The development of a national surveillance system for hospital-acquired infections in Denmark

the Hospital Acquired Infections Database - HAIBA

Sophie Gubbels MD MSc

Department of Infectious Disease Epidemiology
Statens Serum Institut
Artillerivej 5
2300 Copenhagen S
Denmark

PhD thesis

University of Copenhagen
Denmark

2016

Supervisors
Kåre Mølbak, Associate professor, MD DMSc
Department of Infectious Disease Epidemiology
Statens Serum Institut, Copenhagen, Denmark

Brian Kristensen MD PhD
Department of Microbiology Surveillance and Research
Statens Serum Institut, Copenhagen, Denmark

Marianne Voldstedlund MD PhD
Department of Infectious Disease Epidemiology
Statens Serum Institut, Copenhagen, Denmark

Assessment committee
Thomas Benfield, Professor, MD DMSc (Chairperson)
Department of Clinical Medicine
University of Copenhagen, Denmark

Mette Nørgaard, Associate professor, MD PhD
Department of Clinical Epidemiology, Institute of Clinical Medicine
Aarhus University Hospital, Denmark

Marc J.M. Bonten, Professor, MD PhD
Department of Medical Microbiology, University Medical Center Utrecht, the Netherlands
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

This thesis has been submitted to the Graduate School of The Faculty of Health and Medical Sciences, University of Copenhagen on 9 August 2016.

Defence date and venue: 27 January 2017 at the Lecture Hall, Statens Serum Institut, Artillerivej 5, Copenhagen, Denmark

Cover: *Hand hygiene*, by Oliver Gubbels-Khalifé

Printed in Denmark
ISBN 978-87-999602-0-0

Preface

It is an honour to have had the chance to be part of the fascinating journey of building the Danish Hospital Acquired Infections Database (HAIBA). The fact that every person in Denmark has a personal identification number (CPR-number), which is registered everywhere – from the general practitioner, to the tax services, the bank account, the telephone contract and the library – can be quite a shock for persons coming from other countries. Indeed, I had to get used to giving out my number so often. Somehow, it brought me a certain apprehension and fear for misuse of the data. However, I got to know the Danish society as one where trust is a very highly cherished value – although challenged sometimes – and through my work at the Statens Serum Institut I have had the chance to experience the benefits and possibilities this systematic registration can bring. HAIBA is the perfect example of this. It is the first surveillance system for HAI, which is countrywide and requires no additional data entry from any physician, infection control specialist or microbiologist.

Building HAIBA required a set of skills, which branched over a wide range of areas of expertise – epidemiologists, statisticians, microbiologists, infection control nurses, clinical specialists, software developers, it-architects, lawyers, politicians and managers – each with their own jargon and expectations. We all had to try to understand each other and build a system that was optimal for each of us. Communication was the key word. The fact that I did not speak sufficient Danish at the beginning of the project did not make it easier!

It has been a great pleasure to work with so many motivated and knowledgeable persons over the years.

In the first place, I would like to thank the HAIBA group that worked on the development and now on the maintenance of HAIBA on a daily basis. My principal supervisor Kåre Mølbak for being such an inspiration and for all the support; from the overall visions and strategies to the tiniest technical details, from scientific questions to administrative issues. Your door is always open. Brian Kristensen and Marianne Voldstedlund, thank you for giving me more insight in microbiology. It is not an easy field to catch in computer

algorithms that leave no space for human interpretations. Thanks to Jens Nielsen for the great collaboration on the coding of the algorithms. While making so many drawings to make sure that we really captured all situations we possibly could think of, we often had heated discussions, but these always led to an even better result. Kenn Schultz Nielsen, your optimism, even when we face big challenges is phenomenal. Your understanding of surveillance and epidemiology, while also having great insight in IT-architecture provided that bridge between what was needed from a surveillance point of view and the best IT-solutions to get there. Manon Chaine, you started with us as a master student and made yourself indispensable by teaching yourself how to develop the output of HAIBA that is now online. You also did very important work on the development of the case definition for *Clostridium difficile*. Søren Jakobsen, it was pleasure working with you on the project management of HAIBA and discussing different strategies, risk assessments and road maps. Orla Condell, Laura Espenhain, Silvia Funke, Lara Ricotta, Victoria Fernandez de Casadevante and Jonas Kähler, you have strengthened the team at different points in time to assist in validation studies, bringing new ideas and looking at issues from different angles.

The work of HAIBA would, however, not have been possible, had we not had support from many other persons. I will attempt to mention those that were involved since the start in 2011.

During the proof of concept period and the early development of HAIBA Lars Steen Anker, Marlene Haahr and Bodil Bjerg were instrumental. The National Center for Infection Control has given us valuable advice regarding the point prevalence surveys and infection control: Christian Stab Jensen, Elsebeth Tvenstrup Jensen and Jette Holt. In addition, colleagues from the Department of Infectious Disease Epidemiology have supported in many ways: Henrik Bang, Michael Galle, Louise Køhler Olsen, Sofie Holtemann. Others from around the institute shared their valuable experiences with us, particularly Jakob Sandegaard, Nete Nielsen, Katharina Olsen, Mette Fogh Ho-Lanng, Anni Buhr and Camilla Wiberg Danielsen.

The Advisory Forum provided the important link to the regions and kept us sharp with their valuable feedback: Preben Ditlev Cramon, Svend Ellermann-Eriksen, Jørgen H. Engberg, Morten Freundlich, Henrik Friis, Ulrik Gerdes, Annemarie Hellebek, Anette Holm, Elin Kallestrup, Jan Koldbro, Gitte Køtter, Annmarie Lassen, Jesper Laustsen, Bettina Lundgren, Elin Lyngsø, Jens Kjølseth Møller, Henrik C. Schønheyder, Jens Kjær Rasmussen, Jan Utzon and Christian Østergaard.

Also others in the regions have played important roles in the development, validation and implementation of HAIBA: Leif Percival Andersen, Jacob Anhøj, Magnus Arpi, Jonas Rosendal Bager-Elsborg, Paul Daniels Bartels, Lisbeth Kyndi Bergen, María Kristín Björnsdóttir, Ram Dessau, Trine Frederiksen, Per Gundtoft, Kim Oren Gradel, Hans Peder Graversen, Dennis Schrøder Hansen, Anne-Marie Sigsgaard Hansen, Anne-Marie Blok Hellesøe, Ole Heltberg, Jens Otto Jarløv, Thøger Gorm Jensen, Jette Nygaard Jensen, Christoffer Calov Jørgensen, Henrik Kehlet, Poul Kjældgaard, Nina Kling, Jenny Dahl Knudsen, Søren From Knudsen, Annabel Lee Krarup, Jeppe Lange, Lars Lemming, Rita Andersen Leth, Martin Lindbergs-Larsen, Niels Frimodt Møller, Helle Neustrup, Bente Olesen, Kirsten Pedersen, Lasse Pirk, Arne Poulstrup, Steen Rasmussen, Jakob Redder, Thor Schmidt, Lars M. Storm and Lea Toftegaard Weisdorf. In addition, Christina Vandenbroucke-Grauls from the VU University Medical Center in Amsterdam provided useful perspectives in an early stage of the development of the case definitions and always followed the development with interest.

Several committees supported the coordination of HAIBA. The steering committee that oversaw the development of HAIBA: Bodil Bjerg, Søren Brostrøm, Birgitte Drewes, Frederik Gerstoft, Mette Grønholt Harbo, Helle Engslund Krarup, Asja Kunøe, Jesper Myrup, Lisbeth Nielsen, Lars Villiam Pallesen, John Erik Pedersen and Tove Rønne. The internal steering committee that secured collaboration at Statens Serum Institut during the development: Birgitte Drewes, Elsebeth Tvenstrup Jensen, Maria Friis Larsen, Lars Villiam Pallesen, Robert Leo Skov and Heidi Søltoft. The current coordination group for the production system: Anders Brahm, Dorte Vesterholm Lind, Karen Marie Lyng, Jan Poulsen, Vahid Raben, Jean Rygaard and Flemming Per Voss.

For legal and political clarifications, we have had advice from Martin Bagger Brandt, Sara Fini, Ole Jensen, Pia Jespersen, Tyra Grove Krause, Anja Sofie Nielsen, Marie-Louise Paludan, Tove Rønne, and Erika Wolf.

For technical support to different aspects, both IT-development of management of IT-systems, many persons were and still are involved: Judy Eskildsen, Milan Fajber, Mark Hanger, Henrik Mulvad Hansen, Lars Rylander Holm, Stine Holm, Jens Hvidberg, Anders Jensen, Steen Eide Joensen, Dorte Vesterholm Lind, Thomas Tjørnelund Nielsen, Charlotte Nobel, Lise Kristine Højsgaard Schmidt, Peter Spanggaard and Erik Villadsen.

I would like to thank all my colleagues from the Department of Infectious Disease Epidemiology, for being such a positive and inspiring group of people. Special thanks to Tyra Grove Krause for advice and support and to Katrin Gaardbo Kuhn, who became a dear friend.

Of course, I would also like to thank my family for their support. My mother for her interest in my work and for travelling to Denmark, whenever we needed help. Jade, thank you for all your encouragement. With your knowledge of hospital performance and quality indicators and my experiences with HAIBA, we had some very interesting discussions that we both could take back to our different projects. Oliver, you are such a curious and funny little boy. Thank you for dragging me away from my thesis sometimes for some healthy distraction!

Copenhagen, August 2016
Sophie Gubbels

Table of content

Summary in English

Hospital-acquired infections form a large burden on patients and healthcare systems with an estimated 4.5 million hospital-acquired infections in Europe each year and 37,000 deaths due to hospital-acquired infections. At least 20% are thought to be preventable.

When actively used, surveillance plays an important role in the prevention and control of hospital-acquired infections. Active continuous surveillance is, however, laborious and costly. Point prevalence surveys have been used as a more feasible form of surveillance, although these do not allow for analysis of trends over time. Another approach to reduce resources was introduced in the mid-1980's, changing from "facility-wide" or "comprehensive" surveillance of hospital-acquired infections to "priority-directed" surveillance focussing on specific areas, such as departments or types of infections. Since 2000, the use of electronic (semi-)automated surveillance systems has been explored, showing great potential for continuous monitoring, while reducing the labour-intensive manual work for healthcare personnel. The Danish Hospital Acquired Infections Database (HAIBA) is the first nation-wide fully automated surveillance system for hospital-acquired infections.

The aim of this thesis is to describe the surveillance system, to discuss our considerations regarding challenges in terms of data collection, analysis, and interpretation, and ultimately, to discuss how HAIBA can contribute to infection control in the individual hospitals.

HAIBA currently monitors hospital-acquired bacteraemia, urinary tract infections and *Clostridium difficile* infections. Soon, infections after total hip and knee prosthesis will be added. These infections are monitored through case definitions in the form of computer algorithms based on data from the Danish National Patient Registry and the Danish Microbiology Database. Data on antibiotic treatment are also being collected, but are not yet complete for the entire country.
In order to understand registration practices and assess the quality and completeness of data sources, imports of data sources are continuously evaluated. Variations in practices and data quality across the country can pose challenges in the interpretation of data.

The accuracy of the algorithms was also assessed through validation against reference data. Particular attention in this thesis was paid to hospital-acquired bacteraemia and urinary tract infections. Comparison to point prevalence surveys showed a sensitivity of 36% and a specificity of 99% for hospital-acquired bacteraemia. Higher concordance was found when comparing to data from the North Denmark Bacteraemia Research Database: a sensitivity of 50% and a positive predictive value of 75%. The algorithm was also compared to surveillance data from the Department of Clinical Microbiology at Aarhus University Hospital, showing a sensitivity varying between hospitals from 44-56% and a positive predictive value from 82-95%.
The algorithm for hospital-acquired urinary tract infections showed a sensitivity of 50% and a specificity of 94% compared to point prevalence surveys.
Discrepancies between the algorithms and reference data identified areas for improvement, but in some cases also highlighted the limitations of the reference data.

The primary users of HAIBA are the infection control teams and clinical departments. There are also a number of other groups, interested in using data from HAIBA, such as hospital management, regional surveillance collaborations, regional and national politicians, Statens Serum Institut and citizens. Each group may use data in a different way requiring adapted output models. A number of different output models have already been created.

Data currently provided by HAIBA are not adjusted for confounders, making comparisons problematic. This is one of the areas that need further development. Other future developments include new case definitions to monitor more types of infections, including new data sources to refine current and future case definitions and creating a statistical tool to interpret trends over time. HAIBA also opens opportunities for a wide variety of research projects.

However, the most important step at this point is for users to find ways to apply the data. The burden of hospital-acquired infections can only be reduced by changes at the patients' bedside. Now that less resources are needed for data collection, efforts can focus on interventions and finding the best applications for HAIBA to support these.

Summary in Danish – Dansk resumé

Sygehuserhvervede infektioner udgør en stor byrde for patienter og sundhedssystemer med 4,5 millioner sygehuserhvervede infektioner estimeret i Europa hvert år og 37.000 dødsfald. Mindst 20 % af disse menes at kunne forebygges.

Såfremt overvågning anvendes aktivt, spiller den en vigtig rolle i forebyggelse og bekæmpelse af sygehuserhvervede infektioner. Aktiv løbende overvågning er imidlertid arbejdskrævende og omkostningsfuld. Prævalensundersøgelser har været brugt som en mere overkommelig form for overvågning, selvom disse ikke tillader analyse af tendenser over tid. En anden tilgang til en mindre ressourcekrævende overvågning blev indført i midten af 1980'erne, hvor fokus skiftede fra "bred" eller "omfattende" overvågning til "prioriteret" overvågning, der fokuserede på specifikke områder, såsom bestemte afdelinger eller typer af infektioner. Siden 2000 er brugen af elektroniske (semi-) automatiserede overvågningssystemer blevet undersøgt. De viser stor potentiale for løbende overvågning og reducerer samtidig det arbejdskrævende manuelle arbejde med dataindsamling. Hospital Acquired Infections Database (HAIBA) er det første landsdækkende fuldautomatiske overvågningssystem for sygehuserhvervede infektioner.

Formålet med denne afhandling er at beskrive overvågningssystemet, samt at diskutere vores overvejelser med hensyn til indsamling af data, analyse og fortolkning, og i sidste ende, at diskutere hvordan HAIBA kan bidrage til bekæmpelse af infektioner på de enkelte sygehuse.

HAIBA overvåger i øjeblikket sygehuserhvervede bakteriæmier, urinvejsinfektioner og *Clostridium difficile*-infektioner. Infektioner efter total hofte- og knæprotese tilføjes snart. Disse infektioner overvåges gennem anvendelse af case definitioner der er implementeret i form af computeralgoritmer. Disse er baseret på data fra det danske Landspatientregister og den danske Mikrobiologi Database. Data om antibiotisk behandling bliver også indsamlet, men disse er endnu ikke komplette for hele landet.

For at forstå registreringspraksis og vurdere datakildernes kvalitet og hvor komplette de

er, evalueres data løbende. Der beskrives, hvordan variationer i praksis og datakvalitet på landets sygehuse kan udgøre udfordringer i fortolkningen af data.

Kvaliteten af algoritmerne blev vurderet gennem validering mod referencedata. Særlig fokus, i denne afhandling, var på sygehuserhvervet bakteriæmi og sygehuserhvervede urinvejsinfektioner. Sammenlignet med prævalensundersøgelser viste hospitalserhvervet bakteriæmi en sensitivitet på 36 % og en specificitet på 99 %. Højere konkordans blev fundet ved sammenligning med data fra North Danmark Bacteraemia Research Database; en sensitivitet på 50 % og en positiv prædikativ værdi på 75 %. Algoritmen blev også sammenlignet med overvågning af data fra Klinisk Mikrobiologisk Afdeling på Århus Universitetshospital. Denne analyse viste en sensitivitet, der varierede mellem sygehusene fra 44 % til 56 %, og en positiv prædiktiv værdi fra 82 % til 95 %.
Algoritmen for sygehuserhvervede urinvejsinfektioner viste en sensitivitet på 50 % og en specificitet på 94 % i forhold til prævalensundersøgelser.
Uoverensstemmelser med referencedata definerede områder med mulighed for forbedring for algoritmerne, men fremhævede i nogle tilfælde også begrænsninger ved referencedata.

De primære brugere af HAIBA er hygiejneorganisationer og kliniske afdelinger. Der er forskellige andre grupper, der er interesserede i at bruge HAIBA såsom hospitalsledelsen, regional overvågning, regionale og nationale politikere, Statens Serum Institut og borgere. Disse grupper vil bruge data på hver deres måde, og dette kræver tilpassede output-modeller. Nogle forskellige output-modeller er allerede blevet etableret.

De resultater, som i øjeblikket leveres af HAIBA, korrigeres ikke for confounders, hvilket problematiserer sammenligninger. Dette er en af de områder, der kræver yderligere udvikling. Andre fremtidige udviklingsprojekter indeholder nye case definitioner for at overvåge flere typer af infektioner, nye datakilder til at forfine de nuværende og fremtidige case definitioner samt udviklingen af et statistisk redskab til at fortolke tendenser over tid. HAIBA giver også mange muligheder for forskningsprojekter.

Det vigtigste skridt er nu at finde måder at anvende data fra HAIBA. Byrden af sygehuserhvervede infektioner kan kun reduceres ved ændringer in den virkelige verden direkte ”ved patienternes senge”. Da der kræves færre ressourcer til dataindsamling, kan indsatsen fokusere på interventioner og på at finde de bedste anvendelser af HAIBA.

List of Papers

This thesis is based on the following papers.

Paper I **The development and use of a new methodology to reconstruct courses of admission and ambulatory care based on the Danish National Patient Registry.** Gubbels S, Nielsen KS, Sandegaard J, Mølbak K, Nielsen J. Int J Med Inform. 2016 Nov;95:49-59. doi: 10.1016/j.ijmedinf.2016.08.003. Epub 2016 Aug 18.

Paper II **Utilization of blood cultures in Danish hospitals, a population-based descriptive analysis.** Gubbels S, Nielsen J, Voldstedlund M, Kristensen B, Schønheyder HC, Vandenbroucke-Grauls CM, Arpi M, Björnsdóttir MK, Knudsen JD, Dessau RB, Jensen TG, Kjældgaard P, Lemming L, Møller JK, Hansen DS, Mølbak K. Clin Microbiol Infect. 2015 Apr;21(4):344.e13-21. doi: 10.1016/j.cmi.2014.11.018. Epub 2014 Nov 23.

Paper III **National automated surveillance of hospital-acquired bacteraemia in Denmark using a computer algorithm.** Gubbels S, Nielsen J, Voldstedlund M, Kristensen B, Schønheyder HC, Ellermann-Eriksen S, Engberg J, Møller JK, Østergaard C, Mølbak K. (accepted in Infect Control Hosp Epidemiol)

Paper IV **An automated surveillance system for hospital-acquired urinary tract infections in Denmark.** Condell O, Gubbels S, Nielsen J, Espenhain L, Frimodt-Møller N, Engberg J, Møller JK, Ellermann-Eriksen S, Schønheyder HC, Voldstedlund M, Mølbak K, Kristensen B. J Hosp Infect. 2016 Jul;93(3):290-296. doi: 10.1016/j.jhin.2016.04.001. Epub 2016 Apr 19.

Corrigendum to 'An automated surveillance system for hospital-acquired urinary tract infections in Denmark'. J Hosp Infect. 2016 Dec;94(4):410. doi: 10.1016/j.jhin.2016.09.001. Epub 2016 Sep 21.

List of abbreviations

A&E	Accident and Emergency Room
ATC	Anatomical Therapeutic Chemical
AUH	Århus University Hospital
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CD027	*Clostridium difficile* ribotype 027
CFU	Colony-forming units
CI	Confidence Interval
COHA	Community Onset Hospital Acquired *Clostridium difficile* infections
CPR-number	Danish civil registration number
DCM	Department of Clinical Microbiology
DNPR	Danish National Patient Registry
ECDC	European Center for Disease Prevention and Control
EHR	Electronic health records
Epi-MiBa	Copy of Danish Microbiology Database, for epidemiological use
ESBL	Extended-spectrum β–lactamase-producting bacteria
FTP	File Transfer Protocol
FMK	"Fælles Medicinkort" or "Shared Medicine Card"
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HA-bacteraemia	Hospital-acquired bacteraemia
HA-UTI	Hospital-acquired urinary tract infections
HAI	Hospital-acquired infections
HAIBA	Hospital-Acquired Infections Database
HAIR	Hospital-Acquired Infections Registry
HOHA	Hospital Onset Hospital Acquired *Clostridium difficile* infections
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICU	Intensive Care Unit
IPSE	Improving Patient Safety in Europe
MDS	Microbiological Diagnosis System
MiBa	Danish Microbiology Database

MINIPAS	Patient Administrative System for private hospitals
MRSA	Methicillin-resistant *Staphylococcus aureus*
NPV	Negative predictive value
NDBRD	North Denmark Bacteremia Research Database
PCR	Polymerase chain reaction
PPS	Point prevalence surveys
PPV	Positive predictive value
SIRS	Systemic inflammatory response syndrome
SSI	Statens Serum Institut
UTI	Urinary tract infections
VAP	Ventilator-associated pneumonia
VAE	Ventilator-associated events
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization

How to read this thesis

This thesis provides a description of the Hospital Acquired Infections Database (HAIBA) from a detailed level of data analysis through the accuracy of the results to the applicability of the outcomes. HAIBA is discussed in the context of the Danish healthcare system and historical developments in infection control and surveillance, providing a vision of the potential role of HAIBA in the Danish healthcare system.

Chapter 1 provides an introduction to the burden of hospital-acquired infections, and a historical perspective. In addition, some dilemmas are discussed regarding potential conflicting interests of the public and healthcare providers.

Chapter 2 summarizes the objectives of the thesis.

Chapter 3 includes a brief overview of the Danish healthcare system, after which HAIBA is described, including organizational, legal and IT-technical aspects. In addition, a number of epidemiological concepts are discussed that are relevant for HAIBA. Algorithms for *Clostridium difficile* infections, surgical site infections and pneumonia are also briefly described in this chapter. Since the thesis has a particular focus on hospital-acquired bacteraemia and urinary tract infections, these are discussed in detail in Chapters 7 and 8.

Chapters 4, 5 and 6 discuss the content, completeness and validity of the data sources used in HAIBA: the Danish National Patient Registry, the Danish Microbiology database and the regional medicine modules.

In Chapter 9, the requirements for output models for different user groups are discussed as well as possible applications in practice.

Chapter 10 concludes the thesis, by evaluating the attributes of HAIBA as a surveillance system such as validity, timeliness and usefulness, as well as presenting plans for future developments.

1. General introduction

Hospital-acquired infections (HAI) form a large burden both on healthcare systems and on the individual patient in terms of prolonged length of stay and treatment, long-term disability and excess mortality (1,2).

The proportion of preventable HAI depends on the setting, the preventive measures that have already been taken and baseline infection rates. A 2003 systematic review estimated that at least 20% of HAI could be prevented, based on studies reporting a minimum preventable proportion of 10% and the maximum of 70% (3). The largest potential gain was identified for catheter-associated bacteraemia. A 2011 study suggested that 65%-70% of catheter-associated bloodstream- and urinary tract infections (UTI) could reasonably be prevented, as could 55% of ventilator-associated pneumonias (VAP) and surgical site infections (4).

With the increasing emergence of antimicrobial resistant microorganisms, treatment options become more limited and prevention becomes more important than ever.

Surveillance in itself can reduce the incidence of HAI, by raising awareness and improving an active approach (5). As such, it plays an important role in preventive measures. The

prevention and control of HAI requires a partnership between infection control professionals, clinicians, managers and the government, including enhanced real-time surveillance, in combination with implementation of clinical protocols, improved hand hygiene and environmental cleaning, training, audit and legislation (Code of Practice) (6). It is this combination of interventions that can lead to success and surveillance can form the tool to identify the required changes in hospital policy and targeted interventions. In addition, surveillance data can be used to evaluate the impact of the interventions.

Definitions

The terms 'hospital-acquired', 'healthcare-associated', 'nosocomial', or simply 'hospital' infections are often used interchangeably. Sometimes the combinations 'hospital-associated' or 'healthcare-acquired' can be seen too. Generally, all terms refer to infections contracted from the healthcare environment in a broad sense, including from procedures, devices, patients or staff.

The World Health Organization (WHO) states in its guide *Prevention of hospital-acquired infections* nosocomial and hospital-acquired infection as synonyms and defines such an infection as "An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other healthcare facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staff of the facility" (7). Another publication from WHO uses the terms 'healthcare-associated infections', 'nosocomial infections' and 'hospital infections' interchangeably (8).

Some definitions use the term healthcare-associated infections to refer to infections acquired in healthcare facilities outside an admission. The Infectious Diseases Society of America for instance distinguishes hospital-acquired pneumonia and healthcare-associated pneumonia in this way (9). Similarly, Friedman *et al*. suggest a distinction for bacteraemia between community-acquired, healthcare-associated and nosocomial bacteraemia, where healthcare-associated refers to an association with outpatient contacts and nosocomial with hospitalizations (10).

In other cases, healthcare-associated infections refer to both hospitals and other healthcare facilities, such as the surveillance of the European Centre for Disease Prevention and Control (ECDC), which monitors these infections in acute care hospitals and in long term care facilities (11,12).

Centers for Disease Control and Prevention (CDC) also uses the term 'healthcare-associated infections' and focuses on infections that are associated with devices used in medical procedures, such as central line-associated bloodstream infections, catheter-associated urinary tract infections, VAP and surgical site infections (13).

In the Hospital Acquired Infections Database (HAIBA), we have decided to use the term hospital-acquired infections, because data are primarily based on admissions to hospitals. HAIBA does also include outpatient contacts and these will probably become a larger part of HAIBA in the future. Still, these all have to do with hospitals. Information on nursing homes and other non-hospital healthcare facilities are not (yet) included in the Danish National Patient Registry (DNPR). The abbreviation HAI in this thesis in relation to HAIBA therefore refers to hospital-acquired infections. When it is related to other references, it is less clearly defined and reflects the wide variety of terms and understandings of the terms that exist in medical literature, making it more challenging to get an overview of the epidemiology of these infections.

Epidemiology and burden of HAI

A systematic review estimated around 4.5 million HAI each year in Europe and 37,000 deaths due to HAI (5). In 2002, the CDC estimated 1.7 million HAI per year in the United States (US), leading to 99,000 deaths (14). An 2011 report estimated 722,000 HAI and 75,000 deaths from HAI in the US (15).

A European point prevalence survey (PPS) estimated a prevalence of 6.0% of patients with at least one HAI (11). In Denmark, the prevalence of HAI has been estimated twice a year in prevalence studies, coordinated by the Statens Serum Institut (SSI) since 2008 (16). The prevalence of bacteraemia, UTI, respiratory infections, postoperative infections for all

participating hospitals together varied between 6.5% and 9.2% between 2009 and 2014. Intensive care units (ICUs) had the highest prevalence of HAI, varying between 21.6% and 44.8%.

UTI, surgical site infections, bloodstream infections and pneumonia account for more than 80% of all HAI (1). *Clostridium difficile* infections are the most common cause of hospital-acquired gastro-enteritis, accounting for 48% of infections (11).

Depending on different assumptions, direct costs of HAI in the US range from 28-34 billion USD to 36-45 billion USD (17). Costs of surgical site infections are estimated at 1 billion Danish Kroner per year; around 2% of all hospital costs (18). In addition to that, there are the costs of the other types of HAI.

Historical perspective

Without aiming to give a comprehensive overview of the history of surveillance of HAI and infection control, a summary of key events in history will put the work of HAIBA in perspective.

Medieval hospitals

In Europe, the first hospitals were established in the 12th century, usually outside the city walls and with large burial grounds (19). In medieval times, large numbers of hospital patients died of epidemic infections, often smallpox and plague. Postoperative mortality rates of 60-80% were common. There was little knowledge of cause and spread of disease. In addition, the practice of cautery during surgery, in which a burning iron was pushed into the wound until it reached the bone, lead to many surgical site infections. In such a setting it is not surprising that, when a sick person had to enter the hospital, his or her property was disposed of and, in some regions, a requiem mass was held.

On the other hand, in Egypt, knowledge on hygiene seems to have been more advanced at the time. Moses ben Maimon, who lived from 1135 to 1204, taught that cleanliness was the physician's best friend (20). He is supposed to have said: "Never forget to wash your hands after having touched a sick person" and "I dismount from my animal, wash my hands, go forth to my patients."

Advances in medical and public health

In the late 1600s and 1700s, death reports were being used to measure the health of populations (21). Some important advances were made towards the end of the 18th century in terms of infection control and understanding of disease spread. Edward Jenner demonstrated in 1796, that inoculation with cowpox could protect against smallpox (13). Quarantine was introduced for persons suspected of plague. Woollen or cotton goods were checked by having a 'sleeping servant' sleep on them. If this person did not get ill, the goods were considered safe.

In the mid-1800s, Sir Hector Cameron, an associate of Joseph Lister, reported tetanus, erysipelas, septicaemia, pyemia, and gangrene were never absent and often epidemic at the Glasgow Royal Infirmary (19). Hygiene still had little attention. Hospitals had infestations of lice and vermin. Operation rooms were rarely cleaned and thus had faeces, urine, blood and pus on the floors. Hands were never washed before surgery. Disease was believed to spread through bad air and was thought to be influenced by the 'four humours'.

In middle of the 19th century, three persons started using epidemiological methods to identify risk factors for infections: Ignaz Semmelweis in Austria, Oliver Wendell Holmes in the US and Florence Nightingale in India and the Crimea.

Ignaz Semmelweis was a Hungarian obstetrician who led the First Obstetric Clinic in the Vienna General Hospital from 1846 to 1849. Due to a mortality rate of around 10%, his clinic had a very bad reputation among the population and women would rather give birth on the street than be admitted to the clinic. The Second Obstetric Clinic in the same hospital had a much lower mortality rate around 4%. Semmelweis came to the conclusion that the main difference was the personnel; the First Clinic was the teaching service for medical students, the Second Clinic was for the instruction of midwifes. When a friend of his died after having had an accident with a scalpel at a post-mortem examination, Semmelweis made the link to 'cadaverous material' on the hands of doctors and medical students. Semmelweis instructed all personnel to disinfect their hands with chlorine lime. He noted that hand washing was not effective: "The cadaveric particles clinging to the

hands are not entirely removed by the ordinary method of washing hands with soap….For that reason, the hands of the examiner must be cleansed with chlorine, not only after handling cadavers, but likewise after examining patients" (22).
His surveillance data showed a dramatic drop in mortality after the introduction of hand disinfection and implementation of strict control of this practice (23).

The findings of Semmelweis met strong criticism and were discarded by many doctors (19). It did not fit with the leading theories and, at the same time, it was probably felt as an insult to medical doctors that they would not have clean hands.

Around the same time, Oliver Wendell Holmes also observed an association between birth attendants and puerperal fever (19). He also pushed for hand hygiene and used epidemiological methods to prove his theories.

Florence Nightingale did a statistical study of sanitation in India and demonstrated that bad drainage, contaminated water, overcrowding and poor ventilation were causing the high mortality. She successfully campaigned to improve the sanitary conditions of the country. She also campaigned for hospital cleanliness during the Crimean War (19). Her *Notes on Hospitals* had an important impact on the design and management of hospitals (20). It improved situations of overcrowding, poor ventilation and lack of cleanliness.

It was not until Louis Pasteur presented his germ theory of disease in 1875 when a good explanation could be given for the observations of Semmelweis, Holmes and Nightingale. Further discoveries on the germ theory followed soon. In 1876, Robert Koch proved that a bacterium could be a specific infectious agent, through his work on anthrax. In 1886, Pasteur successfully immunized a boy who had been bitten by a rabid dog with inactivated rabies virus.
In response to this new knowledge the use of soap increased in the late 19th century, milk pasteurization was introduced, as well as water treatment systems and sewer systems (24).

Hospitals also became cleaner places and medical techniques improved (19). Joseph Lister published the concept of surgical asepsis in *the Lancet* in 1867 (25). This decreased the post-amputation mortality from 45 to 15% (19). In 1890, William Halsted introduced rubber gloves.

In the 1940s incidence of tuberculosis, diphtheria, pertussis, measles and puerperal sepsis declined, even before the introduction of antibiotics. With the discovery of antibiotics by Alexander Fleming in 1928 a new era started, although it took 17 years before they were introduced in medical practice (26). The fear for infections reduced and they were even thought to disappear as a healthcare problem. However, as early as 1950s epidemics with *Staphylococcus aureus* emerged, related to antibiotic resistance (19).

Infection control and surveillance

In the 1930s, it was suggested to appoint a single individual responsible for collecting data on HAI and to apply epidemiology. The earliest formal infection control programs in the US were introduced in the 1950s (27).

The Study on the Efficacy of Nosocomial Infection Control (SENIC) carried out in the 1970s in the US found that hospitals could reduce their HAI rates by approximately 32%. Four main components of infection surveillance and control program were identified: 1) appropriate emphases on surveillance activities and vigorous control efforts, 2) at least one full-time infection-control practitioner per 250 beds, 3) a trained hospital epidemiologist, and 4) for surgical site infections, feedback of infection rates to practicing surgeons (28). This study is often seen as a landmark in infection control.

Collection of data is time-consuming and costly, particularly when it is done on a daily basis. For this reason, the PPS was introduced. Manual evaluation of each patient was done only on specific study days. PPS have been a component of the Danish infection control programme since 1974 (29), but were first carried out on a regular basis twice a year since 2009 (16).

Since mid-1980s, another approach was introduced with the aim of reducing resources. Focus of surveillance moved away from “facility-wide” or “comprehensive” HAI surveillance, in which continuously all patients were monitored to surveillance on specific areas, e.g. specific departments or types of HAI. This was called “priority-directed” surveillance (23). One form of this was called “surveillance by objective”, in which efforts were matched to the seriousness of the HAI problem (30).

Political interest was reflected in Resolution (72)31 of the Council of Europe, adopted in 1972, aiming to improve hospital hygiene in Europe and promote prevention of HAI. It was up to the individual member states to take measures as they thought suitable (31). In 1984, the Council of Europe again emphasized the importance of hospital hygiene in Resolution (84)20, recommending a strategy for nosocomial infection control. In most countries this did not lead to any specific legislation (32).

It was not until 1994 when a European collaboration was established. The Hospitals in Europe Link for Infection Control through Surveillance (HELICS) network was created as an international partnership of national and regional HAI surveillance systems (33). Its aims were to standardise surveillance methods, to promote and assist the development of new networks, to improve the way results are used in feedback, prevention and cost containment and to promote the integration of surveillance of HAI with routine data collection. In 2005, HELICS surveillance became part of the Improving Patient Safety in Europe (IPSE) network. The European Union, WHO, European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and several major public health institutes supported the IPSE network. In 2008, the surveillance of HAI was transferred to the ECDC under the HAI-net. The surveillance was expanded with a new European protocol for PPS. Surveillance of HAI in long-term care facilities (HALT project) and the support to infection control training in Europe (TRICE project) were continued as outsourced projects.

In the mid-1990s, benchmarking was introduced as quality tool in healthcare (34). Benchmarking involved the process of comparisons between organizations and aimed to identify and implement best practice and improve performance. Public reporting of

information on quality of care of healthcare providers involved the public in the benchmarking process (35).

Patient safety and reduction of the number of preventable medical errors received intensified focus after the report “To Err Is Human” from the Institute of Medicine, published a few years later in 1999 (36).

In line with this, the World Health Assembly adopted resolution WHA55.18 “urging countries to pay the closest possible attention to strengthening healthcare safety and monitoring systems”. Following this resolution the WHO established the World Alliance on Patient Safety, which dedicated its first “Global Patient Safety Challenge” in 2005-2006 to HAI as a major patient safety problem (37).

In Denmark, the Act on Patient Safety came into force in 2004, leading to systematic patient safety work throughout the Danish healthcare system (38).

Approaches to surveillance using information technology

Electronic applications have become a valuable support to surveillance. In 1989, the Central Department of Infection Control at SSI developed surveillance software for HAI, called DANOP (39). This was a minimal dataset for monitoring of surgical site infections. The system was made available for hospitals and was also integrated in WHO’s programme WHOCARE. Between 1991 and 1998 surgical site infections were systematically recorded in a surveillance programme called “Skildvagten” (40). However, in 1995, Poulsen and Jepsen reported no preventive effect of continuous monitoring for surgical site infections (41).

Initiatives exploring possibilities for automated systems have been published since around 2000 (42–61). Many of these systems use algorithms in a semi-automated way, for instance as a first filter to identify patients that need further investigation by manually examining medical records and other available information. Other systems are fully automated and rely solely on electronic data.

There is also a difference in the complexity of automated surveillance systems for HAI. While some systems use simple decision tree algorithms, others use multivariable prediction models. The choice of methodology often depends on the type and the number of data sources available and the requirements of the specific setting.

Terminology

The terms electronic and automated are not always used consistently in scientific literature. For this thesis, the terms were defined as follows:

Electronic surveillance: *surveillance using computerized systems for data retrieval and/or data processing.*

Automated surveillance: *electronic surveillance solely based on algorithmic analysis of electronic health data.*

Semi-automated surveillance: *electronic surveillance based on a combination of algorithmic and manual analysis of health data.*

The limitations of traditional surveillance, regarding manual evaluation of medical records using standardized case definitions, were recognized. The main disadvantages noted were the lack of a standard approach to case finding and difficulty in applying definitions, causing inter-observer differences (62). Automated systems were increasingly seen as promising alternatives, as they removed subjectivity, making them more suitable for analysis over time (63,64).

A 2008 systematic review on automated surveillance systems for HAI concluded that systems based on microbiology data alone had a sensitivity ranging from 63% to 91% and specificity from 87% to >99% (65). Sensitivity when only using administrative data, including discharge diagnoses and pharmacy data, varied from 59% to 96% and specificity

from 95% to >99%. Another systematic review for automated surveillance systems that only use diagnosis codes raised concerns regarding the accuracy of these algorithms (66).

In Denmark, experience with automated surveillance was gained through three main initiatives. The Hospital-Acquired Infections Registry (HAIR) published in 2006 algorithms for hospital-acquired bacteraemia, UTI, pneumonia and surgical site infections (45). This system was further developed in the setting of hospitals in Aarhus county. The algorithms for bacteriaemia and UTI were also evaluated for Lillebælt Hospital in 2015 (52).

The Task Force for Reduction of Hospital-Acquired Infections was established in the Capital Region of Denmark in 2011 (67). The Task Force created surveillance systems for bacteraemia, UTI, surgical site infections, VAP, central venous line associated infections, *C. difficile*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and antibiotic consumption. For bacteraemia and UTI, algorithms were developed for fully automated surveillance.

The Danish Collaborative Bacteraemia Network (DACOBAN) research database contains bacteraemia episodes of three Danish Departments of Clinical Microbiology (DCMs) between 2000 and 2011 (54). The DACOBAN group published an algorithm for bacteraemia in 2012, which they validated against the DACOBAN research database (50,68).

In all Danish automated surveillance systems, the Danish Civil Registration System plays an important role. It was established in 1968 and includes a personal identification number (CPR-number) for all persons alive and living in Denmark (69). From this number both date of birth and sex can be obtained. In addition, individual information was stored in the Civil Registration System, such as place of birth, place of residence, citizenship, continuously updated information on vital status, and the identity of parents and spouses. This registry has become central in the healthcare system over the years. The CPR-number also became the person identifiable key for many other electronic systems, allowing for linkage across systems.

Public interest and hospital engagement

Getting an infection in the hospital, in addition to the condition one is admitted for, is naturally something of great concern for patients and their families. This is often reflected in media attention and decisions from politicians.

While a certain proportion of HAI is preventable, not all HAI are. Mark Cole stated in 2008 that infection control has created its own Sword of Damocles and that "it now needs to deliver sustained improvements to an increasing frail, high risk population" (70). He wrote that the media and policy makers had been largely responsible for the patients' understanding of HAI. He called for clinicians to become more active in shaping the public's understanding, giving patients a more honest account for the aetiology of HAI and that medical science has limitations in prevention. It is interesting to note that the CDC states in its HAI Progress Report that it reports "the progress towards the ultimate goal of eliminating HAI" (71). Although elimination means that it should be reduced to a level where it is no longer a public health threat, in contrast to eradication (which implies complete removal of a disease), this statement may imply to the public that all HAI are preventable.

Also in Denmark, the past years have seen some media attention with strong criticism of infection control and hygiene situations in Danish hospitals. In 2013, journalist Adam Dyrvig Tatt made a documentary in which he spoke with patients who had developed HAI (72). He also went to six hospitals and a slaughterhouse with an ATP-device, which can measure organic material as an assessment of the quality of the cleaning. He claimed that the organic load in those hospitals was higher than in the slaughterhouse.

The Danish author Morten Sabroe, who was himself admitted for surgery in August 2015, wrote on his Facebook page about his experiences and observations of the lack of cleanliness in the hospital. This lead to much response in the media, including calls from the media for patients to report their experiences during hospital stays.

A project in Hvidovre Hospital and Rigshospitalet in 2015 raised media attention as it showed that only 30% of patients washed their hands after toilet use and 60% of healthcare personnel. After installing an alarm that rang when a person had not washed

his or her hands within 10 seconds of flushing the toilet, the proportions went up to 70% and 90%, respectively (73).

The concern of patients regarding HAI was also illustrated by a Danish survey among recently discharged patients (personal communication Søren Thaulow). When asked what factors they found most important when choosing a hospital, most mentioned the waiting time between referral and first contact. Second on the list were HAI, before factors such as knowing how many patients thought that the treatment improved their situation, or the number of medical mistakes. This survey was done in preparation of a project to develop a tool to assist patients when choosing a hospital, an initiative from the Danish Ministries of Health and Finance.

The Task Force for Reduction of Hospital-Acquired Infections, established in 2011 by regional politicians of the Capital Region of Denmark, had the ambitious aim of reducing the incidence of HAI by 50% by the end of 2013 (67). In order to achieve this, surveillance systems had to be put in place to monitor the incidence and reveal any reduction.

While the public may have a somewhat exagerated picture of the hygiene situation in Danish hospitals and expectations may be too high, as Mark Cole suggested, there do seem to be areas that need more attention. In the documentary of Adam Dyrvig Tatt, professor in clinical microbiology at Odense University Hospital Hans Jørn Kolmos confirmed that hospital cleaning has been down prioritized for many years by hospital management. The study on hand hygiene also indicated a clear lack of hand hygiene after toilet use. It is a known challenge to raise compliance to hand hygiene and other infection control measures to optimal levels (74–76). This is influenced by workload and time pressure, working culture, engagement of clinical leadership and financial resources.

It is important for infection control units to assess the costs of HAI and estimate the amount that infection control programs save the hospital in order to be able to compete for hospital budget. For this the primary costs of HAI need to be calculated as the extra length of stay and additional costs due to the infection (77). A systematic review showed that preventive measures have very positive cost-benefit rates (78). In the US benefits of

prevention were estimated to range between 6-7 billion USD (assuming 20% preventable HAI) and 25-32 billion USD (assuming 70% preventable HAI) (17).

However, Pedersen and Kolmos pointed out an interesting dilemma: while it is most favourable from a patient safety point of view to reduce the occurrence of HAI as far as possible, this may not be the optimal point from an economic point of view. There is a point where cost-effectiveness decreases to such an extent that net-costs begin to increase (figure 1.1). This means that from a financial point of view the optimal incidence of HAI will be reached sooner, leaving little financial incentive for hospital management to further reduce HAI. Benchmarking and public reporting to encourage hospitals to optimal levels of patient safety comes naturally as a next step.

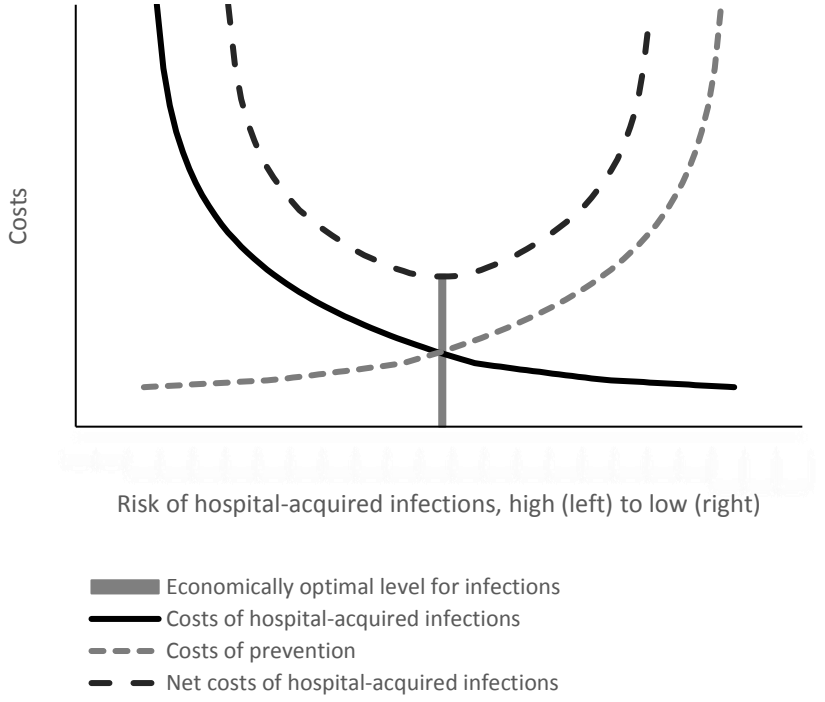


Figure 1.1. The economically optimal level for hospital-acquired infection. Adapted from Pedersen and Kolmos (18).

Some of the first responses to the launch of HAIBA quickly showed that the public expects to be able to compare hospitals. However, from an epidemiological point of view such comparisons are problematic, even more so when without adjustment for confounding.

In addition, rather than identifying best practice, this quickly evolves into pinpointing the worst hospitals. From an infection control point of view, blaming of hospitals may not be the most effective tool to improve hospital hygiene practices.

It is in this field with different forces and interests that HAIBA needs to operate. It is important to emphasize the need for explaining to the public what can and cannot be expected from HAI surveillance and infection control. At the same time the interest, engagement and motivation of healthcare personnel and hospital management needs to be addressed optimally.

2. Objectives

The aim of this thesis is to describe HAIBA as a surveillance system and the algorithms developed, particularly those for hospital-acquired bacteraemia (HA-bacteraemia) and hospital-acquired UTI (HA-UTI).

The specific objectives are:

1. To describe and discuss the system for national surveillance of HAI balancing available data sources and meaningful output for end users (Chapter 3).
2. To describe and discuss the algorithm to relate inpatient and outpatient contacts from the DNPR (Chapter 4).
3. To estimated numbers of courses of admissions and courses of ambulatory care per year and development in their duration (Chapter 4).
4. To gain insight into the underlying data used in HAIBA (Chapters 4, 5 & 6).
5. To describe and discuss the case definition for HA-bacteraemia (Chapter 7).
6. To describe and discuss the case definition for HA-UTI (Chapter 8).
7. To describe and discuss output models supporting end-users (Chapter 9).

3. The surveillance system HAIBA

Surveillance of HAI is a prerequisite for infection control. It is an important tool to identify areas that need additional focus and to evaluate the effect of interventions. Surveillance itself has been suggested to act as an effective intervention, due to the active approach and awareness it generates (5). Generally, four phases can be identified: systematic data collection, data handling, analysis and interpretation, and dissemination to those who need to know. To be effective the dissemination needs to be followed by appropriate action.

Electronic surveillance can provide major improvements to all phases of surveillance. Although data are often still manually entered at the first stage of data collection, human error is eliminated in the following stages. In addition, electronic systems can build in certain validations and corrections to improve this data entry, for example by not accepting empty fields and predefining formats. With systematically collected data, analysis becomes easier and allows for more complex calculations as more data become available and can be handled at the same time. This same aspect may make the interpretation of results possibly more complex. On the other hand, statistical tools can also support interpretation. With electronic systems, sharing of data has become easier allowing for more interesting ways of presenting data.

When automating the surveillance, systematic recording is taken a step further. Rather than entering data on HAI after manual evaluation of medical records, an algorithm analyses existing data sources and systematically identifies cases that meet a predefined set of rules. By using existing data sources, which are maintained in any case for other purposes, the chances are smaller that data are intentionally or unintentionally altered for the desired effect. In addition, the algorithms remove the subjective component that makes traditional surveillance so difficult to interpret. While algorithms may not always register each HAI case correctly, they do produce results that are more consistent.

When building and evaluating surveillance systems there are a number of attributes that can be used to define the quality of the system. For the evaluation of surveillance systems ECDC defined the following attributes: completeness and validity, accuracy in terms of sensitivity, specificity, positive and negative predictive values, timeliness, usefulness, representativeness and other attributes, such as simplicity, flexibility, acceptability, stability, reliability and adequacy (79). Some of these can contradict each other and the optimal balance of attributes is ultimately what makes a system useful (21). Therefore, it is necessary to identify the ones that are most important for the system and accept that others may not be fully achieved. These attributes have been examined during the development of HAIBA and will be discussed in this thesis.

Healthcare setting for HAIBA

The Danish healthcare sector is primarily public. We estimated that public hospitals account for 97.9% of all inpatient contacts (Paper I). Since 2007, Denmark is divided into five regions (figure 3.1). The regions are responsible for the provision of health services; they run the public hospitals and are responsible for the functioning of the primary healthcare sector.

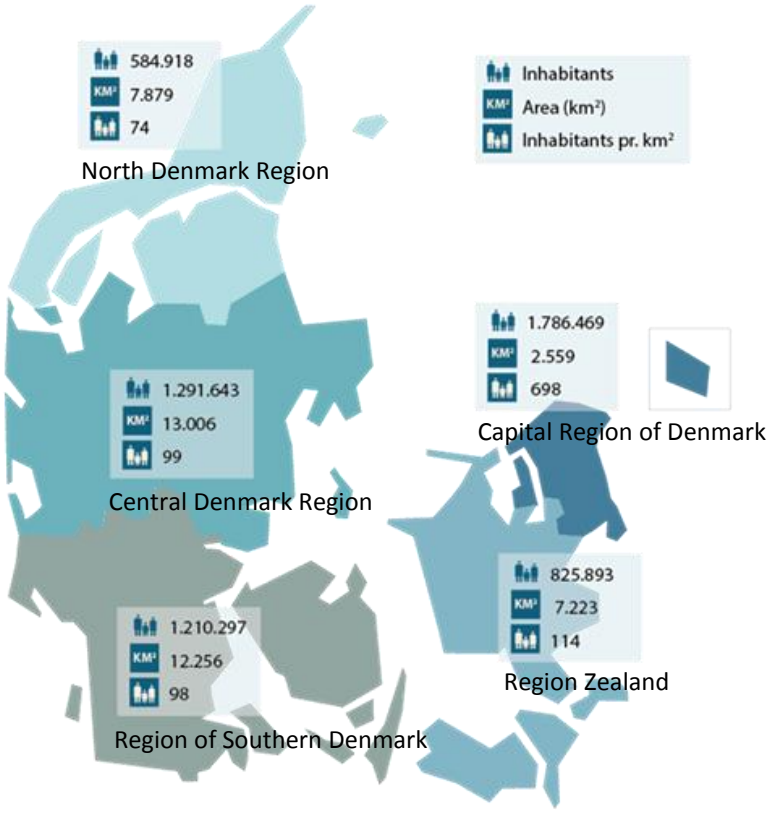


Figure 3.1. Map of Denmark showing the geographic distribution of the five Danish regions.
Source: http://www.regioner.dk/services/in-english/regional-denmark

In order to collaborate, the five regions have organized themselves in an interest organization: Danish Regions. A board of elected regional politicians from the five regions runs Danish Regions. Its mission is "to safeguard the interests of the regions nationally as well as internationally" (80). Amongst others, Danish Regions negotiates the annual financial frames of the regions with the national government. The financing of HAIBA and the Danish Microbiology Database (MiBa) is also included in these negotiations.

Hospital hygiene and infection control in Denmark is organized on regional and hospital level. Every hospital is required to establish a hygiene policy and a hygiene organization. Central in the hygiene organization is the infection control team, typically consisting of infection control nurses and clinical microbiologists and sometimes extended with an epidemiologist and other scientific staff. In some hospitals, the infection control team is located in the Departments of Clinical Microbiology (DCM), in others in the Quality Department. There is no comprehensive overview of the hygiene organizations on

regional and hospital level in Denmark. A first overview was started on the website of SSI (81).

The primary task of an infection control team is to do surveillance of HAI and to respond to signals (82). Response can be to an acute outbreak situation, including isolation of patients, communication with key persons in the hospital, the local public health department and the media. It can also be on a more long-term plan regarding antibiotic stewardship, hand hygiene practice, education, preparedness etc. In recent years, the work of the infection control teams in some regions has been challenged by uncertainties regarding the interpretation of legal basis for access to person identifiable data for the use of quality improvements. Infection control teams need to work closely together with clinical departments, as the actual action for prevention needs to be taken there. It is therefore important that infection control teams present surveillance data to doctors and nurses in these departments in a way that is easy to understand, as they are under time-pressure and not used to interpret epidemiologic data on a daily basis. It is a known challenge to communicate surveillance data in an attractive motivating way that finds response and action in the daily clinical practice (23).

Whether the infection control team is integrated in the DCM or not, the DCM plays an important part in infection control in any case. In 2010, there were 13 DCMs in Denmark, located in 13 public hospitals. These serve all public and private hospitals as well as primary healthcare in their uptake area. The laboratory information systems of the DCMs in Herlev Hospital and Hvidovre Hospital were merged in May 2012, although the DCMs remained independent. In May 2013, the DCM of Hillerød joined their mutual data server.

While much of the healthcare system is run by the five regions, some functions are centrally organized. The SSI has the responsibility for surveillance of notifiable diseases. This responsibility is a shared task for the Department of Infectious Disease Epidemiology and the reference laboratories at SSI. In this role, SSI works closely together with the regions to collect data, to interpret results and to advice on interventions. In addition, the National Center for Infection Control at SSI advises hospitals on hospital hygiene and infection control. This unit also develops national guidelines in this field.

How it all began…

To be able to monitor HAI in a systematic comprehensive way on a national level, there was a need for national surveillance data, which were uniformly collected, gave a complete picture, including patients transferred between hospitals and regions, and was not dependent on manual data entry. In the autumn 2011, SSI was requested by the then Ministry of the Interior and Health (now the Ministry of Health and the Elderly) to investigate the possibilities for creating such a nationwide electronic surveillance system for HAI using existing data sources.

The project started with a feasibility study between September and December 2011. The purpose of this pilot was to investigate the technical feasibility of linking existing data to monitor HAI. This was done using data from two hospitals from two different Danish Regions: the Capital Region of Denmark and the Central Denmark Region. Based on the results of this pilot, the Ministry of Health and the Elderly provided funding of 8 million Danish Kroner (approximately 1.13 million euro) to develop HAIBA and implement it as an operational system over the course of three years; between 2012 and 2014.

HAIBA was launched on 4th March 2015 with data on HA-bacteraemia and *C. difficile* infections (CDI) (83–85). Data on HA-UTI were added in October 2015 (86). Infections after total hip arthroplasty will be included in autumn 2016. HAIBA is located on eSundhed, the portal from SSI and the Danish Health Data Authority where health data are made transparent, and can be found through www.haiba.dk.

Early 2017, a new ministerial order for notifiable diseases is expected to come into force. This will make HAI notifiable diseases, to be monitored through HAIBA.

Goals and objectives

The overall goals of HAIBA are:

- To provide national continuous and automated surveillance data, based on existing data sources for specific frequent HAI, as a basis for a strengthened infection control in hospitals.

- To disseminate results in a manner that can be used by infection control specialists, epidemiologists, clinicians, researchers, hospital management, regional and national policy makers and the public, fitting the needs for each of these target groups.

More specifically, the objectives for surveillance through HAIBA are:

- To monitor trends of HAI over time by department, hospital, region, public/private hospitals and for the entire country.
- To provide continuous and representative estimates of the occurrence and burden of HAI in Denmark.
- To provide infection control teams with data to detect areas that need further attention.
- To provide infection control teams with data to support planning and evaluation of the effect of control measures.
- To provide clinical departments with data that can support improvement in infection control and hygiene.
- To provide data to hospitals and regions to support prioritization of resources.
- To encourage epidemiological research on HAI.
- To stimulate collaboration on infection control across hospitals and regions and with SSI.

Organization and stakeholders in development phase

The project group included a project owner, project manager, an epidemiologist, a statistician, an IT-architect, two microbiologists and four scientists.

An internal steering committee within SSI coordinated the collaboration between the different SSI departments involved in the project: the Departments of Infectious Diseases Epidemiology, Microbiology and Infection Control, IT-Projects and Development, IT-production and Support, It-Standards and Architecture, Health Documentation and the Department of Health Analyses.

An advisory group with representatives from each Danish region advised the project group and secured the necessary bridge to the regional and local infection control organizations.

A steering committee with representatives from the Danish Ministry of Health and the Elderly, the Danish Regions, the Regional Health-IT, the Danish Health and Medicines Authority and SSI oversaw the overall project management.

In order to involve all healthcare workers interested in HAIBA and to create a system that was meaningful and acceptable for the target groups, a stakeholder group was established. This group consisted of approximately 120 persons and met twice over the course of the project. A subgroup of around 30 persons met for one workshop to give specific advice on the output of HAIBA.

Organization and stakeholders in production

Since the launch of HAIBA in 2015, the system has been co-financed as a joint public activity between the Danish government and the five Danish regions, under the finance act that is negotiated each year. Around 2.1 million Danish Kroner (approximately 300,000 euro) is available per year. The financing of HAIBA and organizational structure is combined with MiBa.

MiBa and HAIBA have separate groups responsible for the daily operational work, although several persons play important roles in both and there is close collaboration between the two groups. For HAIBA, this group consists of the same persons who formed the project group in the developmental phase.

In 2015, the National Health Documentation and eHealth Authority was separated from SSI into an independent authority, the Danish Health Data Authority. This authority is responsible for the collection and handling of most of the data imported into HAIBA and for the servers on which HAIBA runs, as well as for parts of the production of MiBa. In order to secure data quality and stable production a shared coordination group for MiBa

and HAIBA was established including the heads of the involved departments from SSI and Danish Health Data Authority.
The advisory group for HAIBA with two representatives from each region was maintained to secure close collaboration with the persons responsible for infection control in the regions and hospitals. MiBa also has a corresponding group of representatives.

After the summer of 2016, a new body will be established that oversees IT-systems in healthcare that are co-financed between the state and the regions. This steering committee will be able to take high-level strategic decisions, without having to open up the financial negotiations and may secure synergy between different systems.

In the process of establishing this steering committee, it became clear that there is a need for a lower level steering committee for MiBa and HAIBA, with representatives from SSI, Danish Health Data Authority and the regions that has a mandate to take more hands-on decisions to do with technical issues.

Legal framework

The following description gives an overview of the legal basis for HAIBA, as clarified at the time of writing. De clarification process is not finalized at this point, and may still reveal new challenges and solutions.

The legal basis for HAIBA to receive and handle data lies in Act nr. 429 from 31 May 2000 regarding handling of information on persons ("persondataloven"). This act includes regulations for collection, archiving, internal use, registration, linking and disclosure of data of persons, as described in § 3, stk. 1, nr. 2.[1]
Handling of general data, which are not traceable to individual persons, is regulated in § 6, stk. 1, nr. 5 and § 6, stk. 1, nr. 6. In § 7, handling of health information of individual persons is described; § 7, stk. 1 prohibits use of these data. This prohibition does not apply when it is necessary for preventive medicine, medical diagnosis, patient treatment and when the person handling the data works in the healthcare sector and has, according to

[1] The Danish system for citation of legislation is maintained throughout this text. For comparison, in the British system § 3, stk. 1, nr. 2 would be written as s. 3(1)(b).

the law, obligation for confidentiality, § 7, stk. 5. This paragraph may also give HAIBA the necessary legal basis to return data to the regions and thus for use on regional and hospital level.
Act nr. 2012 from 14 November 2014 ("sundhedsloven"), § 195 regulates that it is the responsibility of regional councils, municipal boards, healthcare personnel and private persons or institutions running a hospital and others to provide data to central authorities after further specification of the minister of health. Furthermore, § 222 describes that SSI has the task to prevent and control infectious diseases. The nature of this task requires a close collaboration with the regions and exchange of data from the regions to SSI and back.

Act nr. 814 from 27 August 2009 ("epidemiloven"), § 26 forms the basis for the Ministerial order for notifiable diseases, which specifies the surveillance systems for notifiable infectious diseases. This Ministerial order is currently under revision. The new version will also make HAI notifiable. The Ministerial order is expected to come into force early 2017. It remains to be clarified what the legal basis is for the regions to receive data from HAIBA and be able to handle them.

With the legal basis in place, HAIBA still needs to be registered with the Data Protection Agency. Currently, HAIBA is registered as a research database under the title "Sygehuserhvervede infektioner" with number 2015-54-0942. This needs to be changed, in order to be able to send data on individual persons to the regions. HAIBA will be registered as an administrative database, meaning that it can be used for the following purposes: surveillance, patient treatment, quality assurance, research and case investigations.

Epidemiological considerations

Incidence and prevalence

The number of HAI gives an indication of where problems occur. To develop stronger evidence, incidence and prevalence need to be calculated. These can put the data into perspective, taking differences in population size and risk into account.

Incidence refers to the number of new HAI within a defined population and during a specific period, while prevalence refers to the number of active HAI in a defined population during a specific period.

For incidence, there is a choice of four types of calculations (23,87):

- Infection ratio: the number of new HAI divided by the number of patients at risk during a specific period. Infection ratio is often referred to as infection rate.
- Infection proportion: the number of patients with ≥ 1 new HAI divided by the number of patients at risk during a specific period.
- Incidence density: the number of new HAI divided by the number of patient-days at risk during the period of surveillance. The incidence density does not assume complete follow-up of subjects, but it does assume that all time at risk is equal. Often, only the first HAI is included, since the risk of acquiring a second HAI is different from the risk of acquiring the first HAI.
- Cumulative incidence: the number of new HAI divided by the total number of patients free of disease, but at risk of disease at the start of the period. This is also often referred to as the attack rate.

The denominator for incidence density has been debated. The use of catheter days as denominator for HA-UTI showed to have a problematic effect: those departments that had effectively reduced their catheter days, subsequently had a lower denominator and a relatively higher incidence of catheter-associated UTI (88,89). The explanation for this is that the remaining patients with a catheter may be the ones that are at highest risk of developing HA-UTI. In order to distinguish effective and less effective departments it has been suggested to introduce a second indicator, namely the catheter utilization ratio, calculated as catheter days divided by patient days.

In addition, Laupland demonstrated that a denominator based on hospitalizations may introduce hospital admission and referral bias for nosocomial bacteraemia (90). He suggested using a population denominator and standardization of age and sex. In line with this, a study from Funen in the Region of Southern Denmark reported a 28.9% decrease in incidence for nosocomial bacteraemia between 2000 and 2008 calculating nosocomial bacteraemia per 100,000 person years, standardizing for age and sex (91).

This study found that incidence did not change over time when calculating incidence as number of nosocomial bacteraemia per 100,000 hospital bed days.

In the development of HAIBA, we chose to calculate incidence densities for bacteraemia, UTI and CDI. For each patient, only the first HAI within a course of admission was included. To reflect the appropriate hospital population as precisely as possible we chose to use "risk days" rather than bed days from admission to discharge. We defined "risk days" as the days in which a HAI could be registered according to the HAIBA case definitions. For bacteraemia and UTI this meant between >48 hours after admission and ≤48 hours after discharge, or until a HAI occurred. For CDI we also included outpatient contacts as potential exposure. Therefore, these were also included in the denominator calculations (see the description of the CDI case definition later in this chapter). For CDI a new infection was counted if it occurred more than two months (60 days) after the last positive sample, also if this was during the same course of admission.

For surgical site infections, we chose to use the cumulative incidence, i.e. the number of surgical site infections that occurred among all patients that had a primary total hip replacement.

Prevalence may be defined as the proportion of patients with an active HAI during a specific period. When the period is short (i.e. ≤ 1 day) it is called point prevalence, when the period is longer it is referred to as period prevalence (23).

To determine active HAI in HAIBA we defined a duration of illness of 14 days for bacteraemia and UTI after sample taking date/time of the last positive sample and 60 days for CDI. We calculated a time-weighted prevalence proportion as the number of hours that patients with an active infection were present in the department, divided by the number of hours patients at risk were present. Days at risk were determined as the time between >48 hours after admission until discharge. Since prevalence is one of the measures that indicate a type of burden, we also included consecutive HAI during each course of admission for bacteraemia and UTI, not just the first HAI.

Incidence and prevalence are related measures. Duration of infection affects the prevalence estimate: the longer the duration the higher the chance of being included in a prevalence estimate. On the other hand, diseases that are rapidly fatal may have a high incidence, but low prevalence (92). In addition, patients who are admitted for longer are at higher risk of developing an infection and have a higher chance of being included in a prevalence estimate.

The fundamental relationship can be described as follows (23):

$$Prevalence \sim Incidence\ x\ Duration$$

A more detailed variation of this formula was described 1981 by Rhame and Sudderth (93). This calculation is for example used by ECDC when calculating an incidence burden from PPS (11). Two studies assessing the accuracy of the calculation found it useful (94,95). Others question the applicability of the formula (96–98).

Point Prevalence Surveys

Although monitoring by incidence generally is more informative, since it reflects the current risk, prevalence estimates are still used in many settings, as they require fewer resources than continuous daily registrations. PPS are an important reference for HAIBA, both in validation of the algorithms and more in general in assessing how HAIBA surveillance relates to the traditional surveillance. Therefore, it is worth discussing the PPS methodology in more depth and understanding its limitations. This is also motivated by the fact that ECDC encourages the PPS approach.

Between 2009 and 2014, PPS have been carried out twice a year on specific days in spring and autumn. A sample of departments, based on voluntary participation, registered all patients in the department on those specific days and whether these patients had recently undergone surgery, received antibiotic treatment and had catheters. In addition, they registered patients with nosocomial and non-nosocomial bloodstream infections, lower respiratory tract infections and pneumonia, UTI and surgical site infections according to standardized case definitions, adapted from CDC case definitions (99,100). It

was also indicated if the infection was acquired in the current department or another clinical setting. If a patient had more than one type of infection, the infections were registered separately. PPS data are usually reported in aggregate form to SSI. For the purpose of the validation of the HAIBA case definitions hospitals were asked to report their case-based data to SSI.

The main limitations of PPS are that they overestimate the risk of developing a HAI, due to the influence of duration and that the numbers of HAI on individual departments are often too small to detect differences with statistical significance (23).

In the practical carrying out of PPS, there are also a number of challenges. The manual evaluation in PPS is known to introduce large inter- and intrapersonal variation, despite standardized case definitions (101,102). Usually, PPS are carried out by staff from infection control teams, who do not know the patients under surveillance. Generally, they do not visit patients during a PPS, but rely solely on the available medical records and laboratory results to assess if patients have a HAI. Most of the time, staff of the clinical departments, who do know the patients, do not allocate time to fill in information gaps. It is not an easy task to evaluate all available data sources and scan them simultaneously for several different types of HAI, keeping in mind all case definitions and an eye on the clock. In addition, medical records are not always consistently kept, making it necessary to dig deep to find the necessary information. If certain symptoms, such as fever, are not properly recorded, a patient might not fulfil the case definition, while the patients actually did have a HAI. Another practical issue is the fact that the microbiological result may not be available at the time of PPS yet, meaning that a patient may erroneously be classified as not having an infection.

The case definition states that an infection was hospital-acquired if it occurred > 48 hours after admission and there are no signs that the infection was already incubating in the first 48 hours (100). This makes it vulnerable to interpersonal variation, as it is not easy to judge if a HAI was incubating in the first 48 hours. However, in some cases there may be a clear note in the records that will give this information. Recording those patients as

having an infection that was not hospital-acquired and others, where notes were not clear, as hospital-acquired gives a biased result.

There are also a number of limitations in the way the denominator is obtained. When recording all patients that are in the department on a specific day, one will also record patients that later turned out to be discharged within 48 hours. Therefore, this population in the denominator will decrease the prevalence estimate. Similarly, for surgical site infections, the denominator is all patients admitted to a department. These patients have not necessarily had a relevant operation to begin with. In addition, the numerator also combines all different surgical sites, giving a mixed numerator and denominator.

Number reported by Danish media and policy makers

Danish media and policy makers often report that 80,000-100,000 patients get a HAI in Denmark per year. These figures are converted from prevalence estimates from the Danish PPS using the number of admission per year from the DNPR. With a prevalence of 8.0% in 1999 and around 1 million admissions per year, the number of HAI was estimated at 80,000 (8.0% of 1 million). Since the PPS resulted in 9.7% in 2003, the figure was updated to 100,000 HAI per year.

These calculations, however, do not take the duration of illness into account. In addition, they do not represent the number of patients developing a HAI, but the number of HAI during an admission, as a patient can develop more than one HAI and can be admitted more than once per year. Lastly, using the contacts in the DNPR as equivalent for admissions, without the algorithm we presented in Paper I, will likely overestimate the number of admissions.

With data from HAIBA, we estimate an overall median of 20,053 first HAI per admission per year (table 3.1). Although surgical site infections and lower respiratory infections are not yet included in this estimate, it does suggest that the annual number of HAI is substantially lower, than was reported over the past years.

Table 3.1. Number of HAI per year as estimated by HAIBA (extract dd. 3 August 2016).

	2011	2012	2013	2014	2015	Median	(Range)
Bacteraemia	2,758	2,635	2,681	2,835	2,639	2,681	(2,635-2,835)
UTI[1]	13,763	13,685	14,001	13,423	12,962	13,685	(12,962-14,001)
HOHA[2]	2,379	2,091	2,165	1,812	1,642	2,091	(1,642-2,379)
COHA[3]	1,562	1,585	1,934	1,983	2,155	1,934	(1,562-2,155)
Total	20,462	19,996	20,781	20,053	19,398	20,053	(19,398-20,781)

[1] UTI=Urinary tract infection; [2] HOHA=Hospital Onset Hospital Acquired *Clostridium difficile* infection;

[3] COHA=Community Onset Hospital Acquired *Clostridium difficile* infection

Assessment of accuracy of HAIBA algorithms

In the validation of the algorithms from HAIBA, we linked data with reference data on individual patients and generated 2x2 tables. These allowed for calculation of sensitivity and specificity. Sensitivity is the proportion of positives as identified by the algorithm among the true positives, while specificity is the proportion of negatives as identified by the algorithm among all true negatives. These two measurements are interconnected. When sensitivity increases, specificity will decrease. Figure 3.2 shows how a more inclusive test or case definition will increase the number of true positives identified (sensitivity), but also includes false positives and thus decreases specificity.

The sensitivity and specificity are affected by the prevalence of the target condition (103). Figure 3.3 illustrates that the sensitivity is likely to be underestimated when the prevalence is low, which is the case for HAI.

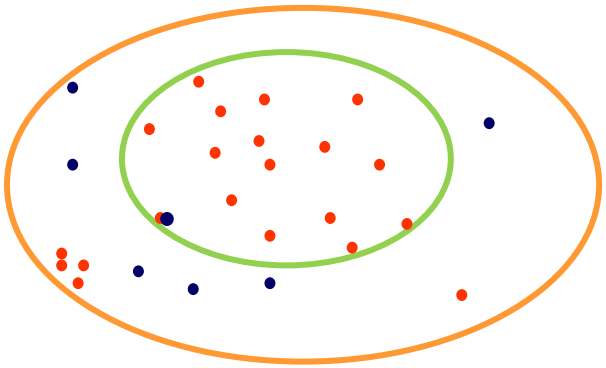


Figure 3.2. Illustration of the relation between sensitivity and specificity, where a narrow test/case definition (in green) identifies mostly true positives (red dots) and few false positives (blue dots) and a wider test/case definition (in orange) includes more true- and false positive.

Two other measures that can be calculated from a 2x2 table are the positive predictive value (PPV) and the negative predictive value (NPV). The former refers to the assessment of how likely it is that a positive result found with the algorithm is a true positive and the latter of how likely it is that a negative result is truly negative. These measures are particularly important when a test is developed as a diagnostic tool that is meant to be used to decide if a patient needs treatment or will have an invasive procedure. For a surveillance tool, they are less important. Nevertheless, they give an indication of the accuracy of the test or case definition. Due to the low prevalence of HAI the PPV is also likely to be low.

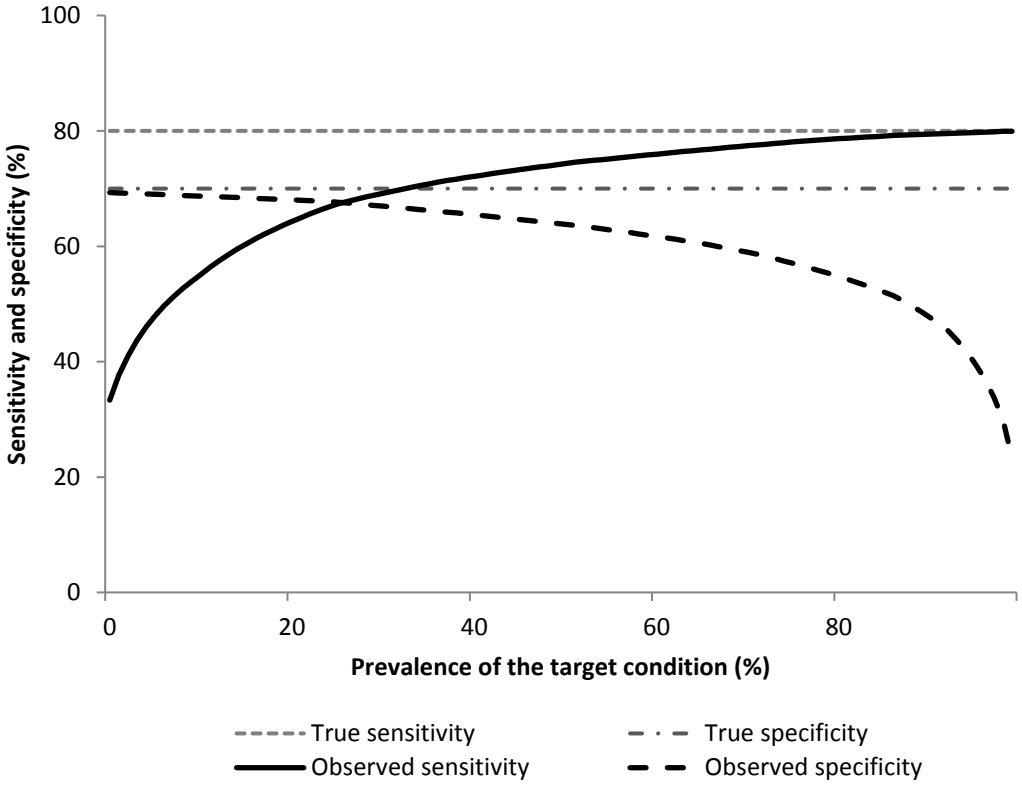


Figure 3.3. Sensitivity will be underestimated most when the prevalence of the target condition is low, and specificity will be underestimated most when the prevalence of the target condition is high. Modified from Biesheuvel *et al.* (103)**.**

The challenge with these validations is to find the optimal reference data. Reference data often have their own limitations, while interpretations of sensitivity, specificity, PPV and

NPV calculations are assuming a reference that represents the truth (103). The optimal reference is often referred to as the gold standard. The term gold standard comes from economists, who used it as a monetary standard, using a stated quantity of gold as the basic unit. The term was first introduced in medical science in its current meaning in 1979 (104). Unlike how the term is often used, a gold standard does not necessarily measure the absolute truth, or the arrow in the bullseye (figure 3.4). It may be the green or the blue one. It is defined as "a time honoured alternative that is considered to be the current standard in the field" and the word standard in this context means "authoritative or recognised exemplar of quality or correctness" (105). A more precise term may be "preferred reference standard".

Figure 3.4. Illustration showing a white arrow representing a test that aims at the true case ascertainment, and green and blue arrows representing tests that have good concordance but do not achieve the true case ascertainment.

With this in mind, comparing HAIBA data to reference data, does not tell us how close HAIBA comes to the truth. It could be the blue arrow, closer to the bullseye, or the green one. All we know is how close HAIBA comes to the reference data. Indeed, discrepancies often revealed limitations of the reference data rather than of HAIBA. For this reason, HAIBA's algorithms were not always modified even if they showed a discrepancy. Each reason for discrepancy was discussed and only adjusted if at all possible with the available

data sources and if this also made sense from a clinical, microbiological or epidemiological point of view. After each change, case definitions were compared again to assess what effect they had had.

The QUADAS-2 tool provides a method for quality assessment of diagnostic accuracy studies (106). The following questions in this tool, which assess the risk of bias, are also relevant to evaluate in relation to validation studies of the HAIBA algorithms:

1. Could the selection of patients have introduced bias?
2. Could the interpretation of the index test have introduced bias? This includes assessment whether the interpretation of the index test was performed blinded to the results of the reference standard.
3. Could the reference standard, its conduct or its interpretation have introduced bias? Important issues here are the earlier mentioned potential for misclassification in the reference standard and whether the interpretation of the reference standard was done without knowledge of the interpretation of the index test.
4. Could the patient flow have introduced bias? This includes evaluation whether all patients were included, so that a 2x2 table could be made, and whether the timing of testing was not too far apart.

Estimates of the accuracy of HAIBA algorithms need to be seen in light of the potential underestimation of sensitivity as well as potential misclassification in reference data. It is also good to keep in mind that HAIBA is not a diagnostic tool for the individual patient. It is a surveillance tool for monitoring of trends among groups of patients. It is therefore particularly important to assess if sensitivity and specificity are constant over time.

Despite their limitations, reference data used to validate the HAIBA algorithms are all derived from existing surveillance systems that are accepted as such. Therefore, estimating how HAIBA relates to them is still meaningful and places HAIBA is the context of HAI surveillance in Denmark.

Case definitions

The initial task given by the Ministry of the Interior and Health was to develop a surveillance system for hospital-acquired bacteraemia, UTI, lower respiratory infections and postoperative infections. Microbiologist, particularly in Region Zealand and the Capital Region of Denmark also wished to include infections with *C. difficile*.

Case definitions were defined in the form of computer algorithms, based on data from the DNPR and the copy of MiBa that has been prepared for epidemiological use (Epi-MiBa). Doing this for a national system, we needed to find a balance between accuracy and simplicity. With local systems it may be possible to refine algorithms with more details, using data that are specifically available in that setting and anticipating specific practices for example in diagnostics or treatment. With a national surveillance, we needed to build algorithms that would be meaningful for all hospitals, using data that are available from all hospitals. Still, local practices affect the data and some of these effects will be discussed in detail in this thesis.

The case definitions for bacteraemia and UTI will be discussed in detail in Chapters 7 and 8. In this chapter, the other case definitions will be discussed in terms of general considerations and choices made.

Clostridium difficile

The Capital Region of Denmark and Region Zealand have seen several outbreaks of *C. difficile* ribotype 027 (CD027) between 2008 and 2011 (107,108). These infections formed a large burden, both on patients in terms of mortality and morbidity, and on the resources in the departments. Much effort has been done in these regions to reduce the incidence of these infections. A surveillance system that could visualize the extent of the problem since 2010 and the expected improved situation after the interventions seemed a useful aim. In addition, we expected that it would be relatively easy to create a case definition, based on microbiological results in relation to admission and discharge data and outpatient contacts.

We developed the case definition, consisting of two parts. Firstly, the identification of laboratory confirmed *C. difficile* (Chaine M. *et al*., manuscript in preparation). Secondly, a definition of whether a CDI was hospital-acquired and whether the onset was in the hospital or in the community (Chaine M. *et al*., manuscript in preparation). This last part was developed as closely as possible to the European case definition for Community Onset Hospital Acquired CDI (COHA) and Hospital Onset Hospital Acquired CDI (HOHA) (109). The case definition defined the following components.

- A CDI was defined as a culture or Polymerase Chain Reaction (PCR) positive for *C. difficile*.
- Results with a specific indication of a non-toxigenic strain were excluded.
- Patients under two years of age were excluded.
- A new case was counted if it occurred >60 days (in hours) after the last positive sample.
- The HOHA risk time was defined as the time between >48 hours after admission and ≤48 hours after discharge.
- The COHA risk time after an outpatient procedure or short admission (≤48 hours) was defined as the time between >48 hours and ≤28 days (in hours) after the procedure or short admission.
- The COHA risk time after a longer admission (>48 hours) was defined as the time between >48 hours and ≤30 days (in hours) after discharge.
- If a new procedure occurred during a COHA risk time then the first period was cut off at 48 hours after the new procedure and a new 48-hour risk time started.
- If a COHA risk time overlapped with a HOHA risk time, then the HOHA risk time overruled.

The different DCMs send their results for CDI in different formats to MiBa, some in free text. Therefore, it took a considerable amount of coding to identify the cases. Several validation studies comparing to local extracts showed a good concordance. The fact that data are not uniformly recorded makes this case definition vulnerable to changes. It needs to be regularly evaluated if the coding is still accurately identifying CDI.

Another limitation is that MiBa is currently not suitable to identify subtypes and toxins. Consequently, these data are not uniformly recorded. A major update of MiBa in the near future should improve both the uniformity of data and the information on subtypes and toxins.

Since CDI is often difficult to treat and can recur over several months there was a need to define when a new episode would be counted. For its surveillance during the past years, the SSI reference laboratory initially used six months after the first positive sample as the cut-off. Later on, this was changed to six months after the last positive sample. The European case definition uses two months since the first positive sample. Sensitivity analyses in HAIBA showed that there is not a large difference between the use of two or six months, but there is between counting the time window from the first or the last positive sample. It was decided for HAIBA to use the European time window of two months. However, it was judged as more correct to count the time since the last positive sample.

Children under two years of age were excluded, because it is uncertain that *C. difficile* is pathogenic at this age.

The part of the algorithm identifying whether *C. difficile* was laboratory confirmed was validated against five local datasets. Preliminary data showed a sensitivity of 99.5% and a PPV of 98.7%. This part of the algorithm will be implemented in the National Register for Enteric Pathogens for national surveillance of CDI – all CDI, not only hospital-acquired – in the next few months.

Surgical site infections

The task of developing surveillance for surgical site infections had to be focused to generate indicators for specific operations. Considerations in the choice of indicators were the availability of data sources for automated surveillance, availability of reference data for validation and whether operations were frequently performed. We decided to prioritize infections after total hip and knee replacement and caesarean section. These are also indicators that are used in other surveillance systems, including that of ECDC (110).

Results for infections after total hip replacement is expected to be made publicly available through HAIBA in autumn 2016. The following components were defined for the computer algorithm:

- Index operations were defined as all total hip replacement, stratified by acute and elective.
- Patients were followed-up for infection for the period of 3-90 days after index operation. For research purposes infections between 91 and 730 days (2 years) were also included.
- Double-sided index operations were followed as two parallel risk periods.
- Only infections that required a re-operation were registered.
- To identify an infection at least three biopsies must have been taken in a time window of 24 hours before and 48 hours after the registered time of re-operation. At least two of these needed to be positive for the same microorganism.

Results of the algorithm were validated against three data sources: (1) a database containing systematic recordings from the Capital Region of Denmark, where surgeons have judged upon re-operation whether there was an infection, (2) a database from Lundbeck for Fast-Track hip and knee surgery, in which the discharge notes were evaluated for infection and (3) an advanced semi-automated computer algorithm.

Specificity varied from 99.6% to 99.9% and sensitivity from 65.3% to 88.9%. Further investigation of discrepancies revealed a number of issues that were related to limitations in HAIBA or the reference data. HAIBA is, by definition, not able to pick up those infections that are so clear for the surgeon that no biopsies are taken. Although that is not according to protocol and means that the opportunity is missed to target 4-6-week treatment more specifically to the agent causing infection, it does happen in practice. Also, cases in which antibiotic treatment was started before the biopsies were taken, may not be picked up, as the culture is often negative. On the other hand, some cases were included in HAIBA, where the re-operation was done because of a fracture and positive biopsies were considered a coincidental finding. Often these patients were treated with antibiotics, to

be on the safe side, but surgeons did not consider them infections that needed to be counted.

A report of the findings will be sent in for comments to the Danish Society of Orthopaedic Surgery in September 2016.

Lower respiratory infections

During the development of a case definition for lower respiratory infections, it became clear that it would not be possible to define a meaningful indicator without the use of X-ray results. It was considered to only use microbiological data, although not all patients with pneumonia will have a sample taken. However, this would mean to create different algorithms for different (groups of) microorganisms. It would be difficult to create an algorithm that decides which infection is hospital-acquired, especially for those microorganisms with a long incubation period, such as *Legionella pneumoniae*. Another option was to use diagnosis codes (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes) (111). Apart from doubts about the quality and completeness of these codes for pneumonia, the difficulty here was that diagnosis codes are not registered in the DNPR with a date of diagnosis. They can only be related to the admission and discharge date/time. It was decided not to proceed with this case definition for the time being. When a national radiology database exists, a case definition for lower respiratory infection can be investigated further. Another approach would be to investigate a case definition focussing on VAP, as this is a more specific entity to identify with an algorithm and it has a high mortality and is often targeted in HAI surveillance. Codes in the DNPR for ventilator treatment have been shown to be useful (112). Still, this will pose challenges, as it is difficult to diagnose a VAP. The National Healthcare Safety Network in the US implemented the use of ventilator-associated events (VAE) for surveillance instead (113). A recent study on the feasibility of electronic surveillance of VAE identifies many challenges still ahead (114).

IT-architecture

Data model

Figure 3.5 shows the overall dataflow in the surveillance system, with the import of data, the processing done inside the HAIBA data warehouse and the output that it generates. In addition, Appendix 1 describes the current production tables in HAIBA, stored in the "REPLIKA data mart" and the "HAIBA data warehouse".

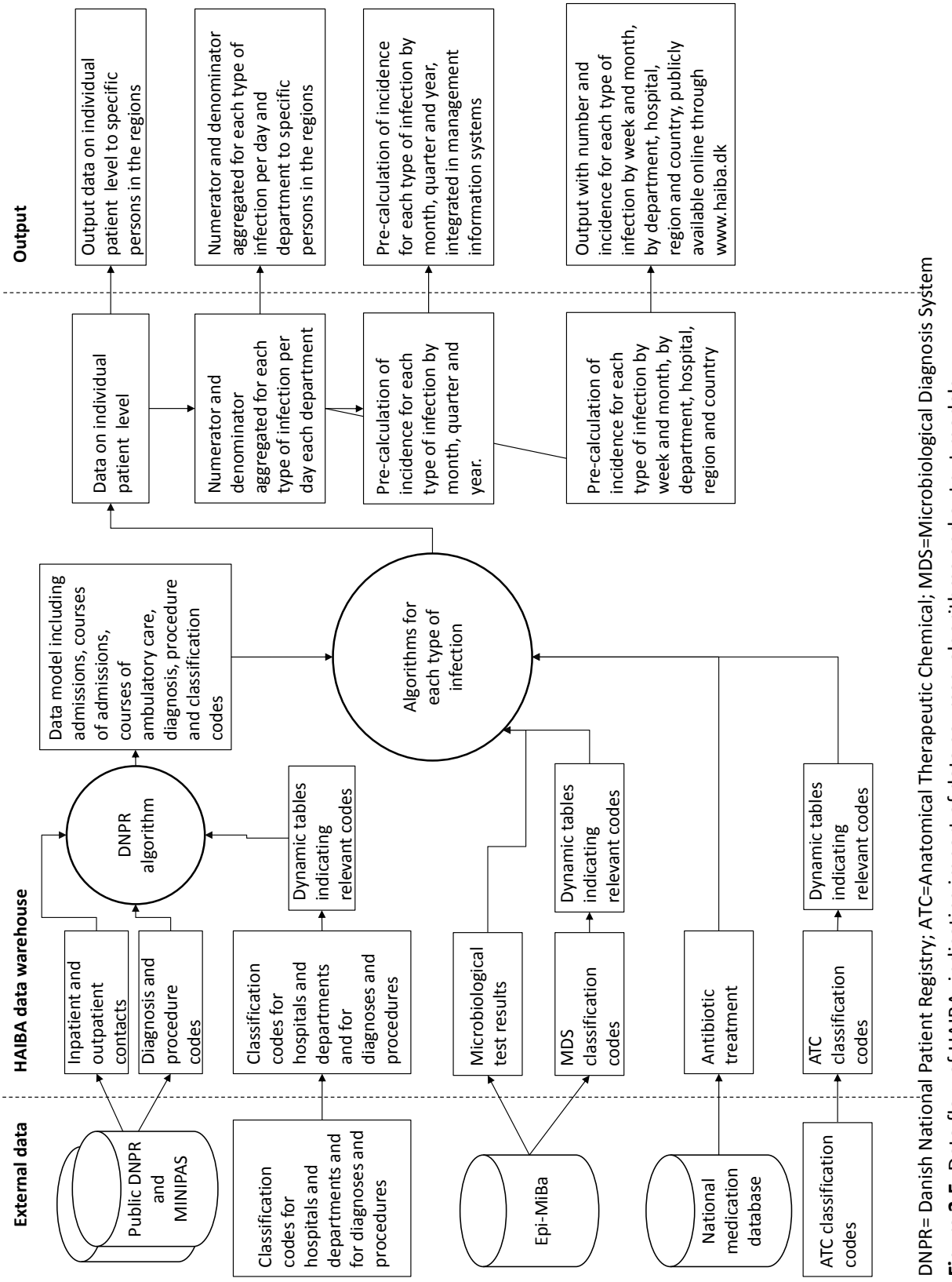
The REPLIKA data mart stores the imports of patient administrative systems from public hospitals (Public DNPR) and private ones (MINIPAS). In addition, classification tables are imported to be able to translate diagnosis, procedure and hospital-department codes to text and to obtain information on their properties (115).

An algorithm has been developed creating coherent courses of admission and courses of ambulatory care (Chapter 4). When data from Public DNPR and MINIPAS have been managed by this algorithm, they are stored as combined datasets in the HAIBA data warehouse. The combined data are referred to as DNPR.

Microbiological data are imported from Epi-MiBa into the HAIBA data warehouse, after data have been mapped to uniform codes (116). Extract criteria are described in Appendix 2. Classification tables are also imported from Epi-MiBa to translate codes from the Microbiological Diagnosis System (MDS) (117). Further details on how these data are integrated in HAIBA are provided in Chapter 5.

As there was no national database for medication given during hospital stay, we had to consolidate the data ourselves from regional medicine modules (Chapter 6). Data are transferred to the HAIBA data warehouse as one data source. In addition, a classification table for codes from the Anatomical Therapeutic Chemical (ATC) classification system is imported to be able to translate codes to text (118).

The import programmes start at 21:30 to check if data sources have been updated. If so, HAIBA starts to import those data.



DNPR= Danish National Patient Registry; ATC=Anatomical Therapeutic Chemical; MDS=Microbiological Diagnosis System

Figure 3.5. Data flow of HAIBA, indicating import of data sources, algorithms and output models.

For those classification tables, where we needed to indicate relevant codes, dynamic classification tables were made. These only contain the codes that actually have been found in HAIBA data. When a new code is being detected, an email is sent out to notify that it needs to be indicated as relevant or not.

Data are then combined according to case definitions in the form of computer algorithms (see earlier in this Chapter, as well as Chapters 7 and 8) and output models are generated (Chapter 9).

HAIBA environments

HAIBA has two environments: a test and a production environment. New developments are written and tested in the test environment using static datasets. When a new version is ready, it is moved to the production environment.

Coding

HAIBA has been coded in .NET c#, Java and SAS Analytics software. External companies have developed the imports from Public DNPR and MINIPAS after specifications from HAIBA. Imports from Epi-MiBa were developed in-house.

For data security reasons and because of the size of these databases it was not possible to import all available data. It was necessary to limit the imports to the necessary tables and variables and define filters. The challenge with development by external companies was that the requirements for imports had to be made at the start of the project, long before we had experience with the case definitions and could investigate which variables and tables we would need.

The DNPR and case definition algorithms were developed in SAS Analytics software. Experiences with application of such vast amounts of data taught us that we needed to work with the data for a considerable period and carry out several validation studies, before it would be possible to describe exactly the requirements to an external company. In addition, new developments in microbiology, coding practice, underlying data of the

data sources require a high level of flexibility for adjustment of the algorithms. Outsourcing would not be feasible nor affordable.

Surveillance on the surveillance system

Every morning, key persons receive an email that shows which steps ran successfully or failed. This email is also sent to the Servicedesk of the Danish Health Data Authority, which coordinates trouble-shooting if necessary. The Servicedesk is planning to monitor the time between failure and solution of the problem. The aim is that data on eSundhed is never older than 48 hours.

With this email system, HAIBA is often the first to notice disturbances in the production of its data sources. Recently, MINIPAS server maintenance was outsourced. This gave problems for HAIBA, because the full load that MINIPAS made every night was no longer finished in 1.5 hours but took up to 11 hours. This meant that HAIBA would not be ready in the morning, at the time it had to stop running. It shows that there is a need for better surveillance on the data sources that HAIBA uses by those who maintain these data sources. It is also necessary to sign agreements with departments responsible for this maintenance, specifying details of the delivery, server accessibly, timely information on service windows and changes in data models and monitoring of the quality and completeness of the data source. This quality assurance becomes more and more important as more surveillance systems are going to apply these data sources for automated daily calculations.

In addition to the data sources monitoring their imports, HAIBA is also planning to develop surveillance for its imports to keep an eye on the importers. This would for example be a daily calculation of all blood cultures and all urine cultures from Epi-MiBa. Automatic thresholds can be installed that warn when the numbers reach above or under the expected limits.

Back-ups

Four times a year we take a snap shot of HAIBA, copying all import data, all tables in the data warehouse, all output data and all algorithm-coding programmes. In addition, back-

ups are made of the output graphs on a monthly basis and analysed for differences compared to the previous back-up. These back-ups have proven to be very useful when we need to investigate certain irregularities observed in the underlying data. Examples of these are shown in Chapter 4 regarding open inpatient contacts and changes in the hospital-department codes.
When performing research on HAIBA it is also important to make a static copy of the relevant data, to be able to reproduce the exact same results later on, since data are highly dynamic.

Timeliness

Evaluating the timeliness of HAIBA and improving it where possible is important for a number of reasons. If HAIBA is to detect or support management of outbreaks, it needs to be as timely as possible. In addition, data from HAIBA become much more relevant and interactive for doctors and nurses if they concern patients that are still in the hospital, making the learning aspect of the data more significant. Lastly, surveillance data always show a certain drop in the last few days, due to the delay in data. Knowing the expected delay will help judging whether a recent decrease in the number or incidence is real or part of the delay. Figure 3.6 gives a schematic overview of the different processes and potential delays that are involved from hospital contact, onset of symptoms and antibiotic treatment, to information for HAIBA and the processing in HAIBA to output for the end-users.

The term real-time surveillance is often used to indicate the timeliness of surveillance systems and refers to the frequency of updating an electronic surveillance system. Most surveillance systems are not real-time, but use batch reporting, in which data are collected for a certain period and then processed (119). This is also the case for HAIBA. Import data are collected for 24 hours to be imported once a night, after which they are processed. Given the fact that it takes 8-10 hours to process data, it would not be feasible to update the data more frequently. In addition, most registrations will not be delayed more than 14 hours, since HAIBA imports at around 22:00 and most new registrations will be made the next day.

The automated transfer to regional File Transfer Protocol (FTP)-servers is integrated in an existing transfer for a number of other datasets, not related to HAIBA. This transfer is scheduled for 02:00, before the HAIBA algorithms are finished. This means that it takes until the next night for output data to be transferred to the FTP-servers of the regions.

Other aspects of timeliness of HAIBA lie in the data collection before it can be imported by HAIBA. This involves the clinical, administrative and IT-processes in each hospital and on regional level. These are more difficult for HAIBA to influence, but nevertheless useful to assess for better interpretation of data.

The first element to be able to include patients in the numerator and denominator is the admission or outpatient contact, or the procedure code for the index operation of a surgical site infection. The new development that hospitals since January 2016 are obliged to register patients upon admission rather than after discharge should give an important reduction of the delay for bacteraemia, UTI and CDI. The size of the reduction remains to be evaluated and may further improve, as the registration becomes part of a routine. Since HAIBA first starts counting risk days from 48 hours after admission, a small delay in registration within 48 hours would not even be noticed.

The practice of registering operation codes for index operations of surgical site infections would need to be investigated. However, our case definition does not count infections within three days of the index operation, so if registration is done within three days it would not add to a delay in HAIBA.

We do know that data in the DNPR are constantly updated, also retrospectively several years back. Therefore, the completeness will still not have reached optimal levels until several months later. This is further discussed in Chapter 4.

When a patient starts having symptoms there is typically a delay before the doctors is informed and a delay before a sample is taken. Between sample taking and receipt in the DCM there may be a delay of a few hours, although delays could be longer in the weekend.

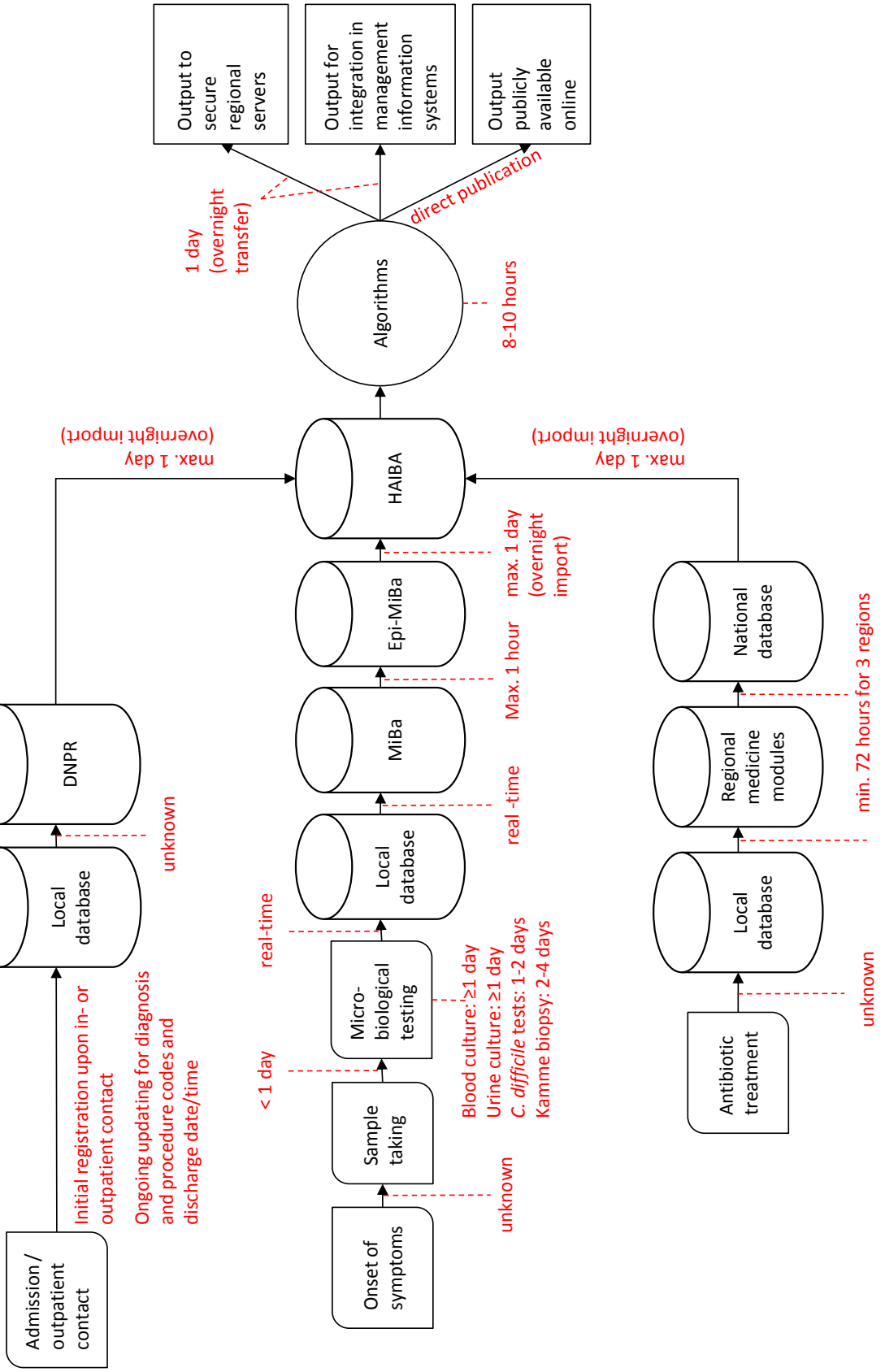


Figure 3.6. Schematic overview of processes that occur between admission and the patient being included in HAIBA output.

The time it takes to process the sample and detect microorganisms varies for different types of samples. Blood cultures should routinely be incubated for five days in automated continuous-monitoring protocols (120). This is adequate for most pathogens, although longer incubations may be needed. However, growth is likely to be detected earlier. The mean time from sample taking to a positive result was reported at 27.6 hours (range 5.1 to 127.5 hours) (121).

Standard urine cultures are incubated for 24 hours, but a study on improving urine culturing technique suggested incubating for 48 hours (122).

The picture for *C. difficile* varies depending on the tests performed. Some DCMs perform a stool culture followed by genotypic toxin profiling by PCR, PCR ribotyping and toxinotyping on positive cultures (123). Other DCMs perform nucleic acid amplification tests detecting toxigenic *C. difficile* directly from faeces. Stool culture takes 24-48 hours (124). The other tests can be done within a day.

Biopsies taken from orthopaedic surgery sites are cultured for 2-4 days (125,126). Final culture results including results on antimicrobial susceptibility testing are usually available within a week.

All results, are simultaneously recorded in the medical record and MiBa. Once an hour these data are transferred to Epi-MiBa.

Often a patient is given antibiotic treatment before the microbiological results is known, even sometimes before sample taking. In theory, this would provide an opportunity for HAIBA to already detect (probable) infections before the microbiological result has been registered. It is not entirely clear if all hospitals register the prescription and administration of medication in real time in their electronic systems. In some regions, the regional medicine module is integrated into the electronic health records (EHR), meaning that data are recorded on regional level in real time. For one region, we know that data are only transferred to the regional database once a week. In addition, several regions

have stated that they prefer to send data with a 72-hour delay, so that the majority of errors will have been corrected before sending to Danish Health Data Authority.

In conclusion, calculation of risk days are most likely timely and so are microbiology results. Naturally, HAIBA cannot directly influence the daily clinical practice and we need to take into account a certain delay from onset of symptoms until a microbiological test result is given. It is unlikely that antibiotic treatment can improve the timeliness of HAIBA. Unfortunately, an additional day is lost in the transfer of data to the regions. This technical issue could be addressed in the future.

Funding and resources

Although electronic systems, such as HAIBA, can save resources by not requiring active registration from clinicians nor from infection control staff, they do cost a considerable amount of time and money to maintain. The vast amounts of information that can be generated with these systems needs to be interpreted and further studied, at national, regional and hospital level. In addition, new developments in the data sources require constant adaptation of the IT-architecture and algorithms. New knowledge and changes in the healthcare system also generate new ideas and wishes for the improvement of the algorithms. Lastly, the output models need to be adapted to additional needs from the end-users.

4. Application of data from the Danish National Patient Registry

The Danish National Patient Registry

The DNPR contains clinical and administrative data on all patients treated in Danish hospitals (127). Each contact with the healthcare system is recorded. In 1977, the DNPR started as a registry for somatic inpatients in public hospitals. It gradually expanded over the years. The main changes were the addition of psychiatric patients, outpatient activities, Accident & Emergency Room (A&E) contacts and private hospitals. Recently, some important changes were made in the data model and underlying data. In January 2014, the DNPR data model combined contacts with the A&E with outpatients contacts, marking them as acute outpatients. At the same time, the Capital Region of Denmark reorganized its on-call service, which meant that patients were no longer seen by their general practitioner, but in the A&E, introducing a new patient population into the acute outpatient category. Since 1 January 2016, hospitals are obliged to register patients in the DNPR upon admission, rather than after discharge.

In order to apply data from the DNPR for HAIBA, or any other epidemiological study, surveillance or policymaking, one needs to understand the data in detail and be aware of changes in the underlying data. While several studies have validated specific diagnosis codes from DNPR, no studies have been published assessing the completeness and accuracy of registrations of admission and discharge dates. This may be a concern, as

many studies use these data to calculate length of stay and number of (re-)admissions, while using contacts as the equivalent to admissions or using an algorithm, but only loosely specifying the details of the algorithm.

We presented a method, which prepares data from DNPR for such applications, by creating coherent courses of admission and ambulatory care.

Extracting data and preparation for use in HAIBA

The import of DNPR consists of two parts: data from public hospitals (Public DNPR) and from private ones (MINIPAS). For each there is a table with data of inpatient and outpatient contacts and a table for diagnosis and procedure codes. Psychiatric hospitals and departments are excluded. This setting is only estimated to have 0.2% prevalence of HAI (128).

A number of classification tables are imported to be able to translate codes and obtain additional information. This includes the national classification system for hospital- and department codes ("Sygehus-afdelingskoder – SHAK" (115)). A new system for hospital-department codes is being developed, which is already integrated in HAIBA for later use ("Sundhedsvæsenets Organisationsregister" (SOR codes, (129)). Diagnosis codes are based on ICD-10 codes and adapted for use in the Danish healthcare system (111,115). Procedure codes are adapted from the Nordic Classification of Surgical Procedures (115,130).

We designed an algorithm with 28 rules that manages transfers between departments, between hospitals and inconsistencies in the data, e.g., missing time stamps, overlaps and gaps (table 1, Paper I). We evaluated the algorithm on data from patients admitted between 1 January 2010 and 31 December 2014 and outpatient contacts starting in that period. This included all somatic patients from public and private hospitals, but not A&E patients before 1 January 2014.

Inpatient contacts and outpatient contacts were handled independently. For outpatient contacts only the first nine rules were applied, setting rules for missing time stamps and

removing overlaps within the same departments. Overlapping courses of ambulatory care between departments were maintained. For inpatient contacts the first nine rules defined admissions. To create courses of admissions overlaps across departments were removed and gaps of four hours or less were closed.

The data model included the main tables for inpatient and outpatient contacts, tables with diagnosis and procedure codes and classification tables (figure 1, Paper I). After the algorithm, there was one main table for admissions, with a many-to-one relation to a table for courses of admission. There was another table for courses of ambulatory care. The main tables were related to tables with diagnosis and procedure codes with a one-to-many relation. In addition, several log files were generated to keep track of errors in the data.

Using the data generated by the algorithm, trends in admissions and ambulatory care were described.

Results of DNPR algorithm

Data from DNPR included 6,822,756 inpatients contacts and 22,480,692 outpatient contacts between 2010 and 2014. Results of the DNPR algorithm illustrated why it is necessary to combine inpatient and outpatient contacts before making estimates of the number of (re-)admissions per year or length of stay.

The DNPR algorithm also revealed some areas that require particular attention. A number of rules showed different patterns in 2013, suggesting an anomaly in data registration and/or the data model. This needs to be further investigated to better understand if it requires further adjustments of the algorithm or at least in the interpretation of data. In addition, known changes in 2014 require additional handling; the combining of the A&E category with outpatient category and the addition of primary healthcare patients from on-call service in the Capital Region of Denmark.

After application of the DNPR algorithm, we estimated an average of 1,149,616 courses of admission per year or 205 hospitalizations per 1000 inhabitants per year. The median

length of stay decreased from 1.58 days in 2010 to 1.29 days in 2014. The number of transfers between departments within a hospital increased from 111,576 to 176,134 while the number of transfers between hospitals decreased from 68,522 to 61,203.

These results likely reflect the dynamics in the healthcare system better than previously published reports.

Discussion

The DNPR has a wealth of information, which is used both for economic analyses and in many epidemiological studies. A more recent application is the integration into automated surveillance systems. HAIBA is one of the first systems to use the DNPR on an automated daily basis, but current developments are moving towards solutions that will allow many more automated systems to draw from DNPR on a daily basis. The national influenza surveillance for example has been using the DNPR algorithm to relate laboratory-confirmed influenza cases to admissions (131).

Experiences from HAIBA showed some areas that need to be further explored, some specifically for HAIBA and some also for the benefit of future systems.

Relating courses of admission to each other

As it is now, HAIBA treats courses of admission independent of each other. This means that if a patient was discharged and admitted again more than four hour later, the algorithm will see it as a new course of admission. Any infections identified within the first 48 hours will not be counted as HAI, although these might be related to the previous admission. This is a simplification that was done for the first version of the DNPR algorithm, but is planned to be handled in a next version.

Completeness and timeliness

In principle, DNPR includes all patients in Denmark since 2003. When looking at historic data before that time, one needs to be aware that certain patient groups were not yet included. When analysing data at different points in time we could observe that data are still being updated; in 2016, data are still being updated as far back as 2010.

Systems that use the DNPR on a daily basis will need to take into account a delay in data registration. This was more relevant before 1 January 2016, when DNPR still was a discharge register. With the change to registration of patients upon admission, the ascertainment of the number of admitted patients will reach completeness earlier. However, registration of discharge date/time is currently delayed by about a month, and therefore requires adaptation of the HAIBA algorithm. Since the summer of 2015, hospitals could voluntarily start to register inpatients upon admission. Particularly in the Capital Region of Denmark, some hospitals started this registration upon admission. Figure 4.1 shows a dramatic increase in risk days for HA-bacteraemia in HAIBA for the Capital Region of Denmark in an extract from 27 November 2015. This is caused by the delay in closing open contacts.

The delay in discharge registration may improve when hospitals have fully integrated this new registration procedure in their daily practice. However, it will probably still be affected by a certain delay.

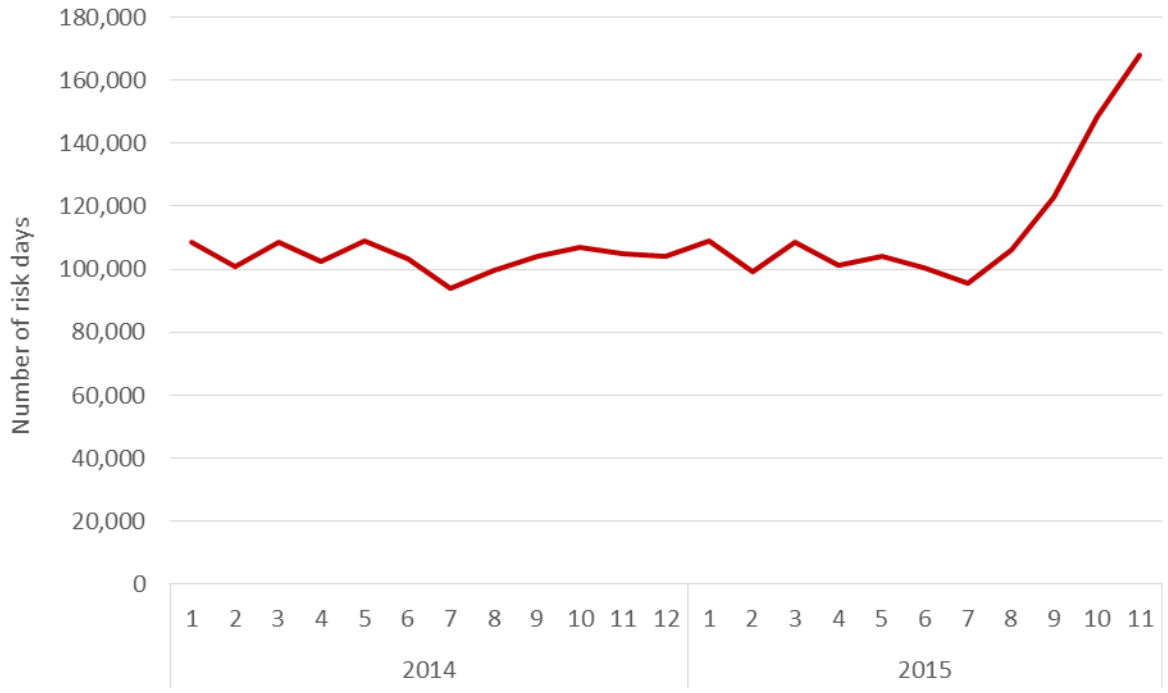


Figure 4.1. Number of risk days related to bacteraemia for the Capital Region of Denmark between 2014 and 2015. Extract dd. 27 November 2015.

As can be seen from figure 4.1, HAIBA needs to handle this situation, either by excluding open contacts, or by a proxy measure that closes the contacts until the definite discharge date has been registered. Since these open contacts can greatly improve the timeliness of HAIBA, we chose the latter. As lengths of stay will differ among different departments, we measured for each department the length of stay of closed contacts. Open contacts were closed at the third quartile of the observed length of stay of their corresponding departments. If a procedure was recorded after this artificial discharge date/time, then the discharge date/time was moved to an hour after the procedure. Figure 4.2 and 4.3 show the number and incidence of HA-bacteraemia between week 40 and 52 of 2015 when using data from 7 January 2016 without open contacts and with the third quartile rule applied on open contacts, and data from 26 March 2016 without open contacts. This way we could assess how well the new rule predicted the real discharge date/time. This is still an early assessment, in which not all hospitals had started registration of open contacts. Primarily the Capital Region of Denmark, Region Zealand and Central Denmark Region had started. This analysis illustrates for all regions the delay that HAIBA has when excluding open contacts. It also shows that the third quartile rule applied on the open inpatient contacts can approach the reality of three months later well. This suggests that this approach can be a valuable improvement to the timeliness of HAIBA. The same analysis will have to be done on later data to evaluate the effect of this new rule now that all hospitals are recording open inpatient contacts and have gained some routine in the registration procedures. A potential delay in registration of diagnosis and procedure codes on open contacts also needs to be evaluated.

Hospital-department codes

To show data per region, hospital and department we use the national classification system for hospital-department codes. This system is integrated in the DNPR. It is being maintained at a national level at the Danish Health Data Authority, but regions do have a certain level of freedom to use the codes. In principle, this system gives regions the possibility to classify hospitals (first four digits), and three levels of departments/units (last three digits/characters). There are a few limitations to this system when applying it to HAIBA. In the SHAK system it is possible to register certain properties to the

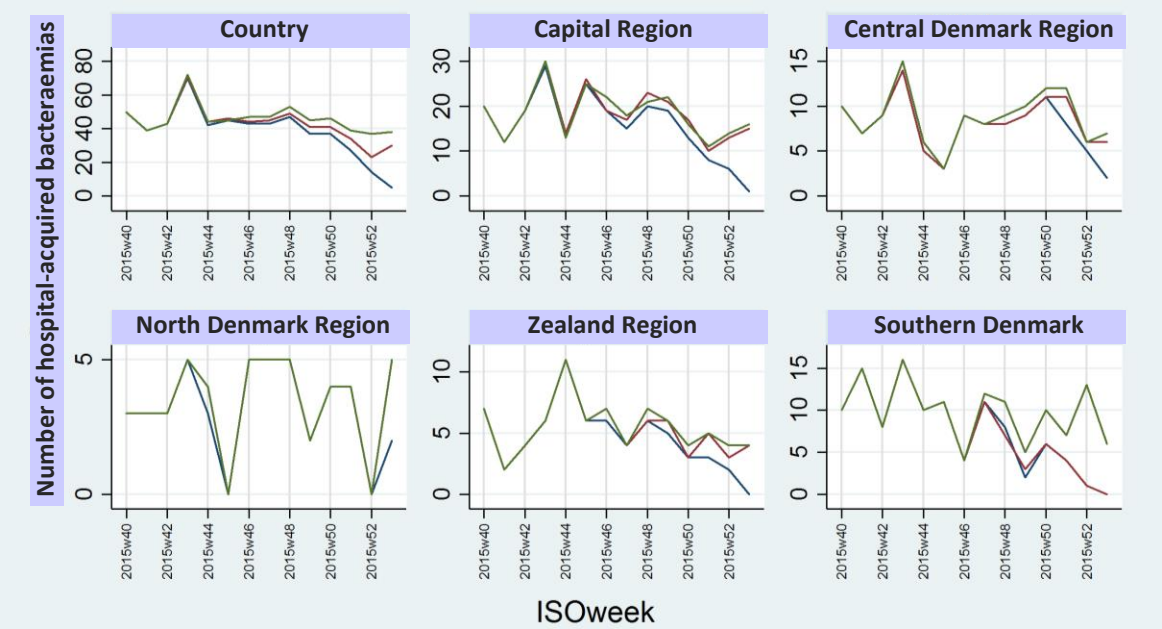


Figure 4.2. Number of hospital-acquired bacteraemias between week 40 and 52 of 2015 for the country and by region, using data from 7 January 2016 without open contacts (blue) and handling open contacts (red) and data from 26 March 2016 without open contacts (green).

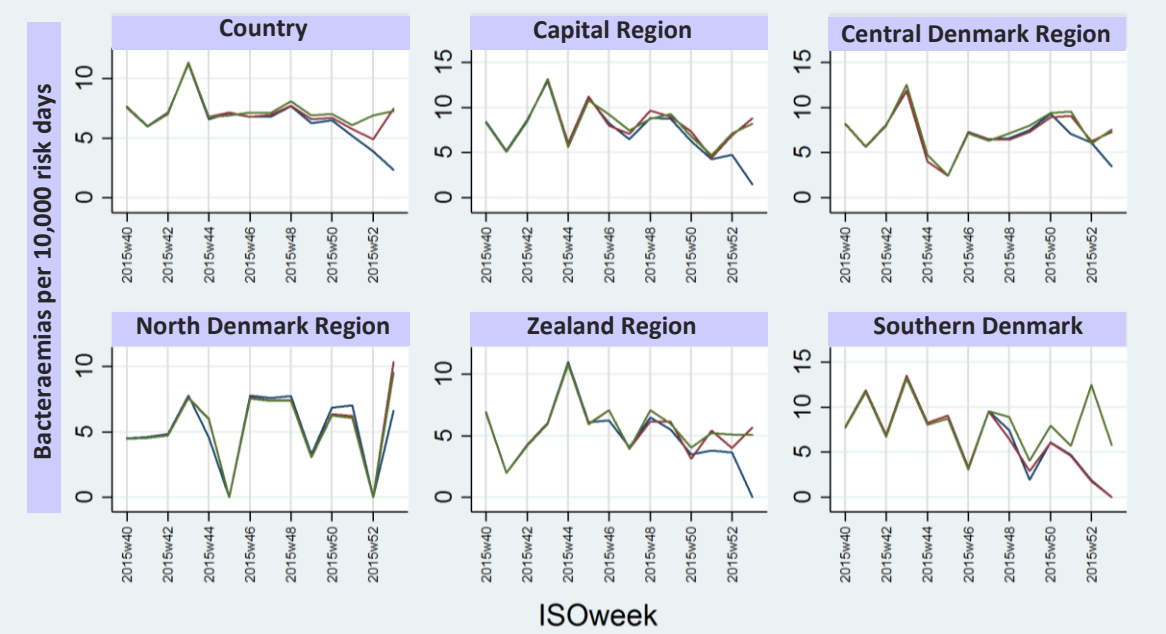


Figure 4.3. Number of hospital-acquired bacteraemias per 10,000 risk days (incidence density) between week 40 and 52 of 2015 for the country and by region, using data from 7 January 2016 without open contacts (blue) and handling open contacts (red) and data from 26 March 2016 without open contacts (green).

departments, for example the specialty, including one main specialty and up to three additional specialities for one department (132). However, the specialties that can be recorded do not allow grouping departments by type of department. It is for example not possible to identify all ICUs from this as they are recorded under the code for anaesthesiology, just like palliative care units and other specialties related to anaesthesiology.

Another difficulty with the registration of ICUs is that in some hospitals, patients remain registered in the department that has the overall responsibility for the patient during ICU admission. This means that HAIBA cannot show any data for these ICUs. Using procedure codes specific for ICU treatment has shown to be an accurate way to identify ICU patients (112). This is currently used in the national influenza surveillance to identify influenza patients in ICUs and could also be considered for HAIBA.

Handling of historical changes in the classifications system also poses challenges. HAIBA uses only the active codes. That means that when the name of a hospital or department was changed, HAIBA will show the new name, also for all retrospective data. This is also valid for situation where the properties of a hospital or department are changed. Figure 4.4 shows an example of the consequences. When comparing data from 7 January 2016 and 26 March 2016, a lower number of bed days was noticed between 2010 and 2012 than after 2012. Stratification by region showed that this was due to a change in the Region of Southern Denmark. Further investigation showed that the hospital code for Svendborg Hospital was changed to a psychiatric hospital. What had happened was that Svendborg Hospital had merged with Odense University Hospital in 2013. All somatic patients were thereafter registered under the code for Odense University Hospital. The psychiatric department continued to use the code for Svendborg Hospital. Therefore, all somatic patients that had been registered in DNPR before the merge were also excluded from HAIBA. Since this change was only recorded in the DNPR early 2016, HAIBA only noticed this change in spring 2016.

Other examples are seen among hospitals in the Capital Region of Denmark, which merged and continued on the code of one of the hospitals. This makes it impossible to

disentangle them after the merge and requires that users combine the old and the new code when judging trends over time. A more practical approach from the point of view of systems like HAIBA that use these data, would be to introduce a new code for the new situation. This may however not be feasible with a limited number of codes available. In addition, there should be documentation on these kinds of changes.

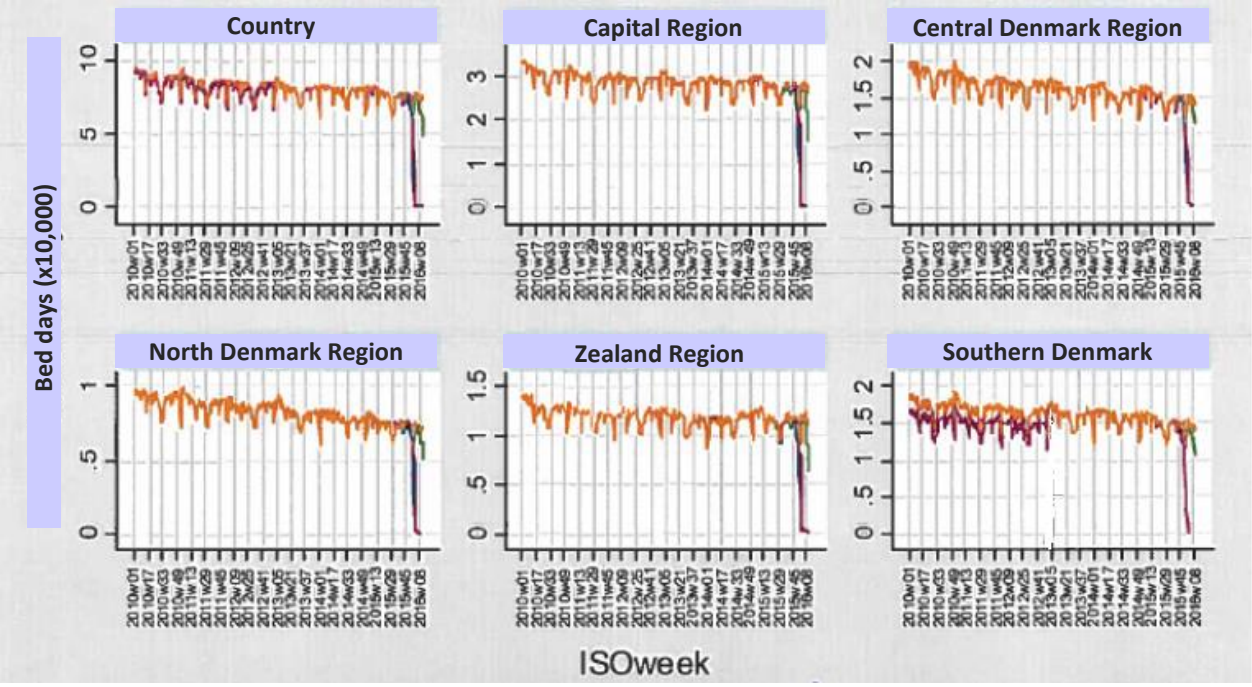


Figure 4.4. Number of bed days among inpatients between 2010 and week 8 of 2016, shown with data from 7 January 2016 (yellow) and from 26 March 2016 (red).

Lastly, Region Zealand chose to give all hospitals in its region the same first four digits. Therefore, it can only use the last three digits to create unique codes for all departments/units in its region, leaving less available codes per hospital. The result is that the codes do not show the unit level. This required adaptation in the HAIBA algorithm, but also means less detail in the data that HAIBA can show for this region.

A new classification system is being developed; the SOR system ("Sundhedsvæsenets Organisationsregister"). HAIBA has been prepared to introduce this system, when it becomes available. However, there are a few concerns regarding the practical application

of this classification. The SOR system has taken the viewpoint of the hospitals and municipalities that will need to make the recordings and has given them the maximum flexibility to create as many levels as they need. In the absence of a variable that indicates what level is being recorded it may be impossible for systems like HAIBA to know what level is being recorded. A large university hospital may for instance use the first level for an overall medicine department, the next for large sub departments such as cardiology, pulmonology, endocrinology, haematology etc. Under each of these there may be several smaller departments and units. A small private hospital might be showing units on the first level. It was our hope that the new system would also be able to handle grouping by types of departments, but it is uncertain that this will be the case. HAIBA has raised these concerns.

Validity of diagnosis and procedure codes

Initially we had planned to use diagnosis codes as substantial components of the case definitions. However, in our collaboration with clinicians we were often warned for the quality of registrations. It is a general impression among clinicians that coding is not done with high precision. An additional complication for the quality of coding is that it has a clear financial incentive. It is favourable to find the codes that provide the highest reimbursement and these codes are actively sought after. A systematic review of the use of diagnosis codes for HAI surveillance indeed concluded that accuracy was limited and highly variable (66). Studies assessing the validity of diagnosis codes in the DNPR, showed that validity varies depending on the disease under investigation (133–145,68,146–150). Completeness of diagnosis codes for bacteraemia for instance were found to vary substantially according to specialty, place of acquisition and microorganism (68). Overall, one third of bacteraemia episodes did not have a relevant diagnosis code in DNPR. A study evaluating 19 diagnosis codes generally used in the Charlson co-morbidity index did report that codes had a consistently high PPV, but was unable to assess sensitivity, specificity and NPV (138).

Operation codes, which are particularly relevant for the case definitions for surgical site infections, are assumed to have a higher accuracy than diagnosis codes, although still affected by reimbursement incentives. This was also confirmed by a Danish study in 2002

(133). Only few studies have examined the sensitivity, specificity, PPV and NPV of operations codes. One study showed high PPV for ICU admission, mechanical ventilation and acute dialysis (112). Another study concluded that the validity for knee cartilage injury in the DNPR is high (151).
Experience from orthopaedic surgeons is that accuracy of additional information such as the side that was operated may be questionable. Validation of the case definition for peri-joint infections after total hip replacement also pointed out that occasionally hip replacements were wrongly coded as knee replacement and vice versa.

Combining acute patients with outpatients

As mentioned, A&E contacts and outpatient contacts were combined in DNPR in January 2014, while in the same month the Capital Region of Denmark moved on-call services from general practitioners to the A&E setting. Figure 4.5 shows the effect of these changes on the number of outpatient contacts in the DNPR. Stratification by region showed that the effect was largest in the Capital Region of Denmark, suggesting that the change in on-call service has a majore influence. This does not affect the results for HA-bacteraemia or UTI, but it may affect the results for COHA CDI.

At the time that the import from DNPR to HAIBA was designed, two aspects were not included, which would have made it possible to disentangle this issue. In order to select only the relevant information for HAIBA we had only selected the patient contacts for inpatients and outpatient, not the A&E patients. With the experience we have today, we would have done this differently, since also an A&E contact could be relevant to include as a potential exposure. In addition, we had not foreseen that we would need an additional variable for “admission mode”. It is this variable that the DNPR used to indicate if an outpatient contact was acute (i.e. an A&E contact) or elective.

These two aspects have recently been included in the import from DNPR, but not yet integrated into the algorithms for CDI and surgical site infections.

Unfortunately, the organizational change from the Capital Region of Denmark cannot be handled with additional variables. The new primary healthcare population has changed

the case-mix after 2014, but only in one region. This is important to realize for all those who make co-morbidity adjustments based on data from DNPR, as variations like these could make co-morbidity adjustments problematic or even useless (152–154).

Differentiating inpatients from outpatients

Unlike in many other countries, admissions in Denmark are not defined as overnight stays. An admission is registered when a patient occupies a bed that has been marked as an inpatient bed. There are over the whole period a large number of admissions under 24 hours. This will in part reflect the reality, but is also driven by cost calculations, as an admission will give a higher reimbursement than an ambulatory care contact.

In addition, with admissions getting shorter the distinction between inpatient and outpatient contacts slowly disappears. This may require a different approach. For example by focussing more on exposures, such as certain procedures.

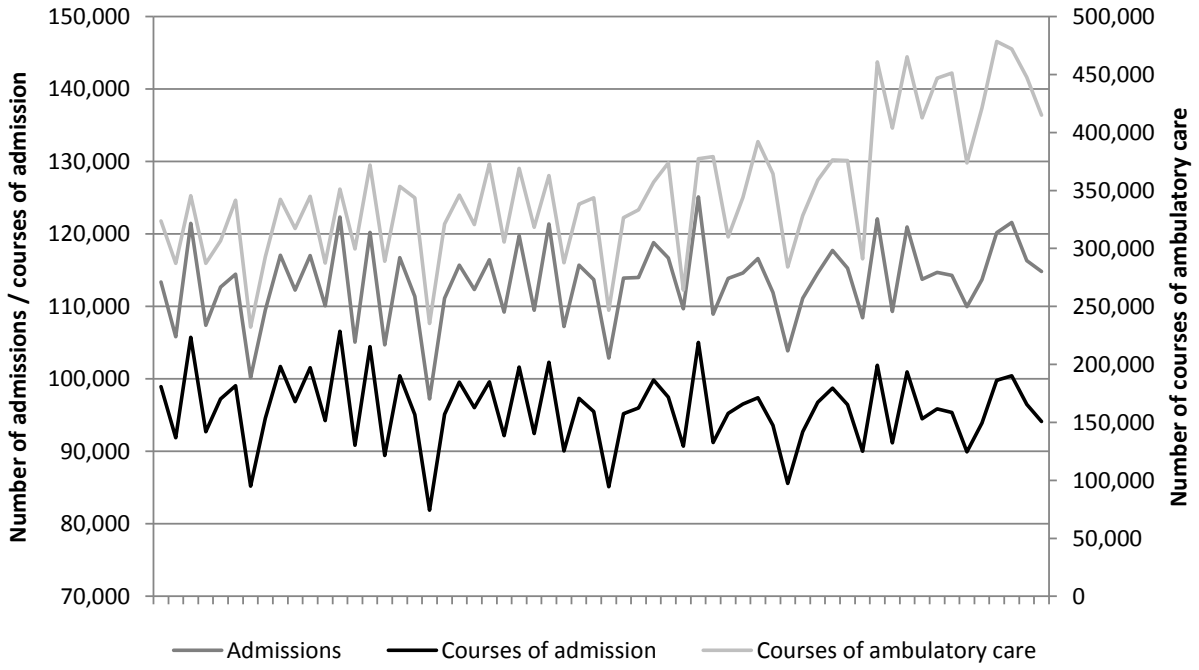


Figure 4.5. The number of inpatient contact, courses of admission (left axis) and courses of ambulatory care (right axis) in Denmark by month of admission/start of ambulatory care. Figure 3 in Paper I.

New data model

A new data model for the DNPR is currently being developed. The description of the design is expected in autumn 2016. With that, HAIBA can start planning the adaptations that will be needed. During 2018 a transition is planned to take place, in which both the old and the new data model will be running. From 2019, only the new data model is expected to be operational.

5. Application of data from the Danish Microbiology Database

The Danish Microbiology Database

MiBa is the national database where all microbiological test results since 1 January 2010 are collected in real-time (155). MiBa covers all microbiology testing in the country, not only from public hospitals, but also from private hospitals and general practitioners. It is a collaboration between all Danish DCMs and SSI. MiBas server is operated by the Capital Region of Denmark. In MiBa, local codes from the different laboratories are translated to key codes. A copy of these translated data, Epi-MiBa, is transferred to a server at SSI. Epi-MiBa serves as a data mart, in which case definitions are registered and transferred to specific surveillance databases, including HAIBA, in real-time (156).

A new application of MiBa is MiBAlert, which flags a patient in the electronic medical record if a patient has been found to have an infection with a resistant microorganism, such as MRSA, Extended-spectrum β–lactamase-producting bacteria (ESBL) or Vancomycin-resistant Enterococci (VRE), within the past months. Using this, a department can directly take action upon admission. This was developed in the Capital Region of Denmark and is planned to be rolled out in the rest of the country, meaning that the alert can be used across hospitals, when patients are transferred. More applications of MiBa regarding antimicrobial resistance are being developed in a new project called eRES.

The new Ministerial Order for notifiable diseases, which is expected in early 2017, will define MiBa/Epi-MiBa as the corner-stone of infectious disease surveillance in Denmark. This will mean that surveillance of most indicators of infections will be derived directly from Epi-MiBa. Clinical microbiologists and physicians may still be contacted for further information regarding the patient. The experiences with HAIBA have been useful for the process ahead, in which all indicators of infections will need to be extracted from Epi-MiBa and handled in order to create an output that can be used by different user groups.

Extracting data and preparation for use in HAIBA

MiBa consolidates laboratory information systems from all DCMs in Denmark. For data performance, security and confidentiality reasons, HAIBA only receives data from Epi-MiBa that are relevant to the case definitions. HAIBA has defined that it needs all blood cultures for the case definition of HA-bacteraemia, all urine cultures for HA-UTI, all investigations relevant for *C. difficile* infection and all investigations relevant for surgical site infections. It is the responsibility of Epi-MiBa to define the right extract criteria and to update them when new codes are being introduced. HAIBA then refines the extracts. Appendix 2 shows the current extract criteria and the refinements that HAIBA puts on them. Technically, these extracts are made with an Extract Transform Load (ETL)-package.

For HAIBA, it is important to be able to have usable time stamps. Epi-MiBa has three date/time variables; the sampling date/time, the date/time the sample was received in the DCM and the date/time the answer was entered into the medical record. HAIBA uses the first two. The date/time the sample was received is always filled out. However, in some cases, the sampling date and/or time is missing. This, and other inaccuracies are handled as follows:

- If the sampling date is missing, then the date of reception in the DCM is used
- If the sampling date is >7 days before the reception date then the reception date is used.
- If the sampling date is after the reception date, then also the reception date is used.

- If the sampling time is missing, and the sampling date is the same as the reception date, then the sampling time is set four hours before reception time.
- If there is still no sampling time, then the time is set to 08:00. In the case of infections after total hip replacement, time is set to 12:00.
- In preparation of the algorithms for bacteraemia and UTI we calculate per DCM for all records that originally had a times stamp how many had a sample at 08:00. If on a given date, there is an increase of >75%, then those that are beyond 75% are set to 09:00. Only those that originally did not have a time stamp are moved to 09:00.
- If there are two or more records with the same CPR-number and sample date/time, then they are combined. The original unique identifiers are kept, as well as the microorganisms recorded in each of the results.

Description of extracts

Figures 5.1 through 5.4 present the numbers of records for each of the extracts by sampling date. This concerns data before they are further refined by HAIBA.

The extracts for UTI, CDI and surgical site infections show large variations over the week, with less samples in the weekend. The moving average fits best at seven days, also suggesting that the variations reflect sampling practices on different weekdays. It should be noted that these extracts also include samples from primary practice, which also explains a lower sampling activity during the weekend. Blood cultures show less variation, as can be expected due to the severity and acute nature of bacteraemia.

All extracts show a lower activity in the summer period. For the urine cultures and samples for surgical site infections, this is a marked dip in July. For blood cultures, there is a more gradual seasonal pattern, with higher activity during winter months and lower during summer months. All extracts show something that looks like a shift around May/June of 2012 with different trends before and after. It needs to be further investigated whether this is a technical issue in MiBa and/or Epi-MiBa or whether this can be explained by changes in the sample taking practice or laboratory testing.

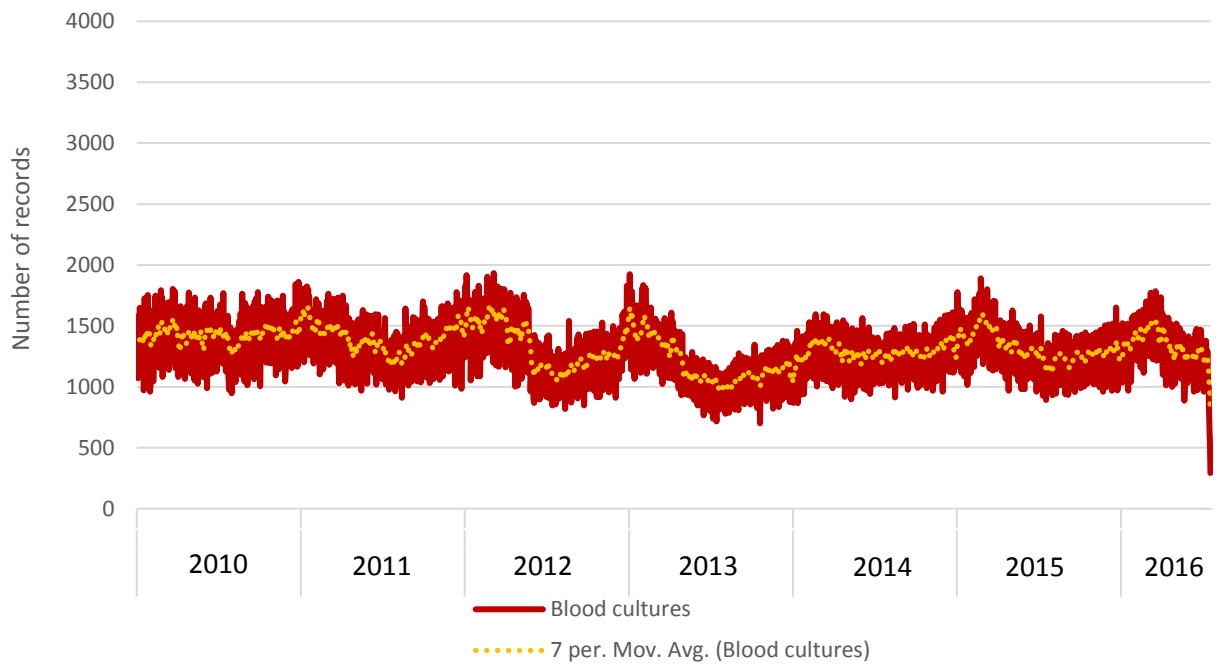


Figure 5.1. Number of records for blood culture extract by sampling date between 1 January 2010 and 18 July 2016, and a seven-day moving average. Extract dd. 19 July 2016.

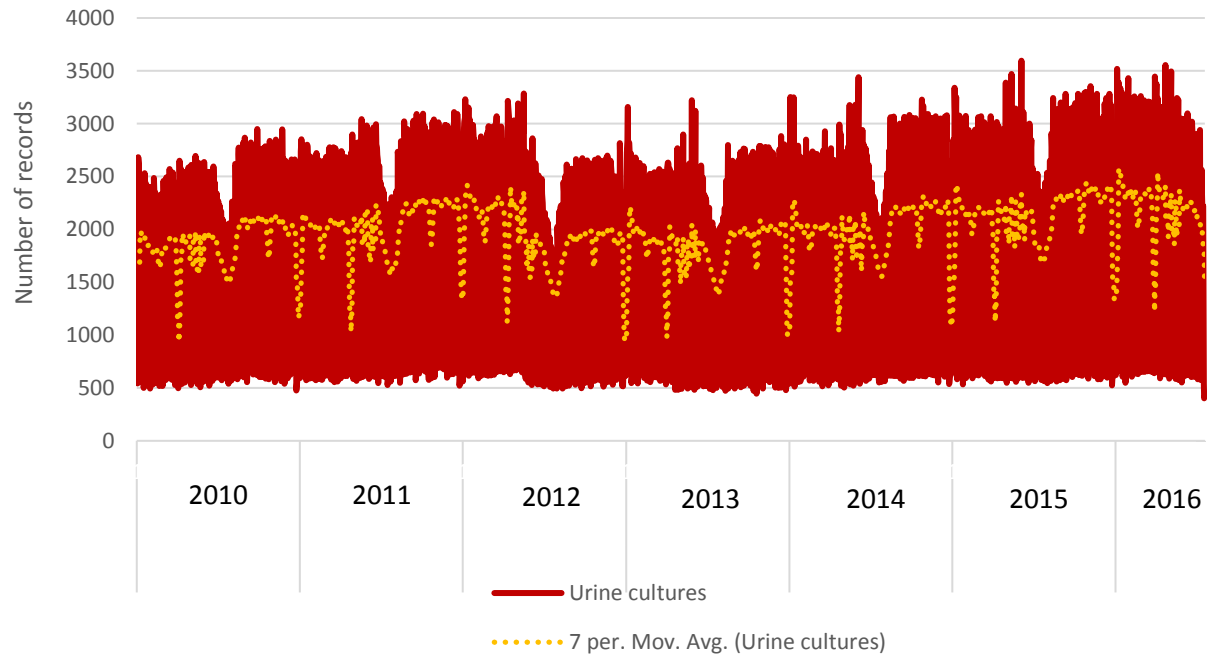


Figure 5.2. Number of records for urine culture extract by sampling date between 1 January 2010 and 18 July 2016, and a seven-day moving average. Extract dd. 19 July 2016.

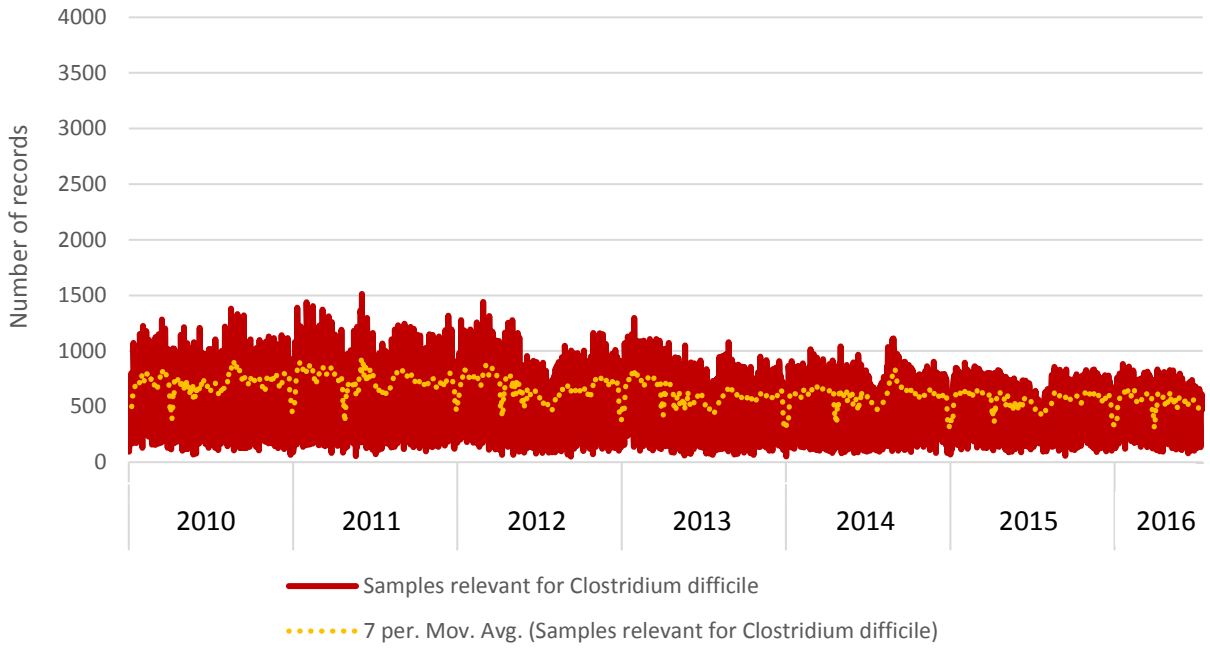


Figure 5.3. Number of records for *Clostridium difficile* infection extract by sampling date between 1 January 2010 and 18 July 2016, and a seven-day moving average. Extract dd. 19 July 2016.

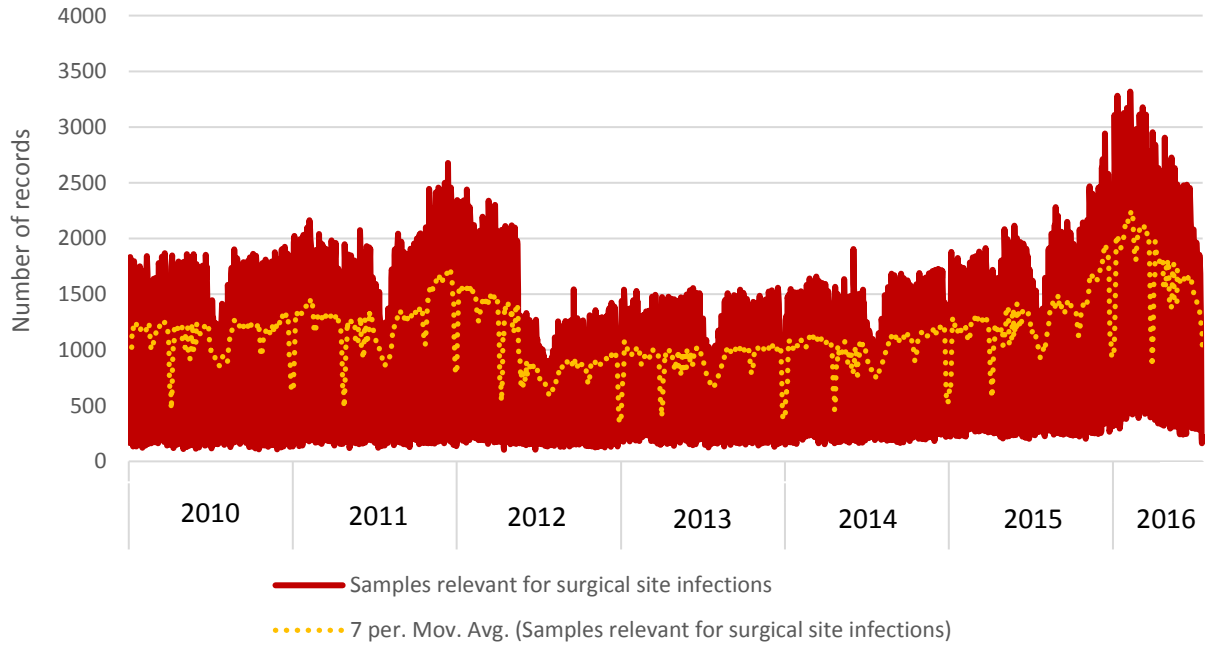


Figure 5.4. Number of records for surgical site infection extract by sampling date between 1 January 2010 and 18 July 2016, and a seven-day moving average. Extract dd. 19 July 2016.

Discussion

Data from MiBa/Epi-MiBa provide the unique opportunity to analyse microbiological data from the whole country. Validation studies of HAIBA showed that the extracts from Epi-MiBa fit well with local data.

In order to monitor completeness of the extracts from Epi-MiBa, HAIBA plans to implement a surveillance similar to what is shown in figures 5.1 through 5.4. This will allow setting alarms that notify if more or less records than expected are being imported. Epi-MiBa will also implement such surveillance on data transferred from MiBa to Epi-MiBa. It would be advisable that also data transferred from the DCMs to MiBa are monitored in a similar way.

Mapping vs uniform reporting

As MiBa is combining data from different laboratory systems, with different coding practices, data are not directly usable for registry-based surveillance. The most sustainable way would be to agree on a common way of reporting and for all laboratory systems to adapt their data delivery. The challenges are at least two-fold: data need to go into the right variables in MiBa and the content of the variables would need to be systematic and without free text. This long process requires consensus on certain microbiological concepts as well as local resources for adaptations of the systems and changes in long used practices. While this process is ongoing, the content of various variables in MiBa is being mapped to uniform codes. This is time-consuming and does not solve all issues. The actual meaning of the concepts may differ, while the code or text is the same. For example, in one DCM the material code for ‘urine’ is used for midstream urine, while in another DCM it is used for all less-well defined and/or inferior ways to collect urine. A uniform practice lies probably far in the future, if it is ever possible. In the meantime, it is important to be aware of these details and for DCMs to inform Epi-MiBa of changes in practice and registration.

Test persons and project samples

During the development of HAIBA, it was noticed that there were some unexpected results with non-existing CPR-numbers. Some of these turned out to be test patients.

While MiBa has a number of 'official' test patients that DCMs and SSI can use to try out what tests will look like in the system, additional test patients seemed to have been created locally. In addition, some of the records represented project samples or samples from quality assurance processes. None of these should be in the surveillance data from HAIBA. All known codes for test patients and project samples are removed from extracts to HAIBA, but if new codes are created, these may not be noticed as such.

Dynamics in the MiBa/Epi-MiBa data model

MiBa and Epi-MiBa are currently undergoing a number of large improvements, which have implications for HAIBA and other systems.

On 7 July 2016, MiBa and Epi-MiBa underwent a major update, which required adaptation of some of the algorithms. Data in HAIBA had to be tested thoroughly to make sure that data were correct and to assess the potential differences in the output tables.

A new major update of MiBa is expected in the near future, in which DCMs will start sending subtyping and resistance data in a more systematic way through a new protocol, called XRTP06. This will open up many more applications for HAIBA and other surveillance systems.

6. Collection and applications of data from regional medicine modules

Background

Including antibiotic treatment in the HAIBA algorithms was a desire from the start of the development of HAIBA. In the absence of data on symptoms, knowledge on treatment could provide important information on the clinical condition of a patient. Combined with microbiological data this would enrich the algorithms considerably. Getting access to antibiotic data proved to be a project of its own and is still not fully achieved.

Since 2009, there is a national system that consolidates data on medicines and vaccinations: the “Fælles Medicinkort (FMK)” or “Shared Medicine Card” (157). With this system, citizens and the persons responsible for their treatment can look up all medication that has been prescribed as well as the vaccinations received, across healthcare providers. The aim is to prevent medical mistakes due to lack of information about medication. However, when a patient is admitted to hospital the FMK is suspended and recording of medication is taken over by the EHR of the hospital. Upon discharge, the relevant medications are entered into FMK again.

The FMK was not a feasible data source for HAIBA, because is it developed for individual patient management and not as a database for epidemiological purposes. Therefore,

HAIBA would not be able to get permission to use the data. Another disadvantage lies in the fact that medication during admission is not recorded in FMK.

For these reasons, we decided to develop our own national database. Since HAIBA's permission to collect medication data is limited to antibiotic treatment, we would only request those from the regions. In October 2012, the IT-board of the Danish Regions ("Regionernes Sundheds-IT, RSI") committed to providing medication data from the regional "medicine modules" to HAIBA and providing resources to prepare data into a uniform format as defined by HAIBA.

In May 2013, the Department of Health Documentation at SSI, now called Department of Data Quality and Content under the Danish Health Data Authority, expressed interest in developing a national database on medication during admission. They could collect data on all medication, not only antibiotics, under the permission of the "omkostnings-database", the database used for financial calculations on the healthcare system.

To prevent a situation in which regions would need to send their medicine data several times in different formats, we agreed that regions would send all medication data to the Department of Data Quality and Content. Before data would be saved in the "omkostningsdatabase" the Department of Data Quality and Content would transfer data on antibiotics to HAIBA. This procedure is an important detail, since HAIBA would not be able to receive data once it has been in the "omkostningsdatabase" and use it for other purposes than pure statistics.

The consolidation of medicine data was challenged by large developments in EHR systems during the same time. In 2007, there were 23 different systems. Between 2007 and 2010, Region Zealand and the Capital Region of Denmark already reduced the number of systems by five (158). By the end of 2013, the aim was to have reduced the number to only five; one in each region. Thus, when HAIBA started with the collection of medicine data in 2011, this process was in full swing. Danish Regions have formulated a collective strategy for IT-systems in healthcare for 2013-2019, in which collaboration among regions and with the state for further IT-development is being prioritized (159).

Data model

Initially, we had identified the variables needed for HAIBA and described the required formats. Region Zealand and the Capital Region of Denmark prepared their data according to these requirements. Data are currently transferred daily. Data from these two regions have been used in the probable case definition for HA-UTI. This case definition was validated against PPS from these regions (Paper IV).

The approach of the Department of Data Quality and Content was to collect data in the original regional formats and analyse them individually, rather than combining them into one coherent database. If necessary, the Department of Data Quality and Content would have a company mapping data into uniform formats. The Northern and Central Regions of Denmark sent their data in this fashion. However, when HAIBA was requested to describe the content of the datasets and requirements for mapping it became clear how difficult it is to interpret some of the data, if one does not know the ins and outs of how the data are recorded. It is more sustainable to have an approach in which the regions take responsibility for delivering data in a predefined format. It also guarantees data quality when regions make changes in their own data models.

Based on these experiences and further discussions with the Department of Medication Statistics under the Danish Health Data Authority, the original data model was improved. It now contains three relational tables (figure 6.1). The main table includes administrative data, such as the patient's CPR-number, date/time of ordering medication, the date/time for each time medication is given. Through a one-to-many relation, a table for medications provides the possibility to register more than one drug, in case of combinations. Similarly, in the indications table more than one indication can be given.
The variables that were identified as relevant can for the most part be provided by all regions. Those that cannot be provided, will be blank and may in future be added.

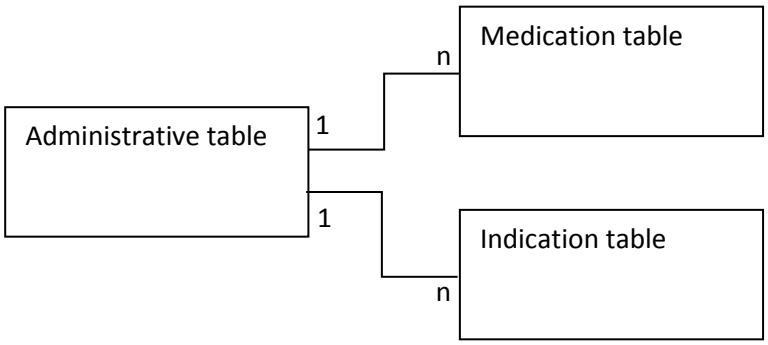


Figure 6.1. Data model for national consolidation of medicine data

Road map

The HAIBA data warehouse currently contains medicine data from Region Zealand and Capital Region of Denmark. Data from the Northern and Central Regions of Denmark have not been made compatible with the original data model, since we are now in the process of developing the new data model. The Southern Region of Denmark was still in a regional consolidation process until the end of 2015. Therefore, the process of collecting data from this region has not taken shape yet.

Discussions with all regions, except the Southern Region of Denmark, are soon to be concluded, resulting in the signing of a data exchange agreement. These regions are preparing their data in the newly defined data model. Table 6.1 gives an overview of data currently available and a time line for the new data model. It will vary from region to region what can be provided in terms of historical data, but none of them will be able to provide data from before 2012.

Hospitals in the Capital Region of Denmark and Region Zealand will, gradually, make a transition to a new EHR. In this process, the medication data will be prepared in the new data model. Data collected from before the transition will be in the old format and will have to be made compatible to the new one by the Department of Data Quality and Content in collaboration with HAIBA.
Northern Denmark Region and Central Denmark Region will start preparing data in the second half of 2016. We will need to clarify what historical data will be available.

It has not been agreed yet when the Southern Denmark Region will be able to provide data for HAIBA.

It will take several years to have a complete database and data from a meaningful period.

Table 6.1. Overview of data availability and expected time line.

Region	Data coverage	IT-system	Data available in new data model	
Capital Region of Denmark	2012 until transition in old format. Prospectively in new format.	Old systems: different systems	21-05-2016	Herlev and Gentofte Hospital
			05-11-2016	Rigshospitalet
		New system: Sundhedsplatformen (Epic (160))	18-03-2017	Nordsjællands Hospital, Amager Hvidovre Hospital and Bornholms Hospital
			20-05-2017	Bispebjerg and Frederiksberg Hospital and Region Psychiatry of Capital Region
Region Zealand	2012 until transition in old format. Prospectively in new format.	Old system: OPUS medicin (161)	23-09-2017	Hospitals in Nykøbing Falster, Næstved, Slagelse and Ringsted
		New system: Sundhedsplatformen (Epic (160))	18-11-2017	Hospitals in Roskilde, Køge and Holbæk and Psychiatry of Region Zealand
Northern Denmark Region	Unknown	OPUS medicin (161)	End 2016?	All hospitals in region
Central Denmark Region	Unknown	Different systems	End 2016?	All hospitals in region
Southern Region of Denmark	Unknown	Since end 2015 all hospitals on COSMIC platform (162)	Unknown	Unknown

Extracting data and preparation for use in HAIBA

Data transferred to the Department of Data Quality and Content each night are filtered for antimicrobial treatment based on the ATC-codes (118). Appendix 3 shows the selected ATC-codes. Subsequently, data are prepared to be used in the HAIBA algorithms. These rules are currently based on the old data model and may need to be adapted when the new data model is available.

- Any records with missing CPR-numbers are removed.

- The start date/time of treatment is being defined as the date/time of ordination or administration, depending on which comes last.
- The end date/time is defined as the ordination end date/time. This variable is systematically missing in some regions. In those cases, the last administration date/time is used instead.
- All records with the same CPR-number and ATC-code with overlapping start date/time and end date/time are combined into one record, showing the first start date/time and last end date/time.
- If the ordination date/time is >365 days in the future it is set to be an open treatment without a closing date/time.

Description of extracts

In HAIBA, data from Capital Region of Denmark and Region Zealand contain information on administration of antibiotic treatment since 2012. Figures 6.2 and 6.3 show that some of these medications were already prescribed between 2010 and 2012. Large differences can be seen per day over that period; with a median of five prescriptions per day in Capital Region of Denmark and seven in Region Zealand, and a maximum number of prescriptions on one day of 4,640 and 2,650, respectively.

Data from Capital Region of Denmark were stable between 2012 and September 2014, in terms of both prescriptions and administrations. The median number of prescriptions in that period was 6,375 (IQR 4,273-7,059) and administrations 5,859 (IQR 5,524-6,128). From October 2014, the numbers increased dramatically and showed three large peaks in January 2015, May-July 2015 and February-April 2016. Further investigation is needed to determine the cause of these peaks.

Data on administration of medicine in Region Zealand were stable from 2012 until June 2016 with a median of administrations of 1688 (IQR 1,579-1,793). There were a few outliers in July 2014 and March 2016 where no administrations were recorded. More variation was observed in administrations between April and October 2015. Prescriptions showed a wider variation on the whole, with a median of 1,722 (IQR 1,292-1,990).

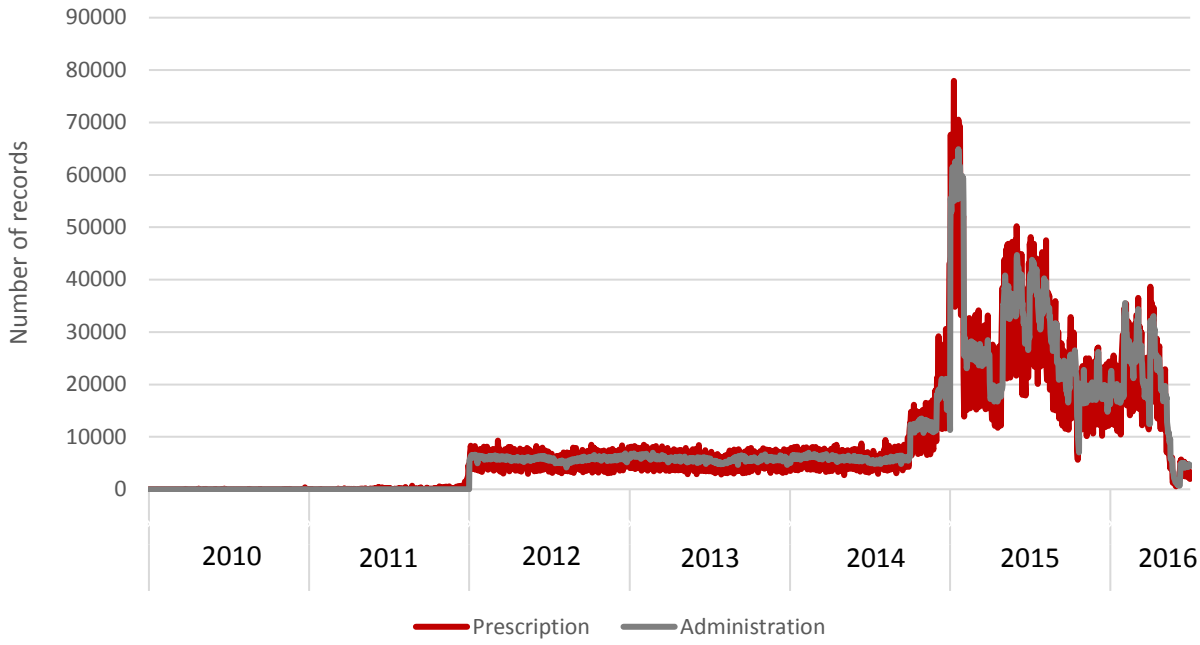


Figure 6.2 Number of prescription and administration records in the import from Capital Region of Denmark between 1 January 2010 and 30 June 2016. Extract dd. 19-07-2016.

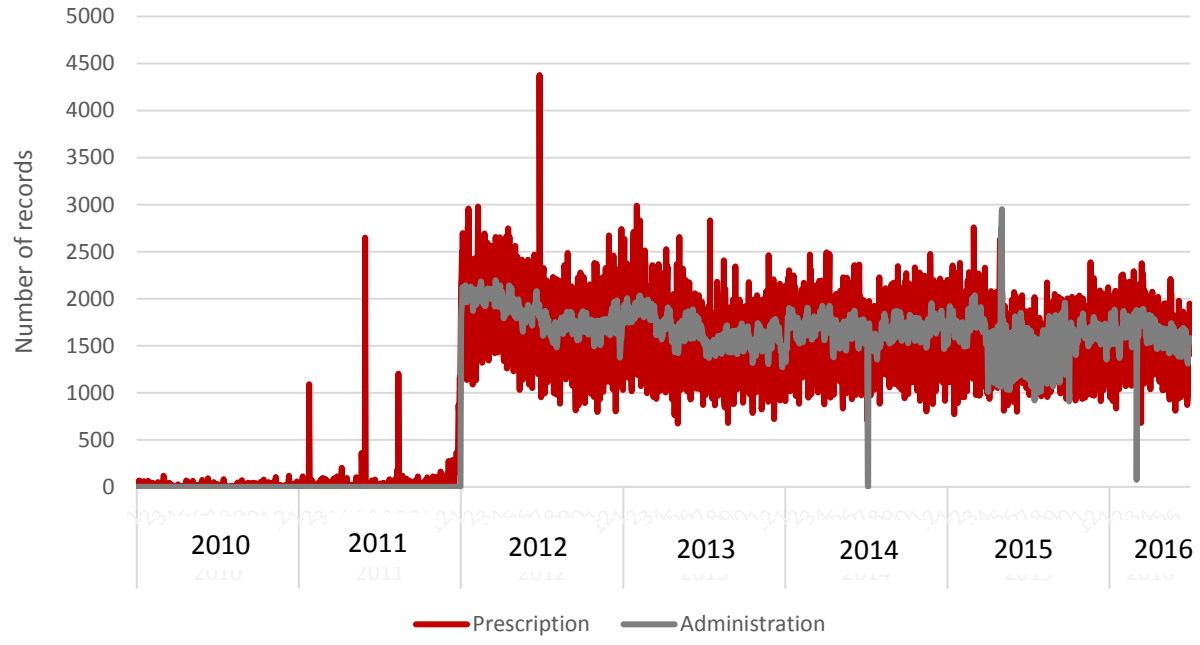


Figure 6.3 Number of prescription and administration records in the import from Region Zealand between 1 January 2010 and 30 June 2016. Extract dd. 19-07-2016.

After applying the rules for preparing medicine data for use in the HAIBA algorithms, the number of records is reduced to only showing one course of treatment with one type of antibiotic (ATC code) per patient. Figure 6.4 shows that this eliminates the large variations. This may suggest that the large peaks in the Capital Region of Denmark have to do with registration practices in which several records are entered for the same course of treatment. The preparation rules seem robust enough not to be affected by these. There are still some high and low outliers on a few days, which should be further investigated.

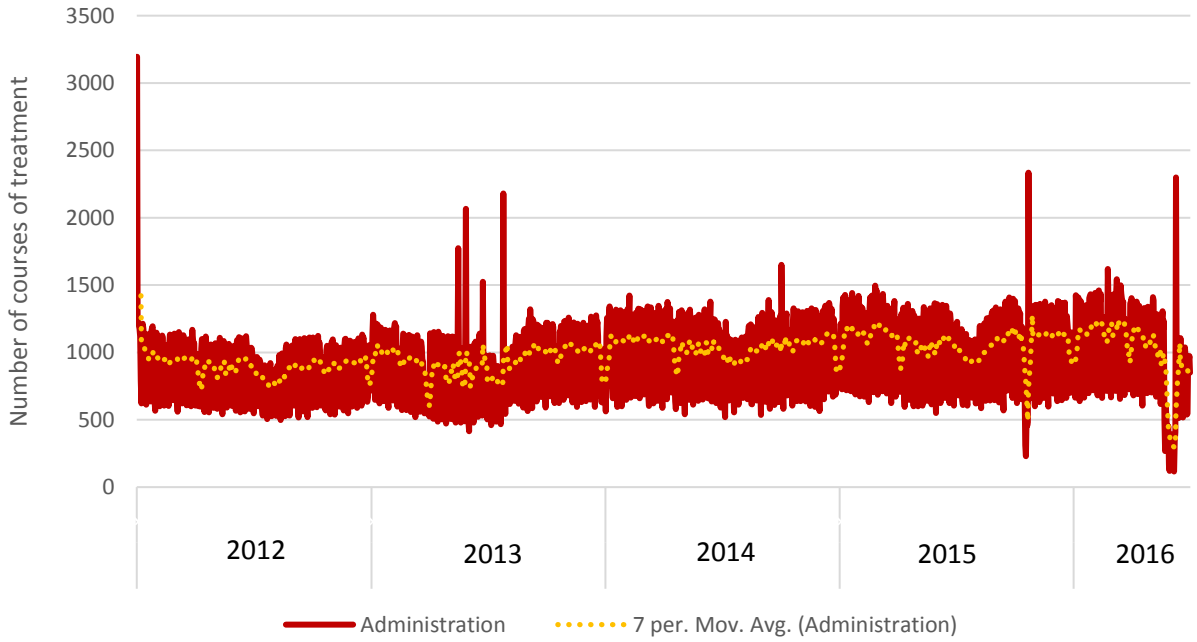


Figure 6.4. Number of courses of antibiotic treatment by administration date in Capital Region of Denmark and Region Zealand between 1 January 2012 and 30 June 2016. Extract dd. 20-07-2016.

Discussion

It has not been easy to consolidate medication data into a national database. However, these efforts are likely to pay off soon. The experiences with this national database illustrate the challenges we face when combining data from different systems.

Since medication data were not yet available for all regions, we made the case definitions that are currently in production independent of antibiotic treatment. We gained some experience with the use of medication data by including them in the algorithm for "probable HA-UTI", as discussed in Paper IV. More work is needed to gain better understanding of the underlying data, for example regarding the unexplained peaks in medication data from Capital Region of Denmark in 2015 and 2016. When data from the other regions also become available, we can start to obtain an overview of antibiotic use in Danish hospitals and explore the full potential of these data.

It will remain a limitation that medical modules do not include data on treatment after discharge. This may particularly be a challenge regarding surgical site infection in which relevant treatment is typically given for a period of four to six weeks. Part of this period most probably takes place after discharge. If FMK becomes available for statistical purposes it would certainly be interesting for HAIBA.

Data quality

In order to secure quality and completeness of the content it is important to sign agreements with each of the regions and between the Department of Data Quality and Content and HAIBA. These agreements will need to clarify the responsibilities of the different partners and describe what each of the partners can expect. In addition, it is important to have documentation from the regions, giving information on coding practice, classification of coding systems and technical specifications, such as how deleted records are being transferred and indicated. It is also important that the Department of Data Quality and Content maintains a surveillance on the imports to detect when imports fail completely or include more or fewer records than expected.

Indication for treatment

Some regions have started registering the indication for treatment in a systematic way, with a coding system or standardized text strings, while others still use free text. The quality of the free text fields is not suitable for use in statistical analysis. Particularly, because the indication for antibiotics generally is written as "against infection" or "against inflammation". If all regions will start registering the indication more specifically and in a

standardized way, e.g. “urinary tract infection”, it would open new interesting opportunities for HAIBA. It would also allow hospitals to evaluate their antibiotic use more constructively.

7. Algorithm for hospital-acquired bacteraemia

Nomenclature

Apart from the various ways of indicating where an infection was acquired, as discussed in Chapter 1, there are also a number of terms used for infections related to bacteria in the blood.

Strictly speaking, bacteraemia means the presence of viable bacteria in the blood. For historical reasons, fungi are also often included in this term. Since not all cases with viable bacteria cause clinical disease, the definition of is sometimes extended with the requirement that a positive blood culture should have been given "significance by a joint clinical and microbiological assessment" (163). Another, more recent, term for a condition in which bacteria or fungi have caused an infection is 'bloodstream infection'.

In 1992, the problem of varying terms and definitions was recognized and new definitions were proposed (164). The term systemic inflammatory response syndrome (SIRS) was introduced and the term sepsis was proposed to be redefined. The terms septicæmia and septic syndrome were proposed to be discarded. SIRS referred to the inflammatory process that can be seen in response to infection, but also in relation to multiple trauma, burns, pancreatitis and other causes. It was suggested that sepsis should be defined as "SIRS, as a result of a confirmed infectious process". The term sepsis includes a continuum

of severity, in which septic shock is the most severe form of 'severe sepsis' (164). Estimates from a few years later, showed that only around 50% of sepsis cases were laboratory confirmed (165). A recent Danish study even showed that only 10% of sepsis patients had bacteraemia (166). This shows that the term sepsis is still used in broader perspective than "SIRS as a result of a confirmed infectious process".

Despite efforts to coordinate terminology, the terms 'bacteraemia', 'blood stream infection' and 'septicaemia' are still used indiscriminately, making literature searches for epidemiology of bacteraemia challenging (167).

In HAIBA, we do not have the possibility of including information on symptoms. It is the presence of pathogenic microorganisms, both bacteria and fungi, in the blood that are being assessed by HAIBA. The following description of the burden of bacteraemia does also include studies on bloodstream infections, clinical sepsis and septicaemia, and specifies the terms as precisely as possible.

Epidemiology of bacteraemia

In a systematic review of 2013, Goto and Al-Hassan estimated 575,00-677,000 episodes of bloodstream infections per year in North America and over 1,200,000 in Europe (168). The European estimates were based on population-based studies in Denmark, Finland and England. This systematic review could not give an estimate of the burden of HA-bacteraemia, due to the limited number of studies. A European PPS from 2011-2012 estimated 312,822 healthcare-associated bloodstream infections per year using the Rhame and Sudderth conversion method (11).

Increases in bacteraemia and sepsis over the past 30 years have been observed in several studies (169–173). Incidence of bloodstream infections has been shown to vary between regions of the world, due to differences in culturing rates, clinical practices, surveillance ascertainment, population demographics and risk factor distribution (172). Incidence of bloodstream infections increases for instance with age and is higher among men (169,174).

Prevalence of healthcare-associated bloodstream infections in Europe was estimated at 0.7% in 2011-2012 (11). Danish prevalence estimates of HA-bacteraemia and sepsis varied from 1.1-1.7% between 2009-2014 (175).

Bacteraemia and sepsis are associated with high mortality, although estimates vary due to different study populations, methodology and definitions. The systematic review from Goto and Al-Hasan reports a mortality of bloodstream infections of 79,000-94,000 deaths per year in North America and 157,000 deaths per year in Europe (168).

In the North Denmark Region, 30-day mortality of community-acquired bacteraemia decreased from 19.0% between 1992 and 1996 to 15.4% between 2002 and 2006 (171). For healthcare-associated bacteraemia (related to other settings than hospitals), 30-day mortality was estimated at 23.4% and 22.0% in those periods and for HA-bacteraemia at 27.9% and 27.7%.

Estimates of mortality of severe sepsis, using mortality within the hospital stay as outcome, vary from 29% to 55% (176–181). These mortality figures are expectedly higher than the overall estimates, since they involve patients who were already severely ill when they developed sepsis, or were admitted to intensive care, because of the severity of the sepsis.

Attributable mortality would be the most precise measure to investigate the true impact of bacteraemia. These studies are however complicated due to the need for strict matching or alternative ways to address competing risks. Pittet *et al*. reported in 1994 a mortality attributable to bloodstream infection of 35% for patients admitted to surgical ICU (182). Length of stay attributable to blood stream infection was estimated at 8 days in ICU and 24 days in the hospital. Nielsen *et al*. showed an excess long-term mortality during 12 years follow up (183). Relative risk of death was increased for all major causes of death among one-year survivors.

The most common microorganisms found in bloodstream infections are *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus pneumoniae* representing 50% or more of all

bloodstream infections (172). *S. pneumonia* often causes community-acquired bacteraemia. The epidemiology of bloodstream infections with *S. pneumonia* varies depending on the childhood vaccination strategies for pneumococcal vaccines (172). The number of bacteraemias caused by *E. coli*, *S. aureus, S. pneumoniae, Enterococcus faecium and Enterococcus faecalis* increased in 27 European countries between 2002 and 2008 (173). The most significant increase was seen for *E. faecium* and the frequency of multi-resistant *E. faecium* also increased. Infections with resistant clones seemed to add to the number of infections rather than replace the infections with susceptible bacteria.

Clinical background

Bacteraemia most often originates from a primary infected site by drainage through the lymphatic system. The most common primary foci are intravascular devices (primarily catheters), the respiratory tract, the urinary tract and various intra-abdominal sites (184). In one-quarter to one-third of patients, no focus can be determined.

Although most studies define death or treatment failure within 4-6 weeks as outcomes, there are also long-term effects. Quality of life is lower and a rapid degradation in cognition and functional capacity is seen during the first year after bacteraemia (185).

Recurrent bacteraemia have been reported to occur in around 10% of patients with bacteraemia (186). The bacteraemia being hospital-acquired or healthcare-associated was found to be a risk factor for recurrence (186,187).

Patients with haematologic malignancies are a particularly vulnerable patient group. Due to chemotherapy induced gastrointestinal mucositis and prolonged periods of neutropenia they are at high risk of developing bacteraemia. A frequent complication among neutropenic cancer patients is bacteraemic pneumonia, mainly caused by *Pseudomonas aeruginosa* and *S. pneumoniae* (188). Immediate antibiotic treatment is needed to prevent severe morbidity and mortality, but is challenged by an increasing presence of multidrug-resistent Gram-negative bacteria, including extended-spectrum β-lactamase-, AmpC β-lactamase-, and carbapenemase-producing Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter baumanni* as well as *Stenotrophomonas maltophilia* (189).

Prompt and targeted antibiotic treatment is important for patients' outcomes. Increased time to notification of a bloodstream infection, defined as the time between blood culture sampling and result, was shown to be independently associated with increased length of stay (121). Therefore, it is important to diagnose early and there is a need for speed and accuracy in blood culture methods. In the 1990s, continuous-monitoring blood culture systems were introduced. Since then, some advances have been made in more rapid identification and susceptibility prediction (120).

Routine surveillance cultures have little clinical benefit (190–192). Blood cultures are more valuable in the presence of relevant clinical symptoms. In daily clinical practice, fever is often used as the decisive factor to take a blood culture. However, one third of patients with bacteraemia are potentially missed in that way (193,194). Decision rules have been suggested, which among other factors include SIRS (193,195). These rules are not applicable for immunocompromised patients and patients suspected of endocarditis (195). The proportion of positive blood cultures is not high and this has not changed much since the 1990's. Estimates vary from 6.3-12.4% (194,196–200). One explanation may be that patients have already received antibiotic treatment before begin cultured. A Danish study showed that more than one-quarter of patients had received antibiotics within 24 hours before blood culture taking (199).

Another challenge with blood cultures are contaminations. False positive cultures increase laboratory work and cause increased length of stay and unnecessary antibiotic treatment. Good practice of blood culture taking is therefore important. Two to four sets of blood samples should be taken from venepuncture at independent sites (120). The volume of blood cultured is directly proportional to the yield of microorganisms. Each set should include paired aerobic and anaerobic culture bottles and should consist of 20-40 mL of blood (120). Proper skin antisepsis before drawing blood is important to prevent bacteria from contaminating the blood sample.

In many cases, interpretation of blood cultures is straightforward. Blood cultures growing *S. aureus*, *S. pneumoniae*, Enterobacteriacea, *P. aeruginosa* and *Candida albicans* can be considered predictive of true bloodstream infection, while *Corynebacterium* spp. and

Propionbacterium spp. almost always represent contamination (120). However, there is a grey zone in which various laboratory data and clinical information need to be combined to come to a conclusion. These situations are important to understand when attempting to develop a computer algorithm. Examples of microorganisms that often pose dilemmas are viridans group streptococci, coagulase-negative staphylococci (CoNS) and enterococci. There are a number of factors that may help identifying the clinical significance, including the number of positive bottles, the site of sampling (catheter versus venepuncture) and the time to positivity (201).

Opportunities for prevention

Apart from the general preventive measures such as hand hygiene and cleaning of the environment, particular focus in the prevention of bacteraemia is needed on the use of central line catheters. This involves aseptic techniques during insertion, catheter manipulation and care, and daily evaluation of necessity (202). In addition, treatment of other infections, such as UTI and surgical site infections is important, before they progress to bacteraemia.

Preventive measures are particularly important in oncology departments, considering the risk of acquiring infections, particularly those with multidrug-resistant gram-negative bacterial infections, and the vulnerability of the patient population. This requires implementation of a bundle of measures including strict adherence to hand hygiene, environmental cleaning and decontamination practices, use of contact precautions for patients known to be colonized or infected with multidrug-resistant gram-negative bacteria and placing high-risk patients in private rooms (189). Screening for colonization with multidrug-resistant gram-negative bacteria followed by appropriate precautions has been shown to be effective in non-haematology departments. Antimicrobial stewardship is also important and requires local protocols and treatment algorithms.

Utilization of blood cultures

Several studies have shown that it is possible to develop an accurate computer algorithm for bacteraemia (42–52). In preparation of the case definition for HA-bacteraemia, we analysed the utilization of blood cultures among the different DCMs in Denmark (Paper

II). Since incidence estimates have been shown to vary between countries and regions, we wanted to gain an understanding of underlying data, to assess how large the differences were between the Danish hospitals, and to understand how these local differences would influence a national case definition in the form of an automated algorithm. Data were analysed per DCM, reflecting the situation in the hospitals served by each DCM.

All blood cultures taken between 1 January 2010 and 31 December 2013, as recorded in Epi-MiBa, were linked to data on courses of admission, derived from the DNPR after application of our DNPR algorithm.

Differences in recording data

This analysis revealed an important challenge in developing an algorithm. DCMs had a different way of recording results from blood cultures. Some would register each culture bottle as a new record, while others would register the conclusion of a set of several bottles as one record. Since time stamps were missing in some cases, it was not always possible to identify bottles belonging to the same culture set from cultures taken at different times. To handle this in the utilization study, blood culture days were defined as days on which a patient had at least one blood culture taken. Positive blood culture days were defined as blood culture days on which at least one sample was positive for a microorganism, classified as pathogenic (see Appendix 4). This approach meant that we would underestimate the blood-culturing activity and it did not account for the volume of blood that was used for each culture. In addition, it did not allow for detection of bacteraemia based on blood cultures that repeatedly isolated likely contaminants.

When translating this into an algorithm for HA-bacteraemia, the most feasible way would be to define a bacteraemia as ‘at least one positive blood culture with at least one pathogen (bacterium or fungus)’. This way the case definition would not be affected by the differences in registration.

Differences and similarities in results of blood cultures

General increases in blood culture days were seen for all DCMs between 2010 and 2013, apart from one university hospital and national referral centre, Rigshospitalet

(Copenhagen), where a slight decrease was seen. Positive results were found in 6.4% of blood culture days; 6.8% for men and 5.9% for women. The proportion of positives among all blood culture days varied among DCMs between 5.5% and 7.2%. The proportion of positives among blood culture days during an admission varied between 5.6% and 7.3% and for those on the day of admission the proportion of positives varied between 6.6% and 8.1%. We observed a higher utilization of blood cultures during the winter months, but a lower yield of positives.

Only small variations were seen in the distribution of microorganisms yielded from blood cultures. Again, Rigshospitalet showed some differences compared to others, with a lower occurrence of *E. coli* and *S. pneumoniae* and a higher occurrence of *E. faecium*.

These minor differences in blood cultures and positive blood cultures between DCMs, strengthened the feasibility of developing an automated surveillance for HA-bacteraemia. They did reveal some challenges for coding, due to different registration practices and showed that data from the algorithm may vary for different patient groups, as was expected.

Case definition

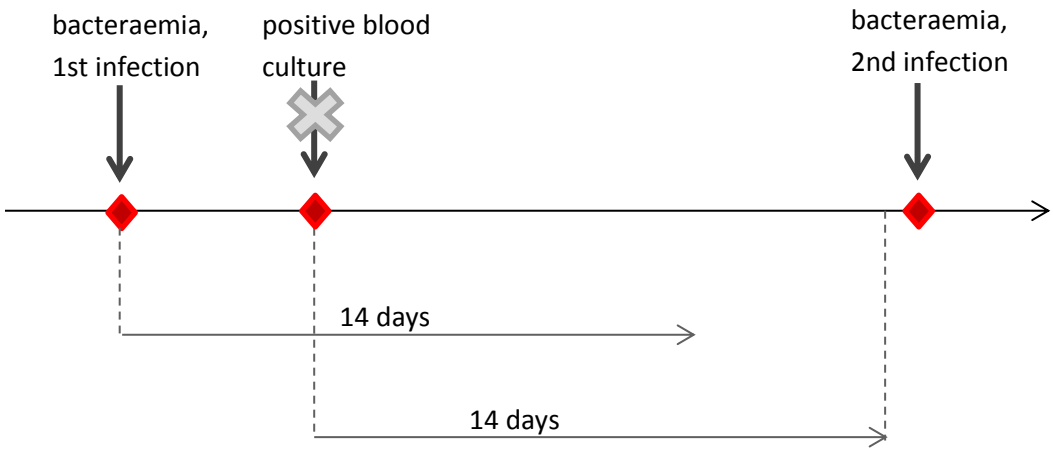
A case definition was developed in the form of a fully automated computer algorithm (Paper III).

In more detail, the following components were specified:

- Bacteraemia was defined as at least one culture positive for at least one microorganism classified as pathogenic (see Appendix 4 for the classification).
- Bacteraemia was assumed to last for 14 days. After that, a new infection could be counted. If a positive sample was found within 14 days, the time window was extended with 14 days and the infection was assumed to still be present (figure 7.1A).
- To be counted as HA-bacteraemia the sampling date had to be between >48 hours after admission and ≤48 hours after discharge and no positive blood culture had to be found in the 14 days before admission nor in the first 48 hours (figure 7.1B).

- Infections were presented at the sample taking date/time.
- An infection was attributed to the departments and hospitals where the patient was according to the DNPR at the date/time of the sample taking. If the sample was taken in the 48 hours after discharge, then the infection was attributed to the department and hospital that discharged the patient.
- Only the first HA-bacteraemia within the course of an admission was counted for incidence calculations. A patient could be counted again for a new infection in a new course of admission, as long as at least 14 days had passed since the previous infection.
- Risk days for incidence density were defined as the days (in hours) from >48 hours after admission to ≤48 hours after discharge, or until an infection occurred.
- Incidence density was calculated as the number of HA-bacteraemia per 10,000 risk days.
- Risk days for prevalence proportion were defined as the days (in hours) from >48 hours after admission until discharge.
- For each day, prevalence was calculated as the number of hours that patients with an active HA-bacteraemia were present in the department, divided by the number of hours patients at risk were present.

A. Time window of 14 days before a new infection is recorded.



B. Relating bacteraemia to course of admission to define HA-bacteraemia and first vs further infections.

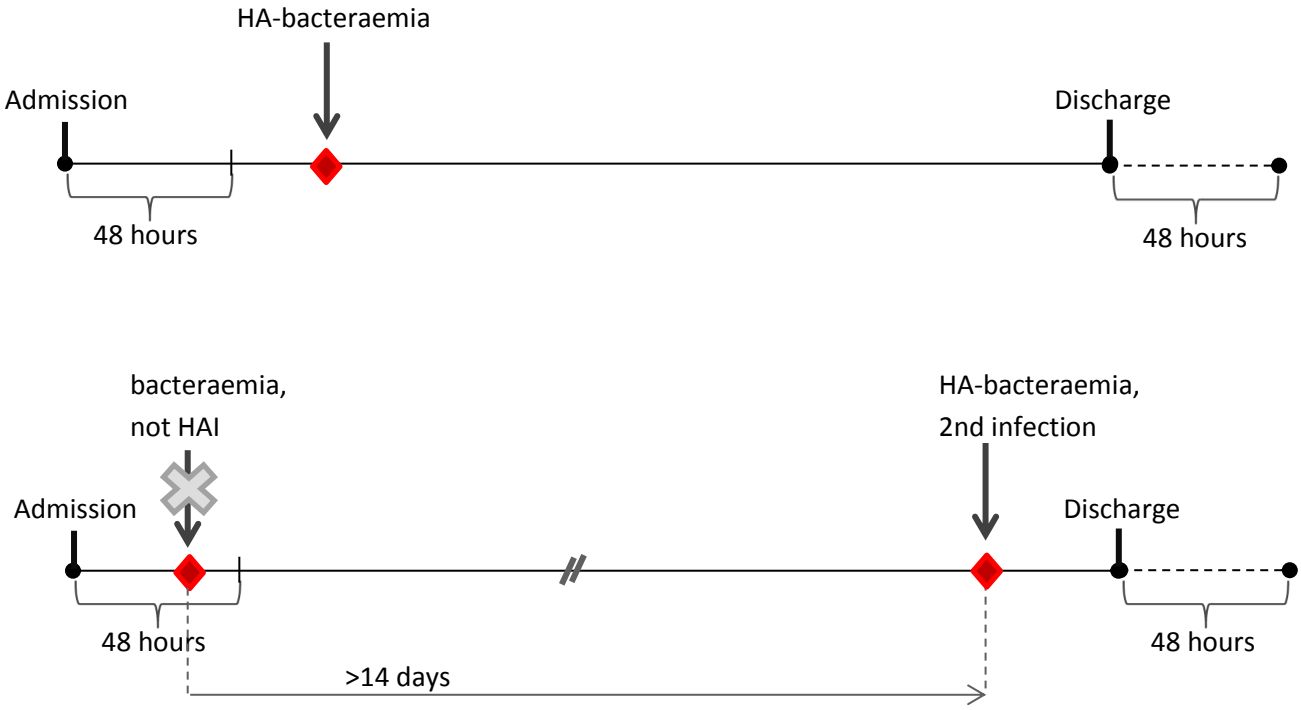


Figure 7.1. Illustrations of the effect of the HA-bacteraemia algorithm on certain situations

Validation

Comparison to Point Prevalence Surveys

The HA-bacteraemia case definition was validated by comparing to data from PPS carried out in 2012 and 2013 in Capital Region of Denmark and Region Zealand (Paper III). In autumn 2012, 66 departments from 10 different hospitals participated in the PPS and in spring 2013, 58 departments from eight hospitals. Apart from bacteraemia (confirmed presence of bacteria/fungi in blood), the PPS case definition also includes patients with clinical symptoms of sepsis and treatment for bacteraemia, but without positive blood cultures (clinical sepsis) (100).

Data were linked using CPR-numbers. Using prevalence calculations from HAIBA, it could then be assessed if HAIBA would have included a HA-bacteraemia on the dates of the PPS.

Sensitivity, specificity, PPV and NPV were calculated and medical records of discrepant cases were further investigated.

This showed a sensitivity of 36.2% (17/47, 95% Confidence Interval (CI) 23.5-51.0%) and a specificity of 99.3% (1926/1939, 95% CI 99.0-99.7%). The PPV was 56.7% (95% CI 40.6-76.1) and NPV 98.5% (95% CI 97.9-99.0). HAIBA was less sensitive for patients in haematology departments and ICUs compared to PPS. Excluding these departments improved the sensitivity to 44.4% (8/18, 95% CI 24.3-70.2).

Pilot study: comparison to North Denmark Bacteremia Research Database

The North Denmark Bacteremia Research Database (NDBRD) includes prospective registration of bacteraemia in the North Denmark Region since 1992 and real-time registration since 1996 (203). Since 2007, clinical data from medical records is included in a structured format. Each case is validated through manual assessment using medical records and microbiological data.

The NDBRD defines a bacteraemia as “an infection with growth in samples from the patients’ blood of one or more bacteria/fungi, which have aetiological meaning after microbiological and clinical assessment” (163). Whether a bacteraemia is hospital-acquired is assessed on a case-by-case basis without a fixed time limit, as described by Garner *et al*. (204). A new episode is recorded after 30 days if it concerns the same microorganism. In case of a different focus, however, a new episode may be recorded earlier.

For comparison, all bacteraemia patients in the North Denmark Region between 1 January 2010 and 31 December 2013 were selected from the NDBRD. From HAIBA, all patients where the algorithm had identified bacteraemia in hospitals in the North Denmark Region in the same period were selected. Data were linked on CPR-number and sampling date with a time window of +/- 3 days. Only the first episodes from each system were included, because of the differences in episode definition.

In total, 822 first episodes of HA-bacteraemia were selected from HAIBA and 1,233 from NDBRD. Of these, 612 episodes were identified by both systems, 210 only by HAIBA and 621 only by NDBRD. This led to a sensitivity of 49.6% (95% CI 46.9-52.5) and a PPV of 74.5% (95% CI 71.5-77.5) for the HAIBA algorithm. One of the reasons for false negatives from HAIBA was the fact that *Staphylococcus epidermidis* was included in bacteraemias in the NDBRD and was classified as a contaminant in HAIBA.

A limitation of this validation was that the NDBRD does not include patients that did not have bacteraemia. Therefore, it was not possible to calculate specificity and NPV. Still, given the high quality of the NDBRD, it is an interesting reference source to compare HAIBA with and get more understanding of the underlying data. Further study is planned to investigate the following questions:

- Are the sensitivity and PPV stable over a period of six years (2010-2015)?
- Clarify the reasons for the discordance between HAIBA and NDBRD, eg. Did HAIBA record some discordant bacteraemia episodes earlier or later in their course of admission in another region?
- Is there difference in concordance for age and sex and between patient groups?
- Is there difference in dominant microorganisms?
- Is there difference in concordance between Aalborg University Hospital and other hospitals in the region?

Evaluation of difference with regional surveillance by Århus University Hospital

The DCM of Århus University Hospital (AUH) had made monthly registrations of bacteraemia since 2004, in order to assess if these concerned community-acquired bacteraemias, hospital-acquired bacteraemias (related to admissions) or healthcare-associated bacteraemias (related to ambulatory care), based on evaluation of medical records. Incidence densities were calculated as the number of episodes/1,000 bed days per month and results were presented in graphs to the leadership of individual hospital departments each quarter of a year.

This surveillance is expected to become redundant with data from HAIBA. A comparison with HAIBA data was carried out, to give the leadership of the clinical departments the

chance to evaluate how HAIBA relates to the surveillance data they were used to (personal communication Rita Andersen Leth).
The study included bacteraemia cases identified in DCM of AUH among patients from Horsens Hospital, Randers Hospital, Skejby and AUH (location Nørrebrogade and Tage Hansens Gade). Data were linked through the CPR-number to an extract from HAIBA containing all patients with HA-bacteraemia, whose samples were taken while they were admitted at these hospitals during 2014.

Overall, 320 HA-bacteraemias were recorded in both systems, 33 only in HAIBA and 307 only in the AUH surveillance (table 7.1). An additional 539 healthcare-associated bacteraemias were recorded in the AUH surveillance.

Sensitivity of the HA-bacteraemia algorithm from HAIBA compared to the HA-bacteraemia surveillance of AUH varied between hospitals from 43.6-55.8% and PPV from 82.2-95.1% (table 7.1). Of the HA-bacteraemias that only HAIBA recorded, 24 were recorded as healthcare associated by the AUH surveillance. The majority of these patients were cancer patients or other immunocompromised patients. These patients are often in outpatient clinics and the AUH surveillance classified them as healthcare-associated, unless it was very clear that they were acquired under an admission. Two bacteraemias were evaluated as contaminations, because these patients were not given any antibiotic treatment. Six bacteraemias were judged to be community-acquired. The difference here may be that HAIBA uses exactly 48 hours and the AUH surveillance uses 2 days. One patient had a complicated course of admission that started and ended in AUH, but had an admission in Herning Hospital in between. A blood culture was taken in Herning Hospital in the evening of the transfer, but without a timestamp. HAIBA then set the time to 08:00 when the patient was still in AUH.

Explanations for the cases that were not detected with HAIBA revealed some interesting areas for improvement of the algorithm (table 7.2). HAIBA's algorithm does not account for re-admissions at this point, meaning that each course of admission is treated independently. In this study, 31 cases would have been detected if the algorithm would takes into account admissions within eight days prior to the admission where an infection

was found. Similarly, it might be useful to add a rule to the algorithm that relates bacteraemia to specific operations, in order to determine whether they were hospital-acquired.

The following three reasons for discrepancies in table 7.2 are specific choices in the HAIBA algorithm. Firstly, we include only the first episode, because the risk of the second episode is not statistically independent of the first. Secondly, HAIBA is able to include transfers across regions, making it possible to account for admission time before transfer into the Central Denmark Region. Thirdly, classification of contamination species in HAIBA has its limitations, as it does not allow for a clinical and microbiological case-by-case evaluation. With the classification, we have prioritized specificity over sensitivity, accepting that some cases will not be detected, even though they were clinically meaningful. Additionally, 114 (37%) cases remain that are indicated with “other reasons”. These would need to be further investigated through medical record evaluation.

Since the DCM of AUH is used to present hospital-acquired and healthcare-associated bacteraemia together, replacing their surveillance with data from HAIBA will make a large difference. With the current HAIBA algorithm, only around 40% of the number of cases will be included: the 353 cases that HAIBA reported divided by the 859 hospital-acquired and healthcare-associated cases that the AUH surveillance recorded.

Table 7.1. Number of concordant and discordant cases between AUH surveillance and HAIBA and the sensitivity and positive predictive value (PPV) of HAIBA relative to AUH surveillance.

Hospital	Concordant	Only HAIBA	Only AUH	Sensitivity in % (95% CI)	PPV in % (95% CI)
Horsens Hospital	33	5	37	47.1 (36.2-59.6)	86.8 (77.4-98.9)
Randers Hospital	34	4	44	43.6 (33.2-55.2)	89.5 (81.0-100.0)
Skejby	96	6	99	49.2 (42.5-56.5)	94.1 (90.0-99.2)
AUH – Nørrebrogade	97	5	77	55.7 (48.7-63.4)	95.1 (91.4-99.8)
AUH - Tage Hansens Gade	60	13	50	54.5 (45.7-64.3)	82.2 (74.1-91.7)
Total	**320**	**33**	**307**	**51.0 (47.2-55.0)**	**90.7 (87.8-93.8)**

Table 7.2. Explanations for those episodes included in AUH surveillance and not in HAIBA.

Hospital	Contami-nation species	Re-admitted <8 days	Operation <30 days	Birth related	2nd episode	Trans ferred	Other
Horsens Hospital	6	3	11	0	2	0	15
Randers Hospital	5	8	16	0	0	0	15
Skejby	20	9	41	4	4	0	21
AUH – Nørrebrogade	15	6	16	0	4	2	34
AUH - Tage Hansens Gade	11	5	4	0	1	0	29
Total	**57**	**31**	**88**	**4**	**11**	**2**	**114**

Epidemiological description of data from HAIBA

An increase in blood cultures and positive blood cultures was observed over time, particularly among patients aged 65 years and older. Blood culture days showed a seasonal pattern with peaks during winter months. For older age groups particularly large peaks were seen in positive blood culture days in the winter of 2013, while children aged 0-4 had peaks that were more consistent during winter months. Positive blood culture days with *S. pneumoniae* showed marked winter peaks for all age groups and for both men and women. A predominance of male patients was seen for bacteraemias due to *S. aureus, E. faecium* and *Klebsiella pneumoniae*.

Ten species, *E. coli, S. aureus, K. pneumoniae, S. pneumoniae, E. faecium, E. faecalis, P. aeruginosa, C. albicans, Enterobacter cloacae* and *Klebsiella oxytoca*, accounted for 74.7% of agents classified as pathogenic.

In 11% of admissions, at least one blood culture was performed; almost 50% of blood cultures were taken at admission. The chance of having a blood culture taken declined over the next days but increased after 4 days of admission (figure 3, Paper II). Blood cultures positive for *E. faecium* increased after day 5 since admission.

After applying the algorithm, national trends generated by HAIBA showed a linear increase between 2010 and 2014 (Paper III). Incidence was higher for men than women (9.6 vs 5.4/10,000 risk days) and highest for ages 61-80 years (9.5/10,000 risk days). The

median daily prevalence was 3.1% (range between daily estimates 2.1-4.7%). Regional incidence varied (6.1-8.1/10,000 risk days) and increased in all regions. Microorganisms found were typical for HA-bacteraemia. Compared to the utilization study, *E. faecium* was more frequently isolated.

Analysis of data for 2011-2015, as presented in the annual report in March 2016, showed a slightly different picture (205). On a national level there was still a statistically significant increase, but for some regions there was no longer a significant increase (table 7.3). Incidence among regions varied considerably from 6.3-8.3 bacteraemias per 10,000 risk days. Similar to the previous analysis, bacteraemia occurred more frequently in older age groups, particularly in the 60-81-year age group and among men. The increase was most marked among men and in the 80+-year age group. For the 60-81-year age group the incidence increased between 2011-2014 and levelled out in 2015.

Discussion

Bacteraemia causes severe disease with high mortality and morbidity. Confirmation of bacteria or fungi in the blood can be difficult as clinical criteria for taking blood cultures are not clear cut, patients may already be under antibiotic treatment and blood cultures may be contaminated. These factors all influence an algorithm for HA-bacteraemia and are potentially different across hospitals. However, assessment of blood culture utilization showed similar utilization among the DCMs in Denmark, suggesting similar practice of blood culture taking across Danish hospitals.

Validation of the algorithm was done using three different data sources, involving four out of five Danish regions: a PPS study at hospitals in the Capital Region of Denmark and Region Zealand, the NDBRD for the entire North Denmark Region and surveillance from AUH covering a large part of Central Denmark Region.

Each of these studies have their strengths and limitations, which need to be taken into account when evaluating their results. The selection of patients in the PPS validation may have introduced bias, since the PPS is based on voluntary participation of hospitals and their choice of departments. The selection of patients should not have introduced any

bias in the validation against NDBRD and the AUH surveillance, as these reference sources included all bacteraemias identified in the respective populations under surveillance.

Table 7.3. Number of cases and incidence of primary hospital-acquired bacteraemias per course of admission, and risk days, by sex, age group and region, 2011-2015 (data extraction from HAIBA on 2 March 2016). From EPI-NEWS 20/2016 (205)

	Number	Number of risk days	Incidence[1] [range in annual incidence]	Annual development (95 % CI)[2]	Trend[3]
Patients, total	13,514	17,774,557	7.6 [7.3-8.1]	1.02 (1.01-1.04)	↑
Men	8,429	8,588,029	9.8 [9.2-10.5]	1.02 (1.01-1.04)	↑
Women	5,085	9,186,529	5.5 [5.3-5.8]	1.02 (1.00-1.04)	–
0-20 years	582	1,742,749	3.3 [3.0-3.7]	1.01 (0.96-1.07)	–
21-40 years	585	1,829,728	3.2 [2.7-3.6]	1.02 (0.96-1.08)	–
41-60 years	2,596	3,336,814	7.8 [7.4-8.2]	1.00 (0.98-1.03)	–
61-80 years	6,955	7,150,366	9.7 [9.4-10.2]	1.01 (1.00-1.03)	–
> 80 years	2,482	3,336,381	7.4 [6.9-8.1]	1.04 (1.02-1.08)	↑
Capital Region of Denmark	5,175	6,271,528	8.3 [7.9-8.6]	1.01 (0.99-1.03)	–
North Denmark Region	1,260	1,851,445	6.8 [5.9-7.6]	1.02 (0.98-1.06)	–
Central Denmark Region	2,499	3,493,682	7.2 [6.4-8.0]	1.04 (1.01-1.07)	↑
Region Zealand	1,666	2,641,253	6.3 [5.8-6.5]	1.02 (0.98-1.05)	–
Region of Southern Denmark	2,914	3,516,651	8.3 [7.9-8.8]	1.03 (1.00-1.06)	↑

[1] Number per 10,000 risk days

[2] Estimate and 95 % confidence interval (CI) calculated using Poisson regression

[3] Annual development shows statistically significantly increasing (↑), decreasing(↓) or unchanged (–) trends from 2011 to 2015 (Poisson regression)

In all studies, the running of the algorithm and manual evaluation of patients for registration in reference data were performed independently. Misclassification may occur in all reference data, but is most likely in the PPS. The strength of the validation against PPS was that it allowed calculating specificity and NPV. This was not possible with the NDBRD and AUH data.

Nevertheless, each study provided valuable information on the quality of the algorithm for HA-bacteraemia and how it relates to other surveillance systems. As expected with a low prevalence, estimates for sensitivity were fairly low, varying between 36.2% and 55.8%. Consequently, specificity was high, with an estimate of 99.3% compared to PPS. PPV showed a large variation from 56.7% in the PPS validation to 95.1% in one of the hospitals of the AUH validation. NPV was estimated from the PPS validation at 98.5%. This reflects our aim to avoid false positives, while accepting false negatives to some extent.

The classification of microorganisms into pathogens and contaminants will always generate some false positives and negatives, because of the absense of human judgement. The choices we made in this respect have mostly led to false negatives. This was illustrated in the NDBRD validation, where HAIBA did not detect some bacteraemias, because blood cultures had grown *S. epidermidis*.

Defining whether a bacteraemia is hospital-acquired leaves more room for improvement on the sensitivity of the HAIBA algorithm. The validation study from AUH gave a couple of interesting leads, including relating courses of admissions to each other and relating bacteraemias to operations and births. In line with this, it could also be interesting to relate bacteraemias to diagnosis of UTI prior to the bacteraemia episode. Both the NDBRD and the AUH surveillance value the information on infections related to ambulatory care. With admissions getting shorter, this group will become larger, making it even more relevant to find a way to include these infections in the algorithm.

The PPS validation showed that HAIBA's algorithm was less sensitive for patients in haematology departments. The AUH surveillance usually considered bacteraemias in these patients as healthcare-associated, because they are regularly visiting the hospital,

either as outpatients or as inpatients. A number of these patients were actually classified as having HA-bacteraemia in HAIBA, but more were probably missed. This reveals the complexity of this specific patient group and an area that could be further explored in HAIBA.

More validation studies are planned. A follow-up with the NDBRD has previously been mentioned here. In addition, the Danish Collaborative Bacteraemia Network (DACOBAN) has gathered much experience with an algorithm for HA-bacteraemia. Discussions at early stages of the development of HAIBA's algorithm were very informative and showed that we faced similar challenges. Comparing the algorithms in more detail may also give new insights for improvements.

With the current algorithm, we estimate a median daily prevalence of 3.1% (range 2.1-4.7%). This is higher than the estimates from Danish PPS, which had a median of 1.1% (range 1.1-1.6%) between 2010-2014 (175). The estimate from the European PPS for 2011-2012 was with 0.7% even lower (11). Since the overall number of infections identified through the HAIBA algorithm were lower than through the Danish PPS, the higher prevalence may have to do with the way HAIBA calculates the denominator, excluding the first 48 hours of each admission as risk time. The PPS includes all patients, also those in the first 48 hours of admission. Differences in underlying concepts and methods may also contribute.

Prevalence estimates in HAIBA could be improved with a few changes. Firstly, it could be considered to define a new episode when a new microorganism has been found. Secondly, when medication data become available, the duration of illness could be more accurately established. These changes will potentially increase the number of infections counted, further approaching the number recorded in PPS. However, a difference in prevalence estimates will remain, given the difference in the denominator.

As expected from the many reports on increasing trends, data generated with HAIBA's algorithm showed an increased incidence density of HA-bacteraemia. However, the number of HA-bacteraemia as reported by HAIBA did not increase. We hypothesized in

paper III that the increase could be driven by a decrease in the denominator, i.e. risk days, although one would also expect less HA-bacteraemia if the length of stay decreased. The fact that this did not decrease may have to do with an aging population and more advanced treatment given at older age.

8. Algorithm for hospital-acquired urinary tract infections

Nomenclature

The terms 'UTI' and 'bacteriuria' are often used interchangeably. However, bacteriuria (or candiduria in the case of *Candida* sp) refers to a significant number of microorganisms in urine as confirmed with urine culture. UTI implicates that microorganisms in the urine led to symptoms. UTI are not always confirmed with urine culture. Bacteriuria is also sometimes defined as "significant growth of bacteria in the urine not associated with symptoms" (206). Others refer to this condition as 'asymptomatic bacteriuria' (207).

With our algorithm, we can assess the presence and amount of bacteria in urine, antibiotic treatment and diagnosis codes, but not symptoms. After considerable deliberation, we defined 'laboratory-diagnosed UTI' as bacteriuria, in the sense of urine cultures yielding significant growth of microorganisms. In addition, we defined 'probable UTI', indicating that a urine culture did not show significant growth, but the patient was given antibiotic treatment and/or recorded with a relevant diagnosis code, suggesting symptoms.

Epidemiology of hospital-acquired urinary tract infections

Estimates from PPS in acute care hospitals in Europe showed a prevalence of HA-UTI at 1.2% (11). The Danish PPS estimated a prevalence of HA-UTI at 1.9-2.5% between 2009 and 2014 (175).

Indwelling urinary catheters are strongly associated with bacteriuria (206,208). The vast majority of HA-UTI are attributable to indwelling catheters; proportions of 70-80% and up to 97% have been reported (207,209).
Despite the fact that HA-UTI are very common and potentially preventable, interest in these infections was low for many decades. Many of the current guidelines are still based on literature from the 1960s to the 1980s. The implementation of a policy by the US Centers for Medicare and Medicaid Services, stating that hospitals would not be reimbursed for costs of catheter-associated UTI acquired by hospitalized patients, renewed interest in HA-UTI (88).

The most common pathogens associated with catheter-associated HA-UTI are Enterobacteriacea, including *E. coli*, *Klebsiella* sp. and *Enterobacter* sp. (209). In ICU settings *P. aeruginosa*, enterococci and *Candida* sp. are more common.
Since 60-80% of hospitalized patients with an indwelling catheter receive antibiotics – usually for other indications, resistant bacteria are often isolated from urine cultures (207).

Clinical background

The most important risk factor for developing catheter-associated bacteriuria is increased duration of catheterization (209). The urinary catheter disrupts the normal host immune mechanisms and a biofilm develops on the internal and external surface, to which microorganisms attach. Microorganisms gain access either extraluminally, from the part of the catheter that lies in the bladder, or intraluminally, from the junction between catheter and collection tube or the drainage port of the collection bag (209). Around one-quarter of patients with an indwelling catheter for two to 10 days develops bacteriuria and nearly all patients catheterized for a month have bacteriuria (206). Many of these patients do not present with symptoms, and are therefore referred to as having asymptomatic bacteriuria.

Other risk factors for catheter-associated bacteriuria include not receiving systemic antibiotic treatment, female sex, diabetes mellitus and older age (209).

The average additional length of stay due to HA-UTI had been estimated at four days (210). One in 27 patients with bacteriuria will develop bacteraemia (206). These secondary bacteraemias have a seven-day mortality of 30% and a 30-day mortality of 40% (211). A systematic review concluded that risk factors for developing bacteraemia secondary to catheter-associated UTI have not been clearly identified (212). However, this review did point out weak evidence for a number of factors, including male sex, immunosuppressive medication, red blood cell transfusion, not receiving antimicrobials, neutropenia, malignancy and liver disease.

Diagnosis

Diagnosis of UTI in the presence of an indwelling catheter is problematic, since almost all patients develop bacteriuria and clinical presentation often is a combination of unspecific and non-localized symptoms (88). In addition, some of the typical symptoms for UTI, such as frequency, urgency and dysuria can be caused by the indwelling catheter itself and therefore cannot be used for diagnosis of UTI in patients with an indwelling catheter (213).

The 2009 International Clinical Practice Guidelines from the Infectious Disease Society of America state that if a patient has an indwelling catheter, urine should be collected with aseptic technique directly from the catheter or tubing (214). A closed drainage system must be maintained. If the patient has had the catheter for more than two weeks at the time of onset of symptoms, a new catheter should be placed and the urine sample should be taken from the fresh catheter. Alternatively, if the catheter can be discontinued, a midstream urine sample should be obtained.

In Denmark, there is no consensus among clinical microbiologists and clinicians on the role of urine cultures in diagnosing UTI among patients with indwelling catheters. Some clinical microbiologists do not find it relevant, because of the difficulties in interpreting results and because the results rarely lead to change in treatment and patients often have been discharged by the time the result becomes available. Therefore, some find it more effective to do a dipstick test. The disadvantage is that a dipstick does not identify bacteria

that do not produce nitrite, such as Enterococci. On the other hand, enterococci do not cause severe UTI.

Another disadvantage of dipsticks is that these do not allow for assessment of a resistance pattern. Therefore, there are clinical microbiologists and clinicians who do find it useful to take a urine culture upon suspicion of a HA-UTI, even among patients with a catheter, in order to establish appropriate treatment. An additional benefit is that it allows for better surveillance.

Interpretation of the urine culture is complicated and is based on the number of colony-forming units (CFU) per mL. The original study by Kass and Finland to determine this threshold dates from the 1950's and was republished in 2002 (215). The authors found that urine cultures with counts between 0 and 10^4 CFU/mL represented contaminations, while those $\geq 10^5$ CFU/mL belonged to patients with symptomatic UTI. The two groups overlapped at around 10^4 CFU/mL and only few patients with low counts developed high counts when a new sample was investigated. They suggested to use $\geq 10^5$ CFU/mL for surveillance purposes. It is important to note that the study from Kass and Finland did not conclude how to interpret cultures for catheterized patients. Stark and Maki found in 1984 that a concentration considerably below 10^5 CFU/mL may still be clinically and epidemiologically important in patients with an indwelling catheter (216). Clinical focus has been on discussing the appropriate thresholds, but the basic uropathogen detection remains unchanged. In 2016, a study was published evaluating a number of enhanced techniques to improve the detection of clinically relevant microorganisms (122).

Due to the limited scientific knowledge, there are various different interpretations being used for the evaluation of catheter-associated UTI and other HA-UTI. Some studies simply disregard urine culturing in patients with indwelling catheters as not reliable for diagnosing symptomatic UTI (217–219). The 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America do propose a decision-making rule for catheter-associated UTI, defining it by "the presence of symptoms or signs compatible with UTI with no other identified source of infection along with $\geq 10^3$ CFU/mL of ≥1 bacterial species" (214). In this guideline, a catheter-associated asymptomatic

bacteriuria is defined by "the presence of ≥10^5 CFU/mL of ≥1 bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI".

For surveillance purposes, a number of definitions have been set. The CDC case definition for PPS defines a UTI as the combination of symptoms compatible with UTI and a urine culture with no more than two species of microorganisms identified, at least one of which is a bacterium of ≥10^5 CFU/mL (213). For those patients without compatible symptoms this case definition assesses whether at least one of the microorganism species in the urine was also found in the blood. If so, those are defined as asymptomatic bacteraemic UTI.

The ECDC case definitions for PPS define a probable UTI by compatible symptoms. A confirmed UTI is defined by compatible symptoms in combination with (1) a urine culture with at least 10^5 CFU/mL of no more than two microorganisms from a voided urine sample, or (2) at least 10^2 CFU/mL of any number of microorganisms collected by an in-and-out catheter, or (3) at least 10^5 CFU/mL of any number of microorganisms in a urinary catheter specimen (220).

In the Danish case definition for PPS a UTI is defined as the combination of compatible symptoms and growth of ≥10^4 CFU/mL of at most two different species of microorganisms (100). No distinction is made between catheter-associated and other HA-UTI.

Opportunities for prevention

Since most HA-UTI are associated with indwelling catheters, prevention strategies aim at minimizing catheter use, appropriate insertion, maintenance and removal (206,221,222). Prophylactic use of antibiotics is not recommended due to the potential selection of antibiotic resistant microorganisms, although it may be justifiable in specific situations (209). Particular focus should be on patients who are at risk of developing bacteraemia secondary to HA-UTI (212).

Considerations in the development of the algorithm

Creating an algorithm for diagnosis of HA-UTI and particularly the group of catheter-associated UTI poses many challenges and is likely to misjudge the reality in some cases. Several studies have already taken on this challenge. A systematic review assessing the accuracy of administrative data for electronic surveillance showed a low sensitivity. In addition, among eight algorithms for HA-UTI, PPV was below 25% in all, except for one semi-automated algorithm where flagged records were further investigated (66). Algorithms using microbiology were more accurate. Some of these were semi-automated, leaving some room for human adjustment (58,59), while others were fully run on pre-defined rules (42,44,48,49,51,52,56,61).

Investigating possibilities for including information on catheters

Since the risk of acquiring UTI is considerably higher among patients with an indwelling catheter and the interpretation of urine cultures is challenged by its presence, we investigated if we could identify catheter-associated UTIs. Unfortunately, procedure codes in the DNPR were incomplete. It was not possible to reliably identify when a patient received a catheter nor for how long the patient had the catheter.

Epi-MiBa contains mapped codes indicating what type of urine sample was collected. Only around 16% of samples from hospitalized patients were indicated to originate from urinary catheters, suggesting that not all catheter urine samples are coded as such. In data from some DCMs catheter urine is included in the general code for ‘urine’. There are anecdotal reports that this is partly driven by a difference in management by the DCMs; some do not investigate catheter urine. Clinicians who would like the sample to be investigated anyway then code it as ‘urine’ or even ‘midstream urine’.

Threshold for significant growth

Setting the threshold for significant growth was challenging, given that there is limited scientific evidence, many different interpretations, and no possibility in HAIBA to assess the presence of a catheter nor symptoms. We decided to follow the threshold from the Danish PPS of $\geq 10^4$ CFU/mL, since that threshold had been thoroughly discussed at the time of the development of the PPS case definitions and was generally accepted in

Denmark for the purpose of surveillance. We chose to keep the algorithm simple and not to develop a classification for microorganisms. We did exclude samples in which mixed flora were reported.

For those samples that fell under the threshold, data were combined with antibiotic treatment to define a probable UTI. The rationale was that taking a urine culture in itself is a proxy for symptoms and if this was also combined with antibiotic treatment, there potentially was a UTI.

Another challenge regarding the quantity of microorganisms found was that this is recorded in Epi-MiBa in free text. Thus, coding is sensitive to changes and needs to be kept up to date regularly.

Defining the length of illness in the algorithm has implications for the definition of a new episode and for prevalence calculations. We set this time to 14 days. This is a simplification of the reality, since length of illness varies considerably between agents causing the UTI. More than 75% of bacteriuria caused by nonenterococcal gram-positive cocci last less than one week, but episodes of bacteriuria due to *E. coli*, *Proteus mirabilis*, and *P. aeruginosa* last on average four to six weeks (218).

Results of dipstick tests taken on the bed side are not registered in MiBa. Practices in taking dipstick tests or urine samples for culture may vary across hospitals, directly affecting the baseline number and incidence of HA-UTI observed in HAIBA. Therefore, it is useful to look at the urine culture utilization to get insight in potential differences in baselines of number and incidence of HA-UTI between hospitals and regions. Figure 8.1 illustrates that in regions where more urine cultures are taken also more HA-UTI are found. Thus, a low incidence does not necessarily mean that there are few HA-UTI, but may reflect a low utilization of urine cultures.

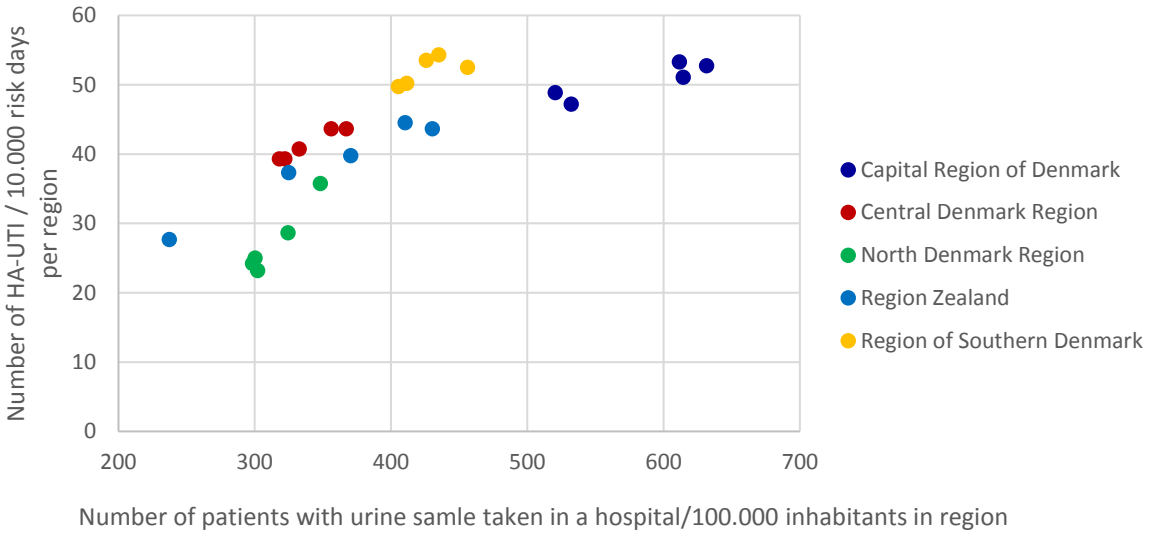


Figure 8.1. The number of patients that had a urine sample taken in a hospital per 100,000 population plotted against the number of laboratory-diagnosed UTI according to HAIBA per 10,000 risk days, by region and by year, 2010 - 2014. Date of analysis 24 August 2015.

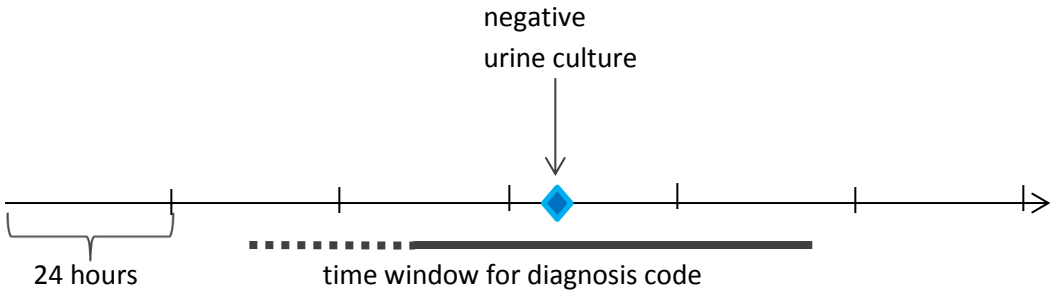
Case definition

The following components were defined for the algorithm for HA-UTI:

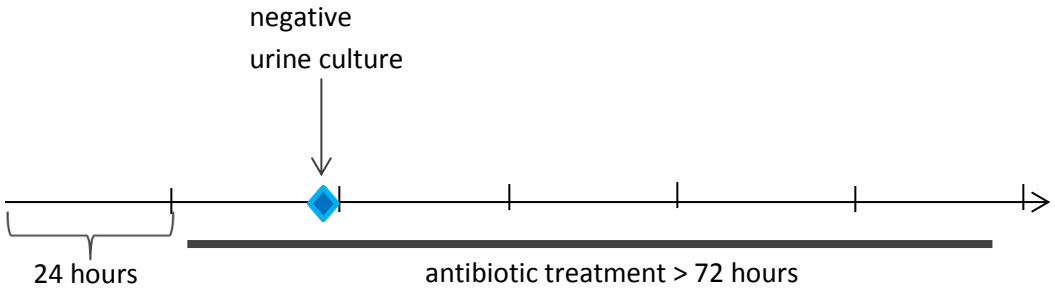
- Patients under one year of age were excluded.
- Laboratory-diagnosed UTI was defined as a urine culture positive for no more than two microorganisms with at least one at 10^4 CFU/mL.
- Probable UTI was defined as a negative urine culture and a relevant diagnosis code or relevant antibiotic treatment.
- Relevant diagnosis codes were defined as codes in Appendix 5. Diagnosis codes do not have a time stamp. To connect them in time to the sampling date/time of the urine sample, the related admission (rather than course of admission) was identified. The relevant time window was defined as 48 hours before start date/time until the end date/time of the admission (figure 8.2A).
- Relevant antibiotic treatment was defined as one of the codes in Appendix 6, independent of the administration mode, started in a time window of 24 hours before sampling date/time and ≤ 48 hours after sampling date/time (figure 8.2B). Treatment given for ≤72 hours was considered prophylaxis and therefore excluded.

- If a laboratory-diagnosed UTI occurred within 14 days (in hours) after one or more probable UTIs then the probable UTIs were excluded (figure 8.2C).
- A UTI was assumed to last for 14 days. After that time window a new infection could be counted (figure 8.2D). If a positive sample was found within 14 days, the time window was extended with 14 days and the infection was assumed to still be present.
- To be counted as HA-UTI the sampling date had to be between >48 hours after admission and ≤48 hours after discharge an no positive urine culture had to be found in the 14 days before admission nor in the first 48 hours (figure 8.2E).
- Infections were presented at the sample taking date/time.
- An infection was attributed to the department and hospital where the patient was according to the DNPR at the date/time of the sample taking. If the sample was taken in the 48 hours after discharge, then the infection was attributed to the department and hospital that discharged the patient.
- Only the first HA-UTI within the course of an admission was counted for incidence calculations. A patient could be counted again for a new infection in a new course of admission, as long as at least 14 days had passed since the previous infection.
- Risk days for incidence density were defined as the days (in hours) from >48 hours after admission to ≤48 hours after discharge, or until an infection occurred.
- Incidence density was calculated as the number of HA-UTI per 10,000 risk days.
- Risk days for prevalence proportion were defined as the days (in hours) from >48 hours after admission until discharge.
- For each day, prevalence was calculated as the number of hours that patients with an active HA-UTI were present in the department, divided by the number of hours patients at risk were present.

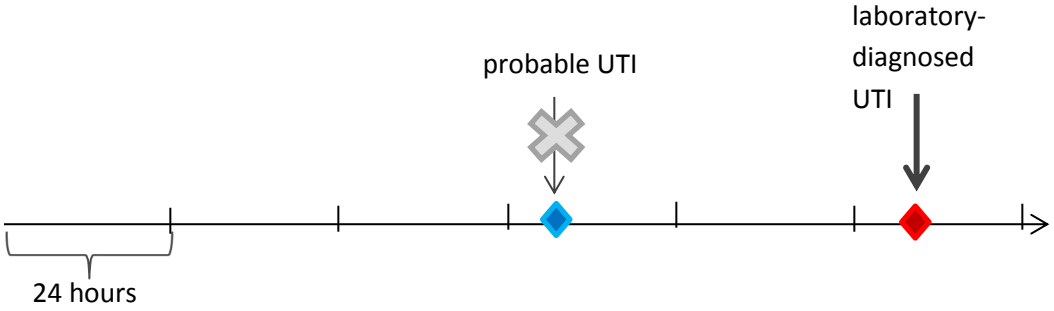
A. Probable UTI based on a negative urine culture and a relevant diagnosis code



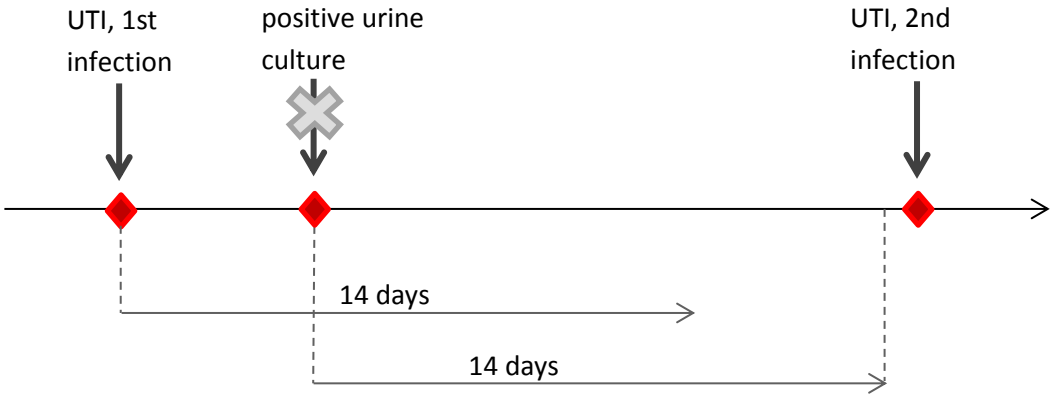
B. Probable UTI based on a negative urine culture and relevant antibiotic treatment



C. Probable UTI excluded if it occurred within 14 days of a laboratory-diagnosed UTI



D. Defining length of UTI and new UTI



E. Relating UTI to course of admission to define HA-UTI and first vs further infections

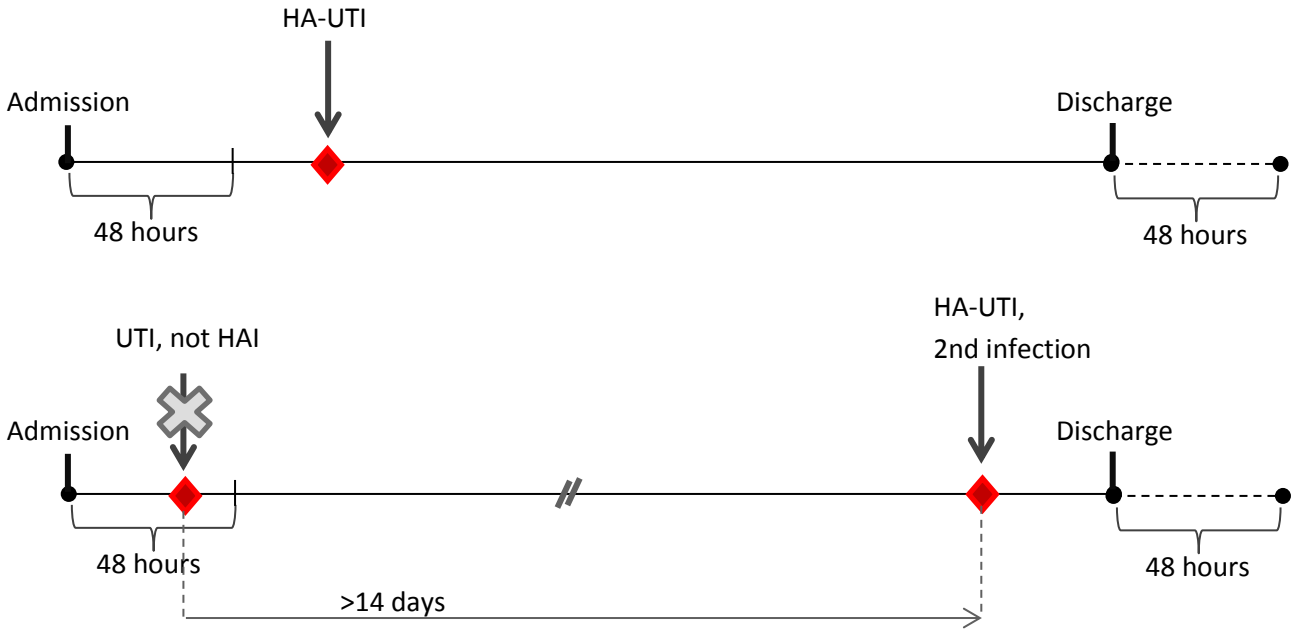


Figure 8.2. Illustrations of the effect of the HA-UTI algorithm on certain situations

Validation

Comparison to PPS

For validation, data were compared to data from the same PPS as used for the validation of HA-bacteraemia, linking through the CPR-number.

Compared to PPS the laboratory-diagnosed HA-UTI algorithm had a sensitivity of 50.0% (26/52, 95% CI 37.4-64.6) and a specificity of 94.2% (1842/1955, 95% CI 93.2-95.3). The PPV was 18.7% (26/139, 95% CI 12.6-25.5) and the NPV was 98.6% (1842/1868, 95% CI 98.1-99.2). Evaluation of medical records of discrepant cases revealed several reasons for discrepancies between HAIBA and PPS. This included laboratory results being unavailable at the time of the PPS; the results considered clinically irrelevant by the surveyor due to an indwelling urinary catheter or lack of clinical signs of infection; and UTIs being considered HA-UTI in PPS eventhough the first sample was taken within 48 hours of admission. A common problem causing discrepancies occurred when patients had pre-existing incontinence or neurological conditions, such as dementia and aphasia. These conditions made it difficult to assess symptoms and therefore the medical record had no

mention of the symptoms required for the PPS case definition. Nevertheless, the clinical team had found it necessary to take a urine sample and culture revealed microorganisms. Positive urine samples in these patients did not always lead to treatment of patients.

No additional benefit was observed from the probable case definition; the algorithm detected 22 more cases of HA-UTI, but only one was also classified as having HA-UTI in the PPS.

Comparison to data from Task Force for Reduction of HAI

The Task Force for Reduction of HAI in the Capital Region of Denmark compared trends in aggregate data from their own algorithm with those from HAIBA. They noted a decrease in number and incidence of HA-UTI in the data from HAIBA in the summer of 2013. This was not observed from the Task Force data (figure 8.3).

A subset of patients was selected from week 29 in 2014 and data from HAIBA and Task Force were linked by CPR-number. This showed a difference in codes used to indicate the specimen material. The Capital Region of Denmark had introduced the use of more specific codes in the summer of 2013. While previously a variety of samples were coded as ‘urine’, these were now coded specifically as ‘urine from urine bottle’, ‘urine from bed pan’, ‘urine from collection bag’. The three new codes were not included in the extract provided by Epi-MiBa, as they represent low quality urine samples. They were, however, included in the algorithm of the Task Force. Figure 8.4 shows the marked increase in the use of these three codes in the three combined DCMs of the Capital Region of Denmark (Herlev, Hvidovre and Hillerød Hospitals). This analysis also showed that Aalborg University Hospital had a stable number of samples coded as such and Viborg stopped using these codes in June 2011.

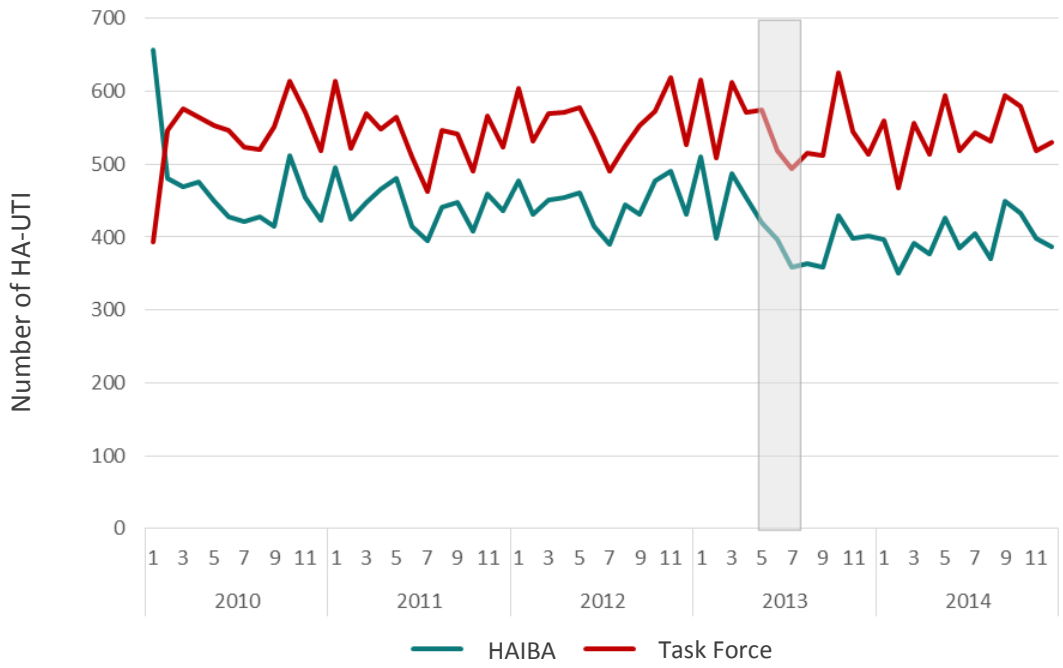
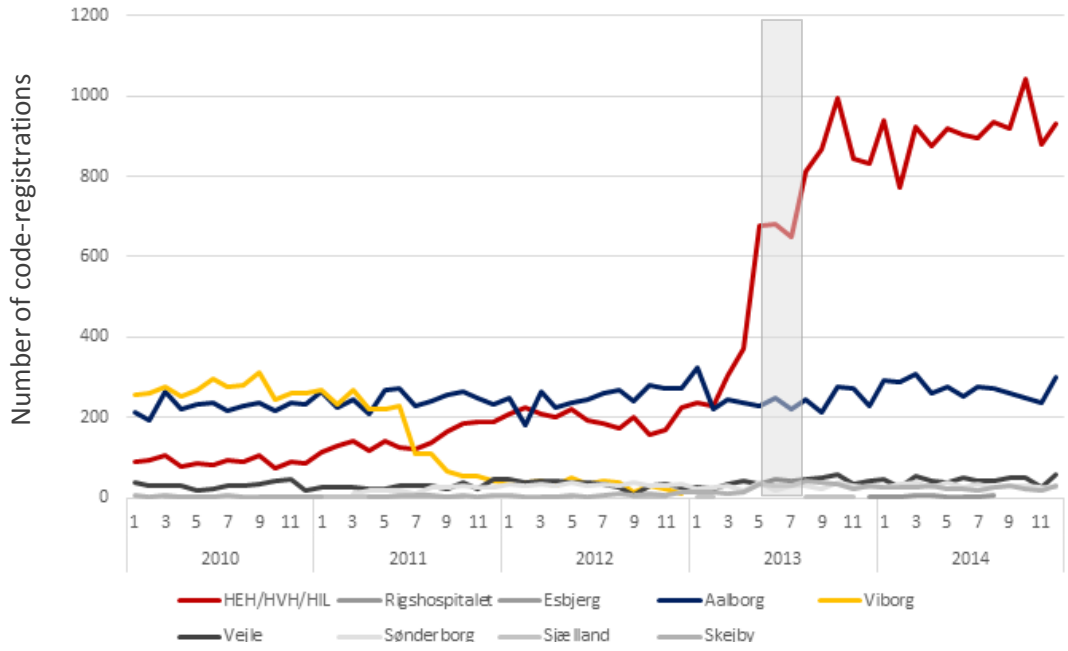


Figure 8.3. Number of HA-UTI in the Capital Region of Denmark as identified by HAIBA (blue) and the Task Force for reduction of HAI (red) between 2010 and 2014. Data analysis dd. 24 August 2015



HEH/HVH/HIL= Herlev, Hvidovre and Hillerød Hospitals

Figure 8.4. Use of codes for 'urine from urine bottle', 'urine from bed pan', 'urine from collection bag' among the different Departments of Clinical Microbiology, between 2010 and 2014. Data analysis dd. 24 August 2015.

Epidemiological description of data from HAIBA

HAIBA detected a national incidence rate of 42.2 laboratory-diagnosed HA-UTI per 10,000 risk-days with an increasing trend between 2010 and 2014 (Paper IV). Incidence increased in all regions. Analysis for the annual report for 2015 also showed an increase between 2011 and 2015, although the trend seemed to become stable in the Capital Region of Denmark. Prevalence was estimated for each day, the median daily prevalence was 4.9% (range 4.0-6.1%). Women had a higher incidence than men (table 8.2), as was expected. Incidence was considerably higher among the older age groups and the increase over time was statistically significant only in the 61-80-year age group.

Discussion

HA-UTI are largely preventable, particularly by reducing the duration of indwelling catheters. With a high risk of infections with resistant microorganisms, surveillance and prevention becomes even more important. While patients with indwelling catheters have a higher risk of developing HA-UTI they are difficult to diagnose, making surveillance and research more challenging.

The case definition was validated against a PPS study carried out in hospitals in the Capital Region of Denmark and Region Zealand. In addition, a number of ad hoc investigations were done in response to findings in trends. As mentioned before, the PPS is based on voluntary participation of hospitals and their choice of departments. This potentially introduced bias in the selection of patients. Identifying cases through the algorithm and PPS were performed independently. PPS has the potential of misclassifying, meaning that false positives from HAIBA could be false negatives from PPS and vice versa. The strength of the validation against PPS was that it allowed calculating specificity and NPV in addition to sensitivity and PPV.

For the ad hoc validations no sensitivity, specificity, PPV and NPV were calculated. They did however give important insights in underlying processes that influence the number of HA-UTI presented in HAIBA.

Table 8.2. Number of cases and incidence of primary hospital-acquired urinary tract infections per course of admission, and risk days, by sex, age group and region, 2011-2015 (data extraction from HAIBA on 2 March 2016). EPI-NEWS 20/2016 (205)

	Number	Number of risk days	Incidence[1] [range in annual incidence]	Annual development (95 % CI)[2]	Trend[3]
Patients, total	68,108	15,856,617	43,0 [41.6-44.0]	1.01 (1.00-1.01)	↑
Men	25,951	7,693,607	33.7 [32.0-35.4]	1.01 (1.00-1.02)	↑
Women	42,157	8,163,010	51.6 [50.4-52.2]	1.01 (1.00-1.01)	↑
1-20 years	810	700,091	11.6 [10.3-13.0]	0.99 (0.95-1.04)	–
21-40 years	3,127	1,778,221	17.6 [17.1-18.8]	1.02 (1.00-1.05)	–
41-60 years	8,916	3,172,153	28.1 [27.6-29.1]	1.00 (0.99-1.01)	–
61-80 years	31,640	6,741,043	46.9 [45.0-48.5]	1.02 (1.00-1.02)	↑
> 80 years	22,459	3,108,298	72.3 [70.6-75.2]	0.99 (0.99-1.00)	–
Capital Region of Denmark	24,582	5,603,751	43.9 [41.0-46.5]	1.03 (1.00-1.05)	↑[4]
				1.00 (0.97-1.02)	–[5]
North Denmark Region	5,643	1,664,450	33.9 [30.6-36.6]	1.05 (1.03-1.07)	↑
Central Denmark Region	12,515	3,050,792	41.0 [38.7-42.7]	1.02 (1.01-1.03)	↑
Region Zealand	9,979	2,405,910	41.5 [37.7-44.0]	1.04 (1.03-1.06)	↑
Region of Southern Denmark	15,389	3,131,715	49.1 [47.0-50.4]	1.01 (1.00-1.02)	↑

[1] Number per 10,000 risk days

[2] Estimate and 95% confidence interval (CI) calculated using Poisson regression

[3] Annual development shows statistically significantly increasing (↑), decreasing (↓) or unchanged (–) trends from 2011 to 2015 (Poisson regression)

[4] Divided into two periods due to changes in the background data: 2011-April 2013

[5] Divided into two periods due to changes in the background data: August 2013-2015

Lessons from validation studies

Underlying data used in the algorithm for HAIBA are directly influenced by the policies in hospitals for when and how to take urine samples and how to interpret urine cultures. Consensus on these aspects would mean a large improvement in the quality of data. One suggestion may be for the Danish Society of Clinical Microbiology to develop a national guideline for urine sample collection. This would need to include uniform indication of the material that is sampled and a uniform policy of DCMs to culture urine samples from indwelling catheters. Implementation of this would remove selection bias from HAIBA data. Importantly, while this may not lead to a substantial improvement on the individual patient on the short term, it would provide more consistent patient care and opportunities for research, which could improve patient care in future. An example of a study could be to evaluate optimal thresholds for urine cultures from patients with indwelling catheters.

Knowing that this is an ambitious and challenging proposal, HAIBA will need to find ways to handle data given the present selection bias. Adjustment for confounders would be important in this respect. A study on urine culture utilization and other means of diagnosing UTI, similar to the one we did for blood cultures, could also give better insight in the differences and potential biases. It may be necessary to supplement such a study with a survey among Danish hospitals on the official and unofficial practices in urine sample collection, culturing and recording.

There are also a few improvements possible to make the algorithm more robust for coding differences. Initially, samples codes as urine from urine bottle, bed pan and collection bag were not included in our extract from Epi-MiBa, based on the theoretical reason that these kind of urine samples are of less quality and are likely to be contaminated. However, data from MiBa show that the use of these codes varies among DCMs and in many DCMs these samples are coded as ‘urine’. It may be useful to consider including these codes. This is an example where requirements for surveillance and microbiology do not necessarily meet and a decision needs to be taken towards one or the other.

Another planned improvement is of a technical nature. Currently, all known and possible future free text strings indicating the numbers of ≥10^4 CFU/mL are coded as such. This requires regular checks to evaluate whether these text strings are still up to date. In addition, it does not allow moving the threshold easily to test the effect of different thresholds. We plan to create a dynamic table which translates the free text into numbers in a semi-automated fashion. This would make the algorithm less vulnerable and more flexible.

In addition, a number of improvements mentioned for HA-bacteraemia would also apply for HA-UTI. This includes relating courses of admission to each other and including outpatient contacts in the algorithm.

The algorithm from the Hospital Acquired Infections Registry (HAIR) made antibiotic treatment a requirement for registering a HA-UTI (52). This would better reflect the clinical situation and only register a HA-UTI if it was symptomatic. We have not included antibiotic treatment in the algorithm for laboratory-diagnosed UTI for a few reasons. In the first place, simply because the medicine database does not cover the entire country yet. However, even when it does, it will be a challenge to identify the relevant antibiotic treatment, as the medication policy may vary among different hospitals. In the case of HAIR, the algorithm was made for one specific hospital. This allowed for a very specific list of relevant antibiotics, adapted to the local treatment policies. For the algorithm of HAIBA we need to accommodate for all hospitals, and therefore create a larger list with potential for false positives.

Therefore, we tried to use medicine data in a more sensitive way by developing a probable case definition on top of the laboratory-diagnosed case definition. From the validation study it showed that this approach was of limited benefit. Making better use of medication data would have to be further investigated.

HAIBA estimated a median daily prevalence of 4.9%. These estimates are considerably higher than the prevalence of 1.9-2.5% reported by the Danish PPS and the 1.2% reported by ECDC (11,175). Unlike with the algorithm for bacteraemia, the algorithm for HA-UTI

does classify more cases as having HA-UTI than the PPS, explaining the higher prevalence. Nevertheless, there is also the difference in denominator, which in PPS includes patients in the first 48 hours of admission, but not in HAIBA. This also adds to a higher prevalence estimate. Other differences in underlying concepts and methods may also contribute to the difference in prevalence estimates.

Considering the high mortality among patients who develop bacteraemia after a UTI, it is particularly useful to focus prevention measures on patients at risk of this. With data from HAIBA, it is possible to study the correlation between UTI and developing a bacteraemia. Subsequently, the patient groups who do and do not develop bacteraemia could be compared to study risk factors.

9. Data for action

The last stage of surveillance, dissemination, is perhaps the most important one. A surveillance system can be brilliantly accurate and very sophisticated, but if it does not reach those that need to know and can make a difference it is useless. And equally important is that those users need to be able to turn the disseminated data into action. Therefore, we need to identify who the users are, what their wishes and needs are and what data models need to be produced to optimally serve them. These aspects are discussed in this chapter. In addition, some ideas are presented on how data can be turned into action.

Surveillance and quality cycles

For quality improvement Plan-Do-Study-Act (PDSA)-cycles are often used. These were for instance recently mentioned by the Asia Pacific Society of Infection Control as a key success factor in the prevention of central line-associated bloodstream infections (202). The PDSA and surveillance cycles can feed each other in several places (figure 9.1). Dissemination of results can be used for planning interventions as well as studying their results. Interventions may be directed at reducing the occurrence of HAI, or at certain practices that improve data quality in the data collection of the surveillance cycle.

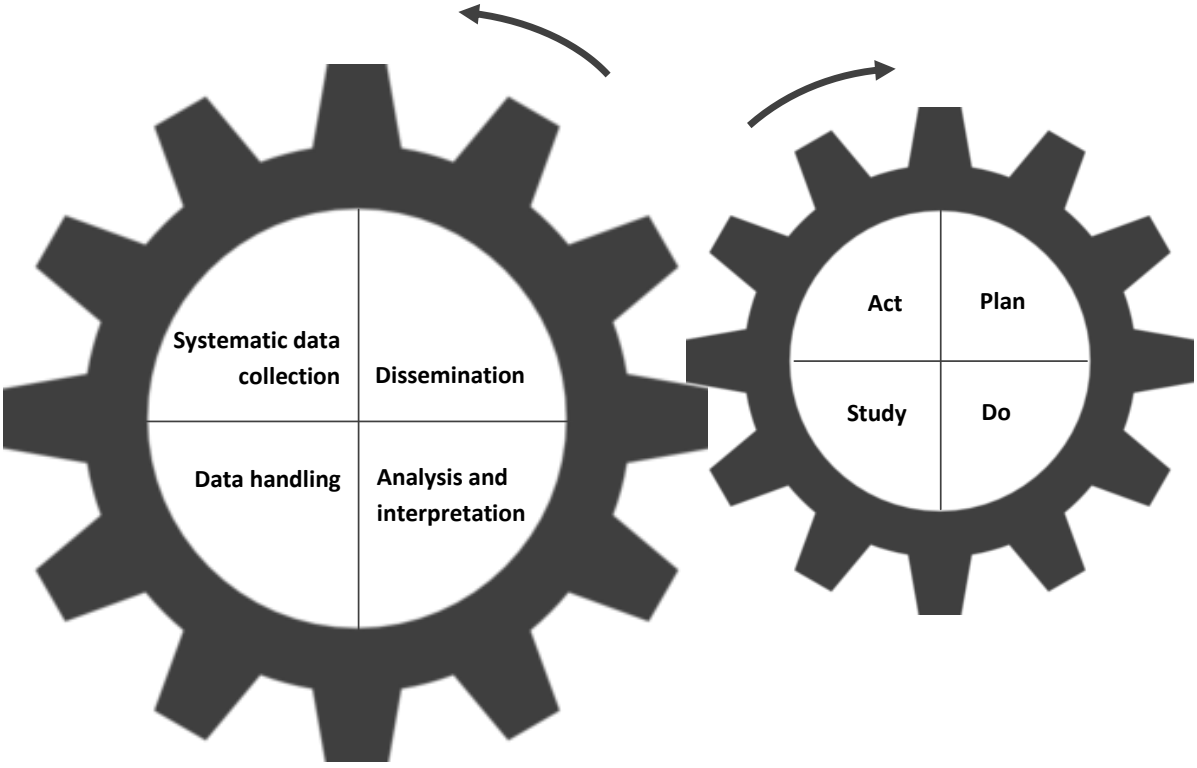


Figure 9.1. A surveillance cycle (left) and PDSA (Plan-Do-Study-Act)-cycle for quality improvement (right).

HAIBA users

The primary users of HAIBA are the infection control teams, who have the responsibility in their hospitals for surveillance and control of HAI. The infection control teams have the experience of communicating epidemiological data to clinical departments in order to improve hygiene practices and other interventions to reduce the occurred of HAI. It is in close collaboration with these teams that the output models are being developed. Results from HAIBA are naturally also aimed at doctors and nurses working in clinical departments, as it is their patients that are under surveillance. Table 9.1 shows for what purposes these and other HAIBA users may want to use HAIBA, and possible applications.

It is important that especially the infection control teams and personnel from clinical departments accept HAIBA as a surveillance system. While many persons from these user groups have been involved in the development of HAIBA over the years, it may still

Table 9.1. Overview of HAIBA user groups, the purpose of surveillance for each of these groups and potential applications of HAIBA.

Level	User group	Purpose	Potential applications
Hospital[1]	Infection control team	Hospital surveillance for infection control	• Evaluation of trends • Evaluation of infection control interventions • Evaluation of quality of operations • Evaluation of treatment of specific infections • Validation of HAIBA • Outbreak detection • Teaching • Research
	Clinical departments	Infection control in individual department/unit	• Evaluation of trends • Evaluation of infection control interventions • Evaluation of quality of operations • Evaluation of treatment of specific infections • Teaching • Research
	Hospital management	Hospital indicators for quality assurance	• Prioritization of resources • Response to media questions
Regional	Regional surveillance collaborations	Regional surveillance for infection control	• Evaluation of trends • Estimation of burden on regional level • Evaluation of interventions • Response to media questions
	Danish Regions / Regional politicians	Regional indicators for quality assurance	• Prioritization of resources • Comparison between hospitals
National	Department of Infectious Disease Epidemiology and National Center for Infection Control at SSI	National surveillance and support to regional and local infection control	• Estimation of burden on national level • Evaluation of trends • Research • Data to support advice to infection control units
	Ministry / National Health and Medicines Authority / national politicians	National indicators for quality assurance	• Reporting for transparency towards citizens • Comparison between hospitals and regions
	Media / citizens	Transparency	• Insight in the quality of the healthcare system • Data to support choice of hospital
International	ECDC	International indicators for burden assessment	• Burden estimates on European level

[1] In some hospitals, the quality control unit and the infection control unit are combined, in other hospitals the quality control unit is connected to the hospital management. Therefore, the quality control unit is not listed in the table.

be perceived as a nationally developed system, distant from the "real world" in the local setting. More efforts are probably needed to create a shared feeling of ownership over HAIBA at hospital level. An added challenge for the acceptability of HAIBA is the phenomenon of "algorithm aversion". Studies have shown that people prefer human judgement to judgement from a computer algorithm, even if they can see that the algorithm performs better (223). As HAIBA is the first national surveillance system for HAI, that completely relies on computer algorithms, some scepticism can be expected. As long as it does not keep us from using it, a critical view can only be good and lead to an even better system.

Output models

Initially, we proposed to make different layers of information, where the more general aggregation levels would be publicly available and the more detailed ones, as well as person identifiable data, sent to the primary users through a login. In October 2012, about 30 representatives from infection control units, clinical departments, hospital and regional management and national institutes were invited for a workshop. The participants were clear in their opinion to open up for all information and make aggregate data publicly available online including the lowest department/unit level.

The advice from the workshop participants formed the basis for the data model that generates data on the website of eSundhed (also accessible through www.haiba.dk). Users can indicate what aggregation level they want to see and if they would like the data presented in a table or graph. There is also the possibility to download data into MS Excel or pdf file format. In addition, the case definitions are documented on this website.

The number of infections is shown online, even if only one or two infections have been identified in a specific department or hospital in a specific week. This is often subject to debate, since this may fall under some definitions of person identifiable data. However, HAIBA follows the policy of eSundhed, which in turn follows the guideline of Statistics Denmark (224). This guideline states that one should not be able to obtain new information on an individual person through a statistics table. If one can only identify a person from the table by knowing all the details, then no new knowledge is being

obtained. In HAIBA, one can only identify a person if one knows that the person had a HAI and when and where a sample was taken. There is no new knowledge gained with that. In addition, data shown in HAIBA are based on algorithms, which may not show a clinical diagnosis that a patient has had.

Initially, this online solution was thought to serve all user groups with aggregate data. However, the first experiences speak for different output models to accommodate the different user groups:

- Infection control teams have indicated that the online data are not flexible enough. They need data per day and in one dataset. That would allow for custom-made calculations.
- Data have not been adjusted for risk and are in general difficult to interpret for persons who do not work with the data and/or know the clinical setting behind the data.
- The hospital-department coding system does not always reflect the names used in daily practice. Many departments do not recognize their department name in the classification system.
- Data on surgical site infections are more sensitive to show by hospital/department as they can be more clearly related to the department or even person responsible for exposure to microorganisms than with bacteraemia, UTI and CDI.
- The speed of the online solution is not so high due to the vast amount of underlying data. A one or two second wait after each choice is often enough to lose interest of the users. This would improve when some levels of aggregation are removed: eg. week and department.

Table 9.2 proposes output models for different purposes. Some of these new output models are currently being tested.

Table 9.2. Requirements and solutions for output models from HAIBA to facilitate the different purposes of surveillance optimally.

Purpose	Requirements for output	Individual patients/ aggregate data	Place: lowest level of aggregation	Time: levels of aggregation	Technical solution	Status
Local and regional surveillance for infection control	Timely; possibility for custom-made aggregations; follow-up individual patients	Individual patients with infections; aggregate numerator and denominator	Department/unit	By day for the past five years and the current year up to today minus 2 days	Daily automated transfer to secure regional servers. Regions control user access.	Aggregate output is in pilot with Capital Region of Denmark. Legal clarification needed for patient level output.
Local and regional indicators for quality assurance	Indicators integrated into hospital management s ystems	Aggregate numerator data and incidence	Department/unit	By month, quarter and year for the past five years. For the current year only the closed month and quarter	Daily automated transfer to Danish Clinical Registries, integrated into hospital management systems.	Datasets are adapted to data model of Danish Clinical Registries and are being tested.
National surveillance and support to regional and local infection control	Insight in all import data, algorithms and output; risk adjustment; trend analysis	Individual patients; aggregate numerator and denominator data	Department/unit	By day for the past five years and the current year up to today minus 1 day	HAIBA data warehouse	In production
National indicators for quality assurance	Indicators on country, region and hospital level; integration in other applications; risk adjustment; trend analysis	Aggregate numerator, denominator and incidence data	Department/unit	By week, month and year. Could be considered to remove the week aggregation	Online data via eSundhed. Annual report of HAIBA in EPI-NEWS and annual report from Ministry of Health and the Elderly.	In production. Data have not been adjusted for confounders and are therefore not suitable for integration into other applications aiming to compare.
Transparency	Dynamic user-friendly system with simple indicators; comparable (risk adjustment)	Aggregate numerator, denominator and incidence data	Department/unit. May be changed to hospital level.	By week, month and year. Could be considered to remove the week aggregation	Online data via eSundhed. Removing some aggregation levels may improve performance	In production. Data have not been adjusted for confounders.
International indicators for burden assessment	ECDC requires PPS using European case definitions and methodology	Aggregate prevalence data	Country	By date of PPS	No solution through HAIBA.	No reporting

A pilot is being carried out with the Capital Region of Denmark to send aggregated data showing number of infections and risk days by day and department/unit. By providing aggregate data by day, the regions are more flexible in calculating incidence figures for any relevant time period, making automated reports for many departments and hospitals in parallel and plot incidence of a hospital against the incidence for the region or the country. It also allows for other types of calculations that may be more motivating for clinical departments, such as the number of days since the last bacteraemia occurred. In addition, hospital and department names can be adapted to fit the local day-to-day practice with more meaningful names and combining hospitals or departments that should be analysed together.

These data are being transferred through a secure connection to a regional FTP-server every night. Once the legal basis is in place for sending person identifiable data, the same secure connection can be used to send a line list of patients that HAIBA identified with the different types of infections, as well as the microorganisms found in their samples, the local laboratory numbers and other relevant information. Eventually, this secure server solution may be replaced by a solution which is integrated in one of the national IT-dissemination systems, such as the 'closed eSundhed' or the National Service Platform. However, these two IT-systems are currently not integrating new systems.

In addition, we have developed an output model for aggregate data to fit the data model from the Danish Clinical Registries. The Danish Clinical Registries provide monthly and quarterly feedback to clinical departments and management information systems and yearly feedback for regional and national clinical audits (225). In June 2016, we started automatic transfer every night. The Danish Clinical Registries will split up the data and send the respective data to each of the regions. The regions are currently testing the data for integration into their management information systems. This output will allow hospitals to generate automated reports in the same way and format as other quality indicators.

With these new ways to present data to the primary users, the purpose of the online interface becomes primarily for transparency purposes. Nevertheless, it can still very well

be used by anyone in the healthcare system who would like to have a quick overview of HAI and who does not have direct access to the hospital management systems or the deliveries to the regional FTP-servers.

Data are also made public through a number of publications. When HAIBA was launched and each time a new case definition was included an article was published in the EPI-NEWS, SSIs weekly epidemiological newsletter (83–86). In addition, SSI publishes annual reports in collaboration with the advisory forum, in which results from HAIBA are further analysed. The first was published in EPI-NEWS in April 2016 (205). HA-bacteraemia and CDI are also included as indicators in the annual report of the healthcare system (226).

A number of systems are interested in incorporating results from HAIBA as quality indicators. This would require development of output models specific for these purposes. For these kind of applications, data first need to be adjusted for confounders, such as age, sex and co-morbidity.

Applications of HAIBA in infection control practice

Investigation of trends and signals

The most prominent application of HAIBA is to follow trends over time. Gradual increases and decreases and sudden changes in number and/or incidence need to be evaluated. In addition, data can been analysed in light of interventions to evaluate the effect. Each time it is important to question whether the trends or signals are real or if they are caused by changes in sampling practices, coding practices, recordings in data sources or changes in the algorithms.

Crucial for the investigation of trends and signals is to be able to evaluate details on patient level. The Department of Infectious Disease Epidemiology at SSI can do this, but it would mean a large step forward when infection control teams are able to access these details too. This will allow validating whether data from HAIBA show a true rise or fall, and looking up additional information on the patients, such as antibiotic resistance data, the clinical history, use of indwelling catheters etc. Apart from manual evaluation, it would even open possibilities for (semi-)automated systems on top of HAIBA, combining

HAIBA data with additional local data, for example biochemistry, antibiotic treatment and even text mining into medical records, if infection control teams wish to make more advanced analyses for surveillance or research.

Data for learning

One application is to present weekly overviews of number and incidence to each clinical department. In the case of infections that do not occur very often it can be more interesting to present the number of days since the last infection. Seeing the number of days increase, can have a motivating effect.

Data from HAIBA, particularly when available at patient level, can be very illustrative for learning purposes. An example could be that a clinical department makes an extract from HAIBA with all patients with HA-UTI in a certain period and evaluates their medical records. This could give information on questions, such as if these patients were treated according to the local guidelines, if their indwelling catheters were changed frequently enough, how the urine samples were taken, if the patients were treated in line with microbiological results, and what could be done to reduce the incidence of HA-UTI in this department. Another example could be at a surgery department, where an extract is drawn with all patients with a specific operation. All patients could be evaluated for having developed HA-bacteraemia and/or HA-UTI.

Outbreak detection

One wish that was expressed from the start of HAIBA's development was to use HAIBA for outbreak detection. In terms of timeliness, this may be possible. There is a certain delay in the system, but this is primarily due to the time until the decision of taking a sample and processing microbiological tests. These processes are also limiting factors when detecting outbreaks in the local setting. Larger outbreaks that occur over a longer period can also be detected by HAIBA. Detection of outbreaks becomes much more relevant when data on microbial aetiology, including sub-typing, becomes more easily accessible through Epi-MiBa. Since HAIBA shows data for the entire country, it could for example identify a cluster of patients across the country having an infection with the same microorganism. Further trace-back could then be done to find the common exposure.

Outbreak detection would require automated thresholds that give off signals of potential outbreaks, which then need to be evaluated. These thresholds need to have a good balance between picking up all outbreaks (high sensitivity) and not giving too many false alarms (high specificity).

Prioritizing resources

HAIBA data need to be used with caution when it comes to prioritization of resources. As mentioned previously, comparison of departments is difficult, especially in the absence of adjustment for confounders. It is possible though to prioritize departments were an increase is seen or, if many departments have an increase, to prioritize those with the highest increase. In addition, when data from HAIBA are analysed on patient level, they can highlight more focused areas for improvement, allowing for resource allocation to targeted interventions.

National surveillance

National surveillance is primarily to support the primary users: the infection control units and clinical departments in the hospitals. The Department of Infectious Disease Epidemiology at SSI monitors the quality of data and investigates national and regional signals. In addition, hospitals can contact the Department of Infectious Disease Epidemiology when they have questions about trends for their hospital or specific departments and discuss what the reasons can be, particularly to investigate if certain coding practices could cause a particular trend.

The National Center for Infection Control at SSI may use data from HAIBA as basis for their advice on infection control and hospital hygiene in personal contact with infection control units and in guidelines.

Questions from the media regarding regional or hospital trends are not answered on the national level by SSI, but are directed to the press contact in the relevant region. These will then contact the relevant persons who are able to interpret the results, generally the infection control teams.

There has been discussion as to what extent the HAIBA group at SSI and the HAIBA advisory forum should actively get involved in discussions on the use of HAIBA at hospital level, or if the task of HAIBA is solely to provide the data. It may not be the task of SSI to interfere in the infection control of hospitals, but particularly the members of the advisory forum who are clinical microbiologists, have a good position to share their insights into the HAIBA system and advise hospitals on the potential applications. A practical way of inspiring the local debates on the application of HAIBA would be an annual national meeting where experiences can be shared, differences in underlying data can be illustrated and debates can be held on needs for further development of HAIBA.

Research

HAIBA opens up many opportunities for research, which can increase understanding of data shown in HAIBA and could generate new knowledge on HAI in general. This is also a good opportunity for collaboration between SSI and regions. Not all studies have to be coordinated by SSI and regional and local researchers are invited to propose and carry out new research.

European surveillance

For European assessment of the burden of HAI, PPS is still the most feasible approach and is advocated by ECDC, as it can be executed by most countries in a standardized way. Current data collection for European surveillance requires completion of an elaborate questionnaire, making it difficult for hospitals to set aside resources and motivate personnel for such elaborate manual work, especially when an automated system is available. HAIBA could provide prevalence estimates, but these are not acceptable for the European surveillance, as they are generated with a different methodology.

There are good reasons for doing European burden assessments at certain time intervals through PPS, but a balance needs to be found between high participation and amount of information requested. If the focus of the European PPS is on the aim of assessing the burden, and registration of additional interesting information is avoided, more hospitals may be willing to participate.

Other European countries are currently exploring the possibilities of developing national or regional electronic surveillance systems and seeking collaboration with HAIBA. It would be useful to invest in a European collaboration at this stage, in order to exchange experiences between countries, assist each other and attempt to develop common case definitions that are acceptable and are possible to create today or in the next few years in most countries.

Application in quality assurance and transparency

In addition to the hands-on infection control, surveillance data are also increasingly used for quality measurement, including benchmarking and public reporting (227). This trend can also be seen in relation to HAIBA. There is, however, little evidence that public release of performance measures and quality measures has an effect on the delivery of healthcare and reduction of HAI rates (228).

The importance of case-mix adjustment when making inter-hospital comparisons has been raised in various publications (228–232). Kritsotakis *et al*. studied the effect of case-mix adjustment on 11 hospitals and showed that ranking changed after case-mix adjustment for eight (72.8%) hospitals (233). Similarly, Kanerva *et al*. examined the effect on their adjustment model on 30 hospitals and found that observed prevalence rates ranked lower than after case-mix adjustment in 11 (38%) of hospitals (234).

Patients, policymakers and politicians may want to see results from hospitals and through that pressure hospitals or specific departments to improve, but we always need to be careful and monitor that the methods are not having the opposite effect or give incentives for unwanted adjustments in the healthcare system. Experiences with transparency of mortality figures have shown that they have effect on mortality, but not necessarily on the quality of healthcare. Surgeons would for example avoid high-risk operations (235). Others have also reported that doctors become more risk avoiding in light of mortality reports (236,237). The policy of the Centers for Medicare & Medicaid Services not to reimburse costs due to selected preventable adverse events, such as catheter-associated UTI, central line-associated bloodstream infection or leaving a foreign object in the body

during surgery, induced a decrease in the rate of these events (238). However, these were likely influenced by a decrease in registration of these events.

A similar effect could be expected with indicators for HAI. Unwanted effects would be that hospitals introduce more bedside tests to avoid sending samples to the DCMs or that orthopaedic surgeons stop taking biopsies upon suspicion of infection. These changes would decrease the numbers of HAI recorded in HAIBA, but also decrease the quality of treatment for infections and the accuracy of antibiotic choice. Therefore, these changes can have a direct effect on antibiotic use, effectiveness of treatment and resistance, while at the same time not reducing the actual occurrence of infections. These adverse effects of transparency tools need to be considered when introducing indicators of HAIBA in national reporting, particular when they are aiming to compare hospitals.

A new version of the Danish Quality Model has been launched this year. Bacteraemia and CDI are included among the indicators (239). The model states that hospitals should use these HAIBA indicators in their quality work. As long as this encourages the hospitals to establish and/or strengthen their internal mechanisms to improve infection control this could be a good way to use HAIBA. If they become benchmarking measures to pinpoint departments that are not doing well enough, or even financially penalizing departments, it becomes questionable how appropriate this is for the improvement of infection control and the reduction of infections, particularly since the indicators are not yet adjusted for confounders.

Another application, that does come close to benchmarking, is a project for the free choice of hospitals. In Denmark, patients may choose a hospital for certain treatments (240). The Ministry of Health and the Elderly together with the Ministry of Finance initiated a project to develop a user-friendly tool that assists patients in their choice. As mentioned in Chapter 1, patients indicated to find the occurrence of HAI a major factor in their choice. Therefore, HAIBA was requested to deliver data. It is however, not appropriate to include HAIBA data as such. If the patient for instance is a young healthy man searching for an arthroscopic knee exploration, HA-bacteraemia will not be a relevant indicator to provide. As long as the tool does not create a profile of the person

searching for information and HAIBA's indicators cannot be adapted to the age, sex and type of treatment, it is not meaningful to include data from HAIBA as indicators in this. Even when it becomes possible to give meaningful indicators, one needs to question if this in the end will actually help the patients and their safety.

10. Conclusions and future perspectives

HAIBA is just at its beginning. The current case definitions and output models form a good basis to build further upon, but have by no means reached the end of their potential. The system is not yet mature enough for all applications envisioned and the different users are only just starting to explore the potential for the improvement of patient safety and the reduction of HAI.

Challenges of using Big Data also apply to HAIBA

Over the past decades, the potential of large datasets for healthcare has been explored and the volume of available data has become larger and larger (241). Big Data is often defined as "data sets so large and complex that they become awkward to work with using standard statistical software" (242). The actual size of the datasets changes as new ways of handling data are being developed, but are currently generally considered in the order of magnitude of terabytes or more. Another way of defining Big Data is by its four dimensions: volume, velocity, variety and veracity, or "the four V's" (241). Each of these also pose challenges for HAIBA and have been illustrated throughout this thesis.

With almost 100GB of data currently in production (see Appendix 1), HAIBA does not involve such vast amounts of data that would usually be considered as Big Data. Part of the reason is because we have reduced the size of data transferred into the HAIBA data

warehouse by predefining variables that we expected to need and filters (extract criteria) to only extract content that we needed. Nevertheless, the software programmes in the current production take 8-10 hours to update the data, meaning that the volume affects the performance, requiring optimizing efficiency at all stages.

Velocity refers to the speed at which new data are accumulated (241). The same analysis will give different results every day, because the content of data sources is constantly updated, also retrospectively. In addition, changes in the data models of DNPR or Epi-MiBa and updates in the HAIBA algorithms may affect results over the entire period. For this reason, HAIBA takes regular updates to be able to compare data at different points in time and investigate the effect of changes in data sources or algorithms. Users also need to be aware that data from HAIBA change from day to day.

If a revision of the algorithms is to be made, it will need to be planned carefully and changes need to be implemented in clusters to limit the number of revisions, since it will potentially change all figures that hospitals have been using from the previous algorithm. The advantage is that the new algorithm can be run on historic data, allowing following trends with a consistent algorithm.

The variety in forms of data sources in HAIBA so far has been limited to the DNPR and Epi-MiBa, but new data sources are expected to be added, to start with medicine modules. Within the data sources variety can also be seen, as they consolidate data from different other databases. In Epi-MiBa for instance data from different DCMs appear in varying formats. In some cases, this can be handled in the algorithms, in others it forms a limitation in the applicability of the data. Combining five medicine modules also poses challenges in this respect. We aim to handle this by agreeing with the regions on a predefined set of variables and formats.

Currently, HAIBA only uses data sources with structured data. As more data sources become available it may be interesting to explore possibilities for semi-structured or unstructured data, such as radiology reports.

Lastly, veracity or rather the uncertainty of data, forms a challenge in Big Data. The larger the datasets, the further removed they are from the reality where data are generated. When working with Big Data, the level of data generation is referred to as "micro-processes". Data models developed on Big Data often make assumptions on the micro-processes, without testing them adequately (242). In the context of branding and understanding customer habits and wishes, Martin Lindstrøm also advocates in his book *Small Data: The Tiny Clues That Uncover Huge Trends* that large companies should lift their eyes from Big Data and supplement them with studies that reveal "Small Data", i.e. information behind data recording (243). In HAIBA, the understanding of clinical and coding practices that lead to the recording in the underlying data sources and changes in these practices over time is also very important if we want to use HAIBA in a meaningful way.

Attributes of the surveillance system

Creating a national surveillance system has several benefits: data sources and case definitions are standardized for the whole country, the system can take into account transfers of patients across hospitals and regions, and the burden of HAI can be measured for all public and private hospitals in one system. In addition, costs for development and maintenance can be shared. Whether the system is also useful depends on how well the attributes are fulfilled.

Acceptability

The fact that HAIBA is a national surveillance system is both an advantage and a challenge. It naturally generates a certain scepticism on a local level. However, HAIBA was built in close collaboration with many experts in hospitals, with the clinical setting in mind. The HAIBA group will need to keep focusing on intensifying engagement and feeling of ownership in the regions and hospitals. It is important in this respect to overcome the phenomenon of "algorithm aversion" (223), and to keep in mind that HAIBA is a surveillance tool and not aiming to replace the diagnostic process. A diagnosis still needs to be made for the individual patient, taking all available information into account, including patient history, physical examination, additional laboratory results and the clinical judgement of the treating doctors.

Completeness and validity

The way that HAIBA uses the DNPR, MINIPAS, Epi-MiBa and medicine modules is new. DNPR and MINIPAS have primarily been used for financial calculations, using Diagnosis-Related Groups (DRG), and registry-based studies. Epi-MiBa has been used for ad hoc extracts and for weekly influenza surveillance. In recent months, Epi-MiBa is increasingly being used for automated surveillance of notifiable diseases. The medicine modules have not been used at national level at all.

HAIBA imports on a daily automated basis, which frequently detects failures in the updates of DNPR and particularly MINIPAS. Since HAIBA aims to provide hospitals with data that can point at specific patients, it sets high requirements to the quality and completeness of data. During the development and validation of the case definitions data are being evaluated in detail, often noticing inaccuracies or changes in registrations, which seemingly have not been noted by those responsible for the original collection of these national data. Examples of this have been observed for all three data sources of HAIBA.

It is important to set aside resources to secure data quality of the original data sources. To some extent, this is done for our data sources regarding the completeness and validity of the individual records. This is referred to as internal completeness and validity (79). However, quality assurance should also include good documentation of the data sources and understanding of the meaning of the variables, a surveillance on the import of data, and a validation of the content, including analysis of the content over time. These are all aspects that can help to assess external completeness and validity (79). Data sources that provide data to other systems also require procedures that inform users well in advance of changes in the systems and service windows. It would be useful if crucial changes are planned in collaboration with epidemiologists and other persons responsible for systems that use these data sources, to secure that data will be usable in the future and retrospectively.

This will only become more important in the future as there are several developments going on to facilitate new (surveillance) systems that will use these data and apply algorithms to them.

On HAIBA's side, validation of its data sources should not stop either. As was illustrated in Chapters 4-6, validation with electronic surveillance never ends. Data models of data sources change, and so do coding and sampling practices. Algorithms may need to be adapted accordingly.

In the process of understanding underlying data, different practices among hospitals and regions were identified. There is for example no consensus on when and how to take urine samples and on the interpretation of urine cultures, particularly in the presence of an indwelling catheter. Another example is the varying practice of registering results for *C. difficile*. Through active use of HAIBA and multidisciplinary discussions of results, HAIBA may be a driving force towards agreements on certain practices.

Accuracy

The validation of algorithms for HA-bacteraemia and HA-UTI showed high specificity and a lower sensitivity. This was to be expected with a low prevalence. However, it is important to further investigate how sensitivity can be improved and if there are specific patient groups that have a particularly low sensitivity. We concluded that the current algorithms give meaningful information for surveillance and discrepancies with other surveillance systems can be explained. Several points of improvement have been identified and will be followed up upon. Despite a low sensitivity, HAIBA can be used as a surveillance system. Important in this respect is to further investigate if sensitivity is constant over time.

Timeliness

Most aspects that HAIBA can influence in timeliness have been optimized and the system has an acceptable timeliness for surveillance and even for outbreak detection. The only substantial improvement that can be made by HAIBA is to find a more timely technical solution for sending secure data to the regions, which is currently delayed until the next night.

Representativeness

HAIBA covers all public and private hospitals in Denmark, except psychiatric departments. Since patients are not actively selected to participate in the surveillance, chances of introducing bias are reduced. They are however not eliminated. Several factors affect whether a patient is included in HAIBA. These include the clinical presentation, which may be different for certain patient groups, such as haematological patients, the decision of a clinician to take a sample, which may vary across departments, and the judgment of a DCM to call a sample positive. Coding practices in the DNPR may also vary from hospital to hospital, affecting for instance the quality of procedure codes for surgical site infections. The introduction of primary healthcare patients into the hospital population in the Capital Region of Denmark is an example of how the selection of patients eligible to contribute to risk days may be affected in one region but not another.

Usefulness

With HAIBA data as a starting point, the infection control teams and clinical departments can now develop ways to apply the results as suits best their local situation. A number of applications are already possible with the current deliveries of aggregate data. Making data available on person-identifiable level would mean a crucial leap in this respect. In order to communicate surveillance data effectively, numbers will need to be translated back to stories of the actual patients. Timeliness can contribute to this, as it is more illustrative and relevant for departments to discuss surveillance data that concern recent patients.

Since politicians and policymakers are also interested in using data from HAIBA, there is a need for further discussion about the appropriate applications in this respect. In all applications, we need to keep in mind that the main aim of HAIBA is to reduce the occurrence of HAI. It is patient safety that should stand first and foremost and adverse effects of transparency and benchmarking should be avoided. In the end, patients are best helped if the actual infections are reduced. It is the internal quality systems inside hospitals and individual departments that need to do this. These often require a safe environment in which problems can be openly discussed without the fear of public blame. Another note of caution is needed regarding the fact that results from HAIBA are not yet

adjusted for confounders and therefore not suitable for comparisons that aim at benchmarking.

Future plans for HAIBA

Including new data sources

Including more data sources can improve the accuracy of case definitions. However, there needs to be a balance between the number of data sources and the resources needed to keep the overview of the quality.

Once medication data is available for the entire country we plan to investigate more thoroughly how the current and future case definitions can benefit from this information, as discussed in Chapter 6. Another feasible addition could be to integrate vital status data from the Danish Civil Registration System. For specific scientific studies it is already possible to combine data from HAIBA with vital status, for example to study 30-day mortality. Whether mortality would also be suitable for ongoing surveillance will need to be discussed further.

There are many other ongoing developments in terms of national registers and consolidation of data. Some of these may be useful for HAIBA in the future. A national database for biochemical results is being developed, which could provide data such as C-reactive protein and leukocyte counts. An implant register is also being developed, which will include a detailed recording of each implant that has been given to a patient. For the first version it was not feasible to integrate the implant register into the DNPR. It is planned to be done when the new DNPR version becomes available, allowing for direct linkage between procedure codes and the implants given. It is uncertain when development of a national radiology database can be expected.

New case definitions

Possibilities for improvements of current algorithms have been discussed in Chapters 4, 7 and 8. However, it is a wish from the advisory forum to first develop more case definitions, before refining the current algorithms, so that more disciplines in the hospitals will get data they can relate to. The next case definitions that are planned to be

developed are infections after total knee arthroplasty and infections after caesarean section.

A national database for radiological data may give the opportunity to develop case definitions for hospital-acquired pneumonia, or more specifically VAP and infections after cholecystectomy. It may also be relevant to investigate possibilities for developing a case definition for gastroenteritis; either generally or focussing on specific agents such as *C. difficile*, norovirus and rotavirus. Other relevant case definitions could focus on specific microorganisms such as influenza or even specific resistant strains, eg. MRSA, ESBL and VRE.

Risk adjustment

Adjustment for confounders is necessary to remove factors that disturb analysis and mask the real trends in the occurrence of HAI and to be able to make comparisons.

There are a number of methods that could be used to adjust for confounders. These include stratification, standardization based on weighted averages, restrictions by excluding unwanted levels of a confounder and a multivariable regression model. Stratification is already used in some of our case definitions; by stratifying the surgical site infections after total hip replacement by acute and elective operations, we have created two patient groups with a different risk for infection. Similarly, the division in COHA and HOHA, where COHA is primarily linked to outpatients and HOHA to inpatients, has created two different risk groups.

Standardization could be considered for example in standardizing regions. This would give incidence rates as if the regions were the same and would allow comparing the observed incidence rate to the standardized rate.

It will need to be explored whether restrictions are necessary or not. In this respect, we could think of excluding the tertiary hospitals of Rigshospitalet and Skejby, or specific specialized departments that are only present in some hospitals.

However, stratification, standardization or restriction will not be enough to adjust for confounders. There will be a need to define a multivariable regression model.

No optimal set of patient-associated parameters has been established so far for case-mix calculation relevant to HAI. Kritsotakis *et al*. proposed the inclusion of demographic characteristics, primary admission diagnosis, Karnofsky functional status index, Charlson comorbidity index, McCabe-Jackson severity of illness classification, use of antibiotics and prior exposures to medical and surgical risk factors (233). Kanerva *et al*. suggested a slightly different set of parameters: admission date, medical specialty, demographics, McGabe classification, prior exposures to urinary tract or central venous catheters, ventilator or preceding surgery and Charlson comorbidity index (234). Both publications used logistic regression models, but we could consider Poission regression as well. This has the benefit of giving relative risk estimates, which are easier to interpret than odds ratios.

For HAIBA, we will need to assess which parameters are reliably available for the entire country in our data sources. Patients' demographics are directly available in HAIBA. The Charlson comorbidity index would also be possible to calculate with diagnosis codes from the DNPR, although we may need to consider importing data from before 2010, depending on the period we decide to use to establish comorbidity over. Procedure codes from DNPR identifying ICU may also provide informative data for adjustment. With procedure and diagnosis codes in DNPR there is potential to assess several other relevant parameters, such as previous surgery and diagnosis upon admission. Use of antibiotics will also be possible to include as a parameter when medicine modules are available for the whole country. The registration of urinary tract catheters seemed incomplete from our assessment and this may also be true for central venous catheters.

The McCabe classification is a severity classification used in ICUs defining three categories: non-fatal disease, ultimately fatal disease and rapidly fatal disease (244). The Karnofsky functional status index is a scoring system originally developed in 1948 to assess the patient's ability to survive chemotherapy for cancer (245). It seems unlikely

that we will be able to derive these parameters from existing national data sources for the use in HAIBA.

A number of parameters, which were not mentioned in the other models, could also be relevant to consider for HAIBA. As sample taking rates differ among hospitals and regions and are directly related to the number of infections detected it may be useful to adjust for this factor. It should be further discussed whether the sample rate as such is suitable. Another option would be to include all samples within the course of an infection until the first positive is found. Since we only include the first HAI within the course of an admission, this adjustment would approach more closely the risk profile we need to adjust for.

Length of stay is to some extent already adjusted for, as it is included in the denominator. However, that is only the case within the period shown, eg within the week or month that is shown. The incidence density assumes a linear increase of risk with length of stay. It should be investigated if that is also the case, or if the risk follows a different pattern over time. If it does, it should also be adjusted for in the multivariable regression model.

It is unclear how Kanerva *et al*. used the admission date in the model, whether to calculate age at admission or to adjust for seasonality. The latter may be interesting to include.

Hospital size or type of hospital (university, non-university, public and private) is also worth considering. Both are a proxy for the complexity of patient population. However, they could also reflect differences in infection control, where it may for example be more challenging to manage a large infection control organization than a small team in a small hospital.

Despite all adjustments, different practices in hospitals may still be affecting the data, but having adjusted for confounding can rule out some of the factors, bringing us closer to understanding what could be the reason for trends and differences between hospitals and regions.

Tool for interpretation of trends

One of the main uses of HAIBA is to follow trends over time. This is already possible with the current algorithms even when sensitivity is not optimal. In order to assist the users in evaluating trends, we plan to develop statistical tools.

To choose the most appropriate methods we need to take a number of issues into consideration. Firstly, we need to establish what the aim of the tool is; whether it is to test gradual trends over time for statistical significance, or to detect outbreaks. Generally, surveillance measures the endemic-disease rate of HAI, which represents 90-95% of all HAI (246). While outbreaks often are caused by the failure of one prevention strategy for a short period, many different (ongoing) issues influence the endemic-disease rates (247). Focus on the endemic-disease rate will have the most impact and may also prevent future outbreaks as it would need to address a combination of many factors.

However, although outbreaks are not frequent and concern less than 10% of cases, outbreak detection may still be worthwhile. Early detection of an outbreak and elimination of the cause may prevent new cases over a short time. These outbreaks may also have a considerable impact on a hospital in terms of public attention. Moreover, outbreak investigations can provide new knowledge on possible sources, mode of transmission and methods for prevention and control (246). Outbreaks are often of political significance and can be used to start new initiatives for improvement.

In the development of a tool, a balance will need to be found for the aggregation level that gives meaningful information and still has enough power. Numbers of HAI may be too small on department level. Certainly when looking by week. However, if the tool aggregates per month, the delay in detection becomes too long. In addition, local outbreaks of small clusters may not be visible on national level, while on the other hand outbreaks of a number of cases across the country would not be identified if we only monitor on hospital level. Probably the best balance would be found in aggregation by week on hospital, regional and national level.

A number of methods could be considered. First of all time series analysis using Poisson or negative binomial regression. Thresholds can be set to be able to create a warning if trends are increasing or decreasing beyond what can be expected. This method can both test for the endemic-disease rate and detect outbreaks.

A number of other tools have been described with the particular aim of detecting outbreaks of infectious diseases. The counted data Poisson Cumulative Sum (CuSum) was first described by Lucas in 1985 (248). The model adds up differences between the expected and the observed. By using a cumulative approach, it can magnify small, abrupt changes that would not be detected by conventional graphic plots of a series of data. A threshold is calculated to detect if the sum significantly rises. After the model has given off a warning by crossing the threshold, the CuSum is decreased with a reference value that needs to be simulated for each disease. This decrease is needed to set CuSum back to its control state from where it can monitor increases again.

The Farrington model, also referred to as the England and Wales model, was described by Farrington *et al*. in 1993 (249). It is used for weekly surveillance reports in England and Wales (250). The model involves a quasi-Poission regression. For this purpose, the model was improved with a weighing process for better sensitivity, as it ignores previous outbreaks by giving more weight to a “normal week” than an “outbreak week”.
This model is also used in outbreak detection of food and waterborne infections in Denmark.

The Salmonella Potential Outbreak Targetting (SPOT) model was described in 1993 by Stern and improved into SPOTv2 in 1999 (251). It was developed for the sparsely populated areas of Australia, where the CuSum and Farrington models did not fit well. The model consists of a baseline calculation based on monthly data from the previous five years.

These three outbreak detection models were tested by Rolfhamre and Ekdahl against surveillance data from Sweden for campylobacteriosis, hepatitis A and tularaemia (252). They found the Farrington and SPOTv2 outperform the CuSum. The main limitation of the

CuSum model was that it did not adjust for previous outbreaks in the baseline. The authors had a slight preference for the SPOTv2 model as it produced fewer warnings without losing PPV, was easier to implement and detected outbreaks slightly faster than the Farrington model.

The Task Force for Reduction of HAI in the Capital Region of Denmark uses the control chart for analyzing increases beyond the expected level (253). This is a method in which data are plotted in a point-and-line graph and control limits are calculated representing the limits of random variation in data. This method does not account for seasonal or other variations. This may still be a useful tool to use on department level for regular evaluation of HAI incidence.

Users of HAIBA will have to keep in mind that a statistical tools will not give information whether these trends are real or artefacts caused by systematic changes, such as hospitals merging and therefore getting a new patient population, enhanced diagnostics, changes in coding practice. They can only assist in active use of data, but not replace it.

Research

HAIBA opens opportunities for research, especially when linking the data to other registries, such as the Danish Civil Registration Register to obtain vital status.
This is for instance planned for a study on CDI, which will assess the clinical burden of these infections on departments and staff and evaluate if the mortality has decreased.

Other examples are studies to further investigate the interaction between different types of infections in HAIBA. HAIBA currently manages each type of infection independently. These infections are, however, not independent. Bacteraemia is often a complication of a UTI or surgical site infection. It would therefore be very useful to get more insight in the correlation between these infections using data derived from HAIBA.

In addition, another PhD project is currently being planned to evaluate the use of HAIBA in infection control practice. When HAIBA has been used for a few years, the effect of its introduction can be studied on the burden of the different types of HAI.

Final remarks

HAIBA algorithms have been shown to provide meaningful data for surveillance on national, regional and hospital level. However, HAIBA results are just numbers if they are not used for action. The task ahead is one in which the users will need to find ways to apply the data and HAIBA needs to keep improving the case definitions and the output models to best support infection control.

While public and political pressure may be needed to put HAI on the agenda and to make sufficient resources available at all levels, we should guard ourselves for potential adverse effects of transparency and benchmarking. The real changes need to be made at the patients' bedside and efforts need to focus on finding the best applications for HAIBA to support this and carry out effective interventions.

This requires a multidisciplinary approach with close collaboration across all stakeholders and sincere efforts to bridge between professions. Surveillance and epidemiology need to meet patient care, infection control, quality improvement, hospital management and IT-development. These fields do not naturally have the same jargon, understanding and requirements, and often compete rather than collaborate. However, it is the synergy between these disciplines that can bring a higher standard to the control of HAI and ultimately reduce its burden, first and foremost on the patient.

References

1. Burke JP. Infection control - a problem for patient safety. N Engl J Med. 2003 Feb 13;348(7):651–6.

2. World Health Organization. Report on the burden of endemic health care-associated infection worldwide [Internet]. 2011. Available from: http://apps.who.int/iris/bitstream/10665/80135/1/9789241501507_eng.pdf?ua=1

3. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. Journal of Hospital Infection. 2003 Aug;54(4):258–66.

4. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. Infect Control Hosp Epidemiol. 2011 Feb;32(2):101–14.

5. Zingg W, Holmes A, Dettenkofer M, Goetting T, Secci F, Clack L, et al. Hospital organisation, management, and structure for prevention of health-care-associated infection: a systematic review and expert consensus. Lancet Infect Dis. 2015 Feb;15(2):212–24.

6. Duerden BI. Responsibility for managing healthcare-associated infections: where does the buck stop? J Hosp Infect. 2009 Dec;73(4):414–7.

7. World Health Organization. Prevention of hospital-acquired infections. A practical guide. 2nd edition [Internet]. 2002. Available from: http://apps.who.int/medicinedocs/documents/s16355e/s16355e.pdf

8. World Health Organization. Health care-associated infections - Fact Sheet [Internet]. Available from: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf

9. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388–416.

10. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002 Nov 19;137(10):791–7.

11. European Centre for Disease Prevention and Control. ECDC Surveillance report - Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012 [Internet]. Available from: http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf

12. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities [Internet]. 2013. Available from: http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-point-prevalence-survey-long-term-care-facilities-2013.pdf

13. Centers for Disease Control and Prevention. Types of Healthcare-associated Infections [Internet]. Available from: https://www.cdc.gov/HAI/infectionTypes.html

14. Klevens RM, Edwards JR, Richards CL, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007 Apr;122(2):160–6.

15. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014 Mar 27;370(13):1198–208.

16. Central Enhed for Infektionshygiejne, Statens Serum Institut. Landsprævelensundersøgelsen [Internet]. Available from: http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Overvaagning/Praevalensundersogelser/Data%20fra%20Praevalensundersogelser.aspx

17. Douglas Scott II R. The direct medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention [Internet]. 2009. Available from: https://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf

18. Pedersen KM, Kolmos HJJ. Hospitalsinfektioners økonomi. 2007.

19. Smith PW, Watkins K, Hewlett A. Infection control through the ages. Am J Infect Control. 2012 Feb;40(1):35–42.

20. Pearson A. Historical and changing epidemiology of healthcare-associated infections. J Hosp Infect. 2009 Dec;73(4):296–304.

21. Buehler JW. Chapter 22 - Surveillance. In: Rothman KJ, Greenland S Modern Epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998. p. 435–57.

22. Harbarth S. Handwashing-the Semmelweis lesson misunderstood? Clin Infect Dis. 2000 Jun;30(6):990–1.

23. Andrus ML, Horan TC, Gaynes RP. Chapter 6 - Surveillance of Healthcare-Associated Infections. In: Bennett & Brachman's Hospital Infections. 5th ed. Wolters Kluwer, Lippincott Williams & Wilkins; p. 73–90.

24. Aiello AE, Larson EL, Sedlak R. Hidden heroes of the health revolution. Sanitation and personal hygiene. Am J Infect Control. 2008 Dec;36(10 Suppl):S128-151.

25. Pitt D, Aubin J-M. Joseph Lister: father of modern surgery. Can J Surg. 2012 Oct;55(5):E8–9.

26. Aminov RI. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. Front Microbiol [Internet]. 2010 Dec 8 [cited 2015 Aug 26];1. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109405/

27. Centers for Disease Control and Prevention. Public Health Focus: Surveillance, Prevention, and Control of Nosocomial Infections [Internet]. [cited 2016 Jun 17]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00017800.htm

28. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol. 1985 Feb;121(2):182–205.

29. Christensen M, Jepsen OB. Reduced rates of hospital-acquired UTI in medical patients. Prevalence surveys indicate effect of active infection control programmes. J Hosp Infect. 2001 Jan;47(1):36–40.

30. Haley RW. Surveillance by objective: a new priority-directed approach to the control of nosocomial infections. The National Foundation for Infectious Diseases lecture. Am J Infect Control. 1985 Apr;13(2):78–89.

31. Reybrouck G, Mertens R. Infection Control and Hospital Hygiene in Belgium. Infection Control and Hospital Epidemiology. 1989;10(4):170–4.

32. Jepsen OB. Towards European Union standards in hospital infection control. Journal of Hospital Infection. 1995 Jun 1;30:64–8.

33. Mertens R, van den Berg J, Fabry J, Jepsen O. HELICS: a European project to standardise the surveillance of hospital acquired infection, 1994-1995. Euro Surveillance. 1996 Apr 1;1(4):154.

34. Camp RC, Tweet AG. Benchmarking applied to health care. Jt Comm J Qual Improv. 1994 May;20(5):229–38.

35. Epstein AM. Rolling down the runway: the challenges ahead for quality report cards. JAMA. 1998 Jun 3;279(21):1691–6.

36. Institute of Medicine. To Err Is Human: building a safer health system [Internet]. 1999. Available from: http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/1999/To-Err-is-Human/To%20Err%20is%20Human%201999%20%20report%20brief.pdf

37. Pittet D, Donaldson L. Challenging the world: patient safety and health care-associated infection. Int J Qual Health Care. 2006 Feb;18(1):4–8.

38. Kristensen S, Badsberg JH, Rischel V, Anhøj J, Mainz J, Bartels P. The patient safety climate in Danish hospital units. Dan Med J. 2015 Nov;62(11):A5153.

39. Statens Serum Institut. CAS-NYT, No 49/1991. Available from: http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Aktuelt/Nyhedsbreve/CEI-NYT/1999%20-%201990/Nr%2049%20-%201991.ashx

40. Statens Serum Institut. CEI-NYT, No 81/1999. Available from: http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Aktuelt/Nyhedsbreve/CEI-NYT/1999%20-%201990/Nr%2081%20-%20April%201999.ashx

41. Poulsen KB, Jepsen OB. Failure to detect a general reduction of surgical wound infections in Danish hospitals. Dan Med Bull. 1995 Nov;42(5):485–8.

42. Bouam S, Girou E, Brun-Buisson C, Karadimas H, Lepage E. An intranet-based automated system for the surveillance of nosocomial infections: prospective validation compared with physicians' self-reports. Infect Control Hosp Epidemiol. 2003 Jan;24(1):51–5.

43. Trick WE, Zagorski BM, Tokars JI, Vernon MO, Welbel SF, Wisniewski MF, et al. Computer algorithms to detect bloodstream infections. Emerging Infect Dis. 2004 Sep;10(9):1612–20.

44. Brossette SE, Hacek DM, Gavin PJ, Kamdar MA, Gadbois KD, Fisher AG, et al. A laboratory-based, hospital-wide, electronic marker for nosocomial infection: the future of infection control surveillance? Am J Clin Pathol. 2006 Jan;125(1):34–9.

45. Leth RA, Møller JK. Surveillance of hospital-acquired infections based on electronic hospital registries. J Hosp Infect. 2006 Jan;62(1):71–9.

46. Leal J, Gregson DB, Ross T, Flemons WW, Church DL, Laupland KB. Development of a novel electronic surveillance system for monitoring of bloodstream infections. Infect Control Hosp Epidemiol. 2010 Jul;31(7):740–7.

47. Woeltje KF, McMullen KM, Butler AM, Goris AJ, Doherty JA. Electronic surveillance for healthcare-associated central line-associated bloodstream infections outside the intensive care unit. Infect Control Hosp Epidemiol. 2011 Nov;32(11):1086–90.

48. Bouzbid S, Gicquel Q, Gerbier S, Chomarat M, Pradat E, Fabry J, et al. Automated detection of nosocomial infections: evaluation of different strategies in an intensive care unit 2000-2006. J Hosp Infect. 2011 Sep;79(1):38–43.

49. de Bruin JS, Adlassnig K-P, Blacky A, Mandl H, Fehre K, Koller W. Effectiveness of an automated surveillance system for intensive care unit-acquired infections. J Am Med Inform Assoc. 2013 Apr;20(2):369–72.

50. Gradel KO, Knudsen JD, Arpi M, Ostergaard C, Schønheyder HC, Søgaard M. Classification of positive blood cultures: computer algorithms versus physicians' assessment - development of tools for surveillance of bloodstream infection prognosis using population-based laboratory databases. BMC Med Res Methodol. 2012;12(1):139.

51. Venable A, Dissanaike S. Is automated electronic surveillance for healthcare-associated infections accurate in the burn unit? J Burn Care Res. 2013 Dec;34(6):591–7.

52. Redder JD, Leth RA, Møller JK. Incidence rates of hospital-acquired urinary tract and bloodstream infections generated by automated compilation of electronically available healthcare data. J Hosp Infect. 2015 Nov;91(3):231–6.

53. Bellini C, Petignat C, Francioli P, Wenger A, Bille J, Klopotov A, et al. Comparison of automated strategies for surveillance of nosocomial bacteremia. Infect Control Hosp Epidemiol. 2007 Sep;28(9):1030–5.

54. Gradel KO, Schønheyder HC, Arpi M, Knudsen JD, Ostergaard C, Søgaard M. The Danish Collaborative Bacteraemia Network (DACOBAN) database. Clin Epidemiol. 2014;6:301–8.

55. Pokorny L, Rovira A, Martín-Baranera M, Gimeno C, Alonso-Tarrés C, Vilarasau J. Automatic detection of patients with nosocomial infection by a computer-based surveillance system: a validation study in a general hospital. Infect Control Hosp Epidemiol. 2006 May;27(5):500–3.

56. Choudhuri JA, Pergamit RF, Chan JD, Schreuder AB, McNamara E, Lynch JB, et al. An electronic catheter-associated urinary tract infection surveillance tool. Infect Control Hosp Epidemiol. 2011 Aug;32(8):757–62.

57. van Mourik MSM, Troelstra A, van Solinge WW, Moons KGM, Bonten MJM. Automated surveillance for healthcare-associated infections: opportunities for improvement. Clin Infect Dis. 2013 Jul;57(1):85–93.

58. Shepard J, Hadhazy E, Frederick J, Nicol S, Gade P, Cardon A, et al. Using electronic medical records to increase the efficiency of catheter-associated urinary tract infection surveillance for National Health and Safety Network reporting. Am J Infect Control. 2014 Mar;42(3):e33-36.

59. Lo Y-S, Lee W-S, Chen G-B, Liu C-T. Improving the work efficiency of healthcare-associated infection surveillance using electronic medical records. Comput Methods Programs Biomed. 2014 Nov;117(2):351–9.

60. Gundtoft PH, Overgaard S, Schønheyder HC, Møller JK, Kjærsgaard-Andersen P, Pedersen AB. The 'true' incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties. Acta Orthop. 2015 Jun;86(3):326–34.

61. Hsu HE, Shenoy ES, Kelbaugh D, Ware W, Lee H, Zakroysky P, et al. An electronic surveillance tool for catheter-associated urinary tract infection in intensive care units. Am J Infect Control. 2015 Jun;43(6):592–9.

62. Tokars JI, Richards C, Andrus M, Klevens M, Curtis A, Horan T, et al. The changing face of surveillance for health care-associated infections. Clin Infect Dis. 2004 Nov 1;39(9):1347–52.

63. Klompas M, Yokoe DS. Automated surveillance of health care-associated infections. Clin Infect Dis. 2009 May 1;48(9):1268–75.

64. Woeltje KF, Lautenbach E. Informatics and epidemiology in infection control. Infect Dis Clin North Am. 2011 Mar;25(1):261–70.

65. Leal J, Laupland KB. Validity of electronic surveillance systems: a systematic review. Journal of Hospital Infection. 2008 Jul;69(3):220–9.

66. van Mourik MSM, van Duijn PJ, Moons KGM, Bonten MJM, Lee GM. Accuracy of administrative data for surveillance of healthcare-associated infections: a systematic review. BMJ Open. 2015;5(8):e008424.

67. Region Hovedstaden. Task Force Forebyggelse af hospitalsinfektioner [Internet]. [cited 2016 Aug 3]. Available from: https://www.regionh.dk/hospitalsinfektioner/om-os/Sider/baggrund.aspx

68. Gradel KO, Nielsen SL, Pedersen C, Knudsen JD, Østergaard C, Arpi M, et al. Low Completeness of Bacteraemia Registration in the Danish National Patient Registry. PLoS ONE. 2015;10(6):e0131682.

69. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull. 2006 Nov;53(4):441–9.

70. Cole M. The true cost of health care associated infection. Journal of Orthopaedic Nursing. 2008;12(3–4):136–8.

71. Centers for Disease Control and Prevention. National and state healthcare associated infections progress report [Internet]. 2016. Available from: http://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf

72. Tatt AD. Hvad du ikke vidste om Danmark. 2013.

73. Hvidovre Hospital. Alarm afslører når du ikke vasker hænder. Available from: https://www.hvidovrehospital.dk/presse-og-nyt/pressemeddelelser-og-nyheder/nyheder-fra-hvidovre-hospital/Sider/alarm-afsloerer-naar-du-ikke-vasker-haender.aspx?rhKeywords=h%C3%A5ndhygiejne

74. Boyce JM. It is time for action: improving hand hygiene in hospitals. Ann Intern Med. 1999 Jan 19;130(2):153–5.

75. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000 Oct 14;356(9238):1307–12.

76. Krein SL, Damschroder LJ, Kowalski CP, Forman J, Hofer TP, Saint S. The influence of organizational context on quality improvement and patient safety efforts in infection prevention: a multi-center qualitative study. Soc Sci Med. 2010 Nov;71(9):1692–701.

77. Haley RW. Measuring the costs of nosocomial infections: methods for estimating economic burden on the hospital. Am J Med. 1991 Sep 16;91(3B):32S–38S.

78. Arefian H, Vogel M, Kwetkat A, Hartmann M. Economic Evaluation of Interventions for Prevention of Hospital Acquired Infections: A Systematic Review. PLoS ONE. 2016;11(1):e0146381.

79. European Centre for Disease Prevention and Control. Data quality monitoring and surveillance system evaluation [Internet]. 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/Data-quality-monitoring-surveillance-system-evaluation-Sept-2014.pdf

80. Danish Regions [Internet]. Available from: http://www.regioner.dk/services/in-english

81. Statens Serum Institut. Infektionshygiejne - Sygehusene/regionerne [Internet]. Available from: http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Organisering/Sygehusene-regionerne.aspx

82. Roth VR, Simmons BP. Chapter 2 - The Healthcare Epidemiologist. In: Bennett & Brachman's Hospital Infections. 5th ed. p. 26–30.

83. Gubbels S, Nielsen J, Voldstedlund M, Chaine M, Espenhain L, Mølbak K, et al. HAIBA-Hospital-Acquired Infections Database, EPI-NEWS, No 9/2015 - Statens Serum Institut. [cited 2016 Feb 23]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2015/No%209%20-%202015.aspx

84. Chaine, M., Gubbels S, Voldstedlund M, Espenhain L, Nielsen J, Mølbak, K., et al. Surveillance of hospital-acquired Clostridium difficile infection through HAIBA, EPI-NEWS, No 10/2015 - Statens Serum Institut. [cited 2016 Jul 8]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2015/No%2010%20-%202015.aspx

85. Gubbels S, Nielsen J, Mølbak K, Voldstedlund M, Kristensen B, Nielsen KS, et al. Hospital-acquired bacteraemia, EPI-NEWS, No 11/2015 - Statens Serum Institut. [cited 2016 Jul 8]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2015/No%2011%20-%202015.aspx

86. Gubbels S, Espenhain L, Condell O, Nielsen J, Mølbak K, Voldstedlund M, et al. Hospital-acquired urinary tract infection, EPI-NEWS, No 51/2015 - Statens Serum Institut. [cited 2016 Jul 8]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2015/No%2051%20-%202015.aspx

87. Lautenbach E. Chapter 8 - Epidemiological Methods for Investigating Infections in the Healthcare Setting. In: Bennett & Brachman's Hospital Infections. 5th ed. Wolters Kluwer, Lippincott Williams & Wilkins; p. 110–20.

88. Nicolle LE. Catheter Matters. Infect Control Hosp Epidemiol. 2016 Mar;37(3):334–6.

89. Wright M-O, Kharasch M, Beaumont JL, Peterson LR, Robicsek A. Reporting catheter-associated urinary tract infections: denominator matters. Infect Control Hosp Epidemiol. 2011 Jul;32(7):635–40.

90. Laupland KB. Defining the epidemiology of bloodstream infections: the 'gold standard' of population-based assessment. Epidemiol Infect. 2013 Oct;141(10):2149–57.

91. Nielsen SL, Pedersen C, Jensen TG, Gradel KO, Kolmos HJ, Lassen AT. Decreasing incidence rates of bacteremia: A 9-year population-based study. J Infect. 2014 Feb 25;

92. Rothman K, Greenland S. Chapter 3 - Measures of Disease Frequency. In: Modern Epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998.

93. Rhame FS, Sudderth WD. Incidence and prevalence as used in the analysis of the occurrence of nosocomial infections. Am J Epidemiol. 1981 Jan;113(1):1–11.

94. Delgado-Rodríguez M, Cueto Espinar A, Rodríguez-Contreras Pelayo R, Gálvez Vargas R. A practical application of Rhame and Sudderth's formula on nosocomial infection surveillance. Rev Epidemiol Sante Publique. 1987;35(6):482–7.

95. Berthelot P, Garnier M, Fascia P, Guyomarch S, Jospé R, Lucht F, et al. Conversion of prevalence survey data on nosocomial infections to incidence estimates: a simplified tool for surveillance? Infect Control Hosp Epidemiol. 2007 May;28(5):633–6.

96. Gastmeier P, Bräuer H, Sohr D, Geffers C, Forster DH, Daschner F, et al. Converting incidence and prevalence data of nosocomial infections: results from eight hospitals. Infect Control Hosp Epidemiol. 2001 Jan;22(1):31–4.

97. Gbaguidi Haore H, Muller A, Talon D, Bertrand X. Estimation of the cumulative incidence of hospital-acquired bacteremia from prevalence data: a formula. Infect Control Hosp Epidemiol. 2005 Apr;26(4):415–7.

98. King C, Aylin P, Holmes A. Converting incidence and prevalence data: an update to the rule. Infect Control Hosp Epidemiol. 2014 Nov;35(11):1432–3.

99. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008 Jun;36(5):309–32.

100. Statens Serum Institut, Department of Microbiology and Infection Control. Definitioner på de fire hyppigste infektioner til brug ved prævalensundersøgelse [Internet]. Available from: http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Smitteberedskab/Infektionshygiejne/Praevalensundersogelser/Foraar%202011/Definitioner%20for%20infektioner_jan2011.ashx

101. Lin MY, Hota B, Khan YM, Woeltje KF, Borlawsky TB, Doherty JA, et al. Quality of traditional surveillance for public reporting of nosocomial bloodstream infection rates. JAMA. 2010 Nov 10;304(18):2035–41.

102. Mayer J, Greene T, Howell J, Ying J, Rubin MA, Trick WE, et al. Agreement in classifying bloodstream infections among multiple reviewers conducting surveillance. Clin Infect Dis. 2012 Aug;55(3):364–70.

103. Biesheuvel C, Irwig L, Bossuyt P. Observed differences in diagnostic test accuracy between patient subgroups: is it real or due to reference standard misclassification? Clin Chem. 2007 Oct;53(10):1725–9.

104. Rudd P. In search of the gold standard for compliance measurement. Arch Intern Med. 1979 Jun;139(6):627–8.

105. Claassen JAHR. The gold standard: not a golden standard. BMJ. 2005 May 14;330(7500):1121.

106. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529–36.

107. St-Martin G, Bacci S, Mølbak K, Olsen KEP, Olesen B, Bruun B. Clostridium difficile, EPI-NEWS, No 13/2009 - Statens Serum Institut. Available from: http://www.ssi.dk/~/media/Indhold/EN%20-%20engelsk/EPI-NEWS/2009/pdf/EPI-NEWS%20-%202009%20-%20No%2013.ashx

108. Olsen KEP, Jensen JN, Torpdahl M, Kjerulf A, Mølbak K. No 7-8/2012 - EPI-NEWS - Statens Serum Institut. [cited 2013 Jul 24]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2012/No%207-8%20-%202012.aspx

109. Kuijper EJ, Coignard B, Tüll P, ESCMID Study Group for Clostridium difficile, EU Member States, European Centre for Disease Prevention and Control. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006 Oct;12 Suppl 6:2–18.

110. European Centre for Disease Prevention and Control. Surveillance of surgical site infections in European hospitals - HAISSI protocol version 1.02 [Internet]. 2012. Available from: http://ecdc.europa.eu/en/publications/Publications/120215_TED_SSI_protocol.pdf

111. ICD-10 Version:2010 [Internet]. [cited 2015 Jul 25]. Available from: http://apps.who.int/classifications/icd10/browse/2010/en

112. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Nørgaard M. Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report. Clin Epidemiol. 2013;5:9–12.

113. Centers for Disease Control and Prevention. Device-associated Module - VAE [Internet]. 2016. Available from: http://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf

114. Klein Klouwenberg PMC, van Mourik MSM, Ong DSY, Horn J, Schultz MJ, Cremer OL, et al. Electronic implementation of a novel surveillance paradigm for ventilator-associated events. Feasibility and validation. Am J Respir Crit Care Med. 2014 Apr 15;189(8):947–55.

115. Danish Health Data Authority. SKS browser - v4.02 [Internet]. [cited 2016 Jul 25]. Available from: http://www.medinfo.dk/sks/brows.php

116. Voldstedlund M, Haarh M, Molbak K, MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. Euro Surveill. 2014;19(1).

117. Møller JK, Jensen TG, Prag J, Tønning B, Pedersen S, Jarløv JO, et al. Elektronisk svar og rekvisition i klinisk mikrobiologi - kodeværk for prøvebeskrivelse [Internet]. Available from: http://www.madsonline.dk/MDS-koder/MDS_Rapport.pdf

118. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - ATC/DDD Index [Internet]. [cited 2016 Aug 3]. Available from: http://www.whocc.no/atc_ddd_index/

119. Institute of Medicine (US) Forum on Microbial Threats. Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions, Workshop Summary [Internet]. Washington (DC): National Academies Press (US); 2007 [cited 2016 Jul 28]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK52867/

120. Kirn TJ, Weinstein MP. Update on blood cultures: how to obtain, process, report, and interpret. Clin Microbiol Infect. 2013 Jun;19(6):513–20.

121. Beekmann SE, Diekema DJ, Chapin KC, Doern GV. Effects of rapid detection of bloodstream infections on length of hospitalization and hospital charges. J Clin Microbiol. 2003 Jul;41(7):3119–25.

122. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S, Brincat C, et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. J Clin Microbiol. 2016 May;54(5):1216–22.

123. Jensen MBF, Olsen KEP, Nielsen XC, Hoegh AM, Dessau RB, Atlung T, et al. Diagnosis of Clostridium difficile: real-time PCR detection of toxin genes in faecal samples is more sensitive compared to toxigenic culture. Eur J Clin Microbiol Infect Dis. 2015 Apr;34(4):727–36.

124. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis. 2008 Jan 15;46 Suppl 1:S12-18.

125. Tillander J, Hagberg K, Hagberg L, Brånemark R. Osseointegrated Titanium Implants for Limb Prostheses Attachments: Infectious Complications. Clin Orthop Relat Res. 2010 May 15;468(10):2781–8.

126. Mikkelsen DB, Pedersen C, Højbjerg T, Schønheyder HC. Culture of multiple peroperative biopsies and diagnosis of infected knee arthroplasties. APMIS. 2006 Jun;114(6):449–52.

127. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011 Jul;39(7 Suppl):30–3.

128. Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, et al. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill. 2012;17(46).

129. Danish Health Data Authority. Sundhedsvæsenets Organisationsregister (SOR) [Internet]. [cited 2016 Aug 9]. Available from: http://sundhedsdatastyrelsen.dk/SOR

130. Nordclass: [Internet]. [cited 2016 Jul 25]. Available from: http://www.nordclass.se/ncsp_e.htm

131. Wendland A, Nielsen J, Chaine M, Emborg HD, Gubbels S, Voldstedlund M, et al. Development and evaluation of a register-based surveillance system for severe influenza virus infections in Denmark. European Scientific Conference on Applied Infectious Disease Epidemiology 2015; 2015 Nov 12; Stockholm, Sweden.

132. Statens Serum Institut. Sygehus-afdelingsklassifikation [Internet]. 2013. Available from: http://www.ssi.dk/graphics/standardkatalog/2.0/publication/439.pdf

133. Lidegaard Ø, Hammerum MS. [The National Patient Registry as a tool for continuous production and quality control]. Ugeskr Laeg. 2002 Sep 16;164(38):4420–3.

134. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28(3):150–4.

135. Jensen AØ, Nørgaard M, Yong M, Fryzek JP, Sørensen HT. Validity of the recorded International Classification of Diseases, 10th edition diagnoses codes of bone metastases and skeletal-related events in breast and prostate cancer patients in the Danish National Registry of Patients. Clin Epidemiol. 2009;1:101–8.

136. Nøjgaard C, Bendtsen F, Matzen P, Becker U. The aetiology of acute and chronic pancreatitis over time in a hospital in Copenhagen. Dan Med Bull. 2010 Jan;57(1):A4103.

137. Erichsen R, Strate L, Sørensen HT, Baron JA. Positive predictive values of the International Classification of Disease, 10th edition diagnoses codes for diverticular disease in the Danish National Registry of Patients. Clin Exp Gastroenterol. 2010;3:139–42.

138. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.

139. Nielsen EH, Lindholm J, Laurberg P. Use of combined search criteria improved validity of rare disease (craniopharyngioma) diagnosis in a national registry. J Clin Epidemiol. 2011 Oct;64(10):1118–26.

140. Wermuth L, Lassen CF, Himmerslev L, Olsen J, Ritz B. Validation of hospital register-based diagnosis of Parkinson's disease. Dan Med J. 2012 Mar;59(3):A4391.

141. Jespersen CG, Borre M, Nørgaard M. Validity of the recorded codes of gonadotropin-releasing hormone agonist treatment and orchiectomies in the Danish National Patient Registry. Clin Epidemiol. 2012;4:145–9.

142. Helqvist L, Erichsen R, Gammelager H, Johansen MB, Sørensen HT. Quality of ICD-10 colorectal cancer diagnosis codes in the Danish National Registry of Patients. Eur J Cancer Care (Engl). 2012 Nov;21(6):722–7.

143. Ruwald MH, Hansen ML, Lamberts M, Kristensen SL, Wissenberg M, Olsen A-MS, et al. Accuracy of the ICD-10 discharge diagnosis for syncope. Europace. 2013 Apr;15(4):595–600.

144. Holland-Bill L, Christiansen CF, Ulrichsen SP, Ring T, Jørgensen JOL, Sørensen HT. Validity of the International Classification of Diseases, 10th revision discharge diagnosis codes for hyponatraemia in the Danish National Registry of Patients. BMJ Open. 2014;4(4):e004956.

145. Lange J, Pedersen AB, Troelsen A, Søballe K. Do hip prosthesis related infection codes in administrative discharge registers correctly classify periprosthetic hip joint infection? Hip Int. 2015 Nov 25;25(6):568–73.

146. Dal J, Skou N, Nielsen EH, Jørgensen JOL, Pedersen L. Acromegaly according to the Danish National Registry of Patients: how valid are ICD diagnoses and how do patterns of registration affect the accuracy of registry data? Clin Epidemiol. 2014;6:295–9.

147. Søgaard M, Heide-Jørgensen U, Nørgaard M, Johnsen SP, Thomsen RW. Evidence for the low recording of weight status and lifestyle risk factors in the Danish National Registry of Patients, 1999-2012. BMC Public Health. 2015;15:1320.

148. Jørgensen LK, Dalgaard LS, Østergaard LJ, Andersen NS, Nørgaard M, Mogensen TH. Validity of the coding for herpes simplex encephalitis in the Danish National Patient Registry. Clin Epidemiol. 2016;8:133–40.

149. Rasmussen NH, Thomsen RW, Rasmussen HH, Søgaard M. Validity of diagnostic coding for undernutrition in hospitals. Clin Nutr. 2016 Apr;35(2):491–5.

150. Poulsen FR, Halle B, Pottegård A, García Rodríguez LA, Hallas J, Gaist D. Subdural hematoma cases identified through a Danish patient register: diagnosis validity, clinical characteristics, and preadmission antithrombotic drug use. Pharmacoepidemiol Drug Saf. 2016 Jul 7;

151. Mor A, Grijota M, Nørgaard M, Munthe J, Lind M, Déruaz A, et al. Trends in arthroscopy-documented cartilage injuries of the knee and repair procedures among 15-60-year-old patients. Scand J Med Sci Sports. 2015 Aug;25(4):e400-407.

152. Nicholl J. Case-mix adjustment in non-randomised observational evaluations: the constant risk fallacy. J Epidemiol Community Health. 2007 Nov;61(11):1010–3.

153. Mohammed MA, Deeks JJ, Girling A, Rudge G, Carmalt M, Stevens AJ, et al. Evidence of methodological bias in hospital standardised mortality ratios: retrospective database study of English hospitals. BMJ. 2009;338:b780.

154. Jacques RM, Fotheringham J, Campbell MJ, Nicholl J. Did hospital mortality in England change from 2005 to 2010? A retrospective cohort analysis. BMC Health Serv Res. 2013;13:216.

155. Den Danske Mikrobiologidatabase [Internet]. Available from: http://miba.ssi.dk/graphics/miba/index.html

156. Bekendtgørelse om Lægers anmeldelse af Smitsomme Sygdomme mv. (Bekendtgørelse nr. 277 af 14/4/2000) med senere tilføjelser (Bekendtgørelse nr. 1102 20/9/2007).

157. Fælles Medicinkort (FMK) [Internet]. Available from: http://sundhedsdatastyrelsen.dk/da/registre-og-services/om-faelles-medicinkort

158. Kromann ME. Danske regioner kasserer 18 EPJ-systemer. Available from: http://www.computerworld.dk/art/215719/danske-regioner-kasserer-18-epj-systemer

159. Danske Regioner, Region Hovedstaden, Region Sjælland, Region Syddanmark, Region Midtjylland, Region Nordjylland. Sammenhængende og ensartede digitale muligheder - Regionernes fælles strategi for digitalisering af sundhedsvæsenet 2013-2019 [Internet]. Available from: http://www.regioner.dk/media/3263/rsi-regionernes-faelles-strategi-for-digitalisering-af-sundhedsvaesenet-2013-2019.pdf

160. Epic Software [Internet]. [cited 2016 Aug 4]. Available from: http://www.epic.com/Software

161. CSC Scandihealth. OPUS Medicin - Nem og sikker medicinordination [Internet]. [cited 2016 Aug 9]. Available from: http://csc.scandihealth.dk/Losninger/Losninger_produktbl_pdf/Journalprodukter/DK-OPUS-Medicin.pdf

162. CGI. Elektronisk patientjournal-EPJ, Sundhedsplatformen Cambio COSMIC [Internet]. Available from: https://www.cgi.dk/elektronisk-patientjournal

163. Schønheyder HC. [Two thousands seven hundred and thirty nine episodes of bacteremia in the county of Northern Jutland 1996-1998. Presentation of a regional clinical database]. Ugeskr Laeg. 2000 May 15;162(20):2886–91.

164. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992 Jun;101(6):1644–55.

165. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA. 1995 Jan 11;273(2):117–23.

166. Henriksen DP, Laursen CB, Jensen TG, Hallas J, Pedersen C, Lassen AT. Incidence rate of community-acquired sepsis among hospitalized acute medical patients-a population-based survey. Crit Care Med. 2015 Jan;43(1):13–21.

167. Søgaard M, Andersen JP, Schønheyder HC. Searching PubMed for studies on bacteremia, bloodstream infection, septicemia, or whatever the best term is: A note of caution. American Journal of Infection Control [Internet]. 2011 Jul 19 [cited 2011 Sep 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21775021

168. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect. 2013 Jun;19(6):501–9.

169. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003 Apr 17;348(16):1546–54.

170. Bearman GML, Wenzel RP. Bacteremias: a leading cause of death. Arch Med Res. 2005 Dec;36(6):646–59.

171. Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis. 2011 Jan 1;52(1):61–9.

172. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect. 2013 Jun;19(6):492–500.

173. de Kraker MEA, Jarlier V, Monen JCM, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. Clin Microbiol Infect. 2013 Sep;19(9):860–8.

174. Uslan DZ, Crane SJ, Steckelberg JM, Cockerill FR 3rd, St Sauver JL, Wilson WR, et al. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. Arch Intern Med. 2007 Apr 23;167(8):834–9.

175. Data fra Landsprævalensundersøgelse [Internet]. Available from: http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Overvaagning/Praevalensundersogelser/Data%20fra%20Praevalensundersogelser.aspx

176. Engel C, Brunkhorst FM, Bone H-G, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med. 2007 Apr;33(4):606–18.

177. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001 Jul;29(7):1303–10.

178. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med. 2004 Apr;30(4):589–96.

179. Brun-Buisson C, Meshaka P, Pinton P, Vallet B, EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med. 2004 Apr;30(4):580–8.

180. Sundararajan V, Macisaac CM, Presneill JJ, Cade JF, Visvanathan K. Epidemiology of sepsis in Victoria, Australia. Crit Care Med. 2005 Jan;33(1):71–80.

181. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med. 2003 Sep;31(9):2332–8.

182. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994 May 25;271(20):1598–601.

183. Nielsen SL, Lassen AT, Gradel KO, Jensen TG, Kolmos HJ, Hallas J, et al. Bacteremia is associated with excess long-term mortality: a 12-year population-based cohort study. J Infect. 2015 Feb;70(2):111–26.

184. Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. Clin Microbiol Rev. 1997 Jul;10(3):444–65.

185. Leibovici L. Long-term consequences of severe infections. Clin Microbiol Infect. 2013 Jun;19(6):510–2.

186. Jensen US, Knudsen JD, Ostergaard C, Gradel KO, Frimodt-Møller N, Schønheyder HC. Recurrent bacteraemia: A 10-year regional population-based study of clinical and microbiological risk factors. J Infect. 2010 Mar;60(3):191–9.

187. Jensen US, Knudsen JD, Wehberg S, Gregson DB, Laupland KB. Risk factors for recurrence and death after bacteraemia: a population-based study. Clin Microbiol Infect. 2011 Aug;17(8):1148–54.

188. Gudiol C, Royo-Cebrecos C, Laporte J, Ardanuy C, Garcia-Vidal C, Antonio M, et al. Clinical features, aetiology and outcome of bacteraemic pneumonia in neutropenic cancer patients. Respirology. 2016 Jul 14;

189. Baker TM, Satlin MJ. The growing threat of multidrug-resistant Gram-negative infections in patients with hematologic malignancies. Leuk Lymphoma. 2016 Jun 24;1–14.

190. Nielsen J, Kolmos HJ, Rosdahl VT. Poor value of surveillance cultures for prediction of septicaemia caused by coagulase-negative staphylococci in patients undergoing haemodialysis with central venous catheters. Scand J Infect Dis. 1998;30(6):569–72.

191. Levin PD, Hersch M, Rudensky B, Yinnon AM. Routine surveillance blood cultures: their place in the management of critically ill patients. J Infect. 1997 Sep;35(2):125–8.

192. Czirók E, Prinz GY, Dénes R, Reményi P, Herendi A. Value of surveillance cultures in a bone marrow transplantation unit. J Med Microbiol. 1997 Sep;46(9):785–91.

193. Lindvig KP, Henriksen DP, Nielsen SL, Jensen TG, Kolmos HJ, Pedersen C, et al. How do bacteraemic patients present to the emergency department and what is the diagnostic validity of the clinical parameters; temperature, C-reactive protein and systemic inflammatory response syndrome? Scand J Trauma Resusc Emerg Med. 2014;22:39.

194. Seigel TA, Cocchi MN, Salciccioli J, Shapiro NI, Howell M, Tang A, et al. Inadequacy of temperature and white blood cell count in predicting bacteremia in patients with suspected infection. J Emerg Med. 2012 Mar;42(3):254–9.

195. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA. 2012 Aug 1;308(5):502–11.

196. Bates DW, Cook EF, Goldman L, Lee TH. Predicting bacteremia in hospitalized patients. A prospectively validated model. Ann Intern Med. 1990 Oct 1;113(7):495–500.

197. Pfitzenmeyer P, Decrey H, Auckenthaler R, Michel JP. Predicting bacteremia in older patients. J Am Geriatr Soc. 1995 Mar;43(3):230–5.

198. Adams NG. Diagnostic use of C-reactive protein in bacteraemic emergency department patients. Emerg Med Australas. 2005 Aug;17(4):371–5.

199. Leth RA, Forman BE, Kristensen B. Predicting bloodstream infection via systemic inflammatory response syndrome or biochemistry. J Emerg Med. 2013 Feb;44(2):550–7.

200. Chase M, Klasco RS, Joyce NR, Donnino MW, Wolfe RE, Shapiro NI. Predictors of bacteremia in emergency department patients with suspected infection. Am J Emerg Med. 2012 Nov;30(9):1691–7.

201. Opota O, Croxatto A, Prod'hom G, Greub G. Blood culture-based diagnosis of bacteraemia: state of the art. Clin Microbiol Infect. 2015 Apr;21(4):313–22.

202. Ling ML, Apisarnthanarak A, Jaggi N, Harrington G, Morikane K, Thu LTA, et al. APSIC guide for prevention of Central Line Associated Bloodstream Infections (CLABSI). Antimicrob Resist Infect Control. 2016;5:16.

203. Schønheyder HC, Søgaard M. Existing data sources for clinical epidemiology: The North Denmark Bacteremia Research Database. Clin Epidemiol. 2010;2:171–8.

204. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988 Jun;16(3):128–40.

205. Gubbels S, Nielsen J, Voldstedlund M, Chaine, M., Mølbak K, Kristensen B, et al. HAIBA 2015, No 20/2016, EPI-NEWS - Statens Serum Institut. [cited 2016 Jul 9]; Available from: http://www.ssi.dk/English/News/EPI-NEWS/2016/No%2020%20-%202016.aspx

206. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. Am J Infect Control. 2000 Feb;28(1):68–75.

207. Nicolle LE. Catheter associated urinary tract infections. Antimicrob Resist Infect Control. 2014;3:23.

208. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. J Infect Dis. 1983 Jul;148(1):57–62.

209. Chenoweth CE, Saint S. Chapter 30 - Urinary Tract Infections. In: Bennett & Brachman's Hospital Infections. 5th ed. Wolters Kluwer, Lippincott Williams & Wilkins; p. 507–16.

210. Mitchell BG, Ferguson JK, Anderson M, Sear J, Barnett A. Length of stay and mortality associated with healthcare-associated urinary tract infections: a multi-state model. J Hosp Infect. 2016 May;93(1):92–9.

211. Melzer M, Welch C. Outcomes in UK patients with hospital-acquired bacteraemia and the risk of catheter-associated urinary tract infections. Postgrad Med J. 2013 Jun;89(1052):329–34.

212. Conway LJ, Carter EJ, Larson EL. Risk Factors for Nosocomial Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria: A Systematic Review. Urol Nurs. 2015 Aug;35(4):191–203.

213. Centers for Disease Control and Prevention. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection UTI]) and Other Urinary System Infection [USI]) Events. Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/7pscCAUTIcurrent.pdf

214. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010 Mar 1;50(5):625–63.

215. Kass EH, Finland M. Asymptomatic infections of the urinary tract. J Urol. 2002 Aug;168(2):420–4.

216. Stark RP, Maki DG. Bacteriuria in the catheterized patient. What quantitative level of bacteriuria is relevant? N Engl J Med. 1984 Aug 30;311(9):560–4.

217. Bergqvist D, Brönnestam R, Hedelin H, Ståhl A. The relevance of urinary sampling methods in patients with indwelling Foley catheters. Br J Urol. 1980 Apr;52(2):92–5.

218. Warren JW, Tenney JH, Hoopes JM, Muncie HL, Anthony WC. A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. J Infect Dis. 1982 Dec;146(6):719–23.

219. Steward DK, Wood GL, Cohen RL, Smith JW, Mackowiak PA. Failure of the urinalysis and quantitative urine culture in diagnosing symptomatic urinary tract infections in patients with long-term urinary catheters. Am J Infect Control. 1985 Aug;13(4):154–60.

220. European Centre for Disease Prevention and Control. Protocol for point prevalence surveys of healthcare-associated infections and antimicrobial use in European long-term care facilities. Available from: http://ecdc.europa.eu/en/publications/publications/halt-3-ltcf-pps-protocol-v2.1.pdf

221. Saint S, Olmsted RN, Fakih MG, Kowalski CP, Watson SR, Sales AE, et al. Translating health care-associated urinary tract infection prevention research into practice via the bladder bundle. Jt Comm J Qual Patient Saf. 2009 Sep;35(9):449–55.

222. Tambyah PA, Oon J. Catheter-associated urinary tract infection. Curr Opin Infect Dis. 2012 Aug;25(4):365–70.

223. Dietvorst BJ, Simmons JP, Massey C. Algorithm aversion: people erroneously avoid algorithms after seeing them err. J Exp Psychol Gen. 2015 Feb;144(1):114–26.

224. Datafortrolighedspolitik i Danmarks Statistik [Internet]. Available from: http://www.dst.dk/ext/292786082/0/Datafortrolighedspolitik-i-Danmarks-Statistik--pdf

225. Danish Clinical Registries [Internet]. Available from: http://www.rkkp.dk/in-english/

226. Kommunernes Landsforening, Danske Regione, Finansministeriet, Økonomi- og og Indenrigsministeriet. Indblik i sundhedsvæsenets resultater 2015 [Internet]. 2015. Available from: http://sum.dk/~/media/Filer%20-%20Publikationer_i_pdf/2015/Indblik-i-sundhedsvaesenets-resultater-maj-2015/Indblik-i-sundhedsvaesenets-resultater-2015-270515.ashx

227. Haustein T, Gastmeier P, Holmes A, Lucet J-C, Shannon RP, Pittet D, et al. Use of benchmarking and public reporting for infection control in four high-income countries. Lancet Infect Dis. 2011 Jun;11(6):471–81.

228. O'Neill E, Humphreys H. Use of surveillance data for prevention of healthcare-associated infection: risk adjustment and reporting dilemmas. Curr Opin Infect Dis. 2009 Aug;22(4):359–63.

229. Archibald LK, Gaynes RP. Hospital-acquired infections in the United States. The importance of interhospital comparisons. Infect Dis Clin North Am. 1997 Jun;11(2):245–55.

230. Sax H, Pittet D, Swiss-NOSO Network. Interhospital differences in nosocomial infection rates: importance of case-mix adjustment. Arch Intern Med. 2002 Nov 25;162(21):2437–42.

231. Harris AD, McGregor JC. The importance of case-mix adjustment for infection rates and the need for more research. Infect Control Hosp Epidemiol. 2008 Aug;29(8):693–4.

232. El-Saed A, Balkhy HH, Weber DJ. Benchmarking local healthcare-associated infections: available benchmarks and interpretation challenges. J Infect Public Health. 2013 Oct;6(5):323–30.

233. Kritsotakis EI, Dimitriadis I, Roumbelaki M, Vounou E, Kontou M, Papakyriakou P, et al. Case-mix adjustment approach to benchmarking prevalence rates of nosocomial infection in hospitals in Cyprus and Greece. Infect Control Hosp Epidemiol. 2008 Aug;29(8):685–92.

234. Kanerva M, Ollgren J, Lyytikäinen O, Finnish Prevalence Survey Study Group. Interhospital differences and case-mix in a nationwide prevalence survey. J Hosp Infect. 2010 Oct;76(2):135–8.

235. Nashef S. The Naked Surgeon: The Power and Peril of Transparency in Medicine. Scribe Publications; 2015.

236. Joynt KE, Orav EJ, Zheng J, Jha AK. Public Reporting of Mortality Rates for Hospitalized Medicare Patients and Trends in Mortality for Reported Conditions. Ann Intern Med. 2016 May 31;

237. DeVore AD, Hammill BG, Hardy NC, Eapen ZJ, Peterson ED, Hernandez AF. Has Public Reporting of Hospital Readmission Rates Affected Patient Outcomes?: Analysis of Medicare Claims Data. J Am Coll Cardiol. 2016 Mar 1;67(8):963–72.

238. Farmer SA, Black B, Bonow RO. Tension between quality measurement, public quality reporting, and pay for performance. JAMA. 2013 Jan 23;309(4):349–50.

239. Sundheds- og ældreministeriet. Nationale mål for sundhedsvæsenet [Internet]. Available from: http://www.sum.dk/Aktuelt/Publikationer/Nye-nationale-maal-april-2016.aspx

240. Frit sygehusvalg, udvidet frit sygehusvalg og ret til hurtig udredning [Internet]. Available from: https://www.sundhed.dk/borger/behandling-og-rettigheder/sygehusvalg/frit-sygehusvalg/

241. Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. Health Information Science and Systems. 2014;2:3.

242. Snijders C, Matzat U, Reips U. 'Big Data': big gaps of knowledge in the field of internet science. International Journal of Internet Science. 2012;7(1):1–5.

243. Lindstrom M, Heath C. Small Data: The Tiny Clues That Uncover Huge Trends. New York City: St. Martin's Press; 2016. 256 p.

244. McCabe WR, Jackson GG. Gram negative bacteremia: I. Etiology and ecology. Arch Intern Med. 1962;110:845–847.

245. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of nitrogen mustards in teh palliative treatment of carcinoma - with particular reference to bronchogenic carcinoma. Cancer. 1948;1(4):634–56.

246. Stamm WE, Weinstein RA, Dixon RE. Comparison of endemic and epidemic nosocomial infections. Am J Med. 1981 Feb;70(2):393–7.

247. Gaynes R, Richards C, Edwards J, Emori TG, Horan T, Alonso-Echanove J, et al. Feeding back surveillance data to prevent hospital-acquired infections. Emerging Infect Dis. 2001 Apr;7(2):295–8.

248. Lucas JM. Counted Data CUSUM's. Technometrics. 1985;27(2):129–44.

249. Farrington CP, Beale AD. Computer-aided detection of temporal clusters of organisms reported to the Communicable Disease Surveillance Centre. Commun Dis Rep CDR Rev. 1993 May 21;3(6):R78-82.

250. Noufaily A, Enki DG, Farrington P, Garthwaite P, Andrews N, Charlett A. An improved algorithm for outbreak detection in multiple surveillance systems. Stat Med. 2013 Mar 30;32(7):1206–22.

251. Stern L, Lightfoot D. Automated outbreak detection: a quantitative retrospective analysis. Epidemiol Infect. 1999 Feb;122(1):103–10.

252. Rolfhamre P, Ekdahl K. An evaluation and comparison of three commonly used statistical models for automatic detection of outbreaks in epidemiological data of communicable diseases. Epidemiol Infect. 2006 Aug;134(4):863–71.

253. Anhøj J, Hellesøe A-MB. The problem with red, amber, green: the need to avoid distraction by random variation in organisational performance measures. BMJ Qual Saf. 2016 Mar 31.

Appendix 1: Overview of tables in HAIBA

Table 1. Tables in the "REPLIKA data mart", used for the import of patient administrative data, including the number of records in each table, the size and a description. Total size 60GB. Data from 4 August 2016.

Nr	Name	Category	# Records	Size (KB)	Description
1	t_adm	Data preparation	43,615,013	6,603,227	Inpatient and outpatient records imported from Public DNPR.
2	t_bes	Data preparation	81,733,164	2,209,484	Outpatient visit records imported from Public DNPR.
3	t_koder	Data preparation	372,370,795	30,130,125	Diagnosis and procedure codes imported from Public DNPR.
4	t_adm	Import DNPR	154,519	12,734	Table to assist in the daily update of inpatient and outpatient records from Public DNPR.
5	t_bes	Import DNPR	929,632	26,414	Table to assist in the daily update of outpatient visit records from Public DNPR.
6	t_koder	Import DNPR	2,429,049	201,344	Table to assist in the daily update of diagnosis and procedure codes from Public DNPR.
7	t_log_sync	Import DNPR	638	23	Daily import status from Public DNPR.
8	t_log_sync_history	Import DNPR	483,376,074	18,104,156	Instructions from DNPR regarding data manipulations such as records that need to be deleted or changed.
9	t_adm	Import MINIPAS	2,236,706	441,688	Inpatient and outpatient records imported from MINIPAS.
10	t_bes	Import MINIPAS	2,700,197	183,984	Outpatient visit records imported from MINIPAS.
11	t_koder	Import MINIPAS	14,426,873	2,193,898	Diagnosis and procedure codes imported from MINIPAS.
12	t_log_sync	Import MINIPAS	671	31	Daily import status from MINIPAS.
13	MinipasImporterStatus	Import MINIPAS	781	55	Daily import status from MINIPAS with extended error information.
14	t_log_sync_history	Import MINIPAS	87,243	6,789	Instructions from MINIPAS regarding data manipulations such as records that need to be deleted or changed.
15	T_MINIPAS_SYNC	Import MINIPAS	1,682,889	216,508	Patient identification numbers from MINIPAS. Table is used to check if there are new or changed records in the import.

Table 2. Tables in the "HAIBA data warehouse", including the number of records in each table, the size and a description. Total size 31GB. Data from 4 August 2016.

Nr	Name	Category	# Records	Size (KB)	Description
1	Admin	Administration	21	8	Daily status of the entire HAIBA updating process. Sent out as email notification to key persons.
2	Admin_history	Administration	11,299	711	History of daily status of the entire HAIBA updating process.
3	Dummy_StartDate	Administration	1	8	Indicates start date shown in the online interface. This automatically moves a year after 1 January.
4	Text	Administration	83	31	Text used in the online documentation.
5	Title	Administration	35	8	Titles used in the online documentation.
6	Class_Public_Private	Import hospital classifications	6	8	Classification table showing codes for public/private hospitals (SHAK system (115)).
7	Class_ Region	Import hospital classifications	5	8	Classification table showing region codes (SHAK system (115)).
8	Class_SHAK	Import hospital classifications	21,644	3,016	Original classification table for hospital/department/unit codes (SHAK system (115)).
9	Class_SKS	Import hospital classifications	85,273	7,648	Original classification table for diagnosis and procedure codes (SKS system (115)).
10	Class_SOR	Import hospital classifications	3,914	180	Original classification table for hospital/department codes (SOR system (129)).
11	Class_Type_Hospital	Import hospital classifications	30	8	Original classification table for types of hospitals, i.e. somatic and psychiatric hospitals (SHAK system (115)).
12	FGRImporterStatus	Import hospital classifications	3,252	188	Daily status of import specified for SKS, SHAK and SOR codes.
13	ImporterStatus	Import hospital classifications	711	39	Overall daily import status of SKS, SHAK and SOR codes, with extended error information.
14	Class_Dynamic_ Diagnosis	Data preparation	39,693	2,844	Table indicating diagnosis codes relevant to HAIBA case definitions.

15	Class_Dynamic_ Procedures	Data preparation	12,646	1,633	Table indicating procedure codes relevant to HAIBA case definitions.
16	Class_Dynamic_ SHAK	Data preparation	3,451	813	Table indicating hospital/department codes relevant for HAIBA.
17	Data_Course_ Admission	DNPR algorithm	8,573,087	356,266	Courses of admission after DNPR algorithm.
18	Data_Inpatients	DNPR algorithm	10,125,686	957,578	Admissions after DNPR algorithm, including course of admission identifier.
19	Data_Outpatients	DNPR algorithm	32,758,706	2,879,898	Courses of ambulatory care after DNPR algorithm.
20	Data_Diagnosis	DNPR algorithm	82,677,095	3,075,242	Diagnosis codes after DNPR algorithm.
21	Data_Procedures	DNPR algorithm	139,526,627	11,208,758	Procedures codes after DNPR algorithm.
22	Error_Rule1	DNPR algorithm	6	8	Records affected by DNPR algorithm rule 1.
23	Error_Rule8	DNPR algorithm	0	0	Records affected by DNPR algorithm rule 8.
24	Error_Rule10	DNPR algorithm	1322	203	Records affected by DNPR algorithm rule 10.
25	Error_Rule26	DNPR algorithm	38	8	Records affected by DNPR algorithm 26.
26	Proc_type_error	DNPR algorithm	198	23	Procedure codes without procedure date and time.
27	Recnum	DNPR algorithm	2,314,579	150,023	The original and new record numbers for those that were changed due to the DNPR algorithm.
28	Removed_Diagnosis_Rule 20	DNPR algorithm	1,353,088	46,844	Log file, showing records that were removed due to rule 20.
29	Removed_Procedures_Rul e25	DNPR algorithm	2,103,617	113,875	Log file, showing records that were removed due to rule 25.
30	Data_Header	Import Epi-MiBa	12,259,330	5,072,336	Main import table from EpiMiBa containing all samples that meet the extract criteria.
31	Data_Isolate	Import Epi-MiBa	4,234,101	307,711	Import table from EpiMiBa, containing information on isolates, i.e. culture results.

32	Data_Quantitative	Import Epi-MiBa	2,507,508	215,320	Import table from EpiMiBa, containing information, i.e. PCR results and quantity of microorganisms in urine cultures.
33	Class_Prefix	Import Epi-MiBa classifications	9	8	Description of prefix codes used in EpiMiBa.
34	Class_TabAnalysis	Import Epi-MiBa classifications	625	63	Original classification table for analysis codes imported from EpiMiBa.
35	Class_TabInvestigation	Import Epi-MiBa classifications	988	55	Original classification table for investigation codes imported from EpiMiBa.
36	Class_TabLabSection	Import Epi-MiBa classifications	16	8	Original list of departments of clinical microbiology imported from EpiMiBa.
37	Class_TabLocation	Import Epi-MiBa classifications	794	39	Original classification table for location codes imported from EpiMiBa.
38	Class_TabMicroorganism	Import Epi-MiBa classifications	1,641	78	Original classification table for microorganism codes imported from EpiMiBa.
39	Class_TabOrganization	Import Epi-MiBa classifications	15,222	1,164	Original classification table for departments requesting a test imported from EpiMiBa.
40	Class_TabSpecimen	Import Epi-MiBa classifications	636	63	Original classification table for specimen codes imported from EpiMiBa.
41	EpimibaImporterStatus	Import Epi-MiBa classifications	799	55	Daily import status from Epi-MiBa.
42	Class_Dynamic_ Analysis	Data preparation	175	16	Table indicating analysis codes relevant to HAIBA case definitions.
43	Class_Dynamic_ Investigation	Data preparation	267	31	Table indicating investigation codes relevant to HAIBA case definitions.
44	Class_Dynamic_ Location	Data preparation	358	39	Table indicating location codes relevant to HAIBA case definitions.
45	Class_Dynamic_ Microorganism	Data preparation	1,098	86	Table indicating microorganism codes relevant to HAIBA case definitions.

46	Class_Dynamic_ Specimen	Data preparation	102	16	Table indicating specimen codes relevant to HAIBA case definitions.
47	Testperson_ny	Data preparation	83	8	Known test patients in EpiMiBa.
48	Data_Bact	Output - person level	15,788,294	946,752	Output data on patient level after application of the algorithm for HA-bacteraemia.
49	Data_CDI	Output - person level	43,913,210	2,726,052	Output data on patient level after application of the algorithm for CDI.
50	Data_UTI	Output - person level	15,903,958	1,011,904	Output data on patient level after application of the algorithm for HA-UTI
51	Data_Bact	Online output - aggregate	883,692	92,813	Output dataset with aggregated HA-bacteraemia data per day and department/unit. These data are used for the online interface.
52	Data_CDI	Online output - aggregate	3,411,352	383,906	Output dataset with aggregated CDI data per day and department/unit. These data are used for the online interface.
53	Data_UTI	Online output - aggregate	883,548	92,797	Output dataset with aggregated HA_UTI data per day and department/unit. These data are used for the online interface.
54	Date_table	Online output - aggregate	9,132	2,078	Table with the date dimensions, for aggregation to weeks, months and years in the online interface.
55	Dim_HAIBA_HAI_TYPE	Online output - aggregate	11	8	List of types of infection used in the online interface.
56	Dim_HAIBA_HAI_TYPE_AL L	Online output - aggregate	11	8	Full list of types of infection used in the online interface.
57	Dim_SHAK	Online output - aggregate	3,004	695	List of hospital/department used in the online interface.
58	Dim_Time	Online output - aggregate	2,192	156	Date table used in the online interface.
59	FACT_HAIBA	Online output - aggregate	5,372,086	262,844	Dataset with aggregate results for all types of infections combined, prepared for the online interface.

60	Haiba_0	Clinical registries output - aggregate	4	192	Metadata describing the tables in the delivery to the Danish Clinical Registries. This is part of the daily delivery to the Danish Clinical Registries via a secure FTP-server.
61	Haiba_1	Clinical registries output - aggregate	4	192	Metadata on the properties in the Haiba_2a dataset. This is part of the daily delivery to the Danish Clinical Registries via a secure FTP-server.
62	Haiba_2a	Clinical registries output - aggregate	456,627	69,504	Actual aggregated data from HAIBA, with pre-calculated data by month, quarter of a year and year for each department/unit. This is part of the daily delivery to the Danish Clinical Registries via a secure FTP-server.
63	Haiba_7	Clinical registries output - aggregate	348	192	Metadata on the hospital-department codes used. This is part of the daily delivery to the Danish Clinical Registries via a secure FTP-server.
64	HAIBA_Hovedstaden	Regions output - aggregate	2,616,287	316,096	Aggregate data by day for departments/units in Capital Region of Denmark and in total for the country. To be sent to the region via a secure FTP-server.
65	HAIBA_Midtjylland	Regions output - aggregate	1,858,256	228,096	Aggregate data by day for departments/units in Central Region of Denmark and in total for the country. To be sent to the region via a secure FTP-server.
66	HAIBA_Nordjylland	Regions output - aggregate	965,656	112,576	Aggregate data by day for departments/units in Northern Danmark Region and in total for the country. To be sent to the region via a secure FTP-server.
67	HAIBA_Sjælland	Regions output - aggregate	1,383,472	147,968	Aggregate data by day for departments/units in Region Zealand and in total for the country. To be sent to the region via a secure FTP-server.
68	HAIBA_Syddanmark	Regions output - aggregate	1,826,006	229,312	Aggregate data by day for departments/units in Southern Denmark Region and in total for the country. To be sent to the region via a secure FTP-server.

Appendix 2: Extract criteria from Epi-MiBa

Table 1. Two-step extract process for the algorithm of hospital-acquired bacteraemia, in which Epi-MiBa first defines the blood samples and HAIBA subsequently selects those blood samples that had relevant microbiological investigations.

Step 1: Extract based on MDS material codes (by Epi-MiBa)	
MDS Code	**Text**
10001	Whole blood
10002	Whole blood from peripheral vein
10003	Whole blood from catheter
10160	Blood (blood culture bottle)
10164	Blood from umbilical cord (blood culture bottle)
10165	Blood from peripheral vein (blood culture bottle)
10166	Blood from catheter (blood culture bottle)
10167	Blood from artery (blood culture bottle)

Step 2: Refinement based on MDS investigation codes (by HAIBA)	
MDS Code	**Text**
10002	Aerobic culture (bacteria)
10003	Aerobic and anaerobic culture (bacteria)
10011	Culture and resistance
10040	Anaerobic culture (bacteria)
10045	Aerobic and anaerobic culture in blood culture bottle
10122	Staphylococcus aureus (MRSA) (culture)
10190	Listeria monocytogenes (culture)
10410	Actinomyces (culture)
12127	Staphylococcus aureus (MRSA) (DNA/RNA and culture)
17000	General bacteriological investigation (=culture) and bacterial DNA/RNA
20001	Culture (fungi)
20010	Culture (yeasts)
59015	Staphylococcus aureus (MRSA) (investigation for)
12129	Code not mapped, but included not to miss important information
12300	Code not mapped, but included not to miss important information

MDS=Microbiological Diagnosis System

Table 2. Two-step extract process for the algorithm of hospital-acquired urinary tract infections, in which Epi-MiBa first defines the urine samples and HAIBA subsequently selects those urine samples that had relevant microbiological investigations.

Step 1: Extract based on MDS material codes (by Epi-MiBa)	
MDS[1] Code	**Text**
30001	Urine
30010	Urine – first-void
30070	Urine from renal pelvis
30080	Urine from reservoir {Bricker, Melchior}
30090	Urine – cystoscopy
30110	Urine – mid-stream
30111	Urine – mid-stream (dip slide)
30120	Urine from catheter
30121	Urine from catheter (dip slide)
30122	Urine from indwelling catheter
30123	Urine disposable catheter {sterile technique}
30124	Urine disposable catheter {clean technique}
30125	Urine from ureteral catheter
30126	Urine from nephrostomy catheter
30127	Urine – suprapubic puncture
30128	Urine from suprapubic catheter
30129	Urine from double J stent
30135	Urine (boric acid tube)
30136	Urine – mid-stream (boric acid tube)
30137	Urine from catheter (boric acid tube)
30138	Urine from indwelling catheter (boric acid tube)
30140	Urine (dip slide)

Step 2: Refinement based on MDS investigation codes (by HAIBA)	
MDS[1] Code	**Text**
10002	Aerobic culture (bacteria)
10011	Culture and resistance

[1] MDS=Microbiological Diagnosis System

Table 3. Two-step extract process for the algorithm for *Clostridium difficile* infections. Step 1 consists of three different sets of codes, of which at least one should be present. Step 2 excludes certain findings.

Step 1: Extract based on MDS investigation-, or MDS analysis codes or microorganism codes (by Epi-MiBa)	
MDS[1] Code	**Text**
Step 1a: MDS investigation codes	
10800	Culture (pathogenic intestinal bacteria)
10801	Culture (pathogenic intestinal bacteria and E.coli)
10834	Clostridium difficile (culture)
12115	Clostridium difficile DNA/RNA
15110	Clostridium difficile toxin A
15111	Clostridium difficile toxins
41150	Microscopy and culture (parasites and pathogenic intestinal bacteria)
59001	Diarrhoeal investigation
59002	Intestinal bacteria DNA/RNA
Step 1b: MDS analysis codes	
113	Clostridium difficile binary toxin
114	Clostridium difficile PCR
115	Clostridium difficile ribotype 027
116	Clostridium difficile toxin
117	Clostridium difficile toxin A+B
118	Clostridium difficile toxin B
Step 1c: microorganism codes	
5316	Clostridium difficile
Step 2: Refinement (by HAIBA)	
Exclusion of results that specifically state findings of non-toxigenic strains	

[1] MDS=Microbiological Diagnosis System

Table 4. Two-step extract process for algorithms for surgical site infections, where step 1 creates a general extract and step 2 specifies for infections after hip or knee replacement.

Step 1: Extract based on MDS material codes (by Epi-MiBa)	
MDS[1] Code	Text
10020	Haematoma
10063	Bone marrow (blood culture bottle)
10300	Synovial fluid
20050	Collection
20200	Pus
40000	Tissue
40010	Biopsy
40030	Bone tissue
40034	Medullary cavity - tissue from
40035	Package: Kamme biopsies
40037	Periosteum
40038	Cartilage
40040	Muscle tissue
40062	Synovial membrane
40065	Joint capsule - tissue
40300	Aspirate (blood culture bottle)
50000	Swap
50110	Tissue - swap
50330	Swap from abscess
50450	Aspirate - swap
50465	Pus - swap
50498	Medullary cavity - swap from
50500	synovial fluid - swap
50502	Joint - swap
50504	Joint capsule - swap
50508	Joint tendon - swap
50538	Osteosynthesis material (cement) - swap
50539	Implant material - swap
50540	Osteosynthesis material - swap
50541	Osteosynthesis material internally - swap
50542	Osteosynthesis material externally - swap
50680	Muscle tissue - swap
60001	Aspirate
60002	Aspirate (ultrasound guided)
60010	Abscess - aspirate
70330	Implant material
70350	Prosthesis material
70400	Osteosynthesis material

Step 2: Specification for infections after total hip replacement based on MDS material codes (by HAIBA)	
MDS[1] Code	**Text**
40000	Tissue
40010	Biopsy
40030	Bone tissue
40035	Package: Kamme biopsies

[1] MDS=Microbiological Diagnosis System

Appendix 3: Extract criteria from medicine modules

Table 1. Codes used to select relevant antimicrobial treatment.

ATC[1] code	Text
A01AB	Antiinfectives and antiseptics for local oral treatment
A02BD	Combinations for eradication of Helicobacter pylori
A07A	Intestinal antiinfectives
A07F	Antidiarrheal microorganisms
B05CA	Antiinfectives
C05AB	Antibiotics
D01	Antifungals for dematological use
D06	Antibiotics and chemotherapeutics for dermatological use
D07C	Corticosteroids, combinations with antibiotics
D09AA	Medicated dressings with antiinfectives
D10AF	Antiinfectives for treatment of acne
G01	Gynecological antiinfectives and antiseptics
J01	Antibacterials for systemic use
J02	Antimycotics for systemic use
J04	Antimycobacterials
J05	Antivirals for systemic use
L01D	Cytotoxic antibiotics and related substances
P01	Antiprotozoals
P02	Anthelmintics
P03A	Ectoparasiticides, incl. scabicides
R02AB	Antibiotics
S01A	Antiinfectives
S01C	Antiinflammatory agents and antiinfectives in combination
S02A	Antiinfectives
S02C	Corticosteroids and antiinfectives in combination
S03A	Antiinfectives
S03C	Corticosteroids and antiinfectives in combination

[1] ATC= Anatomical Therapeutic Chemical. The ATC-classification is a hiearchical system; only the highest levels are presented, but all codes belonging under these are also included in the extract.

Appendix 4: Classification of microorganisms for use in case definition for bacteraemia

Table 1. Microorganisms classified as pathogens

Code	Text
203	Abiotrophia defectiva
202	Abiotrophia species
26901	Absidia corymbifera
403	Achromobacter denitrificans
40000	Achromobacter insolitus
410	Achromobacter piechaudii
401	Achromobacter species
402	Achromobacter xylosoxidans
40143	Acid-alcohol-fast rods
40047	Acidaminococcus intestini
40051	Acinetobacter pittii
22601	Acremonium species
705	Actinobacillus species
706	Actinobacillus ureae
709	Actinobaculum massiliae
22501	Actinobaculum schaalii
40052	Actinobaculum species
40053	Actinobaculum urinale
40054	Actinomyces europaeus
911	Actinomyces funkei
913	Actinomyces georgiae
901	Actinomyces gerencseriae
912	Actinomyces graevenitzii
902	Actinomyces israelii
903	Actinomyces meyeri
904	Actinomyces naeslundii
905	Actinomyces neuii
906	Actinomyces odontolyticus
40055	Actinomyces oris
88019	Actinomyces radicidentis
907	Actinomyces radingae
908	Actinomyces species
910	Actinomyces turicensis
914	Actinomyces urogenitalis
909	Actinomyces viscosus
40138	Aerococcus sanguinicola
1002	Aerococcus urinae
1202	Aeromonas hydrophila
40057	Aeromonas media
1201	Aeromonas punctata
1203	Aeromonas salmonicida
1205	Aeromonas sobria
1206	Aeromonas species
1207	Aeromonas veronii
40001	Aggregatibacter aphrophilus
21302	Aggregatibacter actinomycetemcomitans
21301	Aggregatibacter aphrophilus
40002	Aggregatibacter segnis
40001	Aggregatibacter species
1501	Alcaligenes denitrificans
1502	Alcaligenes faecalis
40003	Alcaligenes piechaudii
1503	Alcaligenes species
88018	Alistipes finegoldii
40004	Alistipes species
40005	Alloiococcus otitidis
28301	Alloiococcus species
28401	Anaerobiospirillum species
40060	Anaerococcus tetradius
88017	Anaerococcus hydrogenalis
23401	Anaerococcus prevotii
23402	Anaerococcus species
28501	Anaerotruncus colihominis
2004	Arcanobacterium bernardiae
2001	Arcanobacterium haemolyticum
2003	Arcanobacterium species
40062	Arcobacter species
88016	Arthrobacter cumminsii
28701	Arthrobacter species
2202	Aspergillus flavus
2203	Aspergillus fumigatus
2204	Aspergillus glaucus
2210	Aspergillus nidulans
2205	Aspergillus niger
2207	Aspergillus species
2208	Aspergillus terreus

2209	Aspergillus versicolor
28801	Atopobium minutum
28802	Atopobium parvulum
28803	Atopobium rimae
27001	Aureobasidium pullulans
26102	Avibacterium gallinarum
2401	Bacillus anthracis
2402	Bacillus cereus
88022	Bacillus sphaericus
40064	Bacillus subtilis
40065	Bacillus weihenstephanensis
2501	Bacteroides caccae
2502	Bacteroides coagulans
2514	Bacteroides dorei
2503	Bacteroides eggerthii
2504	Bacteroides fragilis
2505	Bacteroides fragilis-group
40201	Bacteroides intestinalis
2506	Bacteroides massiliensis
2520	Bacteroides nordii
2507	Bacteroides ovatus
40202	Bacteroides pyogenes
2508	Bacteroides species
2509	Bacteroides stercoris
2510	Bacteroides thetaiotaomicron
2511	Bacteroides uniformis
2512	Bacteroides ureolyticus
2513	Bacteroides vulgatus
40203	Bacteroides xylanisolvens
40204	Bacteroides zoogleoformans
40205	Bartonella species
40207	Beauveria species
40132	Bergeyella zoohelcum
3002	Bifidobacterium adolescentis
3003	Bifidobacterium breve
40208	Bifidobacterium dentium
40209	Bifidobacterium pseudocatenulatum
3001	Bifidobacterium species
40210	Bilophila species
30126	Bilophila wadsworthia
3005	Blautia
3301	Bordetella bronchiseptica
3305	Bordetella holmesii
3304	Bordetella species
30127	Bordetella trematum
3401	Branhamella catarrhalis
3501	Brevibacterium casei
30128	Brevibacterium ravenspurgense
3502	Brevibacterium species
30129	Brevundimonas aurantiaca
3603	Brevundimonas diminuta
3601	Brevundimonas species
3602	Brevundimonas vesicularis
3702	Brucella melitensis
3701	Brucella species
30130	Budvicia species
30131	Bulleidia extructa
40006	Burkholderia cenocepacia
3902	Burkholderia cepacia
3905	Burkholderia cepacia complex
30132	Burkholderia fungorum
3903	Burkholderia gladioli
3904	Burkholderia multivorans
3906	Burkholderia pseudomallei
3901	Burkholderia species
4001	Buttiauxella agrestis
28901	Butyricimonas virosa
4101	Campylobacter coli
4102	Campylobacter concisus
4103	Campylobacter fetus
4110	Campylobacter gracilis
4104	Campylobacter jejuni
4105	Campylobacter jejuni/coli
4106	Campylobacter lari
30133	Campylobacter rectus
4107	Campylobacter species
4108	Campylobacter sputorum
4109	Campylobacter upsaliensis
40067	Campylobacter ureolyticus
4201	Candida albicans
4202	Candida dubliniensis
4228	Candida fermentati
4203	Candida glabrata
4214	Candida guilliermondii
4204	Candida inconspicua
4230	Candida intermedia

4215 Candida kefyr
4216 Candida krusei
4217 Candida lambica
4218 Candida lipolytica
4219 Candida lusitaniae
4210 Candida magnoliae
4211 Candida norvegensis
4208 Candida palmioleophila
4205 Candida parapsilosis complex
4221 Candida pelliculosa
30004 Candida robusta
4209 Candida rugosa
4212 Candida sake
4206 Candida species
4207 Candida tropicalis
4236 Candida utilis
4237 Candida valida
4301 Capnocytophaga canimorsus
4302 Capnocytophaga cynodegmi
40068 Capnocytophaga gingivalis
4304 Capnocytophaga ochracea
4305 Capnocytophaga species
4306 Capnocytophaga sputigena
4401 Cardiobacterium hominis
40069 Cardiobacterium species
40070 Carnobacterium maltaromaticum
30135 Catabacter hongkongensis
29001 Caulobacter species
30136 Cedecea neteri
40072 Chromobacterium species
40073 Chromobacterium violaceum
5002 Chryseobacterium gleum
5003 Chryseobacterium indologenes
40074 Chryseobacterium luteola
5001 Chryseobacterium species
40074 Chryseomonas luteola
5201 Citrobacter amalonaticus
5202 Citrobacter braakii
5203 Citrobacter farmeri
5204 Citrobacter freundii
5205 Citrobacter koseri
5206 Citrobacter sedlakii
5207 Citrobacter species
5208 Citrobacter werkmanii
5209 Citrobacter youngae
40211 Clostridium aldenense
5303 Clostridium baratii
5305 Clostridium beijerinckii
5306 Clostridium bifermentans
5308 Clostridium butyricum
5309 Clostridium cadaveris
5311 Clostridium celatum
5313 Clostridium clostridioforme
5316 Clostridium difficile
30137 Clostridium disporicum
5320 Clostridium glycolicum
5321 Clostridium hastiforme
40212 Clostridium hathewayi
5323 Clostridium indolis
5324 Clostridium innocuum
5327 Clostridium limosum
5328 Clostridium malenominatum
5330 Clostridium novyi
5333 Clostridium paraputrificum
5334 Clostridium perfringens
5336 Clostridium ramosum
5339 Clostridium septicum
5340 Clostridium sordellii
5341 Clostridium species
5342 Clostridium sphenoides
5344 Clostridium sporogenes
5346 Clostridium subterminale
5347 Clostridium symbiosum
5348 Clostridium tertium
22701 Collinsella aerofaciens
5404 Comamonas kerstersii
40076 Comamonas kerstersii
5402 Comamonas species
5403 Comamonas testosteroni
40077 Corynebacterium aquaticum
30139 Corynebacterium argentoratense
5604 Corynebacterium diphtheriae
40078 Corynebacterium kroppenstedtii
30141 Corynebacterium massiliense
40079 Corynebacterium mucifaciens
40080 Corynebacterium resistens

30142 Corynebacterium riegelii
40082 Corynebacterium tuberculostearicum
40096 Cronobacter sakazakii
27201 Cryptococcus neoformans
5703 Cupriavidus pauculus
40085 Curtobacterium species
26501 Delftia acidovorans
26502 Dermabacter hominis
40008 Dermabacter species
26503 Desulfovibrio piger
26504 Desulfovibrio species
40011 Dialister micraerophilus
26505 Dialister pneumosintes
26506 Dialister species
5706 Dietzia
26508 Edwardsiella tarda
40086 Edwardsiella tarda
5708 Eggerthella
22801 Eggerthella lenta
40089 Eggerthia catenaformis
6701 Eikenella corrodens
6702 Eikenella species
22301 Elizabethkingia meningoseptica
40090 Empedobacter species
27301 Empedobacter brevis
7102 Enterobacter aerogenes
7103 Enterobacter amnigenus
7104 Enterobacter asburiae
7101 Enterobacter cancerogenus
7105 Enterobacter cloacae
5709 Enterobacter cloacae-complex
7107 Enterobacter dissolvens
7108 Enterobacter gergoviae
40092 Enterobacter hormaechei
5710 Enterobacter intermedius
40094 Enterobacter kobei
40095 Enterobacter ludwigii
7109 Enterobacter species
7401 Enterococcus avium
7402 Enterococcus casseliflavus
7403 Enterococcus cecorum
7404 Enterococcus columbae
7405 Enterococcus dispar
7406 Enterococcus durans
7407 Enterococcus faecalis
7408 Enterococcus faecium
7409 Enterococcus gallinarum
7410 Enterococcus hirae
7411 Enterococcus malodoratus
7412 Enterococcus mundtii
7414 Enterococcus raffinosus
7415 Enterococcus saccharolyticus
40097 Enterococcus saccharolyticus
7417 Enterococcus species
27401 Epidermophyton floccosum
27302 Erwinia species
40099 Erwinia species
27303 Erysipelothrix rhusiopathiae
7705 Escherichia species
40100 Escherichia albertii
7702 Escherichia coli
7703 Escherichia fergusonii
7704 Escherichia hermannii
7705 Escherichia species
7706 Escherichia vulneris
7801 Eubacterium contortum
7803 Eubacterium limosum
40101 Eubacterium moniliforme
7802 Eubacterium species
7805 Ewingella americana
7806 Ewingella species
40103 Exiguobacterium aurantiacum
27601 Exophiala dermatitidis
29101 Facklamia hominis
40014 Facklamia languida
30144 Facklamia species
23101 Finegoldia magna
40032 Finegoldia magna
40032 Finegoldia species
8301 Flavobacterium species
40213 Flavonifractor plautii
30146 Francisella philomiragia
8401 Francisella tularensis
22405 Fusarium dimerum
22402 Fusarium oxysporum
22401 Fusarium solani

22404	Fusarium species
85011	Fusobacterium glutinosum
8501	Fusobacterium gonidiaformans
8502	Fusobacterium mortiferum
8503	Fusobacterium naviforme
8504	Fusobacterium necrogenes
8505	Fusobacterium necrophorum
8506	Fusobacterium nucleatum
8510	Fusobacterium periodonticum
85012	Fusobacterium pseudonecrophorum
8508	Fusobacterium species
8509	Fusobacterium varium
8601	Gardnerella species
8602	Gardnerella vaginalis
8701	Gemella haemolysans
8702	Gemella morbillorum
40015	Gemella sanguinis
8703	Gemella species
8801	Geotrichum candidum
40016	Globicatella sanguinis
29201	Globicatella species
30147	Globicatella sulfidifaciens
40018	Gordonia bronchialis
30148	Gordonia sputi
26401	Granulicatella adiacens
26402	Granulicatella elegans
26403	Granulicatella species
102	Yeast
5711	Haematobacter massiliensis
18536	Haemolytic streptococci
18523	Haemolytic streptococci group A
18503	Haemolytic streptococci group B
18512	Haemolytic streptococci group C
18541	Haemolytic streptococci group F
18513	Haemolytic streptococci group G
9402	Haemophilus haemolyticus
9403	Haemophilus influenzae
9404	Haemophilus parahaemolyticus
9405	Haemophilus parainfluenzae
9406	Haemophilus species
9501	Hafnia alvei
40020	Hafnia species
27801	Helcococcus kunzii
30149	Helcococcus species
40022	Helicobacter cinaedi
9701	Helicobacter pylori
9702	Helicobacter species
27901	Histoplasma capsulatum
22201	Hydrogenophaga flava
30152	Kerstersia gyiorum
10601	Kingella denitrificans
10602	Kingella kingae
10707	Klebsiella species
23	Klebsiella oxytoca
10702	Klebsiella oxytoca
10705	Klebsiella pneumoniae
10703	Klebsiella pneumoniae subsp. ozaenae
10706	Klebsiella pneumoniae subsp. rhinoscleromatis
10707	Klebsiella species
10708	Klebsiella terrigena
40093	Kluyvera intermedia
10801	Kluyvera ascorbata
10802	Kluyvera cryocrescens
10803	Kluyvera species
23501	Kocuria kristinae
23502	Kocuria rosea
23504	Kocuria species
23503	Kocuria varians
30172	Kosakonia cowanii
30154	Kurthia species
40214	Lactobacillus brevis
40215	Lactobacillus jensenii
40216	Lactobacillus plantarum
40217	Lactobacillus sakei
11401	Leclercia adecarboxylata
11402	Leclercia species
11503	Legionella pneumophila
11504	Legionella species
28101	Leifsonia aquatica
30157	Leptotrichia amnionii
11801	Leptotrichia buccalis
40104	Leptotrichia goodfellowii
11802	Leptotrichia species
11903	Leuconostoc mesenteroides
11904	Leuconostoc species
12101	Listeria grayi

12103 Listeria ivanovii
12104 Listeria monocytogenes
12107 Listeria species
5733 Macrococcus caseolyticus
25901 Mannheimia haemolytica
5714 Massilia timonae
5715 Methylobacterium
29301 Microbacterium species
40025 Micrococcus lylae
5717 Microaerophilic streptococcus
12701 Moellerella species
12804 Moraxella catarrhalis
12901 Morganella morganii
12903 Morganella morganii, subsp. morganii
12902 Morganella morganii, subsp. sibonii
12904 Morganella species
13105 Mycobacterium avium
13107 Mycobacterium chelonae
13102 Mycobacterium fortuitum
13112 Mycobacterium marinum
30167 Mycobacterium smegmatis
13118 Mycobacterium species
13116 Mycobacterium tuberculosis
13202 Mycoplasma hominis
5719 Mycoplasma salivarium
22901 Myroides odoratus
22902 Myroides species
13312 Neisseria animaloris (CDC group 4a)
13311 Neisseria elongata
13315 Neisseria elongata spp. elongata
13303 Neisseria gonorrhoeae
13305 Neisseria meningitidis
40108 Neisseria subflava
13314 Neisseria zoodegmatis (CDC group 4b)
13404 Nocardia farcinica
13405 Nocardia nova
13406 Nocardia otitidiscaviarum
13402 Nocardia species
18530 Non-haemolytic streptococci anginosus group
18537 Non-haemolytic streptococci bovis group
18529 Non-haemolytic streptococci milleri group
18531 Non-haemolytic streptococci mitis group
18539 Non-haemolytic streptococci mutans group
18532 Non-haemolytic streptococci salivarius group
40112 Obesumbacterium proteus
13500 Ochrobactrum anthropi
40113 Ochrobactrum intermedium
13501 Ochrobactrum species
13502 Odoribacter splanchnicus
13503 Oerskovia species
5721 Oerskovia turbata
16504 Oligella species
16505 Oligella ureolytica
16506 Oligella urethralis
29401 Paecilomyces species
29501 Paenibacillus amylolyticus
29503 Paenibacillus species
29504 Paenibacillus turicensis
29601 Pandoraea apista
14302 Pantoea agglomerans
14301 Pantoea species
29701 Parabacteroides distasonis
29702 Parabacteroides merdae
40116 Parabacteroides species
5722 Paracoccus
40117 Paracoccus yeei
23201 Parvimonas micra
25901 Pasteurella canis
14608 Pasteurella dagmatis
14612 Pasteurella multocida
14613 Pasteurella multocida subsp. multocida
14602 Pasteurella multocida subsp. septica
14614 Pasteurella pneumotropica
14615 Pasteurella species
14616 Pasteurella stomatis
5723 Pectobacterium carotovorum
40120 Pediococcus acidilactici
40142 Pediococcus pentosaceus
14701 Pediococcus species
14801 Penicillium species
14901 Peptococcus niger
14902 Peptococcus species
23001 Peptoniphilus asaccharolyticus
23002 Peptoniphilus harei
40030 Peptoniphilus lacrimalis
23000 Peptoniphilus species

15001 Peptostreptococcus anaerobius
40031 Peptostreptococcus harei
15006 Peptostreptococcus species
23003 Photobacterium damselae
40133 Photorhabdus luminescens
40033 Plesiomonas shigelloides
15200 Pneumocystis jirovecii
15501 Porphyromonas asaccharolytica
15502 Porphyromonas endodontalis
5724 Porphyromonas gingivalis
15503 Porphyromonas species
15601 Pragia species
15701 Prevotella bivia
15702 Prevotella buccae
15703 Prevotella buccalis
15704 Prevotella corporis
15705 Prevotella denticola
15706 Prevotella disiens
15707 Prevotella intermedia
15713 Prevotella loescheii
15708 Prevotella melaninogenica
15712 Prevotella nigrescens
15709 Prevotella oralis
15710 Prevotella oris
15711 Prevotella species
5725 Propionimicrobium lymphophilum
15901 Proteus mirabilis
15903 Proteus penneri
15904 Proteus species
15905 Proteus vulgaris
16001 Providencia alcalifaciens
16003 Providencia rettgeri
16004 Providencia rustigianii
16005 Providencia species
16006 Providencia stuartii
40200 Pseudoflavonifractor capillosus
16102 Pseudomonas aeruginosa
16103 Pseudomonas alcaligenes
16128 Pseudomonas brenneri
16109 Pseudomonas fluorescens
5726 Pseudomonas fragi
30170 Pseudomonas koreensis
16111 Pseudomonas luteola
16114 Pseudomonas mendocina
40034 Pseudomonas monteilii
40035 Pseudomonas oleovorans
16127 Pseudomonas oryzihabitans
16129 Pseudomonas otitidis
5727 Pseudomonas pseudoalcaligenes
16120 Pseudomonas putida
16121 Pseudomonas species
16122 Pseudomonas stutzeri
40037 Pseudomonas veronii
29801 Psychrobacter phenylpyruvicus
30171 Psychrobacter species
16401 Rahnella aquatilis
5728 Ralstonia mannitolilytica
22101 Ralstonia pickettii
18401 Raoultella ornithinolytica
18402 Raoultella planticola
18403 Raoultella species
10708 Raoultella terrigena
18403 Raoultella terrigena
1401 Rhizobium radiobacter
1402 Rhizobium species
1406 Rhizopus microsporus
1407 Rhizopus oryzae
1408 Rhizopus species
16601 Rhodococcus equi
16602 Rhodococcus species
1603 Rhodotorula glutinis
1604 Rhodotorula mucilaginosa
16701 Rhodotorula species
40039 Roseomonas species
40040 Rothia aeria
16901 Rothia dentocariosa
16902 Rothia mucilaginosa
16903 Rothia species
40041 Ruminococcus gnavus
17001 Saccharomyces cerevisiae
30073 Salmonella Agbeni
17167 Salmonella Aberdeen
30073 Salmonella Agbeni
17101 Salmonella Agona
30075 Salmonella Alachua
17188 Salmonella Albany

27108 Salmonella Altona
17113 Salmonella Anatum
17167 Salmonella Apeyeme
17115 Salmonella Bareilly
17149 Salmonella Blockley
27111 Salmonella Bonn
17117 Salmonella Bovismorbificans
17118 Salmonella Braenderup
17150 Salmonella Brandenburg
17175 Salmonella Bredeney
17172 Salmonella Chester
17208 Salmonella Choleraesuis
17209 Salmonella Colindale
17109 Salmonella Concord
17121 Salmonella Corvallis
17119 Salmonella Derby
17120 Salmonella Dublin
27115 Salmonella Duisburg
17180 Salmonella Eastbourne
17152 Salmonella Emek
17102 Salmonella enterica
17197 Salmonella enterica subsp. diarizonae
27120 Salmonella enterica subsp. houtenae
17181 Salmonella enterica subsp. indica
17104 Salmonella Enteritidis
17122 Salmonella Give
17123 Salmonella Hadar
17154 Salmonella Haifa
17124 Salmonella Heidelberg
27119 Salmonella Hoboken
17125 Salmonella Hvittingfoss
17156 Salmonella Indiana
17126 Salmonella Infantis
17127 Salmonella Java
17193 Salmonella Javiana
17158 Salmonella Kentucky
27136 Salmonella Kingston
17159 Salmonella Kottbus
27125 Salmonella Liverpool
17194 Salmonella Livingstone
30101 Salmonella Loubomo
17128 Salmonella Manhattan
17160 Salmonella Mbandaka
17184 Salmonella Mikawasima
17131 Salmonella Montevideo
17161 Salmonella Muenchen
17162 Salmonella Muenster
17106 Salmonella Napoli
17133 Salmonella Newport
17135 Salmonella Oranienburg
30108 Salmonella Othmarschen
17136 Salmonella Panama
17105 Salmonella Paratyphi A
17111 Salmonella Paratyphi B
17127 Salmonella Paratyphi B var. Java
17137 Salmonella Poona
17138 Salmonella Reading
17163 Salmonella Rissen
17227 Salmonella Rubislaw
17139 Salmonella Saintpaul
17140 Salmonella Sandiego
17141 Salmonella Schwarzengrund
17165 Salmonella Senftenberg
17166 Salmonella serovar 4,5,12:i:-
17199 Salmonella serovar 9,12:-:-
17166 Salmonella serovar O:4,5, 12 H:i
17199 Salmonella serovar O:9,12 H:- :-
17108 Salmonella species
17143 Salmonella Stanley
17185 Salmonella Stanleyville
27130 Salmonella Strathcona
17144 Salmonella Tennessee
17145 Salmonella Thompson
17110 Salmonella Typhi
17146 Salmonella Typhimurium
17171 Salmonella Umbilo
17148 Salmonella Virchow
30118 Salmonella Winston
30118 Salmonella Winston
17186 Salmonella Worthington
40219 Sarcina species
17004 Scedosporium species
40221 Selenomonas species
40222 Serratia ficaria
17401 Serratia fonticola
17402 Serratia liquefaciens

17403 Serratia marcescens
17404 Serratia odorifera
17405 Serratia plymuthica
17406 Serratia rubidaea
17407 Serratia species
17501 Shewanella algae
17502 Shewanella putrefaciens
17503 Shewanella species
17603 Shigella flexneri
17604 Shigella sonnei
17605 Shigella species
103 Mold
5730 Slackia exigua
40224 Sneathia sanguinegens
5731 Solobacterium moorei
40225 Sphingobacterium multivorum
40226 Sphingobacterium species
40227 Sphingobacterium spiritivorum
17802 Sphingomonas paucimobilis
17801 Sphingomonas species
5732 Staphylococcus arlettae
17902 Staphylococcus aureus
40042 Staphylococcus carnosus
17911 Staphylococcus lugdunensis
17925 Staphylococcus pasteuri
17926 Staphylococcus pettenkoferi
40045 Staphylococcus pseudointermedius
17912 Staphylococcus saprophyticus
17923 Staphylococcus schleiferi
40046 Staphylococcus xylosus
18101 Stenotrophomonas maltophilia
18102 Stenotrophomonas species
40169 Stomatococcus species
5736 Streptobacillus moniliformis
40229 Streptobacillus species
5737 streptococ group D
18504 Streptococcus alactolyticus
18505 Streptococcus anginosus
18552 Streptococcus anginosus-group
40230 Streptococcus canis
18508 Streptococcus constellatus
18542 Streptococcus cristatus
18543 Streptococcus dysgalactiae
18538 Streptococcus dysgalactiae subsp. equisimilis
18507 Streptococcus equinus
18533 Streptococcus gallolyticus
18511 Streptococcus gordonii
18534 Streptococcus infantarius
18515 Streptococcus intermedius
18550 Streptococcus lutetiensis
5738 Streptococcus massiliensis
5739 Streptococcus minor
18516 Streptococcus mitis
18553 Streptococcus mitis group
18517 Streptococcus mutans
18518 Streptococcus oralis
18540 Streptococcus ovis
18519 Streptococcus parasanguinis
40231 Streptococcus pluranimalium
18521 Streptococcus pneumoniae
18544 Streptococcus pseudopneumoniae
5740 Streptococcus pseudoporcinus
18524 Streptococcus salivarius
18551 Streptococcus salivarius group
18526 Streptococcus sanguinis
18525 Streptococcus sanguis
5741 Streptococcus sobrinus
18545 Streptococcus suis
40232 Streptococcus thermophilus
18528 Streptococcus vestibularis
40233 Streptomyces species
40121 Sutterella wadsworthensis
104 Fungus
5742 Tatumella
40122 Tissierella praeacuta
40123 Tropheryma whipplei
40124 Trueperella bernardiae
40125 Turicella otitidis
40126 Turicella species
40127 Ureaplasma parvum
40128 Ureaplasma species
40129 Vagococcus species
20401 Veillonella parvula
20402 Veillonella species
20501 Vibrio alginolyticus
20503 Vibrio cholerae

20506	Vibrio fluvialis
20509	Vibrio metschnikovii
20510	Vibrio mimicus
20511	Vibrio parahaemolyticus
20512	Vibrio species
20513	Vibrio vulnificus
5743	Wautersiella falseni
40130	Weeksella species
40131	Weeksella virosa
40170	Wohlfahrtiimonas chitiniclastica
5744	Wolinella
5745	Xanthomonas
40135	Yersinia bercovieri
21101	Yersinia enterocolitica
21106	Yersinia pseudotuberculosis
21107	Yersinia species
5748	Yokenella

Table 2. Microorganisms classified as contaminants

Code	Text
30058	Absidia species
60	Acinetobacter baumanii
61	Acinetobacter calcoaceticus
62	Acinetobacter haemolyticus
63	Acinetobacter johnsonii
64	Acinetobacter junii
65	Acinetobacter lwoffii
66	Acinetobacter radioresistens
67	Acinetobacter species
68	Acinetobacter ursingii
1004	Aerococcus christensenii
1001	Aerococcus species
1003	Aerococcus viridans
30059	Altanaria species
40063	Bacillus circulans
2404	Bacillus licheniformis
2405	Bacillus pumilus
2406	Bacillus simplex
2403	Bacillus species
3004	Bifidobacterium longum
30008	Chrysosporium species
30012	Cladosporium species
5623	Corynebacterium accolens
5601	Corynebacterium afermentans
5602	Corynebacterium amycolatum
5603	Corynebacterium bovis
5624	Corynebacterium glucuronolyticum
5608	Corynebacterium jeikeium
5609	Corynebacterium kutscheri
5625	Corynebacterium macginleyi
5611	Corynebacterium minutissimum
5626	Corynebacterium propinquum
5613	Corynebacterium pseudodiphtheriticum
5615	Corynebacterium pseudotuberculosis
5617	Corynebacterium simulans
5618	Corynebacterium species
5619	Corynebacterium striatum
5620	Corynebacterium ulcerans
5621	Corynebacterium urealyticum
5622	Corynebacterium xerosis
30014	Cryptococcus albidus
10025	Enterobius vermicularis
30031	Geotrichum species
10030	Iodamoeba bütschlii
11201	Lactobacillus casei
30155	Lactobacillus catenaformis
11206	Lactobacillus curvatus
11207	Lactobacillus delbrueckii
11208	Lactobacillus fermentum
11205	Lactobacillus gasseri
11209	Lactobacillus paracasei
11202	Lactobacillus rhamnosus
11203	Lactobacillus salivarius
11204	Lactobacillus species
11302	Lactococcus garvieae
11305	Lactococcus lactis
11303	Lactococcus lactis subsp. cremoris
11304	Lactococcus lactis subsp. lactis
11301	Lactococcus species
40023	Macrococcus caseolyticus
40024	Macrococcus species
30033	Magnusiomyces capitatus
7810	Malassezia furfur
7811	Malassezia species
12403	Micrococcus luteus
12401	Micrococcus species

30034	Microsporum audouinii
30035	Microsporum canis
30037	Microsporum gypseum
12801	Moraxella atlantae
12803	Moraxella canis
12805	Moraxella lacunata
12806	Moraxella lincolnii
12807	Moraxella nonliquefaciens
12808	Moraxella osloensis
12810	Moraxella species
30044	Mucor species
13301	Neisseria cinerea
13302	Neisseria flavescens
13304	Neisseria lactamica
13306	Neisseria mucosa
13308	Neisseria sicca
13309	Neisseria species
13310	Neisseria weaveri (CDC group M-5)
18535	Non-haemolytic streptococci
15801	Propionibacterium acnes
15802	Propionibacterium avidum
15803	Propionibacterium granulosum
15804	Propionibacterium propionicum
15805	Propionibacterium species
1404	Rhizomucor species
17901	Staphylococcus auricularis
17903	Staphylococcus capitis
17922	Staphylococcus caprae
17930	Staphylococcus chromogenes
17920	Staphylococcus coagulase-negative
17904	Staphylococcus cohnii
40044	Staphylococcus condimenti
17905	Staphylococcus epidermidis
17906	Staphylococcus haemolyticus
17907	Staphylococcus hominis
17908	Staphylococcus hyicus
17909	Staphylococcus intermedius
17910	Staphylococcus lentus
17921	Staphylococcus saccharolyticus
17913	Staphylococcus sciuri
17914	Staphylococcus simulans
17915	Staphylococcus species
17924	Staphylococcus species (CNS)
17916	Staphylococcus warneri
18527	Streptococcus species
10046	Trichomonas vaginalis
1411	Trichophyton mentagrophytes
1412	Trichophyton rubrum
1415	Trichophyton species
1417	Trichophyton tonsurans
1418	Trichophyton verrucosum
1419	Trichophyton violaceum
33312	Trichosporon asahii
33310	Trichosporon mucoides
33309	Trichosporum inkin
33304	Verticillium species

Table 3. Results considered negative

Code	Text
13522	Aerobe Gram negative rods
13523	Anaerobe bacteria
13524	Anaerobe Gram negative cocci
13525	Anaerobe Gram negative rods
13526	Anaerobe Gram positive cocci
13506	Anaerobe Gram positive rods
13519	Cocci
13520	Cocci in clusters
13527	Gram negative cocci
13508	Gram negative diplococci
13509	Gram negative rods
13528	Gram negative rods (enterobacteria)
13510	Gram negative rods (enterobacteria)
13513	Gram positive branching rods
13514	Gram positive cocci
13515	Gram positive cocci in clusters
13516	Gram positive cocci in chains
13511	Gram positive coryneforme rods
13512	Gram positive diplococci
13517	Gram positive rods
88886	Negative
10036	Schistosoma haematobium

Appendix 5: Classification of relevant diagnosis codes for probable urinary tract infections

Table 1. Diagnosis codes considered relevant for the case definition for probable urinary tract infections.

Diagnosis code[1]	Text
DA600	Herpesviral infection of genitalia and urogenital tract
DN080B	Glomerular disorders in sepsis
DN308A	Abscess of bladder
DN34	Urethritis and urethral syndrome
DN390	Urinary tract infection, site not specified
DO088E	UTI[2] following abortion and ectopic and molar pregnancy
DO23	Infections of genitourinary tract in pregnancy
DO233	Infections of other parts of urinary tract in pregnancy
DO234	Unspecified infection of urinary tract in pregnancy
DO239	Other and unspecified genitourinary tract infection in pregnancy
DO862	Urinary tract infection following delivery
DP001	Fetus and newborn affected by maternal renal and UTI
DP393	Neonatal urinary tract infection
DR827B	Abnormal findings on microbiological examination of urine
DT814U	Infection following a procedure, not elsewhere classified
DT835	UTI due to prosthetic device, implant and graft
DT835A	UTI due to implant
DT835B	UTI due to prosthetic device
DT835C	UTI due to graft
DT839	Complication of urogenital prosthesis, implant or transplant unspecified
DZ038A	Observation for suspected UTI
DZ038B	Observation for suspected UTI without specification

[1] Danish modification of ICD-10 classification

[2] UTI=urinary tract infection

Appendix 6: Classification of antibiotic treatment for probable urinary tract infections

Table 1. Codes considered relevant for the case definition for probable urinary tract infections.

ATC[1] code	Text
J01CA01	ampicillin
J01CA02	pivampicillin
J01CA04	amoxicillin
J01CA08	pivmecillinam
J01CA11	mecillinam
J01CE01	benzylpenicillin
J01CR02	amoxicillin and enzyme inhibitor
J01DI54	ceftolozan and enzyme inhibitor
J01EA01	trimethoprim
J01EB02	sulfamethizol
J01EE01	sulfamethoxazol and trimethoprim
J01MA01	ofloxacin
J01MA02	ciprofloxacin
J01MA12	levofloxacin
J01XE01	nitrofurantoin

[1] ATC= Anatomical Therapeutic Chemical

Paper I

The development and use of a new methodology to reconstruct courses of admission and ambulatory care based on the Danish National Patient Registry.

Gubbels S, Nielsen KS, Sandegaard J, Mølbak K, Nielsen J.

Int J Med Inform. 2016 Nov;95:49-59.
doi: 10.1016/j.ijmedinf.2016.08.003. Epub 2016 Aug 18.

International Journal of Medical Informatics 95 (2016) 49–59

Contents lists available at ScienceDirect

International Journal of Medical Informatics

journal homepage: www.ijmijournal.com

The development and use of a new methodology to reconstruct courses of admission and ambulatory care based on the Danish National Patient Registry

Sophie Gubbels[a,*], Kenn Schultz Nielsen[b], Jakob Sandegaard[c], Kåre Mølbak[a], Jens Nielsen[a]

[a] Department of Infectious Disease Epidemiology, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
[b] Department of IT-Projects and Development, Danish Health Data Authority, Artillerivej 5, 2300 Copenhagen S, Denmark
[c] Department of Data Quality and Content, Danish Health Data Authority, Artillerivej 5, 2300 Copenhagen S, Denmark

ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form 6 August 2016
Accepted 17 August 2016

Keywords:
Re-construction algorithm
Electronic health records
Hospital admissions
Ambulatory care
Denmark

ABSTRACT

Introduction: The Danish National Patient Registry (DNPR) contains clinical and administrative data on all patients treated in Danish hospitals. The data model used for reporting is based on standardized coding of contacts rather than courses of admissions and ambulatory care.
Methods: To reconstruct a coherent picture of courses of admission and ambulatory care, we designed an algorithm with 28 rules that manages transfers between departments, between hospitals and inconsistencies in the data, e.g., missing time stamps, overlaps and gaps. We used data from patients admitted between 1 January 2010 and 31 December 2014.
Results: After application of the DNPR algorithm, we estimated an average of 1,149,616 courses of admission per year or 205 hospitalizations per 1000 inhabitants per year. The median length of stay decreased from 1.58 days in 2010 to 1.29 days in 2014. The number of transfers between departments within a hospital increased from 111,576 to 176,134 while the number of transfers between hospitals decreased from 68,522 to 61,203.
Conclusions: We standardized a 28-rule algorithm to relate registrations in the DNPR to each other in a coherent way. With the algorithm, we estimated 1.15 million courses of admissions per year, which probably reflects a more accurate estimate than the estimates that have been published previously. Courses of admission became shorter between 2010 and 2014 and outpatient contacts longer. These figures are compatible with a cost-conscious secondary healthcare system undertaking specialized treatment within a hospital and limiting referral to advanced services at other hospitals.

1. Introduction

The secondary and tertiary healthcare provision in Denmark is predominantly public and management and policy making occurs primarily on a national level and in the five Danish Regions [1]. The development and use of common standards for information and communication technology plays a large role in the organization of the Danish healthcare sector.

Administrative and clinical data on patient contacts with the Danish secondary and tertiary healthcare system are recorded locally and gathered daily in the Danish National Patient Registry (DNPR) [2]. This registry was established in 1977. Originally, it only covered somatic inpatients, but over the years, the registry expanded. Since 1995, also outpatient activities, Accident & Emergency Room (A&E) contacts and psychiatric departments have gradually been included. In 2003, notification of inpatient and outpatient contacts from private hospitals became compulsory [3]. Before 2014, A&E patients were recorded as a separate category. From 1 January 2014, these have been recorded as acute outpatients. In addition, since 1 January 2014 the Capital Region of Denmark reorganized its on-call service, after which patients, who would previously have been seen by a general practitioner, were seen in the A&E. The consequence is that, for this region, primary sector patients are now recorded as acute outpatients in the DNPR. Initially, the DNPR was a discharge registry, meaning that data were first sent to the DNPR after discharge. Since 1996, open outpatient

* Corresponding author.
E-mail addresses: gub@ssi.dk (S. Gubbels), ksn@ssi.dk (K.S. Nielsen), sandegaard@live.dk (J. Sandegaard), krm@ssi.dk (K. Mølbak), nls@ssi.dk (J. Nielsen).

http://dx.doi.org/10.1016/j.ijmedinf.2016.08.003

contacts have been registered and since June 2015, hospitals could voluntarily register inpatients that were still admitted. The latter became obligatory from 1 January 2016. Data are entered in the DNPR in accordance with specifications made by Danish Health Data Authority to secure a certain level of standardization and data quality.

Due to the contact based design of the DNPR, in which each inpatient contact with a new department is registered as a new event, and sometimes even several (overlapping) contacts are recorded for the same department, courses of admission cannot directly be deducted. DNPR does for example not disentangle contacts representing transfers within the same course of admission from records that represent a new admission. Outpatient contacts are registered as the period in which the patient was in ambulatory care at a specific department, with visits/consultations related to them. Registration practice of outpatient contact varies between hospitals: where some hospitals record new outpatient contacts regularly, other hospitals keep an outpatient contact open for years. All registrations of inpatients and outpatients are manually entered and may therefore contain inaccuracies, for example in the exact time of admission and discharge, leading to overlaps and gaps in the course of an admission and course of ambulatory care.

Using a large registry for scientific studies and surveillance systems poses many challenges, particularly when data are primarily recorded for administrative and economic purposes. A system that is driven by reimbursements has certain forces driving the coding practice [4–6]. Variations in content, completeness and validity of data between different groups and over time create an additional challenge as these may make adjustments for co-morbidity problematic or even useless [7–9]. A recent review article compiled validation studies performed on the DNPR, showing varying levels of completeness and validity of diagnosis codes [10]. So far, no validation studies were published assessing the accuracy of registrations of admission and discharge dates in the DNPR, although many scientific studies and policy documents use these data to calculate length of stay and numbers of (re-)admissions in relation to specific diseases and for the healthcare system as a whole. In 2014 alone, 12 articles were published using the DNPR to calculate numbers of admissions and/or length of stay (PubMed search with search terms '*National Patient Register Denmark hospitalization*' and '*National Patient Registry Denmark hospitalization*'; limited to English original articles and publication date in 2014. Full text articles were screened for length of stay calculations or analyses of numbers of (re-)admissions). These studies were either done using the DNPR as it is, with the contacts as equivalents to admissions and courses of ambulatory care [11–19], or with a loosely specified algorithm to create courses of admission [20–22]. This variety of practices makes interpretation of results and comparison with other studies difficult.

In this article, we present a method, which can standardize the way DNPR data are used for epidemiological studies, surveillance and policymaking. We describe how registrations can be related to each other using an algorithm ("DNPR algorithm") to reconstruct a complete and coherent picture from inpatient contacts to admissions within the same department, to courses of admission across departments and hospitals as well as from outpatient contacts to courses of ambulatory care within the same department. Using this algorithm, we describe and discuss trends in hospital admissions and ambulatory care and identify areas for further research.

This work was done as a prerequisite for the development of a national automated surveillance system to monitor hospital-acquired infections: the Danish Hospital-Acquired Infections Database (HAIBA) [23]. However, the DNPR algorithm will also be relevant when using DNPR for other surveillance, research and planning purposes. It also gives insight in data quality, as well as dynamics and trends in the utilization of the Danish secondary and tertiary healthcare system. The experiences with this algorithm will be of value for other countries planning to develop an administrative patient system or applying data from existing patient registries.

2. Methods

2.1. Definitions

Inpatient: A patient who occupies a hospital bed for medical care or treatment

Outpatient: A patient who receives medical care or treatment at a hospital, but is not admitted

Ambulatory Care: medical care or treatment an outpatient receives

Inpatient contact: A single registration in the DNPR for an inpatient

Outpatient contact: A single registration in the DNPR for an outpatient

Admission: A coherent hospital stay within the same hospital department as identified with the DNPR algorithm (can include more than one inpatient contact)

Course of admission: A coherent hospital stay across departments and hospitals as identified with the DNPR algorithm (can include more than one admission)

Course of ambulatory care: A coherent period of ambulatory care within the same hospital department as identified with the DNPR algorithm (can include more than one outpatient contact)

2.2. Study population and period

We used data of inpatients admitted between 1 January 2010 and 31 December 2014, and outpatients with contacts starting in that same period. Data included somatic inpatients and outpatients from all private and public hospitals in Denmark, but not A&E contacts before 1 January 2014. Data were extracted on 1 October 2015.

2.3. Data flow and output data model

Data flow and the output data model are shown in Fig. 1. DNPR retrieves data from the five Danish regions. Data from public and private hospitals are collected in separate databases each containing both administrative and clinical information (diagnosis and procedure codes). National classification tables were used to allow translating codes for hospitals, departments as well as diagnosis and procedure codes [24]. The codes also include information on whether data are from the public or private sector and from which Danish region.

Patients were identified by their CPR number, a civil registration number that each person in Denmark receives upon birth or immigration [25].

Data on inpatient and outpatient contacts from both public and private hospitals contained the patients' CPR numbers, dates and times of admission and discharge (with hours being the lowest level of detail) and hospitals and departments where the patients were admitted or received ambulatory care. Each contact has a unique contact identifier, which is the key to linking the contacts to data on diagnosis, procedures and visits.

Diagnosis codes are entered upon discharge according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) [26], and adapted for use in the Danish healthcare system [24]. Additional information to the diagnosis codes may also be entered, here referred to as additional diagnosis codes. Diagnosis codes and additional diagnosis codes do not have a date and time of diagnosis, but can be related to the period between the start and end date and time of the corresponding inpatient or outpatient contacts.

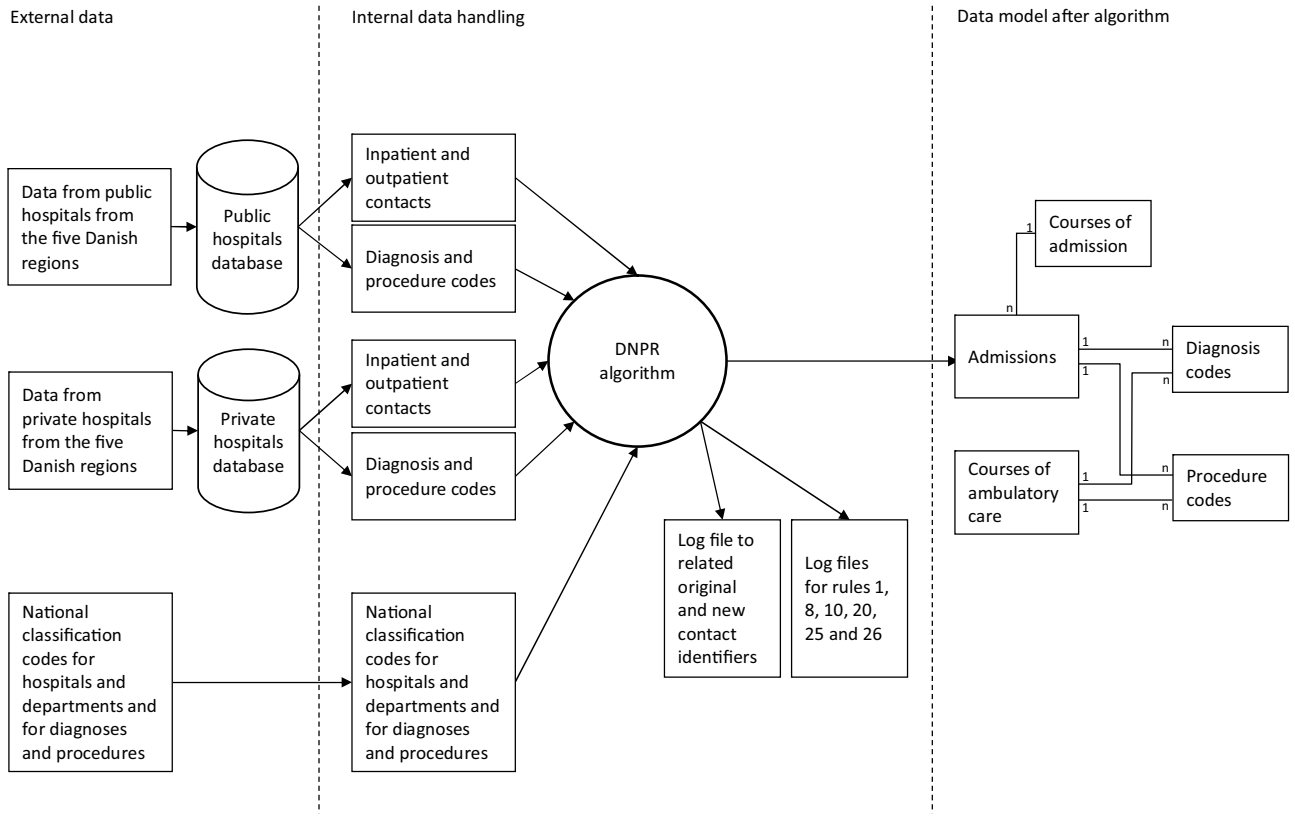


Fig. 1. Data flow showing import of data, tables forming the input for the DNPR algorithm and the resulting data model.

Procedure codes are based on the Nordic Classification of Surgical Procedures [27], and adapted to the Danish healthcare system [24]. Hospital departments enter procedure codes, and additional information (additional procedure codes), with the date and time of procedure and the department that performed the procedure. For this study, we limited procedure codes to treatment (B), operations (K), anesthesia and intensive care (N), and examinations (U) to eliminate clinically irrelevant procedures.

Diagnosis and procedure codes are related to inpatient and outpatient contacts through the unique contact identifier.

In this study, data on inpatient and outpatient contacts, diagnosis and procedure codes as well as classification data were imported and used as input to the DNPR algorithm creating coherent courses of admission and courses of ambulatory care. The DNPR algorithm produced log files and an output database with five tables containing: admissions, the corresponding courses of admission, courses of ambulatory care and diagnosis and procedure codes for both inpatients and outpatients (Fig. 1).

2.4. The DNPR algorithm

To establish a coherent database managing transfers between departments and hospitals, connecting related outpatient contacts, and modifying inconsistencies in data, such as overlaps and gaps, an algorithm with 28 rules was defined (Table 1). Rules 1–9 and 17 applied both to inpatient and outpatient contacts, while rules 10–16 applied only to inpatient contacts. Rules 18–21 applied to diagnosis codes and rules 22–28 to procedure codes. Since a patient may be admitted and at the same time be in ambulatory care, inpatient and outpatient contacts were handled independently. In addition, the DNPR algorithm allowed overlap in courses of ambulatory care at different departments, since a patient can be in ambulatory care for independent medical reasons at the same time.

In more detail, to clean the database, records with relevant data missing were deleted and stored in a log file (rule 1). Contacts that were open at the time of extraction were closed at the extraction date (1 October 2015, in the presented dataset) at 23:00 (rule 2). Hospital codes for one specific region (Region Zealand) were formatted, since this region used the same hospital code for all hospitals in the region and indicated the hospital name as part of the department code (rule 3). Situations in which the time of discharge was not or incorrectly registered were handled (rules 4–8). Overlapping contacts at the same hospital and department were related (rule 9). For outpatient contacts, this was the final rule, creating courses of ambulatory care. For inpatient contacts this rule created "admissions".

Time overlap in admissions across departments were removed to eliminate registrations, where an inpatient was recorded to be admitted at more than one department at the same point in time (rules 10–12). Time-gaps between discharge from one department and admission to another department were handled, defining a gap of 4 h or less as a transfer and more than 4 h as a new admission (rules 13 and 14). Course of admission was defined and registered (rules 15 and 16).

Whenever the above rules affected the linking of diagnosis and procedure codes to admissions and courses of ambulatory care this was managed through the contact identifier (rule 17). The corresponding diagnosis and procedure codes also needed to be updated in this respect (rules 18 and 22).

Diagnosis codes, which were associated to inpatient or outpatient contacts deleted in rules 1, 8 and 10 were removed and written to a log file (rule 20). Duplicate diagnosis and additional codes were handled (rules 19 and 21).

Table 1
DNPR algorithm: set of rules, which were applied to relate contacts with the healthcare system to coherent admissions, courses of admission and courses of ambulatory care.

Nr.	Description of rules	Valid for
1	Contacts which lacked information in one or more of the following variables were excluded: contact identification number, CPR number, patient type (inpatient or outpatient), hospital code, department code, date of admission/start of ambulatory care. If the date of admission was after the date of discharge then it was considered an error. These contacts were written to a log file.	Inpatients and outpatients
2	If the date of discharge was not registered, then the patient was recorded as a current patient and the date of discharge/end of ambulatory care was set at the extraction date at 23:00.	Inpatients and outpatients
3	For all hospitals in Region Zealand, the hospital code was always 3800. The first three letters in the text field for the departments indicated the hospital name. In this step these three letters were moved to the hospital code.	Inpatients and outpatients
4	If a contact had a date of discharge/end of ambulatory care, but no time and there were one or more procedure codes connected to the contact on the same day, then the time of the last procedure plus one hour (parameter) was used as time of discharge/end.	Inpatients and outpatients
5	If a contact had a date of discharge/end of ambulatory care, but still no time and the discharge/end date was the same as the admission/start date, then the time was set at the admission/start time plus one hour (parameter).	Inpatients and outpatients
6	If a contact had a date of discharge/end of ambulatory care, but still no time of discharge/end, then the time was set to 23:00 (parameter).	Inpatients and outpatients
7	If the time of one or more procedures was after the time of discharge/end of ambulatory care (but still on the same day) then the time of discharge/end was moved to the time of the last procedure plus one hour (parameter).	Inpatients and outpatients
8a	If the time of admission/start of ambulatory care was registered to be after the time of discharge/end of ambulatory care, but was registered for the same day, then the time of admission/start was set to the time of discharge/end minus one hour (parameter).	Inpatients and outpatients
8b	If the date of admission/start of ambulatory care was registered to be after the date of discharge/end of ambulatory care, then it was considered a mistake. The contact was removed from the system and written in a log file.	
9	If there were two or more contacts with the same CPR number, hospital and department and overlap in the admission/start and discharge/end dates, then these were combined into one, hereafter referred to as 'admission' for inpatients and 'course of ambulatory care' for outpatients covering the combined period between admission/start and discharge/end. Procedure and diagnosis codes connected to all contacts were kept.	Inpatients and outpatients
10	If there were admissions with the same CPR number and exactly the same date and time of admission/start and discharge/end, but on different hospitals and/or departments. It was not possible to know which department was the correct one, and therefore both admissions were removed and written to a log file.	Inpatients
11	If there was overlap in the date and time of admission and discharge for the same CPR number across departments or hospitals, then the date and time of the first admission was kept. The date and time of admission of the next admission was moved forward in time to the date and time of discharge of the previous admission. This rule was repeated for subsequent overlaps. In some cases new overlapping admissions were created, which were then solved with the same rule, until no overlap existed.	Inpatients
12	If the period between admission and discharge of one admission was registered within another admission with a longer period for the same CPR number, but by another hospital and/or department, the longer admission was split up, resulting in two admissions before and after the shorter admission. In some cases new overlapping admissions were created with this situation, which were subsequently solved with the same rule, until no overlap existed.	Inpatients
13	If a patient was transferred to another department in the same hospital a maximum of four hours (parameter) between time of discharge and admission was allowed to relate the two contacts to the same course of admission.	Inpatients
14	If a patient was transferred to another hospital a maximum of four hours (parameter) between time of discharge and admission was allowed to relate the two contacts to the same course of admission.	Inpatients
15	If two contacts for the same patient on the same department were recorded, where the date and time of discharge for the first contact was the date and time of admission of the second contact these contacts were recorded as one.	Inpatients
16	The course of admission was determined by relating all admissions which together formed a coherent chain without any gaps. All admissions belonging to the same course of admission received the same course of admission identification number.	Inpatients
17	Contacts that were merged or removed (through rules 9 and 15) received the contact identifier of the active admission or course of ambulatory care they belonged to.	Inpatients and outpatients
18	Diagnosis codes were updated with the new contact identifiers to correspond with the identifiers that resulted from rule 17.	Diagnosis codes
19	If an additional diagnosis code was the same as the main diagnosis code then the field for the additional code was set to be empty.	Diagnosis codes
20	Rules 1, 8 and 10 could lead to removal of contacts or admissions. The diagnosis codes connected to these were removed and written to a log file.	Diagnosis codes

Table 1 (*Continued*)

Nr.	Description of rules	Valid for
21	If a diagnosis code or a combination of a main diagnosis code and an additional diagnosis code occurred more than once within the same identifier, then only one was kept.	Diagnosis codes
22	Procedure codes were updated with the new contact identifiers to correspond with the identifiers that resulted from rule 17.	Procedure codes
23	In the table for procedures, the time was updated to be 8:00 (parameter) if time was missing.	Procedure codes
24	If the additional procedure code was the same as the main procedure code then the field for the additional code is set to be empty.	Procedure codes
25	Rules 1, 8 and 10 could lead to removal of contacts or admissions. The procedure codes connected to these were removed and written to a log file.	Procedure codes
26	If the date of a procedure was after the discharge date of the admission or course of ambulatory care it was connected to, then it was considered an error. The procedure was removed and written to a log.	Procedure codes
27	If a procedure code or a combination of a main procedure code and an additional procedure code occurred more than once within the same identifier, then only one was kept.	Procedure codes
28	The hospital codes from hospitals in Region Zealand, who executed the procedures, were adapted to the same format as in the inpatient and outpatient tables (see also rule 3).	Procedure codes

Procedure codes were removed and written to a log file if associated to inpatient or outpatient contacts deleted through rules 1, 8 and 10 (rule 25). Procedure codes with only a date of procedure but no time were set to 8:00 (rule 23), and any procedure code with a date after the date of discharge was deleted and written to a log file (rule 26). Duplicate procedure and additional codes were handled (rules 24 and 27). Finally, hospital codes for hospitals from Region Zealand, which had performed a procedure, had to be formatted, similar to the step in rule 3 (rule 28).

Since different applications may require different interpretations of the course of admission and course of ambulatory care we aimed to keep the algorithm as flexible as possible. We included the possibility to adjust parameters for different requirements. These parameters are indicated in Table 1. The algorithm was developed in-house using SAS software (SAS Institute Inc., Cary, NC, USA) and is available upon request.

2.5. Validation and monitoring of the algorithm

The DNPR algorithm and its coding were tested for accuracy and consistency by examining the registrations of samples of patients at different stages during the development, where necessary followed by corrections or adjustments to optimize the algorithm.

We monitored how many times each rule was used in order to observe how the algorithm affected data, how accurate the original data were and to follow trends over time and identify if there were changes in practice of registration, which may require adjustment of the rules.

For rules 1–8, we counted the number of contacts. For the remaining rules, we counted final admissions, courses of ambulatory care, diagnosis and procedure codes affected by a rule at least once; meaning that if a rule had been applied more than once to the same final registration, then this was only counted once.

In addition, the rules in the algorithm where gaps were closed between time of discharge and time of a new admission (rules 13 and 14) were validated for the appropriateness of a 4-h threshold. This was done by plotting cumulative numbers of admissions before the algorithm and after applying rules 1–12 by time since discharge from a previous admission.

2.6. Epidemiological description of trends in hospitalization

The resulting output model made it possible to analyze trends over time in numbers of admissions, courses of admission and courses of ambulatory care by year and stratified by public and private hospitals. As patients may be transferred between public and private hospitals within the course of an admission, stratification in public and private was not possible for the course of admission. Data were analyzed by the start year.

Duration of courses of admissions and courses of ambulatory care as well as number of transfers between departments and hospitals during courses of admission were also analyzed. To assess the length of stay we calculated the total number of bed days and ambulatory care days per year on data before and after application of the DNPR algorithm. We also calculated the median length of stay and its interquartile range on data after application of the DNPR algorithm. This epidemiological description also allowed us to evaluate what effects the algorithm had and if these effects could be explained.

2.7. Ethical considerations

This study was approved by the Danish Data Protection Agency as part of the development of the Danish Hospital-Acquired Infections Database (registration number 2015-54-0942).

3. Results

Data from DNPR between 1 January 2010 and 31 December 2014 contained inpatient contacts from 138 hospitals (54 public and 84 private hospitals) and outpatient contacts from 331 hospitals (59 public and 272 private hospitals). In this period, 6,822,756 inpatient contacts and 22,480,692 outpatient contacts were registered.

3.1. Monitoring and validation of rules

Table 2 shows how many times each of the rules were applied on contacts, admissions, courses of admission and ambulatory care, diagnosis and procedure codes. There were no contacts removed due to missing essential data (rule 1). Monitoring the use of rule 2, showed that our data still contained 58,194 open courses of ambulatory care, which started in 2010. Rule 2 was naturally used more frequently for the courses of ambulatory care that started in the later years. Open inpatient contacts were first introduced in 2015 and therefore not present in this study. Time of discharge was missing in some contacts, mostly outpatient contacts. For outpatient contacts this could often be solved by setting the end time an hour after the last procedure (rule 4) or an hour after the start time, if the end date was the same as the start date (rule 5). Still, it was necessary for a large number of contacts, mostly outpatient contacts, to

Table 2
The number of times each rule was applied on inpatient and outpatient contacts (rules 1–9, 17), admissions (rules10–16), diagnosis codes (rules 18–21) and procedure codes (rules 22–28) by start year.

Rule	2010		2011		2012		2013		2014		Mean	
	Inpatients	Outpatients	Inpatients	Outpatients	Inpatients	Outpatients	Inpatients	Outpatients	Inpatients	Outpatients	Inpatients	Outpatients
1	0	0	0	0	0	0	0	0	0	0	0	0
2	–	58,194	–	98,929	–	148,744	–	288,486	–	360,643	–	190,999
3	205,156	451,360	217,882	453,936	220,710	453,149	220,754	490,652	234,071	618,765	219,715	493,572
4	272	1,959,560	412	2,082,861	639	2,069,156	651	1,995,066	777	1,154,457	550	1,852,220
5	8262	577,926	9076	582,528	8353	545,642	8926	527,033	7701	381,203	8464	522,866
6	27,628	1,111,796	24,550	1,143,926	23,847	1,152,813	22,949	1,082,715	24,707	487,722	24,736	995,794
7	17,840	49	24,424	62	35,464	344	43,141	109,768	47,975	320,148	33,769	86,074
8a	2	0	0	0	3	0	4	0	0	2	2	0
8b	0	0	0	0	0	0	0	0	0	0	0	0
9	8506	226,737	7408	248,026	6447	240,990	6461	237,630	6420	236,314	7048	237,939
10	156	–	166	–	110	–	286	–	138	–	171	–
11	119,436	–	130,992	–	157,846	–	161,053	–	174,901	–	148,846	–
12	10,246	–	10,648	–	10,148	–	8160	–	8644	–	9569	–
13	2639	–	2533	–	2645	–	3466	–	3428	–	2942	–
14	14,357	–	13,806	–	13,348	–	12,513	–	12,072	–	13,219	–
15	1880	–	1822	–	1912	–	1808	–	1933	–	1871	–
16	1,341,368	–	1,342,551	–	1,363,225	–	1,362,152	–	1,391,707	–	1,360,201	–
17	311	2640	378	2805	146	4299	164	4072	200	6152	240	3994
	diagnoses	procedures	diagnoses	procedures	diagnoses	procedures	diagnoses	procedures	diagnoses	procedures	diagnoses	procedures
18	357,275	–	399,643	–	385,877	–	373,106	–	329,398	–	369,060	–
19	70	–	124	–	113	–	270	–	322	–	180	–
20	386	–	394	–	219	–	1717	–	350	–	613	–
21	1,689,484	–	1,784,775	–	1,943,063	–	2,030,146	–	2,352,363	–	1,959,966	–
22	–	825,872	–	1,024,504	–	1,199,312	–	1,229,188	–	1,359,809	–	1,127,737
23	–	366,670	–	410,919	–	482,461	–	605,733	–	656,059	–	504,368
24	–	141	–	172	–	570	–	792	–	1162	–	567
25	–	265	–	309	–	257	–	1061	–	267	–	432
26	–	0	–	0	–	0	–	0	–	0	–	0
27	–	3,617,757	–	4,173,028	–	4,384,383	–	4,811,222	–	5,579,165	–	4,513,111
28	–	1,614,704	–	1,734,982	–	1,902,905	–	2,088,698	–	2,327,818	–	1,933,821

If a rule was not applicable it is indicated with a '–', while a 0 means that the rule was applicable, but not applied.

choose a fixed time, here set at 23:00 (rule 6). In an increasing number of contacts, the end time was adjusted as it had been registered before the procedure time (rule 7); the increase was particularly large for outpatients, from only 49 in 2010 to 320,148 in 2014. Rule 9 showed that particularly outpatient contacts had overlap in time for the same person in the same hospital and department. In addition, on rare occasions an inpatient was recorded as admitted to two different departments, sometimes even different hospitals at exactly the same admission and discharge date and time (rule 10), leading to 856 contacts (428 duplicates). This occurred most often for contacts that started in 2013. Diagnosis and procedure codes that were removed, because they belonged to these contacts also showed a marked peak in 2013 (rule 20 and 25, respectively).

Validation of rules 13 and 14, in which gaps between discharge and admission were closed if these were 4 h or less, is shown in Fig. 2. The original data contained contacts that had negative time between discharge and a following admission, meaning that there was overlap between two admissions. Overlap was handled through application of rules 11 and 12. Fig. 2 shows an initial steeper increase within the first 4 h after discharge and then a steady increase. From this, we concluded that gaps of 4 h or less could be closed to represent the same course of admission. Larger gaps were considered readmissions. This resulted in 228,302 readmissions between 4 and 48 h after another discharge (190,687 to the same hospital and 37,615 to another hospital), representing 4.0% of all courses of admission between 2010 and 2014.

For 1,845,299 diagnosis codes and 5,638,685 procedure codes the linking contact identifier was changed, because the admissions these used to be related to had been removed or integrated into another admission (rules 18 and 22 respectively). The process of combining contacts to admissions or courses of ambulatory care and grouping their diagnosis and/or procedure codes led to an even larger number of double registrations of the same diagnosis and/or procedure codes, for instance when two departments had registered the same code on overlapping contacts (rules 21 and 27 respectively). This occurred increasingly over the study period. In only few cases, the additional diagnosis code was the same as the primary diagnosis code (rule 19). This increased from 70 in 2010 to 322 in 2014. Similarly, a small but increasing number of cases had the same additional procedure code and main procedure code (rule 24) with 141 in 2010 and 1162 in 2014.

A few additional steps were required for procedure codes to clean the data; for 2,521,842 procedure codes time of the procedure was missing and set to 8:00 (rule 23) and for all contacts from Region Zealand the codes of the hospitals that had performed the procedure had to be updated (rule 28). Rule 26 was an internal check and showed that no procedure codes were placed after discharge.

The effect of the DNPR algorithm can also be observed from the number of inpatients and outpatients and the number of bed days and ambulatory care days before and after the algorithm (Table 3). The number of inpatients and outpatients before the use of the algorithm was higher than the number of admissions and courses of ambulatory care after application of the algorithm. The number of bed days on the other hand was higher after the use of the algorithm, while the number of ambulatory care days was lower after the use of the algorithm.

3.2. *Epidemiological description of trends in the use of the secondary and tertiary healthcare system*

On average 1,364,551 inpatient contacts were recorded per year between 2010 and 2014, giving an average of 1,360,201 admissions per year after application of the algorithm and 1,149,615 courses

Table 3
The number of inpatient and outpatient contacts, inpatient admissions, courses of admission, courses of ambulatory care and diagnosis and procedure codes, as well as dynamics in terms of duration of these registrations and number of transfers by year of admission/start of care.

	Type of hospital	2010	2011	2012	2013	2014	Mean per year
General overview before the algorithm							
# Inpatient contacts	all	1,346,965 (100)	1,346,718 (100)	1,366,591 (100)	1,366,537 (100)	1,395,945 (100)	1,364,551 (100)
before algorithm (%)	public	1,316,123 (97.7)	1,319,484 (98.0)	1,343,609 (98.3)	1,344,026 (98.4)	1,374,185 (98.4)	1,339,485 (98.2)
	private	30,842 (2.3)	27,234 (2.0)	22,982 (1.7)	22,511 (1.6)	21,760 (1.6)	25,066 (1.8)
# Bed days per year (%)	all	4,449,644 (100)	4,249,544 (100)	4,149,216 (100)	4,041,473 (100)	3,966,264 (100)	4,171,228 (100)
	public	4,407,295 (99.0)	4,216,956 (99.2)	4,106,885 (99.0)	4,002,817 (99.0)	3,927,284 (99.0)	4,132,247 (99.1)
	private	42,349 (1.0)	32,587 (0.8)	42,331 (1.0)	38,656 (1.0)	38,980 (1.0)	38,981 (0.9)
# Outpatient contacts	all	3,984,696 (100)	4,223,086 (100)	4,230,407 (100)	4,472,992 (100)	5,569,511 (100)	4,496,138 (100)
before algorithm (%)	public	262,095 (6.6)	251,849 (6.0)	247,503 (5.9)	281,229 (6.3)	304,636 (5.5)	269,462 (6.0)
	private	3,722,601 (93.4)	3,971,237 (94.0)	3,982,904 (94.1)	4,191,763 (93.7)	5,264,839 (94.5)	4,226,669 (94.0)
# Ambulatory care	all	299,896,809 (100)	371,600,674 (100)	437,115,817 (100)	499,340,174 (100)	580,991,411 (100)	437,788,977 (100)
days per year (%)	public	294,494,930 (98.2)	366,698,588 (98.7)	432,186,535 (98.9)	494,515,847 (99.0)	575,471,814 (99.0)	432,673,543 (98.8)
	private	5,401,879 (1.8)	4,902,086 (1.3)	4,929,282 (1.1)	4,824,327 (1.0)	5,519,597 (1.0)	5,115,434 (1.2)
General overview after the algorithm							
# Inpatient admissions	all	1,341,368 (100)	1,342,551 (100)	1,363,225 (100)	1,362,152 (100)	1,391,707 (100)	1,360,201 (100)
after algorithm (%)	public	1,310,825 (97.7)	1,315,740 (98.0)	1,340,352 (98.3)	1,339,980 (98.4)	1,370,141 (98.5)	1,335,408 (98.2)
	private	30,543 (2.3)	26,811 (2.0)	22,873 (1.7)	22,172 (1.6)	21,566 (1.5)	24,793 (1.8)
# Bed days per year (%)	all	4,539,284 (100)	4,335,964 (100)	4,236,630 (100)	4,128,432 (100)	4,057,067 (100)	4,259,475 (100)
	public	4,479,033 (98.7)	4,289,917 (98.9)	4,183,554 (98.7)	4,080,133 (98.8)	4,007,457 (98.8)	4,208,019 (98.8)
	private	60,252 (1.3)	46,047 (1.1)	53,076 (1.3)	48,299 (1.2)	49,610 (1.2)	51,457 (1.2)
# Courses of admission	all[a]	1,159,750 –	1,151,136 –	1,143,566 –	1,139,256 –	1,154,370 –	1,149,616 –
# Courses of	all	3,708,812 (100)	3,910,565 (100)	3,921,420 (100)	4,182,024 (100)	5,249,560 (100)	4,194,476 (100)
ambulatory care (%)	public	3,449,743 (93.0)	3,661,915 (93.6)	3,678,776 (93.8)	3,905,878 (93.4)	4,952,285 (94.3)	3,929,719 (93.7)
	private	259,069 (7.0)	248,650 (6.4)	242,644 (6.2)	276,146 (6.6)	297,260 (5.7)	264,754 (6.3)
# Ambulatory care	all	297,363,687 (100)	366,930,184 (100)	430,410,853 (100)	490,708,939 (100)	568,751,713 (100)	430,833,075 (100)
days per year (%)	public	292,010,710 (98.2)	362,114,512 (98.7)	425,686,144 (98.9)	486,047,691 (99.1)	563,397,159 (99.1)	425,851,243 (98.8)
	private	5,352,978 (1.8)	4,815,672 (1.3)	4,724,709 (1.1)	4,661,247 (0.9)	5,354,555 (0.9)	4,981,832 (1.2)
Characteristics of courses of admission and ambulatory care (after the algorithm)							
Median days in course of admission – M (Q1;Q3)	all[a]	1.58 (0.54;4.04)	1.42 (0.50;3.92)	1.33 (0.46;3.88)	1.33 (0.46; 3.79)	1.29 (0.46;3.67)	1.38 (0.46;3.88)
# Transfers between departments in same hospital	all[a]	111,576 –	122,892 –	154,222 –	160,599 –	176,134 –	145,085 –
# Transfers between hospitals	all[a]	68,522 –	68,523 –	65,437 –	62,297 –	61,203 –	65,196 –
Median days course of	all	0.33 (0.04;58.0)	0.46 (0.04;62.6)	0.6 (0.04;70.2)	1.6 (0.04;86.6)	0.50 (0.04;35.9)	0.54 (0.04;60.5)
ambulatory care – M	public	0.50 (0.04;65.6)	0.58 (0.04;70.5)	1.6 (0.04;78.4)	3.9 (0.04;97.4)	0.88 (0.08;40.1)	1.04 (0.04;68.0)
(Q1;Q3)	private	0.04 (0.04;0.04)	0.04 (0.04;0.04)	0.0 (0.04;0.04)	0.0 (0.04;0.04)	0.04 (0.04;0.04)	0.04 (0.04;0.04)

[a] Courses of admission cannot be shown by public and private hospitals, as patients may be transferred between public and private hospitals within one course of admission.

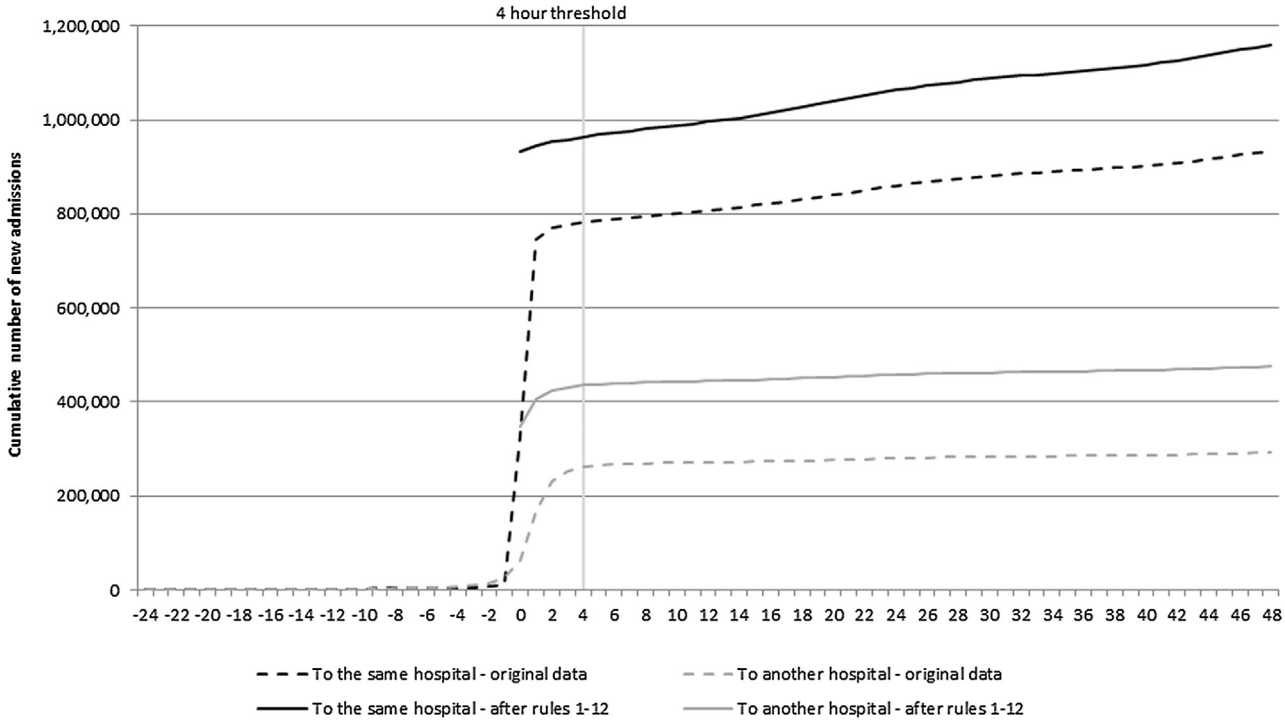


Fig. 2. Cumulative number of new admissions and the time since discharge of a previous admission in hours based on the original data and after applying rules 1–12 of the DNPR algorithm.

of admission per year. The overall proportion of inpatient contacts in public hospitals comprised 98.2% (Table 3). It should be noted that 1520 admissions, which started after 1 January 2010 belonged to a course of admission starting before 2010 and are therefore not included in the analyses for courses of admission. Of these, 1508 admissions (99%) started within the first five months of 2010. This illustrates a more systematic difference between the tables for admissions and courses of admission; also for the following years there are some admissions counted for a year later than the course of admission they belong to.

The number of courses of admission did not change over time. Of the courses of admission 86.56% included only one admission, 10.22% included two admissions, 2.30% included three and the remaining 0.92% ranged from four to 47 admissions. Among these courses of admission 5,624,679 (97.85%) involved only public hospitals, 121,944 (2.12%) involved only private hospitals and 1455 (0.03%) included at least one transfer between a public and a private hospital.

The number of bed days, calculated after the algorithm, showed a decreasing trend from 4,539,284 days in 2010 to 4,057,067 in 2014 (Table 3). In line with this, the median length of stay decreased from 1.58 days in 2010 to 1.29 days in 2014. While the number of transfers between departments increased from 111,576 to 176,134 in this period, the number of transfers between hospitals decreased from 68,522 to 61,203.

Per year, an average of 4,496,138 outpatient contacts were recorded, resulting in an average of 4,194,476 courses of ambulatory care. Outpatient contacts were more frequently carried out in private hospitals than inpatient contacts, with 94% of contacts in public and 6% in private hospitals (Table 3).

The number of courses of ambulatory care for public hospitals increased between 2010 and 2014 from 3,449,743 to 4,952,285. For private hospitals, courses of ambulatory care initially decreased from 259,069 in 2010 to 242,644 in 2012 and then increased to 276,146 in 2013 and 297,260 in 2014.

The ambulatory care days, calculated after the algorithm, increased from 3,708,812 days in 2010 to 5,249,560 in 2014 (Table 3). This was reflected in the median duration, which increased from 0.33 days in 2010 to 1.58 days in 2013. This dropped however to 0.50 days in 2014.

Fig. 3 visualizes the number of inpatient admissions, after applying the algorithm, as well as the courses of admission and the courses of ambulatory care by start month. As was also observed from the numbers in Table 3, the overall trends over the five years were stable for the numbers of admissions and courses of admission. Numbers of courses of ambulatory care gradually increased between 2010 and 2013 and showed a marked increase in 2014. This increase in 2014 was particularly high for outpatients from the Capital Region of Denmark (data not shown), suggesting that it primarily represents the addition of the primary healthcare patients from the on-call service in the Capital Region of Denmark. In addition, there was a seasonal trend, which was present in all three measures: a decrease was seen each year in July and to a lesser extent in December, closely followed by an increase in the subsequent months. Towards the end of 2014 all three measures decreased as a result of the cutoff of the dataset, this decrease set in earlier for courses of ambulatory care than for admissions and courses of admission.

4. Discussion

We have developed a methodology, which constructs coherent courses of admission and courses of ambulatory care. The DNPR algorithm does not correct wrongly entered data, but handles the data in order to create the courses of admission and ambulatory care and provides improved possibilities for analysis of Danish secondary and tertiary healthcare data and for population-based research and surveillance purposes.

It is a limitation that there are no reference data to compare the outcome of the algorithm with. We need to rely on logical rules and thorough analysis of specific aspects, many of which have been

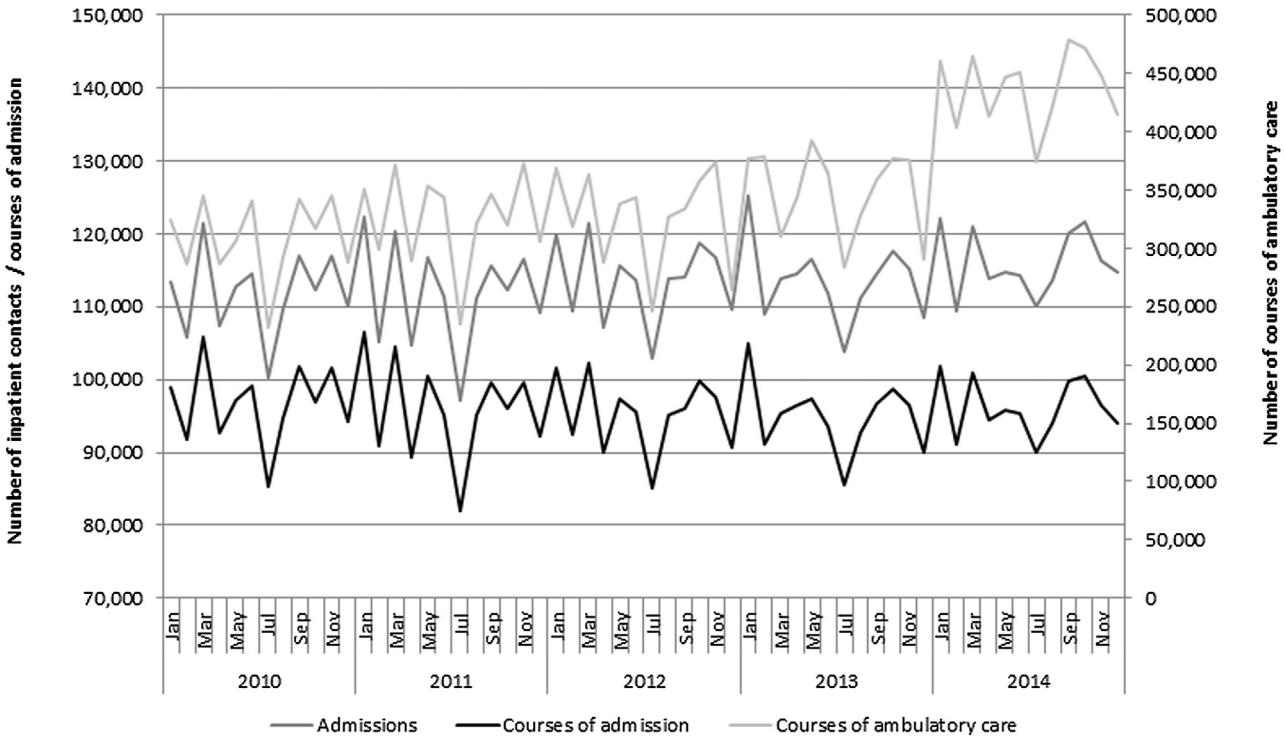


Fig. 3. The number of admissions, courses of admission (left axis) and courses of ambulatory care (right axis) in Denmark by month of admission/start of ambulatory care.

discussed here. Over the years, as we gain more experience and as recording practices change, new irregularities are expected to be found. In the near future, we may for instance need to revisit rule 2, which closes open contacts on the extraction date. Since 1 January 2016, hospitals are registering inpatient contacts upon admission rather than after discharge. The delay with which the discharge date and time is registered needs to be investigated in order to evaluate if rule 2 is suitable.

Another limitation lies in the fact that we have included all contacts starting from 1 January 2010. This means that those that started earlier and were still open in 2010, were excluded. This could potentially affect our estimates of the duration of courses of admission and particularly ambulatory care, as the long courses would be less represented mostly in 2010. However, by calculating the median and interquartile range, the extremely long courses did not affect the measurements.

4.1. Effects of the DNPR algorithm

Registrations in the DNPR contain overlaps and gaps for inpatient contacts between discharge from one department and admission to another. This was illustrated in Fig. 2, where time between discharge and subsequent admission was further explored. The figure showed that rules 1–12 effectively removed the overlaps between admissions and that the rule of 4 h was sufficient to close most gaps. For gaps within the same hospital the cumulated number of gaps still showed a steady increase between 4 and 48 h and one could argue that the cut-off should be extended. However, the longer the gap the more likely it becomes that a patient was in fact discharged and readmitted rather than a registration gap within the same course of admission. In our algorithm, the 4 h were set as a parameter, which means that this can be adjusted according to the needs of a particular purpose. Fig. 2 also showed that the number of admissions after applying rules 1–12 started at a higher level both for gaps within the same hospital and for gaps between hospitals. One reason for this is that all the registrations that used to contain overlap have been set to have no time between discharge and subsequent admission. Another reason may be the use of rule 12, where more admissions were created than the original number of overlapping admissions within each other.

When applying rule 10 of the DNPR algorithm it became apparent that in some cases the same patient was recorded in different departments, sometimes even in different hospitals, but with the same admission date and time and the same discharge date and time. We discarded both admissions, because it was not possible to determine in which department the patient actually was. Fortunately, this situation only happened in very few cases (428 duplicates). It did occur more often in 2013, which was also reflected in a marked increase in the use of the rules applied to the diagnosis and procedure codes related to these admissions, suggesting that data entry practices may not be consistent over time.

Also in the evaluation of other rules we observed differences over time, with rules 7, 11, 19, 21, 24 and 27 being increasingly used over the 5-year period. This may have to do with the general increase in inpatient and outpatient contacts in the DNPR. For some rules, e.g. rule 7 for outpatient contacts, the increase was too large to be only explained as such and may suggest a change in coding practice at the hospitals.

4.2. Trends in the use of the secondary and tertiary healthcare system

We estimated an average number of 1.36 million admissions and 1.15 million courses of admission to private and public hospitals per year in Denmark. With a Danish population of 5.6 million in the first quarter of 2012 [28], we estimate an admission rate (based on course of admission) of 205 per 1000 population.

To compare, Statistics Denmark estimated from the DNPR a total of 1,2 million admissions in 2012 (9), and only a very small increase in 2013 [30]. The admission rate was estimated at 214 per 1000 population. The estimates from Statistics Denmark were based on the

number of times a patient was admitted to a department and only included public hospitals [31]. This will likely give an overestimate for public hospitals, since patients should not be counted more than once within the course of an admission. The course of admission, as constructed with the algorithm, would therefore better reflect the real number of hospital admissions.

In addition, the algorithm affected the number of bed days and ambulatory care days leading to longer length of stay and shorter ambulatory care. Removal of overlap reduced the length, while closure of gaps added to it. In addition, inpatient and outpatient contacts, which had a discharge date but no time of discharge, often were recorded with a duration of $\leq$0 h. The algorithm created a positive duration for these situations. Although the algorithm makes assumptions and might not always recreate the exact reality, it would probably come closer to the real situation. The length of stay and length of ambulatory care is therefore likely be underestimated if one used the DNPR directly.

The number of courses of admission was stable between 2010 and 2014. Duration of admission tended to decrease over the entire period. This was also reported by Statistics Denmark [29] and is in line with the trend to send patients home sooner. However, considering that 4.0% of courses of admission may represent a readmission within 48 h, one could wonder if patients are being sent home too early. It would be interesting to investigate whether these persons represent a specific group of patients. It has been described that early readmissions (within 6 days of discharge) are more likely to be avoidable [32–35]. It is also worth noting that over the whole period there is a large number of admissions under 24 h. This will in part reflect the reality, but is also driven by cost calculations, as an admission will give a higher reimbursement than an ambulatory care contact. In the DNPR a patient can be registered as an inpatient, when the patient occupied a hospital bed. This is in contrast with many other countries, where an admission means that the patient stayed overnight.

Despite this financial incentive to register patients as inpatients, the number of courses of ambulatory care increased as well as the number of ambulatory care days. This suggests a shift towards ambulatory care, as can be expected from the development of discharging patients earlier. The marked increase in 2014, however, has a different reason, namely the merge of A&E patients with outpatients and the introduction of acute outpatient contacts from the on-call service in the Capital Region of Denmark. The fact that the median length of ambulatory care dramatically dropped in 2014 also points towards this. For this study, information on the A&E patient category was not available for 2010–2013, nor was a variable that can distinguish between acute and elective outpatients from 2014 onwards. For future work, these two aspects will need to be included. However, acute patients from primary healthcare in the Capital Region of Denmark can (at the present) not be distinguished from other acute outpatients in the DNPR.

The number of transfers between departments increased over time, while the number of transfers between hospitals decreased. This may reflect a shift in the Danish healthcare system, where hospitals become larger and comprise more medical specialties, limiting the need to transfer a patient to another hospital for further treatment. Overall, the figures are compatible with a cost-conscious secondary healthcare system undertaking at an increasing rate specialized treatment at various units within the hospital of admission and, on the other hand, if possible, reducing referral to advanced services at other hospitals.

Private hospitals deliver only a small proportion of healthcare in Denmark. This study showed that the contribution of private clinics to hospital admissions even decreased in the past years and that the length of ambulatory care was considerably shorter than for public hospitals. This is in line with the type of treatment, which private hospitals typically perform, i.e. well-defined medical conditions with a well-defined treatment, while public hospitals provide treatment for chronically ill patients in need of treatment in the secondary sector.

The yearly July and December dips that were observed in numbers of courses of ambulatory care, admissions and courses of admission can be explained by a reduced activity in elective care over the summer holiday period and during Christmas holidays. The dips in December and the subsequent increases in January may also be because budgets are running out towards the end of the year and elective care is postponed to the start of the next year, when the new budgets are available.

4.3. Recommendations and future use of the DNPR algorithm

As expected from current policy in healthcare, our data show that hospital stays are becoming shorter and the number of outpatient contacts is increasing. In our current DNPR algorithm, courses of admission and ambulatory care were handled independently, but with these shifts towards ambulatory care certain risks, such as hospital-acquired infections, will also shift more and more to the outpatient setting, making it more important to develop a way to relate courses of ambulatory care to courses of admission. It is important to further understand the coding practices of inpatient and outpatient contacts and ideally to standardize them at the registration level. Awareness of the critical changes made to the DNPR in 2014, concerning A&E patients in the whole country and primary sector patients in the Capital Region of Denmark, is also crucial. These changes, as well as variations we observed over time in the application of the rules from the algorithm highlight the need for caution when using data from DNPR in co-morbidity adjustments [7–9].

The DNPR algorithm is being used to relate occurrence of infections to courses of admission and ambulatory care in order to identify hospital-acquired infections. This application forms the basis for the automated surveillance of hospital-acquired infections in Denmark. For the present study, data were limited to 2010–2014 and for somatic patients. However, the algorithm can be run on the entire DNPR. As such, the outcome of the DNPR algorithm can also be used as the backbone for other surveillance systems and for relating other illnesses to courses of admission and defining length of stay. It may also be used for various other purposes including healthcare planning, research, burden-of-illness and economic analyses. A new version of the data model of DNPR is being developed and expected in a couple of years. This new version is expected to have the useful addition that hospitals will indicate relations between hospital contacts over the course of disease.

In conclusion, we were able to develop an algorithm that creates coherent courses of admission and ambulatory care and showed why it is necessary to use such an algorithm when assessing the number of admissions and length of stay. The development highlighted important insights in the underlying data and data quality. A number of these issues can potentially influence research and surveillance applications. We urge those responsible for the quality of the DNPR and all those using data to be aware of irregularities in the data and to handle them in order to avoid biased results.

Author contributions

SG, JN and KSN designed the data model. JN and KSN developed the data model and collected the data. SG and JN designed the algorithm. JN programmed the algorithm. SG analyzed the data and drafted the manuscript. KM monitored the progress of design at each stage. JS provided valuable insights in the design of the DNPR and interpretation of results of this study. JN, KM, JS and KSN revised the manuscript.

Summary points

What was already known before the study

- Data in the Danish National Patient Registry (DNPR) are based on registration of each contact with the healthcare system and do not directly allow analysis of course of admission and course of ambulatory care.
- Estimates for number of hospitalizations were available for Denmark, but based on a methodology that likely overestimated the numbers.
- Many population-based studies use the DNPR to assess numbers of (re)admissions and length of stay; some use the contacts as admissions and some use their own algorithm to correct for transfers within the same course of admission.

What this study has added to the body of knowledge

- A reconstruction algorithm needs to be used to create coherent courses of admission and ambulatory care.
- The effect of systematic changes in the data model and registration of outpatients in the Capital Region of Denmark in 2014 affect the patient populations recorded.
- In 2013, data showed different patterns which need to be further investigated.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We would like to thank Søren Jakobsen (Department IT development and projects, Danish Health Data Authority), Brian Kristensen (Department of Microbiology and Infection Control, Statens Serum Institut), Erik Villadsen, Kristian Nielsen, Jonas Kähler and Karen Marie Lyng (Department of Data Quality and Content, Danish Health Data Authority).

References

[1] IT brings the Danish health sector together, 2008. https://www.sundhed.dk/content/cms/24/4224_it-brings-the-danish-health-sector-together.pdf.
[2] T.F. Andersen, M. Madsen, J. Jørgensen, L. Mellemkjoer, J.H. Olsen, The Danish National Hospital Register. A valuable source of data for modern health sciences, Dan. Med. Bull. 46 (1999) 263–268.
[3] E. Lynge, J.L. Sandegaard, M. Rebolj, The Danish National Patient Register, Scand. J. Public Health 39 (2011) 30–33.
[4] C. Preyra, Coding response to a case-mix measurement system based on multiple diagnoses, Health Serv. Res. 39 (2004) 1027–1045.
[5] L. Serdén, R. Lindqvist, M. Rosén, Have DRG-based prospective payment systems influenced the number of secondary diagnoses in health care administrative data? Health Policy Amst. Neth. 65 (2003) 101–107.
[6] U. Nimptsch, Disease-specific trends of comorbidity coding and implications for risk adjustment in hospital administrative data, Health Serv. Res. 51 (2015) 981–1001.
[7] J. Nicholl, Case-mix adjustment in non-randomised observational evaluations: the constant risk fallacy, J. Epidemiol. Community Health 61 (2007) 1010–1013.
[8] M.A. Mohammed, J.J. Deeks, A. Girling, G. Rudge, M. Carmalt, A.J. Stevens, R.J. Lilford, Evidence of methodological bias in hospital standardised mortality ratios: retrospective database study of English hospitals, BMJ 338 (2009) b780.
[9] R.M. Jacques, J. Fotheringham, M.J. Campbell, J. Nicholl, Did hospital mortality in England change from 2005 to 2010? A retrospective cohort analysis, BMC Health Serv. Res. 13 (2013) 216.
[10] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H.T. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, Clin. Epidemiol. 7 (2015) 449–490.
[11] K. Rostgaard, T.R. Nielsen, J. Wohlfahrt, H. Ullum, O. Pedersen, C. Erikstrup, L.P. Nielsen, H. Hjalgrim, Sibship structure and risk of infectious mononucleosis: a population-based cohort study, Int. J. Epidemiol. 43 (2014) 1607–1614.
[12] J.M.C. Strid, C.F. Christiansen, M. Olsen, P. Qin, Hospitalisation for chronic obstructive pulmonary disease and risk of suicide: a population-based case-control study, BMJ Open 4 (2014) e006363.
[13] L. Holland-Bill, H. Xu, H.T. Sørensen, J. Acquavella, C. Sværke, H. Gammelager, V. Ehrenstein, Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients, Ann. Epidemiol. 24 (593–597) (2014) 597–618.
[14] E.N. Glassou, A.B. Pedersen, T.B. Hansen, Risk of re-admission, reoperation, and mortality within 90 days of total hip and knee arthroplasty in fast-track departments in Denmark from 2005 to 2011, Acta Orthop. 85 (2014) 493–500.
[15] L. Underbjerg, T. Sikjaer, L. Mosekilde, L. Rejnmark, Postsurgical hypoparathyroidism-risk of fractures, psychiatric diseases, cancer, cataract, and infections, J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 29 (2014) 2504–2510.
[16] M. Moberg, J. Vestbo, G. Martinez, J.E.A. Williams, S. Ladelund, P. Lange, T. Ringbaek, Validation of the i-BODE index as a predictor of hospitalization and mortality in patients with COPD participating in pulmonary rehabilitation, COPD 11 (2014) 381–387.
[17] S.K. Berg, J. Svanholm, A. Lauberg, B. Borregaard, M. Herning, A. Mygind, A.V. Christensen, A.I. Christensen, O. Ekholm, K. Juel, L. Thrysøe, Patient-reported outcomes at hospital discharge from heart centres, a national cross-sectional survey with a register-based follow-up: the DenHeart study protocol, BMJ Open 4 (2014) e004709.
[18] D. Skovgaard, P. Hasbak, A. Kjaer, BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography, PLoS One 9 (2014) e96736.
[19] M.H. Ruwald, A.-K. Numé, M. Lamberts, C.M. Hansen, M.L. Hansen, M. Vinther, L. Kober, C. Torp-Pedersen, J. Hansen, G.H. Gislason, Incidence and influence of hospitalization for recurrent syncope and its effect on short- and long-term all-cause and cardiovascular mortality, Am. J. Cardiol. 113 (2014) 1744–1750.
[20] C.C. Jørgensen, P. Kjaersgaard-Andersen, S. Solgaard, H. Kehlet, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group, Hip dislocations after 2,734 elective unilateral fast-track total hip arthroplasties: incidence, circumstances and predisposing factors, Arch. Orthop. Trauma Surg. 134 (2014) 1615–1622.
[21] B. Vest-Hansen, A.H. Riis, H.T. Sørensen, C.F. Christiansen, Acute admissions to medical departments in Denmark: diagnoses and patient characteristics, Eur. J. Intern. Med. 25 (2014) 639–645.
[22] M. Lindberg-Larsen, C.C. Jørgensen, T. Bæk Hansen, S. Solgaard, A. Odgaard, H. Kehlet, Re-admissions, re-operations and length of stay in hospital after aseptic revision knee replacement in Denmark: a two-year nationwide study, Bone Jt. J. 96–B (2014) 1649–1656.
[23] S. Gubbels, J. Nielsen, M. Voldstedlund, M. Chaine, L. Espenhain, K. Mølbak, B. Kristensen, K. Schultz Nielsen, S. Jakobsen, Regional HAIBA working group, HAIBA-Hospital-Acquired Infections Database, EPI-NEWS, No 9/2015—Statens Serum Institut, (n.d.). http://www.ssi.dk/English/News/EPI-NEWS/2015/No%209%20-%202015.aspx (accessed 23.02.16.).
[24] Danish Health Data Authority, SKS browser—v4.02, (n.d.). http://www.medinfo.dk/sks/brows.php (accessed 25.07.16.).
[25] C.B. Pedersen, H. Gøtzsche, J.O. Møller, P.B. Mortensen, The Danish civil registration system. a cohort of eight million persons, Dan. Med. Bull. 53 (2006) 441–449.
[26] ICD-10 Version:2010, (n.d.). http://apps.who.int/classifications/icd10/browse/2010/en (accessed 25.07.15.).
[27] Nordclass:, (n.d.). http://www.nordclass.se/ncsp_e.htm (accessed 25.07.16.).
[28] Folketal den 1. i kvartalet efter kommune, køn, alder, civilstand, herkomst, oprindelsesland og statsborgerskab – Statistikbanken – data og tal, (n.d.). http://www.statistikbanken.dk/statbank5a/selectvarval/saveselections.asp (accessed 12.03.14.).
[29] Denmark Statistics, Lidt flere indlæggelser, 2013. http://www.dst.dk/pukora/epub/Nyt/2013/NR617.pdf.
[30] Denmark Statistics, Fortsat stigning i ambulante behandlinger, 2013. http://www.dst.dk/pukora/epub/Nyt/2013/NR618.pdf.
[31] Quality declaration: Hospitalization—Statistics Denmark, (n.d.). http://www.dst.dk/en/Statistik/dokumentation/declarations/hospitalization.aspx (accessed 25.07.16.).
[32] A. Clarke, Are readmissions avoidable? BMJ 301 (1990) 1136–1138.
[33] C. van Walraven, A. Jennings, M. Taljaard, I. Dhalla, S. English, S. Mulpuru, S. Blecker, A.J. Forster, Incidence of potentially avoidable urgent readmissions and their relation to all-cause urgent readmissions, CMAJ Can. Med. Assoc. J. J. Assoc. Med. Can. 183 (2011) E1067–1072.
[34] C. van Walraven, C. Bennett, A. Jennings, P.C. Austin, A.J. Forster, Proportion of hospital readmissions deemed avoidable: a systematic review, CMAJ Can. Med. Assoc. J. J. Assoc. Med. Can. 183 (2011) E391–402.
[35] C.H.K. Yam, E.L.Y. Wong, F.W.K. Chan, F.Y.Y. Wong, M.C.M. Leung, E.K. Yeoh, Measuring and preventing potentially avoidable hospital readmissions: a review of the literature, Hong Kong Med. J. Xianggang Yi Xue Za Zhi Hong Kong Acad. Med. 16 (2010) 383–389.

Paper II

Utilization of blood cultures in Danish hospitals, a population-based descriptive analysis.

Gubbels S, Nielsen J, Voldstedlund M, Kristensen B, Schønheyder HC, Vandenbroucke-Grauls CM, Arpi M, Björnsdóttir MK, Knudsen JD, Dessau RB, Jensen TG, Kjældgaard P, Lemming L, Møller JK, Hansen DS, Mølbak K.

Clin Microbiol Infect. 2015 Apr;21(4):344.e13-21.
doi: 10.1016/j.cmi.2014.11.018. Epub 2014 Nov 23.

Utilization of blood cultures in Danish hospitals: a population-based descriptive analysis

S. Gubbels[1], J. Nielsen[1], M. Voldstedlund[1], B. Kristensen[2], H. C. Schønheyder[4,5], C. M. J. E. Vandenbroucke-Grauls[6], M. Arpi[7], M. K. Björnsdóttir[3], J. Dahl Knudsen[8], R. B. Dessau[9], T. Gorm Jensen[10], P. Kjældgaard[11], L. Lemming[12], J. K. Møller[13], D. Schrøder Hansen[14] and K. Mølbak[1]

1) *Department of Infectious Disease Epidemiology,* 2) *Department of Microbiology and Infection Control, Statens Serum Institut,* 3) *Department of Clinical Microbiology, Rigshospitalet, Copenhagen,* 4) *Department of Clinical Microbiology Aalborg University Hospital, Aalborg,* 5) *Department of Clinical Medicine, Aalborg University, Aalborg, Denmark,* 6) *Department of Medical Microbiology and Infection Control, VU University Medical Center, Amsterdam, The Netherlands,* 7) *Department of Clinical Microbiology, Herlev Hospital, Herlev,* 8) *Department of Clinical Microbiology Hvidovre Hospital, Hvidovre,* 9) *Department of Clinical Microbiology, Zealand Region, Slagelse,* 10) *Department of Clinical Microbiology, Odense University Hospital, Odense,* 11) *Department of Clinical Microbiology, Sygehus Sønderjylland, Sønderborg,* 12) *Department of Clinical Microbiology, Aarhus University Hospital, Aarhus,* 13) *Department of Clinical Microbiology, Vejle Hospital, Vejle and* 14) *Department of Clinical Microbiology, Hillerød Hospital, Hillerød, Denmark*

Abstract

This national population-based study was conducted as part of the development of a national automated surveillance system for hospital-acquired bacteraemia and ascertains the utilization of blood cultures (BCs). A primary objective was to understand how local differences may affect interpretation of nationwide surveillance for bacteraemia. From the Danish Microbiology Database, we retrieved all BCs taken between 2010 and 2013 and linked these to admission data from the National Patient Registry. In total, 4 587 295 admissions were registered, and in 11%, at least one BC was taken. Almost 50% of BCs were taken at admission. The chance of having a BC taken declined over the next days but increased after 4 days of admission. Data linkage identified 876 290 days on which at least one BC was taken; 6.4% yielded positive results. Ten species, *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Enterococcus faecium, Enterococcus faecalis, Pseudomonas aeruginosa, Candida albicans, Enterobacter cloacae* and *Klebsiella oxytoca,* accounted for 74.7% of agents for this purpose classified as pathogenic. An increase in BCs and positive BCs was observed over time, particularly among older patients. BCs showed a seasonal pattern overall and for *S. pneumoniae* particularly. A predominance of male patients was seen for bacteraemias due to *S. aureus, E. faecium* and *K. pneumoniae.* Minor differences in BCs and positive BCs between departments of clinical microbiology underpin the rationale of a future automated surveillance for bacteraemia. The study also provides important knowledge for interpretation of surveillance of invasive infections more generally.

Keywords: Blood cultures, Denmark, epidemiology, hospital admissions, utilization
Original Submission: 27 June 2014; **Revised Submission:** 13 November 2014; **Accepted:** 17 November 2014
Editor: D. Raoult
Article published online: 23 November 2014

Corresponding author: S. Gubbels, Department of Infectious Disease Epidemiology, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
E-mail: gub@ssi.dk

Introduction

Bacteraemia is a severe condition associated with high mortality [1–5]. Blood cultures (BCs) continue to be the only practical method to diagnose bacteraemia [6]. Since 1 January 2010 the

http://dx.doi.org/10.1016/j.cmi.2014.11.018

Danish Microbiology Database (MiBa) has collected microbiological test results from all departments of clinical microbiology (DCMs) in Denmark [7]. This provided the unique opportunity to study BC utilization on a national level. Combining these data with administrative information from the National Patient Registry (NPR [8]) allowed us to also study BCs in relation to hospital admissions.

It is of fundamental interest to study the epidemiology and utilization of BCs to evaluate clinical practices and to understand trends observed in surveillance for invasive infections, including those acquired in healthcare. Differences in BC utilization, e.g. between laboratories, patient populations and changes over time, may give rise to artefacts in surveillance systems due to different levels of ascertainment. We conducted a national population-based study describing the utilization of BCs in Denmark to understand to which extent local differences may affect the interpretation of surveillance of bacteraemia. This assessment was done as part of the development of an automated surveillance system for hospital-acquired infections in Denmark; such a system will depend on a meaningful pooling of data from various DCMs.

Methods

Data sources

MiBa is a real-time database that automatically receives a copy of every electronic microbiology report delivered by all Danish DCMs [7]. An extract from MiBa was obtained comprising all BCs with a sampling date between 1 January 2010 and 31 December 2013. This extract included the sampling date and time (the latter if available), cultured microorganisms and the DCM that carried out the test. Each patient was identified in MiBa through the civil registration (CPR) number, a unique identifier given to each person living in Denmark encrypting date of birth and sex [9].

In January 2010 Denmark had 13 DCMs. Although remaining independent DCMs, the laboratory information systems of the DCMs in Herlev and Hvidovre merged in May 2012, and the DCM in Hillerød joined this mutual data server in May 2013. In January 2013 the DCMs in Herning and Viborg merged. For this article, the DCMs were analysed in the new composition (named by their geographic location).

The NPR includes administrative data on somatic inpatients since 1977 [8]. Individual patients were identified through the CPR number. We used an extract comprising patient administrative data between 1 January 2010 and 31 December 2013. Only those patients who were admitted and discharged within this period were selected; others were excluded, as these would affect analyses on BCs in relation to the number of days since admission. Data included date and time of admission and discharge and the responsible departments and hospitals. The NPR included one record for each admission to a department; each time a patient was transferred to another department, this was registered as a new record. We developed an algorithm relating these inpatient transfers to form a complete course of admission, here referred to as an admission.

The data from MiBa and NPR were linked using the CPR number. Patients with temporary CPR numbers, such as foreign travellers, were excluded from analysis. Similarly, those CPR numbers derived from MiBa which led to an age calculation of <0 or ≥ 100 years were excluded, as we could not confirm whether these CPR numbers were correct.

Definitions

To enable automatic classification and avoid misclassification of contaminants as pathogens, we considered the following microorganisms as contaminants: *Acinetobacter* spp., *Aerococcus* spp. (except *A. urinae*), *Bacillus* spp. (except *B. anthracis* and *B. cereus*), *Corynebacterium* spp. (except *C. diphtheriae*), *Lactobacillus* spp., *Lactococcus* spp., *Micrococcus* spp., *Moraxella* spp. (except *M. catarrhalis*), *Neisseria* spp. (except *N. animaloris, N. canis, N. elongate, N. gonorrhoeae, N. zoodegmatis* and *N. meningitidis*), *Propionibacterium acnes, Staphylococcus* spp. (except *S. aureus, S. saprophyticus, S. lugdunensis* and *S. schleiferi*). Most DCMs identify *Streptococcus* spp. and nonhemolytic streptococci to the species level, especially if the microorganism is considered the etiological agent for bacteremia. Thus, when reported at the genus level, findings were assessed as contaminants.

Microorganisms not listed as contaminants were considered pathogens.

A blood culture day (BCD) was defined as a day on which a patient had at least one blood sample taken for culture. The reason for this measure was the practice in some DCMs to register each bottle of a BC set as an individual sample, while other laboratories registered a set of bottles. The time of sampling was not always available, making it impossible to distinguish between multiple bottles from one set and sets of bottles drawn at different moments in time on the same day.

A positive BCD was defined as a BCD on which at least one culture yielded growth of at least one pathogenic microorganism.

Data analysis

General demographics were described for patients who had BCs taken. Age at first blood sample and sex were derived from the CPR number. BCDs and positive BCDs were observed over time and by sex and age groups (0–4, 5–24, 25–44, 45–64, 65–74, 75–84 and 85–99 years). When stratifying by

age group, the number of BCDs were calculated per 100 000 population, using population data from Denmark Statistics for the first quarter of 2012 (http://www.statistikbanken.dk/statbank5a/selectvarval/saveselections.asp).

The ten most frequently found pathogenic microorganisms were identified. These were determined by BCD, meaning that different pathogenic species from the same BCD were included but counted only once. Differences in the distribution of these ten pathogenic microorganisms among the DCMs were analysed. Furthermore, the five most frequently found pathogenic microorganisms were observed over time and stratified by age group and sex of the patients.

BCDs and positive BCDs were studied in relation to admissions and stratified by DCM. On the national level, BCDs, positive BCDs and the percentage of positive BCDs were studied over a period of 30 days since hospital admission, with day 1 being the day of admission. In addition, BCDs and positive BCDs were observed over this 30-day period per 100 patients in hospital on each of the days since admission in order to adjust for the fact that the number of patients decreases on the days after admission.

Data management and analysis were performed by SAS software (SAS Institute, Cary, NC, USA).

Ethical considerations

This study was approved by the Danish Data Protection Authority as part of the development of the Danish Hospital Acquired Infections Database (registration number 2012-41-1269).

Results

A total of 408 179 unique patients had at least one BC taken within the study period. Of these, 413 were excluded because their CPR numbers led to an age calculation outside the 0- to 99-year age range. Finally, there were 407 766 patients, 205 417 (50.4%) men and 202 349 (49.6%) women. The mean age was 57 years (median 64 years).

Distribution by time and person

The total number of BCDs was 876 290; 55 992 (6.4%) of these were positive BCDs. The number of BCDs increased slightly over time for both men and women (Fig. 1). In addition, seasonal variation occurred, with more BCDs in the winter months. A slight general increasing trend was also seen for positive BCDs, mostly for men. However, there was no seasonal variation of positive BCDs, which means that the percentage of positive BCDs was lower during winter months. Overall, the proportion of positive BCDs for men was 6.8% and for women 5.9%. Over the entire period, more positive BCDs were recorded for men.

Considering the incidence of BCDs among age groups, the increase in BCDs and positive BCDs over the 4 years was

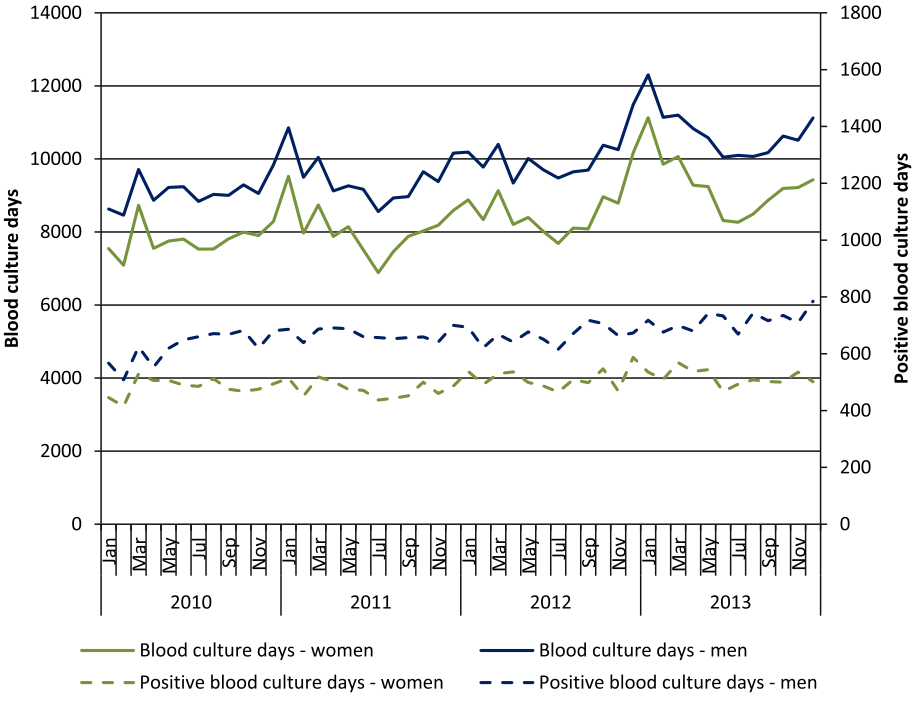


FIG. 1. Number of blood culture (BC) days and positive BC days stratified by sex between 2010 and 2013.

mainly seen among patients aged 65 years and over. In these age groups, seasonal variation was also observed, with a particularly large peak in the winter of 2013. The youngest age group of children (0–4 years) also showed a seasonal pattern in BCDs, with more consistent increases in the winter. Seasonal variation in positive BCDs was not distinctive in any age group.

Trends over time varied among DCMs. The general increase in BCDs was observed for all, except for the DCM at the university hospital and national referral centre, Rigshospitalet, in Copenhagen, where a slight decrease was seen. The increases were most considerable for the DCMs in Herlev/Hvidovre/Hillerød, in Slagelse, Odense and in Aarhus. These DCMs, as well as those in Aalborg and Herning/Viborg, also showed most marked seasonal variation in BCDs. The DCMs in Herlev/Hvidovre/Hillerød and Slagelse were the largest contributors to the increase in positive BCDs.

Microbiological findings

The ten most frequently isolated pathogenic microorganisms are presented in Table 1. Together, the top ten accounted for 74.7% of all pathogenic microorganisms. Of the bacterial species that were considered contaminants, 77.2% were coagulase negative staphylococci (excluding *S. saprophyticus, S. lugdunensis* and *S. schleiferi,* as these were considered pathogens).

The DCM at Rigshospitalet saw a lower occurrence of *E. coli* and *S. pneumoniae* than the other DCMs and a higher occurrence of *E. faecium* (Table 1). Otherwise, there were only small variations in the distribution between the DCMs.

Increasing trends were seen for *E. coli* and *S. aureus* (Fig. 2). These increasing trends affected both men and women, but only in age groups of 65 years and older. *S. pneumoniae* showed a clear seasonal variation, with increases during winter. This trend was seen among men and women and in all age groups. *S. aureus, E. faecium* and *K. pneumoniae* were more often found among men (male:female ratio of 1.7:1.0, 1.6:1.0 and 1.6:1.0, respectively), while *E. coli* and *S. pneumoniae* were found equally among the sexes.

BCs in relation to admissions

Between 2010 and 2013 there were 4 587 295 admissions; in 506 797 of these (11%) there was at least one BCD. As patients may be transferred to other hospitals, several DCMs may be involved in culturing blood samples during the course of one admission. For 498 245 admissions (98.3%), only one DCM was recorded, for 8337 (1.7%) two, for 205 (0.04%) three and for ten (<0.01%) four. If two DCMs were involved on the same day, only the one that tested the first sample was included in Table 2. Of the total of 876 290 BCDs, 827 106 (94.4%) occurred during an admission and 432 164 (49.3%) coincided with the day of admission. The 5.6% of BCDs that were not taken during an admission were taken during the 3 days before an admission or up to 30 days after an admission. The percentage of positive BCDs did not vary substantially between DCMs.

The number of BCDs decreased more after admission than the number of positive BCDs, resulting in a percentage of positive BCDs that showed an initial decrease but a steady increase from day 4 since admission (Fig. 3A). The number of BCDs and positive BCDs per 100 admitted patients also showed an initial decrease, followed by a steady increase from day 4 (Fig. 3B). When observing the five most common pathogens in relation to the admission, all showed a marked decrease after the day of admission. Only *E. faecium* increased again after day 5 and decreased after day 9.

Discussion

The availability of national microbiology data in combination with admission data on all Danish patients created the unique opportunity to make a population-based descriptive analysis of

TABLE 1. Ten most common pathogenic microorganisms per blood culture day according to department of clinical microbiology between 2010 and 2013

Departments of clinical microbiology	*Escherichia coli*		*Staphylococcus aureus*		*Klebsiella pneumoniae*		*Streptococcus pneumoniae*		*Enterococcus faecium*		*Enterococcus faecalis*		*Pseudomonas aeruginosa*		*Candida albicans*		*Enterobacter cloacae*		*Klebsiella oxytoca*		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
Aalborg	1814	41.2	738	16.7	395	9.0	391	8.9	198	4.5	240	5.4	202	4.6	154	3.5	139	3.2	137	3.1	4408
Aarhus	2040	37.0	931	16.9	508	9.2	476	8.6	437	7.9	330	6.0	229	4.1	217	3.9	179	3.2	173	3.1	5520
Esbjerg	628	39.8	279	17.7	139	8.8	122	7.7	67	4.2	102	6.5	69	4.4	85	5.4	42	2.7	44	2.8	1577
Herlev/Hvidovre/ Hillerød	5339	42.1	2201	17.3	1110	8.7	1145	9.0	702	5.5	812	6.4	439	3.5	298	2.3	317	2.5	326	2.6	12 689
Herning/Viborg	1332	38.0	634	18.1	345	9.8	345	9.8	160	4.6	285	8.1	121	3.4	70	2.0	97	2.8	120	3.4	3509
Odense	1616	32.8	787	16.0	415	8.4	324	6.6	568	11.5	437	8.9	211	4.3	233	4.7	182	3.7	147	3.0	4920
Rigshospitalet	567	20.0	610	21.5	327	11.5	78	2.7	523	18.4	245	8.6	114	4.0	168	5.9	132	4.6	78	2.7	2842
Slagelse	2676	42.1	1077	16.9	630	9.9	586	9.2	272	4.3	363	5.7	230	3.6	152	2.4	178	2.8	198	3.1	6362
Sønderborg	577	45.2	224	17.5	116	9.1	108	8.5	48	3.8	77	6.0	37	2.9	22	1.7	36	2.8	32	2.5	1277
Vejle	923	44.2	324	15.5	179	8.6	187	9.0	127	6.1	118	5.6	90	4.3	39	1.9	47	2.2	55	2.6	2089
Total	17 512	38.7	7805	17.3	4164	9.2	3762	8.3	3102	6.9	3009	6.7	1742	3.9	1438	3.2	1349	3.0	1310	2.9	45 193

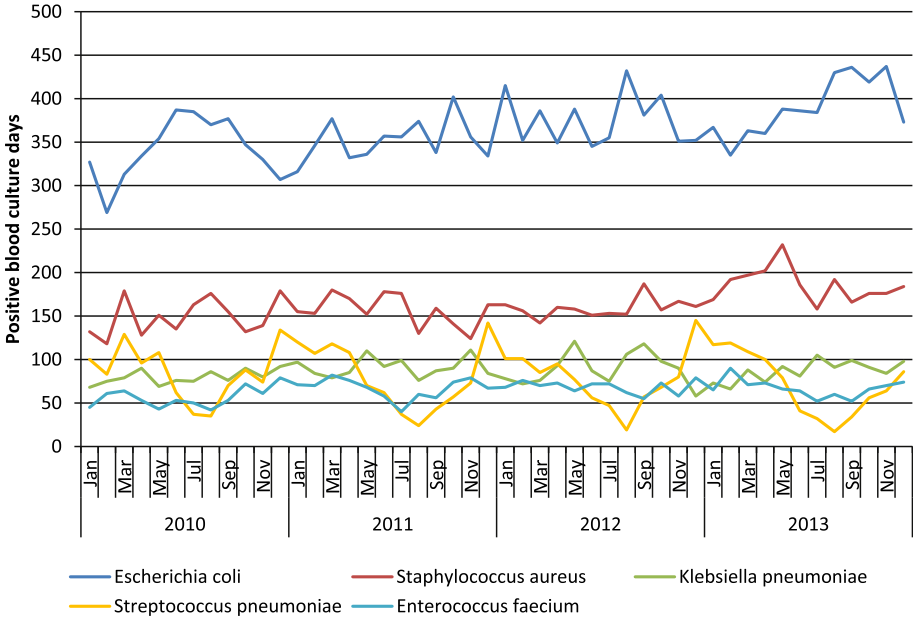


FIG. 2. Frequency of five most common pathogens per blood culture day between 2010 and 2013.

the utilization and general results of BCs in Denmark and to analyse trends. This study showed increases in BC activity and seasonality over the period between 1 January 2010 and 31 December 2013. It provided important insights in differences between DCMs and among the patient population in terms of age and sex. The BCDs and percentage of positive BCDs were shown to decrease in the first 4 days of admission and to increase after that.

Our study was subject to several limitations. Because of varying registration practices, we were unable to assess the blood volume of each BC and distinguish culture sets (several bottles for a BC obtained at one time point) from individual culture bottles. The measure we used as a proxy, the BCD, may therefore underestimate blood-culturing activity. However, it does reflect the daily decision by the clinical team to test a patient for bacteraemia. The definition of positive BCDs will also give rise to an underestimation, as the positive rate is dependent on the volume of blood that was used for culture. Another reason for underestimation is that the BCDs do not include BCs where likely contaminants were repeatedly isolated and hence could be ruled to be clinically relevant. Classifying all nonspeciated streptococci as contaminants may also add to an underestimation of positive BCDs, as may the classification of species commonly considered contaminants in Denmark, which in rare cases may be etiologic agents (e.g. *Acinetobacter baumanii*). This was done to be certain that BCDs counted as positive reflected well-defined and true cases of bacteraemia and not just contaminated samples. Conclusions drawn from

TABLE 2. Number of BCs and percentage of positive BC days in relation to admission according to department of clinical microbiology between 2010 and 2013

	BC days total		BC days during admission		BC days at day of admission	
Departments of clinical microbiology	***n***	**% positive**	***n***	**% positive**	***n***	**% positive**
Aalborg	82 762	6.6	79 175	6.6	42 070	7.6
Aarhus	125 205	5.5	116 953	5.6	59 598	6.7
Esbjerg	31 991	5.9	30 487	6.0	17 489	6.6
Herlev/Hvidovre/Hillerød	216 717	7.2	205 932	7.3	113 921	7.9
Herning/Viborg	77 188	5.6	73 557	5.6	42 618	6.6
Odense	91 050	6.7	83 592	6.9	38 009	8.0
Rigshospitalet	67 660	5.5	62 225	5.7	15 152	8.1
Slagelse	113 766	6.9	109 842	6.9	65 868	7.6
Sønderborg	26 104	6.0	24 498	6.2	13 248	7.5
Vejle	43 847	5.9	40 845	6.1	24 191	7.2
Total	876 290	6.4	827 106	6.5	432 164	7.4

BC, blood culture.

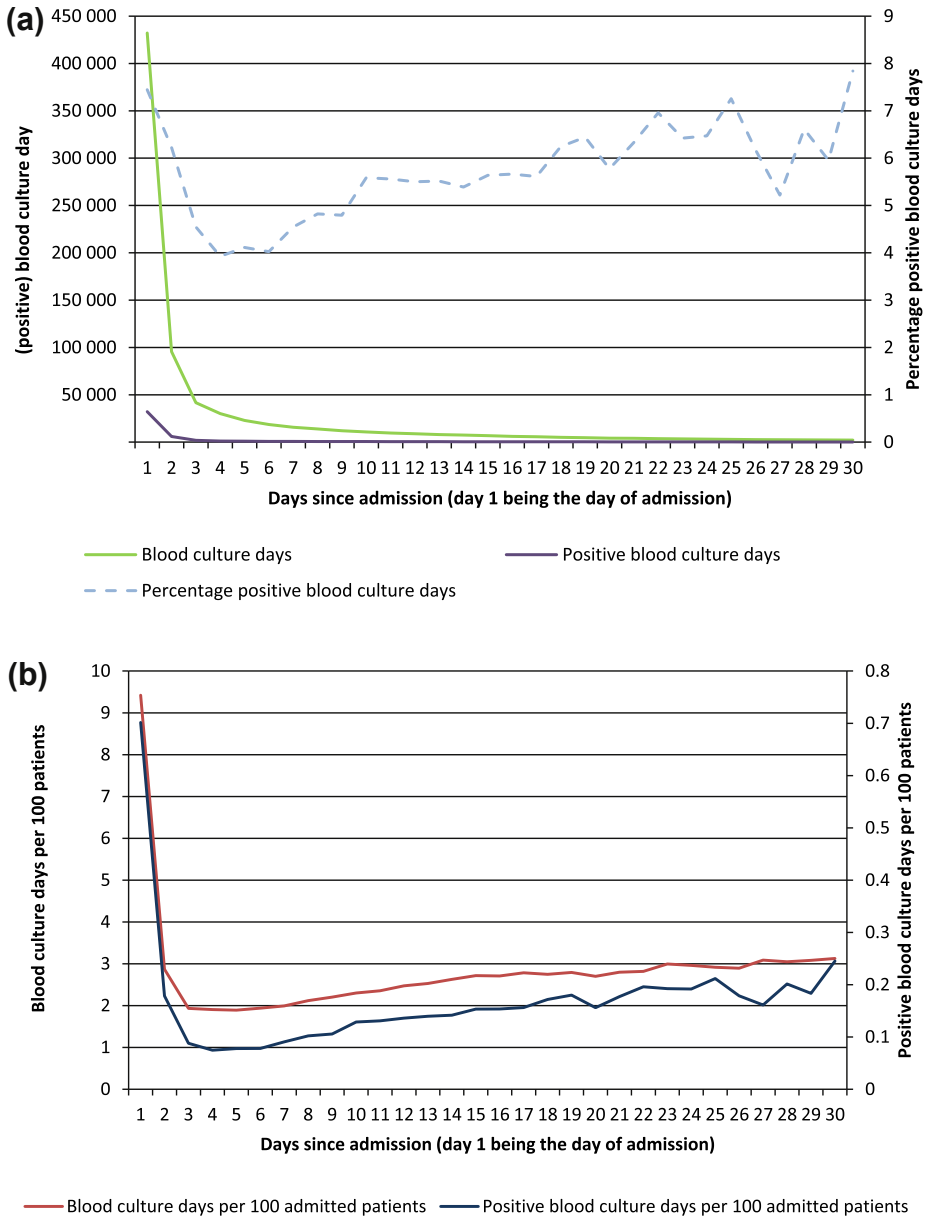


FIG. 3. (a) Number of blood culture (BC) days, positive BC days and percentage of positive BC days in relation to days since admission between 2010 and 2013. (b) Number of BC days and positive BC days per 100 admitted patients in relation to days since admission between 1 January 2010 and 31 December 2013.

automated systems should be judged with caution, and our rationale was to prioritize specificity while being aware that absolute numbers of BCDs may be underestimated.

Lastly, numbers of positive vs. negative BCDs late in the course of admission may be biased by clinicians' attempts to take repeated BCs until a negative appears, e.g. in cases of endocarditis or candidemia. The magnitude and direction of this bias is difficult to assess.

For these reasons, the measures of BCDs and positive BCDs may be difficult to compare to other studies in absolute numbers. They do, however, standardize the data and therefore allow following trends over time and studying differences by age group, sex and DCM.

To further understand differences between DCMs, it would have been useful to assess patients' clinical characteristics which led to the decision to take a BC. However, these data were not available from the sources used in the present study. It was also not possible to group departments to which patients were admitted by their specialty, e.g. to identify intensive care units, departments of surgery, internal medicine and paediatrics. The

NPR and MiBa do provide the name of each specific department. Nonetheless, these names do not always contain information on the specialty, and the registries do not contain an unambiguous classification of the type of department. It would also have been informative to analyse the findings for each DCM in relation to the patient population it serves—for example, in terms of number of patients and length of stay. This information was, however, only available on a national level, not by DCM. As a follow-up study, it would be of interest to apply a comorbidity index based on ICD-10 codes from the NPR.

At the beginning of 2010, the increases observed in BCDs and positive BCDs may have been due to the starting up phase of MiBa, but the BC activity showed a steady increase over all 4 years, suggesting a real increase. The increasing trend is also in line with other studies that have seen substantial increases in incidence rates of bacteraemia over longer periods of time [1,10–12]. This can partly be explained by an aging population. Organizational changes in acute care in Danish hospitals, which have taken place during the same period, may also have contributed to the increase. Thirdly, the introduction of sepsis packages in several Danish hospitals since April 2010, describing interventions to reduce mortality from sepsis through correct and timely diagnostics and treatment (http://www.patientsikkertsygehus.dk/pakker/alle-pakker/sepsispakken.aspx), can also be a reason for the increase in BC activity. The differences in trends over time we observed between DCMs may be due to differences in the patient population the DCMs served, but other factors, such as BC methodology, also need to be taken into account in the interpretation of time trends of bacteraemia [13]. The general increase in positive BCDs was mainly due to an increase in *E. coli* bacteraemias and to a lesser extent to *S. aureus* bacteraemias. It would be interesting to further investigate if the increase in *E. coli* included an increase in extended-spectrum β-lactamase-producing bacteria. The observed trends over time will need to be confirmed using time-series analysis when data become available for a longer period of time.

The seasonal trends in BC activity with increases in the winter coincided with the influenza seasons. The seasons of 2010–2011 and 2012–2013 had a higher influenza activity in Denmark than the season of 2011–2012 [14]. Our data on the BC activity show a similar trend with more marked increases in the seasons of 2010–2011 and 2012–2013. An explanation could be that patients admitted with fever and respiratory symptoms are commonly tested for bacteraemia. The finding that the seasonal variation was more marked in some DCMs may suggest that some hospitals received more patients with fever and respiratory symptoms than others and/or that some hospitals have different practices for testing these patients. The increase in BC testing did not lead to an increase in positive BCs during winter. Therefore, the percentage of positive BCs was lower, suggesting that the decision to take a BC may be influenced by expectations of the clinical team or by the presence of fever rather than signs and symptoms of bacterial vs. viral infections. The occurrence of *S. pneumoniae* did show a seasonal trend with peaks in the winter. This was not notable in the overall picture of positive BCs because *S. pneumoniae* bacteraemias accounted for a small percentage of the total number of positive BCs.

The number of positive BCDs was higher among men, which is in line with other studies showing higher incidences of bacteraemia among men [11,15]. The higher number of positive BCDs among men was mainly due to *S. aureus, E. faecium* and *K. pneumoniae*. As mentioned before, once data are available for a longer period of time, time-series analysis will allow confirmation of these trends.

The finding of *E. coli, S. aureus* and *K. pneumoniae* as the most common microorganisms was to be expected. Although an upsurge of *E. faecium* is well described in Denmark, it was a surprise that *E. faecium* was found to be more frequent than *E. faecalis* [16,17]. This may have to do with the way we analysed the data, i.e. including a microorganism only once per BCD.

Differences in the percentage of positive BCDs between the DCMs were small. This finding is of importance for the construction of a system for automated surveillance of nosocomial bacteraemia. The upcoming automated system is based on the rationale that data from different DCMs and patient populations can be pooled meaningfully. The main outlier was the DCM at Rigshospitalet, which is a tertiary hospital with highly specialized national functions. This DCM had a different ranking of pathogens, which we cautiously ascribe to a different patient population with more comorbidities, complications and susceptibility to opportunistic infections. Other variations between the DCMs may be due to differences in sample size, timing of antimicrobial treatment, antibiotic treatment policies and blood volume taken.

The number of BCDs during admission showed an expected pattern, in which close to 50% of BCDs occurred on the day of admission, followed by a decrease over the following days. Moreover, the results of BCDs per 100 patients showed that the risk of having a BC taken increases with longer admissions. As the positive BCDs per 100 patients and the percentage positive of BCDs also continued to increase, it can be concluded from our data that the risk of getting bacteraemia also increases with the length of stay. Many patients with suspected invasive illness at admission will receive antimicrobial treatment cover after 48 hours' admission, and this may in part explain the turning point we observed. Another explanation for the increase from day 4 may be the occurrence of hospital-

acquired bacteraemia. The finding that *E. faecium,* which is often found in hospital-acquired bacteraemias, increased at day 5 of admission may further support this. Computer algorithms to determine hospital-acquired bacteraemia showed 48 hours to be a useful threshold [18–20]. Other studies have suggested 72 hours [21]. Our approach of showing positive BCDs per 100 patients and percentage of positive BCDs cannot give a clear suggestion for the number of hours to be used as a threshold, but the increases we observed after day 4 may strengthen the previous assumptions that a threshold in a computer algorithm can be used.

In conclusion, we observed an overall increase in BC utilization and positive BCDs, most prominently among the older age groups, and mostly caused by *E. coli* and to a lesser extent *S. aureus*. The activity in terms of BCDs showed a seasonal pattern, driven by negatives rather than positives, possibly related to the influenza seasons and the seasonality of *S. pneumoniae*. The distribution of pathogens differed among DCMs, possibly due to differences in patient populations. A predominance of men was seen for bacteraemias due to *S. aureus, E. faecium* and *K. pneumoniae*. The proportion of positive BCDs was similar between DCMs. It decreased in the first 4 days of admission and increased after that.

These trends and differences provide important insights, which will soon be used to create a nationwide electronic surveillance system for hospital-acquired bacteraemia, which will show data for the whole country, as well as by region, hospital and each individual clinical department. The minor differences in the BCDs and positive BCDs among DCMs underpin the rationale and meaningfulness of such a surveillance system. Nonetheless, we found differences, particularly in the findings of specific pathogens, which suggest that factors such as clinical characteristics of the patient population are influencing the results. The different patterns between age groups, sex and DCMs that serve tertiary hospitals further illustrated this. This is particularly important to keep in mind when attempting to compare results from departments or hospitals with each other or to regional and national results. It shows the need for age, sex and comorbidity adjustment when standardizing national surveillance statistics.

This type of analysis, in which routine databases are linked, may also create opportunities for public health surveillance in other countries, especially when they face restrictions on the use of clinical databases for public health purposes. The study provides important baseline data for the interpretation of surveillance data for invasive infections more generally, in particular when the aim is to compare surveillance figures from various populations and healthcare systems, and where case ascertainment is highly dependent on diagnostic practices.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

Acknowledgements

We thank K. S. Nielsen and S. Jakobsen, Department IT Development, and projects at Statens Serum Institut, the MiBa Board of Representatives and all departments of clinical microbiology in Denmark.

References

[1] Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am 2011;52:61–9.

[2] Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med 2007;33:606–18.

[3] Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54.

[4] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19:501–9.

[5] Leibovici L. Long-term consequences of severe infections. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19:510–2.

[6] Kirn TJ, Weinstein MP. Update on blood cultures: how to obtain, process, report, and interpret. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19:513–20.

[7] Voldstedlund M, Haarh M, Molbak K, MiBa Board of Representatives. The Danish microbiology database (MiBa) 2010 to 2013. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 2014;19.

[8] Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health 2011;39:30–3.

[9] Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish civil registration system. A cohort of eight million persons. Dan Med Bull 2006;53:441–9.

[10] Madsen KM, Schønheyder HC, Kristensen B, Sørensen HT. Secular trends in incidence and mortality of bacteraemia in a Danish county, 1981–1994. APMIS 1999;107:346–52.

[11] Uslan DZ, Crane SJ, Steckelberg JM, Cockerill 3rd FR, St Sauver JL, Wilson WR, et al. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. Arch Intern Med 2007;167:834–9.

[12] Skogberg K, Lyytikäinen O, Ruutu P, Ollgren J, Nuorti JP. Increase in bloodstream infections in Finland, 1995–2002. Epidemiol Infect 2008;136:108–14.

[13] Søgaard M, Engebjerg MC, Lundbye-Christensen S, Schønheyder HC. Changes in blood culture methodology have an impact on time trends of bacteraemia: a 26-year regional study. Epidemiol Infect 2011;139:772–6.

[14] Krause T, Knudsen L, Emborg H, Gubbels S, Mazick A, Nielsen J, et al. Week 23, 2013. Epi-News. Copenhagen: Statens Serum Institut; 2013.

[15] Laupland KB, Kibsey PC, Gregson DB, Galbraith JC. Population-based laboratory assessment of the burden of community-onset bloodstream infection in Victoria, Canada. Epidemiol Infect 2013;141:174–80.

[16] Lester CH, Sandvang D, Olsen SS, Schønheyder HC, Jarløv JO, Bangsborg J, et al. Emergence of ampicillin-resistant *Enterococcus faecium* in Danish hospitals. J Antimicrob Chemother 2008;62:1203–6.

[17] Pinholt M, Ostergaard C, Arpi M, Bruun NE, Schønheyder HC, Gradel KO, et al. Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark, 2006–2009: a population-based cohort study. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2014;20:145–51.

[18] Trick WE, Zagorski BM, Tokars JI, Vernon MO, Welbel SF, Wisniewski MF, et al. Computer algorithms to detect bloodstream infections. Emerg Infect Dis 2004;10:1612–20.

[19] Gradel KO, Knudsen JD, Arpi M, Ostergaard C, Schønheyder HC, Søgaard M. Classification of positive blood cultures: computer algorithms versus physicians' assessment—development of tools for surveillance of bloodstream infection prognosis using population-based laboratory databases. BMC Med Res Methodol 2012;12:139.

[20] Pokorny L, Rovira A, Martín-Baranera M, Gimeno C, Alonso-Tarrés C, Vilarasau J. Automatic detection of patients with nosocomial infection by a computer-based surveillance system: a validation study in a general hospital. Infect Control Hosp Epidemiol Off J Soc Hosp Epidemiol Am 2006;27:500–3.

[21] Bellini C, Petignat C, Francioli P, Wenger A, Bille J, Klopotov A, et al. Comparison of automated strategies for surveillance of nosocomial bacteremia. Infect Control Hosp Epidemiol Off J Soc Hosp Epidemiol Am 2007;28:1030–5.

Paper III

National automated surveillance of hospital-acquired bacteraemia in Denmark using a computer algorithm.

Gubbels S, Nielsen J, Voldstedlund M, Kristensen B, Schønheyder HC, Ellermann-Eriksen S, Engberg J, Møller JK, Østergaard C, Mølbak K.

(accepted in Infect Control Hosp Epidemiol)

ORIGINAL ARTICLE

Accepted in: *Infection Control and Hospital Epidemiology*

Copyedited version

National Automated Surveillance of Hospital-Acquired Bacteremia in Denmark Using a Computer Algorithm

Running title: AUTOMATED HOSPITAL-ACQUIRED BACTEREMIA SURVEILLANCE

Sophie Gubbels, MD, MSc;[1] Jens Nielsen, PhD;[1] Marianne Voldstedlund, MD, PhD;[1]
Brian Kristensen, MD, PhD;[2] Henrik C. Schønheyder, DMSc;[3,4]
Svend Ellermann-Eriksen, MD, DMSc, PhD;[5] Jørgen H. Engberg, MD, PhD;[6]
Jens K. Møller, DMSc;[7] Christian Østergaard, MD, PhD;[8] Kåre Mølbak, MD, DMSc[1]

Affiliations: 1. Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen, Denmark; 2. Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark; 3. Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark; 4. Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; 5. Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark; 6. Department of Clinical Microbiology, Slagelse Hospital, Slagelse, Denmark; 7. Department of Clinical Microbiology, Vejle Hospital, Vejle, Denmark; 8. Department of Clinical Microbiology, Hvidovre Hospital, Hvidovre, Denmark.

Address correspondence to Sophie Gubbels, Department of Infectious Disease Epidemiology
Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (gub@ssi.dk).

PREVIOUS PRESENTATION: A description of the algorithm, but not the comparison study, was presented at the European Scientific Conference on Applied Infectious Disease Epidemiology in Stockholm, Sweden, on November 11, 2015.

BACKGROUND. In 2015, Denmark launched an automated surveillance system for hospital-acquired infections, the Hospital-Acquired Infections Database (HAIBA).

OBJECTIVE. To describe the algorithm used in HAIBA, to determine its concordance with point prevalence surveys (PPSs), and to present trends for hospital-acquired bacteremia

SETTING. Private and public hospitals in Denmark

METHODS. A hospital-acquired bacteremia case was defined as at least 1 positive blood culture with at least 1 pathogen (bacterium or fungus) taken between 48 hours after admission and 48 hours after discharge, using the Danish Microbiology Database and the Danish National Patient Registry. PPSs performed in 2012 and 2013 were used for comparison.

RESULTS. National trends showed an increase in HA bacteremia cases between 2010 and 2014. Incidence was higher for men than women (9.6 vs 5.4 per 10,000 risk days) and was highest for those aged 61–80 years (9.5 per 10,000 risk days). The median daily prevalence was 3.1% (range, 2.1%–4.7%). Regional incidence varied from 6.1 to 8.1 per 10,000 risk days. The microorganisms identified were typical for HA bacteremia. Comparison of HAIBA with PPS showed a sensitivity of 36% and a specificity of 99%. HAIBA was less sensitive for patients in hematology departments and intensive care units. Excluding these departments improved the sensitivity of HAIBA to 44%.

CONCLUSIONS. Although the estimated sensitivity of HAIBA compared with PPS is low, a PPS is not a gold standard. Given the many advantages of automated surveillance, HAIBA allows monitoring of HA bacteremia across the healthcare system, supports prioritizing preventive measures, and holds promise for evaluating interventions.

Hospital-acquired (HA) bacteremia is one of the most common hospital-acquired infections (HAIs). A systematic review estimated 1,200,000 episodes of bloodstream infections per year in Europe as well as 157,000 related deaths.[1] HA bacteremia is estimated to occur 312,822 times per year across acute-care hospitals.[2]

Because continuous manual surveillance of HAI is laborious and costly, point prevalence studies (PPSs) were introduced. In Denmark, PPSs have been performed twice a year since 2009 in hospitals that volunteer to do so. Between 2010 and 2014, the median prevalence of HA bacteremia was 1.1% overall (range, 1.1%–1.6%) and 20.4% in intensive care units (ICUs; range, 12.8%–31.9%).[3] However, PPSs are difficult to standardize because of interobserver and intraobserver variations.[4,5] Several Danish initiatives have explored the possibilities of electronic surveillance, either semiautomated combined with manual components, or fully automated.[6–9] An international systematic review indicated great promise for electronic surveillance.[10] Based on these studies, we developed an algorithm for HA bacteremia for use in the national automated surveillance that provides continuous incidence data for all Danish hospitals: the Danish Hospital-Acquired Infections Database (HAIBA). HAIBA has been publicly available since March 2015.[11]

On a local level, a variety of data sources may be available for electronic surveillance that allow the use of complex algorithms and/or additional manual evaluations, including analyses of administrative, microbiological, and biochemical data, as well as medical records. However, not all local settings have access to all these sources nor resources for continuous

manual evaluation. On a national level, fully automated systems with few data sources may be more feasible. However, potential differences in registration and utilization practices need to be accounted for. An earlier article described an analysis of blood culture utilization across Departments of Clinical Microbiology (DCMs) in Denmark and indicated the feasibility of such surveillance.[12]

The objectives of the present article were (1) to describe the data sources and algorithm created for HA bacteremia, (2) to determine its concordance with the traditional way of monitoring HAIs (ie, PPS), and (3) to present resulting national and regional figures of HA bacteremia.

METHODS

Data Sources in HAIBA

We used 2 data sources in this study: the Danish Microbiology Database (MiBa) and the Danish National Patient Registry (DNPR). Data were linked by unique civil registration numbers (CPR numbers). The data extraction was conducted on November 18, 2015.

The MiBa includes microbiological test results from all Danish DCMs.[13] We extracted data for all blood cultures with sampling dates between January 1, 2010, and December 31, 2014. Information included sampling date and time, microbiological tests requested, and microorganisms identified.

The DNPR includes administrative information on all inpatient and outpatient contacts with the secondary and tertiary healthcare system.[14] This information includes date and time of admission and discharge as well as codes for hospitals and departments. We created an algorithm that related separate contacts to create coherent courses of admission.[15]

Algorithm

A case of HA bacteremia was based on at least 1 blood culture positive for a bacterial or fungal pathogen drawn between 48 hours after admission and 48 hours after discharge. Supplementary Table 1 describes the algorithm in detail.

Incidence Calculation

Incidence was calculated as incidence density: the number of HA bacteremias per 10,000 risk days. Only the first bacteremia in a course of admission was included because subsequent bacteremia cases are not statistically independent in the same patient.[16] Risk days were calculated from the number of hours that passed from 48 hours after admission until the sample was acquired for the first positive blood culture or 48 hours after discharge. Each case was attributed to the department where the patient was located at the time of sampling. If a case had a sampling date or time within 48 hours after discharge, the infection was attributed to the discharging department.

Prevalence Calculation

Prevalence was estimated for each day in the period 2010–2014, calculated as the number of hours that patients with a HA bacteremia were in a particular department on a given day divided by the total number of risk days in the same department on that day. The duration of a bacteremia episode was arbitrarily set at 14 days. If a positive blood culture with a pathogen was found within 14 days, a new 14-day window began. Each case was attributed to the department where the patient was admitted on the date for which the prevalence was calculated. In the prevalence calculation, consecutive episodes within a course of admission were also included. A new HA bacteremia case was counted if it occurred after the duration of the previous one. Risk days were counted from >48 hours after admission until discharge.

Trend Analysis

Incidence of HA bacteremia was described by sex and by age at admission. Patients with temporary CPR numbers (eg, travelers) were excluded from age-group analyses because their CPR numbers did not allow for reliable age calculation. This exclusion involved 0.3% of all data. The 10 most frequently occurring microorganisms were identified among HA bacteremia cases. Trends in incidence of HA bacteremia were analyzed using Poisson regression for each region, age group, and sex, with risk days as exposure (ie, the denominator). Annual increase was calculated using monthly time units. We assessed whether it was reasonable to assume a trend. The median daily prevalence and range between daily prevalence estimates were calculated for each region and the entire country, as well as by age group and sex.

Comparison to PPSs

Data from PPSs were collected in autumn 2012 and spring 2013 from Danish hospitals in the Capital Region of Denmark and Region Zealand on a voluntarily basis. In autumn 2012, 66 departments from 10 hospitals participated and in spring 2013, 58 departments from 8 hospitals participated.

Data included CPR numbers of all patients present on the day of the PPS and whether patients had a HA bacteremia. Case definitions used in the Danish PPS were adapted from the 2008 Centers for Disease Control and Prevention (CDC) case definitions.[17,18] Apart from bacteremia (confirmed presence of bacteria/fungi in blood), the PPS case definition included patients with symptoms of sepsis and treatment for bacteremia without positive blood cultures (clinical sepsis). Patients were evaluated manually by teams of 2 infection control specialists using medical records and electronic laboratory and medication systems.

Prevalence data from the algorithm were linked to PPS data using CPR number and date of PPS. Sensitivity and specificity were calculated, and 95% confidence intervals (CI) were calculated assuming binomial distribution. Discordant cases were evaluated to assess reasons for discrepancies, using notes from the PPS and, when possible, medical records. Information on department specialty was also analyzed, based on PPS data.

Software

Coding was conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

RESULTS

Trends in Incidence and Prevalence

Between January 1, 2010, and December 31, 2014, a total of 13,704 first episodes of HA bacteremia per course of admission were identified by the algorithm, with an incidence of 7.4 per 10,000 risk days (range, 6.9–8.1) (Table 1). The incidence among men was higher than among women. Significantly increasing trends in incidence were observed (Figure 1 and Table 1). The number of HA bacteremia cases did not change (data not shown).

Incidence increased with age, reaching the highest incidence among patients aged 61–80 years. We observed an increase in incidence over time in all age groups, but the increase was only statistically significant in the 2 oldest age groups. Regional incidence varied between 6.1 and 8.1 per 10,000 risk days and showed an increasing trend. A median daily prevalence of 3.1% (range between daily estimates, 2.1%–4.7%) was estimated, showing minimal regional variation. While incidence of HA bacteremia was highest among 61–80-year-old patients, the prevalence of HA bacteremia was similar among the 3 oldest patient groups. Prevalence, like incidence, was higher among men than women.

Microbiological Findings

Among 13,704 cases of HA bacteremia (including double infections and only first episodes within courses of admission), 277 different microorganisms were identified. The general distribution reflected the older age groups (Table 2). However, younger patients showed some differences. *Staphylococcus aureus* was most frequent in the 3 youngest age groups. In the age group of 0–20 years, Group B streptococci (GBS) and non-hemolytic streptococci of the *S. mitis* group were among the 10 most frequently identified microorganisms, and among 21–40-year-old patients, Group A streptococci were among the top 10. The distribution of microorganisms among men and women was similar; the same 10 microorganisms were found in a slightly different order (data not shown).

Comparison of HAIBA With PPS

PPS data were collected from 2,146 patients. Because of incorrect or missing CPR numbers, 11 patients were excluded. Of the remaining 2,135 patients, 28 were registered on 2 PPS days and 1 was registered on 3 PPS days. Furthermore, when linking PPS data to HAIBA, another 179 records were excluded either because admissions lasted ≤48 hours, because patients were recorded in the DNPR as outpatients or because the patient was not recorded at all in the DNPR on the prevalence date. Notably, none of these patients were reported as having HA bacteremia.

Finally, the study included 1,986 records from 1,959 patients: 1,541 records from the Capital Region and 445 from Region Zealand. Among them, 47 (2.2%) were reported with HA bacteremia, 43 of 1,541 (2.8%) occurred in the Capital Region and 4 of 445 (0.9%) occurred in Region Zealand. Comparison with HAIBA showed that 17 cases were identified in both HAIBA and PPS, 13 were identified only in HAIBA, and 30 were identified only in PPS.

We ascertained 2 main reasons that HAIBA identified HA bacteremia not reported by PPS (Table 3). First, in 6 cases, laboratory results were not known at the time of the PPS, whereas HAIBA was able to count these patients and date their infections retrospectively. Second, 6 patients had HA bacteremia but were not reported in the PPS, probably because they no longer had bacteremia at the time of the PPS. The majority missed by HAIBA (55%) had only negative blood cultures or no samples taken at all; most were admitted to intensive care units (ICUs) or hematology departments. When examining medical records, it was difficult to determine whether these patients had clinical sepsis due to underlying illnesses or were being treated for various other conditions.

Overall, HAIBA reached a sensitivity of 36.2% (17 of 47; 95% CI, 23.5%–51.0%) and a specificity of 99.3% (1,926 of 1,939; 95% CI, 99.0%–99.7%). When excluding the ICUs and hematology departments, this sensitivity increased to 44.4% (8 of 18; 95% CI, 24.3%–70.2%), and specificity increased to 99.5% (1,743 of 1,751, 95% CI, 99.3%–99.9%).

DISCUSSION

In this study, we describe an algorithm for continuous national monitoring of HA bacteremia in Denmark, using existing data sources (ie, HAIBA), thus avoiding administrative burden and interpersonal differences in classification of infections.

The algorithm used in this study has 3 main components: detection of pathogens, classification of origin and, for prevalence calculations, definition of new episodes.

The determination of whether a microorganism is pathogenic or a likely contaminant is not always straightforward. If contaminants are repeatedly isolated, they may have clinical relevance (eg, as a cause of catheter-associated bacteremia). For the HA bacterimia

algorithm, we classified microorganisms as pathogens and contaminants, prioritizing specificity over sensitivity. A few differences were observed in the most frequent microorganisms compared to our blood-culture utilization study. *Enterococcus faecium* and *Candida glabrata* were more frequently cultured in samples from HA bacteremia. Both microorganisms are associated with prior or concomitant antimicrobial treatment, and these cases likely reflect an increased burden of illness and increased length of stay. Reassuringly, *Streptococcus pneumoniae*, which typically causes community-acquired bacteremia (and is ranked fourth among all positive blood cultures), was not found among the top 10 microbial causes of HA bacteremia. GBS bacteremia in the youngest age group may be explained by high incidence among neonates. This pathogen may become more important in older age groups in the future, particularly among patients with diabetes.[19] The larger representation of particularly pathogenic microorganisms among younger patients is related to less comorbidity.

The second component of the algorithm involves categorization of bacteremia as HA at the 48-hour cutoff. This cutoff was introduced in the 1970s to standardize surveillance when assessment of medical records and other clinical details was impossible.[20] More recently, the CDC introduced this cut-off in its PPS methodology.[21] The Danish PPS describes an HAI as one that is neither confirmed nor under incubation upon admission. The incubation period is defined as ≥48 hours unless the patient underwent an invasive procedure.[18] Other electronic surveillance systems are also using a 48-hour cutoff.[6,9,22–24] The number of (positive) blood cultures was shown to decrease soon after admission (day 1) and to increase from day 4 onward.[12] This finding may also suggest that 48 hours is a useful cutoff.

For prevalence calculations, subsequent infections were included, as is done in PPS, requiring a cutoff for duration of infection, after which new bacteremia cases can be counted. In the future, it may be possible to refine the estimation of duration by including data on antibiotic treatment.

An algorithm eliminates subjectivity of personal judgment, but it may misclassify in some cases. We evaluated how the HA bacteremia algorithm we created for use with HAIBA related to PPS because it is expected to replace the PPS method in Denmark. Our results showed high specificity but low sensitivities of 36% for all departments and 44% when excluding ICUs and hematology departments. However, PPS is not a gold standard, and re-evaluation of medical records showed that, for several patients, it was debatable whether they had bacteremia/clinical sepsis. Therefore, the real sensitivity of the algorithm may well be higher.

The potential underestimation of HA bacteremia in the ICU and among hematological patients may becaused by the exclusion of contaminants that may have clinical relevance in patients with central venous catheters. However, PPSs may have overestimated HA bacteremia in this group. Neutropenic and leukopenic fever are difficult to distinguish from bacteremia. Patients are, by protocol, given antibiotics as a precaution for developing bacteremia, making it difficult to culture microorganisms. Finally, many ICU patients have (multiple) organ failure, which can be mistaken for bacteremia/clinical sepsis. Although it is challenging to identify HA bacteremia in these patients with an algorithm, it may be useful to investigate the possibility of including antibiotic treatment and/or chemotherapy visits. However, such additions may introduce false positives, which might make HAIBA less acceptable for hospitals.

The increasing trend in national incidence of HA bacteremia seen in HAIBA is in line with a European study.[25] However, in contrast to the European study, the number of HA bacteremia cases did not increase, and the

trend seems driven by a decreasing denominator (ie, risk days). Length of stay decreased in Denmark over the studied period.[26] However, with shorter admissions we would also expect a decrease in the number of HA bacteremia cases. The fact that this was not seen could have been related to an aging population and more advanced treatment given at older age. Incidence did increase over time among the oldest age groups, while it remained stable for other age groups.

Although the number of cases identified by HAIBA was lower than by PPS, the estimated prevalence was higher; HAIBA estimated a median prevalence of 3.1% (range between daily estimates 2.1%–4.7%) between 2010 and 2014 versus 1.1% (range, 1.1%–1.6%) by PPS over the same period.[3] This finding can be explained by several factors, including the fact that HAIBA excludes admissions ≤48 hours from the denominator and differences in underlying concepts and methods.

Incidence of HA bacteremia varied between regions and hospitals, possibly due to differences in patient population in terms of case mix and complexity of treatment. A marked difference was also seen in incidence and prevalence between men and women. Other studies have also reported this difference.[27–29] Several studies have reported that men were more likely to develop bacteremia secondary to urinary catheter–associated bacteriuria than women.[30–32] However, the indication for catheterization (eg, obstruction) could be a confounder in these studies.[33] In line with this finding, we observed that *Escherichia coli* was the most common pathogen among patients >60 years of age.

Further investigation of patient populations is particularly important when data are to be used for interfacility comparisons, requiring adjustment for confounders.[34]

The strength of HAIBA lies in comparing hospitals and departments with themselves over time. By doing so, it can support prioritization in infection control and can serve as a tool to evaluate interventions and for audits. Hospitals will receive data on individual patients with HA bacteremia to further investigate signals and trends. When HAIBA has been actively used for a substantial period its effect on in incidence, morbidity and mortality should be evaluated.

ACKNOWLEDGMENTS

We thank the members of the HAIBA Advisory Forum, Kim Gradel (Center for Clinical Epidemiology, South, Odense University Hospital and Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark) and Christina Vandenbroucke-Grauls (Department of Medical Microbiology and Infection Control, VU University Medical Center, Amsterdam, the Netherlands) for their feedback regarding the algorithm. We thank Kenn Schultz Nielsen (Department of IT-Projects and Development, Danish Health Data Authority) for his involvement in the development of HAIBA. We also thank Christian Stab Jensen (Department of Microbiology and Infection Control, SSI) and all of the infection control nurses and medical doctors who collected data for the PPS. We also thank Manon Chaine (Department of Infectious Disease Epidemiology, SSI) for her assistance in data entry of the PPS data.

The Danish Data Protection Authority approved this study as part of the development of HAIBA (registration no. 2015-54-0942).

Financial support: This work was funded by the Danish Ministry of Health and the Elderly as part of the development of HAIBA.

Potential conflicts of interest: All authors report no conflict of interest relevant to this article.

REFERENCES

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;19:501–509.
2. ECDC Surveillance report—Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. European Centre for Disease Prevention and Control website. http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf. Published 2013. Accessed November 24, 2016.
3. Department of Microbiology and Infection Control, Landsprævalensundersøgelsen. Statens Serum Institute website. http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Overvaagning/Praevalensundersogelser/Data%20fra%20Praevalensundersogelser.aspx. Published 2015. Accessed November 24, 2016.
4. Lin MY, Hota B, Khan YM, et al. Quality of traditional surveillance for public reporting of nosocomial bloodstream infection rates. *JAMA* 2010;304:2035–2041.
5. Mayer J, Greene T, Howell J, et al. Agreement in classifying bloodstream infections among multiple reviewers conducting surveillance. *Clin Infect Dis* 2012;55:364–370.
6. Leth RA, Møller JK. Surveillance of hospital-acquired infections based on electronic hospital registries. *J Hosp Infect* 2006;62:71–79.
7. Schønheyder HC, Søgaard M. Existing data sources for clinical epidemiology: The North Denmark Bacteremia Research Database. *Clin Epidemiol* 2010;2:171–178.
8. Gradel KO, Knudsen JD, Arpi M, Ostergaard C, Schønheyder HC, Søgaard M, Danish Collaborative Bacteraemia Network (DACOBAN). Classification of positive blood cultures: computer algorithms versus physicians' assessment—development of tools for surveillance of bloodstream infection prognosis using population-based laboratory databases. *BMC Med Res Methodol* 2012;12:139.
9. Redder JD, Leth RA, Møller JK. Incidence rates of hospital-acquired urinary tract and bloodstream infections generated by automated compilation of electronically available healthcare data. *J Hosp Infect* 2015;91:231–236.
10. Leal J, Laupland KB. Validity of electronic surveillance systems: a systematic review. *J Hosp Infect* 2008;69:220–229.
11. Hospital-Acquired Infections Database (HAIBA). Sundhedsdatastyrelsen website. http://www.esundhed.dk/sundhedskvalitet/HAIBA/Sider/HAIBA_report.aspx. Accessed November 24, 2016.
12. Gubbels S, Nielsen J, Voldstedlund M, et al. Utilization of blood cultures in Danish hospitals: a population-based descriptive analysis. *Clin Microbiol Infect* 2015;21:344.e13–e21.
13. Voldstedlund M, Haarh M, Molbak K, MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. *Euro Surveill* 2014;19.
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
15. Gubbels S, Nielsen KS, Sandegaard J, Mølbak K, Nielsen J. The development and use of a new methodology to reconstruct courses of admission and ambulatory care based on the Danish National Patient Registry. *Int J Med Inf* 2016;95:49–59.
16. Ostrowsky B. Chapter 1: Epidemiology of Healthcare-Associated Infections. In: Jarvis WR ed. *Bennett & Brachman's Hospital Infections*. 5th ed. Philadelpia, PA: Lippincott Williams & Wilkins; 2007:3–24.
17. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated

infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.

18. Definitioner på de fire hyppigste infektioner til brug ved prævalensundersøgelser - modificeret efter CDC's definitioner til danske forhold. Statens Serum Institut website. http://www.ssi.dk/~/media/Indhold/DK%20-%20dansk/Smitteberedskab/Infektionshygiejne/Praevalensundersogelser/Foraar%202011/Definitioner%20for%20infektioner_jan2011.ashx. Published 2011. Accessed November 24, 2016.
19. Ballard MS, Schønheyder HC, Knudsen JD, et al. The changing epidemiology of group B streptococcus bloodstream infection: a multi-national population-based assessment. *Infect Dis Lond Engl* 2016;48:386–391.
20. McGowan JE, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972), with special reference to hospital-acquired cases. *J Infect Dis* 1975;132:316–335.
21. CDC/NHSN surveillance definitions for specific types of infections. Centers for Disease Control and Prevention website. http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf. Published 2016. Accessed November 24, 2016.
22. Woeltje KF, McMullen KM, Butler AM, Goris AJ, Doherty JA. Electronic surveillance for healthcare-associated central line-associated bloodstream infections outside the intensive care unit. *Infect Control Hosp Epidemiol* 2011;32:1086–1090.
23. Leal J, Gregson DB, Ross T, Flemons WW, Church DL, Laupland KB. Development of a novel electronic surveillance system for monitoring of bloodstream infections. *Infect Control Hosp Epidemiol* 2010;31:740–747.
24. Pokorny L, Rovira A, Martín-Baranera M, Gimeno C, Alonso-Tarrés C, Vilarasau J. Automatic detection of patients with nosocomial infection by a computer-based surveillance system: a validation study in a general hospital. *Infect Control Hosp Epidemiol* 2006;27:500–503.
25. de Kraker MEA, Jarlier V, Monen JCM, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. *Clin Microbiol Infect* 2013;19:860–868.
26. Gubbels S, Schultz Nielsen K, Sandegaard J, Mølbak K, Nielsen J. The development and use of a new methodology to reconstruct courses of admission and ambulatory care based on the Danish National Patient Registry. *Int J Med Inform* 2016;95:49-59.
27. Uslan DZ, Crane SJ, Steckelberg JM, et al. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. *Arch Intern Med* 2007;167:834–839.
28. Cohen B, Choi YJ, Hyman S, Furuya EY, Neidell M, Larson E. Gender differences in risk of bloodstream and surgical site infections. *J Gen Intern Med* 2013;28:1318–1325.
29. Moon H-W, Ko YJ, Park S, Hur M, Yun Y-M. Analysis of community- and hospital-acquired bacteraemia during a recent 5-year period. *J Med Microbiol* 2014;63:421–426.
30. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J Infect Dis* 1983;148:57–62.
31. Saint S, Kaufman SR, Rogers MAM, Baker PD, Boyko EJ, Lipsky BA. Risk factors for nosocomial urinary tract-related bacteremia: a case-control study. *Am J Infect Control* 2006;34:401–407.
32. Greene MT, Chang R, Kuhn L, et al. Predictors of hospital-acquired urinary tract-related bloodstream infection. *Infect Control Hosp Epidemiol* 2012;33:1001–1007.
33. Conway LJ, Carter EJ, Larson EL. Risk factors for nosocomial bacteremia secondary to urinary catheter-associated bacteriuria: a systematic review. *Urol Nurs* 2015;35:191–203.
34. Harris AD, McGregor JC. The importance of case-mix adjustment for infection rates and the need for

more research. *Infect Control Hosp Epidemiol* 2008;29:693–694.

35. Møller JK, Jensen TG, Prag J, et al. Elektronisk svar og rekvisition i klinisk mikrobiologi - kodeværk for prøvebeskrivelse. MADS website. http://www.madsonline.dk/MDS-koder/MDS_Rapport.pdf. Accessed November 24, 2016.

FIGURE 1. Incidence per 10,000 risk days of hospital-acquired bacteremia per month in Denmark for all patients and by sex between 2010 and 2014. Data were acquired November 18, 2015.

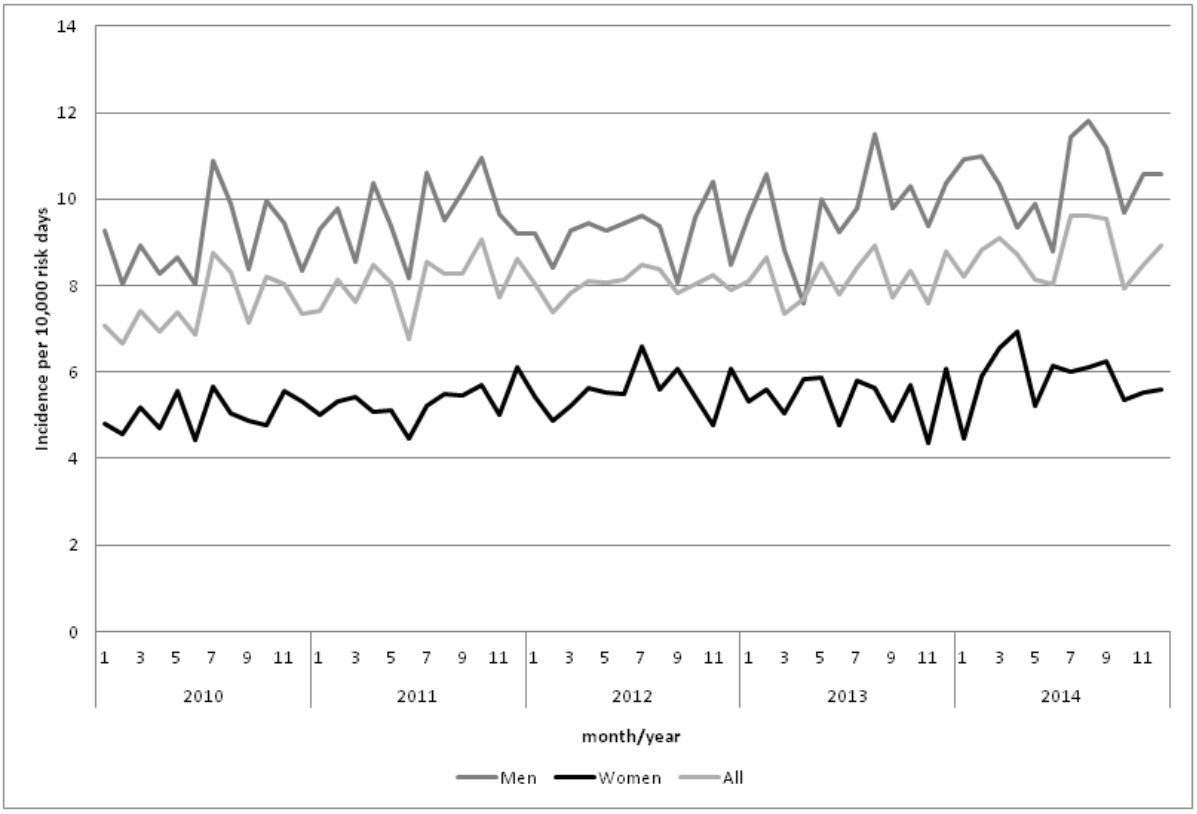


TABLE 1. Incidence and Prevalence of Hospital-Acquired Bacteremia in Denmark, Stratified by Sex, Age,[a] and Region Between 2010 and 2014[b]

Variable	No. of First HA Bacteremia per Course of Admission	No. of Risk Days	Overall Incidence per 10,000 Risk Days (Yearly Range)	Yearly Increase in Incidence[c] (95% CI)	Median Daily Prevalence (Range Between Daily Estimates)[d]
National, all patients	13,704	18,486,552	7.4 (6.9–8.1)	1.04 (1.02–1.05)	3.1 (2.1–4.7)
Men	8,507	8,873,512	9.6 (9.0–10.5)	1.03 (1.02–1.05)	3.7 (2.5–5.5)
Women	5,197	9,613,040	5.4 (5.0–5.8)	1.03 (1.01–1.05)	2.5 (1.5–4.2)
Age 0–20 y	632	1,842,907	3.4 (3.0–3.8)	1.04 (0.98–1.09)	1.3 (0.4–2.4)
Age 21–40 y	593	1,969,758	3.0 (2.6–3.6)	1.03 (0.98–1.09)	1.3 (0.5–2.6)
Age 41–60 y	2,709	3,491,370	7.8 (7.4–8.2)	1.01 (0.99–1.04)	3.9 (1.9–5.2)
Age 61–80 y	6,999	7,336,070	9.5 (9.0–10.2)	1.03 (1.01–1.05)	3.8 (2.5–5.7)
Age >80 y	2,453	3,449,604	7.1 (6.4–8.1)	1.06 (1.03–1.09)	3.7 (2.1–5.8)
Capital Region of Denmark	5,288	6,508,805	8.1 (7.8–8.6)	1.02 (1.00–1.04)	3.1 (2.2–5.4)
North Denmark Region	1,297	1,940,886	6.7 (5.9–7.5)	1.04 (1.00–1.08)	3.0 (1.4–7.0)
Central Denmark Region	2,554	3,670,824	7.0 (6.4–8.1)	1.05 (1.02–1.08)	3.1 (1.5–5.1)
Region Zealand	1,657	2,717,600	6.1 (5.5–6.5)	1.04 (1.01–1.08)	2.8 (0.8–4.9)
Region of Southern Denmark	2,908	3,648,437	8.0 (7.3–8.7)	1.04 (1.01–1.07)	3.3 (1.6–5.4)

NOTE. HA, hospital-acquired.

[a] Patients with temporary CPR numbers were excluded from age group analysis, as these CPR numbers do not allow for reliable age calculations.

[b] Data were acquired on November 18, 2015.

[c] Trend in incidence estimated using Poisson regression.

[d] Daily prevalence estimates for January 2010 were excluded because they were unreliable due to the start-up phase of the data.

TABLE 2. Proportion of the 10 Most Frequent Pathogens[a] Among All Pathogens Identified in Hospital-Acquired Bacteremia Cases and Stratified by Age Group[b]

All patients (N=20,198)	**%**	**Patient age, 0–20 y (N=922)**	**%**	**Patient age, 21–40 y (N=908)**	**%**	**Patient age, 41–60 y (N=3,929)**	**%**	**Patient age, 61–80 y (N=10,381)**	**%**	**Patient age, >80 y (N=3,582)**	**%**
Escherichia coli	19.4	*Staphylococcus aureus*	27.4	*S. aureus*	17.1	*S. aureus*	17.5	*E. coli*	20.0	*E. coli*	25.8
S. aureus	16.9	*E. coli*	10.9	*Enterococcus faecium*	12.6	*E. coli*	16.2	*S. aureus*	14.8	*S. aureus*	19.3
E. faecium	12.1	*E. faecalis*	7.4	*E. coli*	12.3	*E. faecium*	14.3	*E. faecium*	13.5	*E. faecium*	7.6
Klebsiella pneumoniae	6.1	*E. faecium*	6.0	*K. pneumoniae*	7.5	*K. pneumoniae*	6.4	*K. pneumoniae*	6.2	*E. faecalis*	6.6
E. faecalis	6.0	*C. albicans*	5.6	*E. faecalisT*	6.3	*E. faecalis*	5.4	*E. faecalis*	5.9	*K. pneumoniae*	5.4
Candida albicans	4.7	Group B streptococci	4.2	*Pseudomonas aeruginosa*	3.0	*C. albicans*	5.2	*C. albicans*	5.1	*P. aeruginosa*	4.5
P. aeruginosa	3.9	*K. pneumoniae*	4.0	*E. cloacae*	2.6	*E. cloacae*	3.5	*P. aeruginosa*	4.2	*C. albicans*	3.6
E. cloacae	3.1	Streptococcus mitis group	3.4	*C. albicans*	2.4	*P. aeruginosa*	3.1	*E. cloacae*	3.1	*C. glabrata*	3.0
C. glabrata	2.6	*P. aeruginosa*	3.4	*C. glabrata*	2.2	*K. oxytoca*	2.5	*C. glabrata*	2.8	*E. cloacae*	2.4
K. oxytoca	2.5	*E. cloacae*	3.3	Group A streptococci	1.8	*C. glabrata*	2.3	*K. oxytoca*	2.7	*K. oxytoca*	2.4

[a] Pathogens according to the classification as presented in Supplementary Table 1.

[b] Patients with temporary CPR numbers were excluded from age group analysis, as these CPR numbers do not allow for reliable age calculations.

TABLE 3. Patient Characteristics, Specialty of Participating Departments and Microbiological Findings of Patients Included in the Comparison of Data From the Danish Hospital-Acquired Infections Database (HAIBA) and Point Prevalence Survey (PPS) Data

Comparison Group (No. of cases)	Median Age, y (Range)	Ratio of Men:Women	Specialty of Participating Departments (No. of cases)[a]	Explanation for Discrepant Result	No. of Discrepant Cases (%)
Identified in both systems (n=17)	62 (52–74)	12:5	Hematology (n=6) ICU (n=3) Other departments (n=8)		
Identified in HAIBA but not by PPS (n=13)	65 (56–85)	9:4	ICU (n=5) Other departments (n=8)	• Result of blood culture came in after the date of the PPS. • First positive blood culture was taken more than a week before the date of the PPS (8, 10, 12 (2×), 13, and 14 d). The conclusion may have been that the patient no longer had bacteremia. • It is unclear why this patient was not reported by PPS. *Enterococcus faecalis* had been obtained from a blood culture sample taken >48 h after admission and 3 d before PPS, the result being available one day before the prevalence date. Clinical information on the laboratory form stated that the patient was under observation for sepsis.	6 (46) 6 (46) 1 (8)
Identified by PPS but not in HAIBA (n=30)	62 (56–70)	20:10	Hematology (n=11) ICU (n=9) Other departments (n=9)	• Only negative blood cultures • First positive blood culture was taken within 48 h of admission. 2 patients had had invasive procedures and 1 had recently been admitted. • First positive blood culture was taken >14 d before the date of the PPS (1, 4, and 7 d beyond the 14 d). Medical records showed that they were still under antibiotic treatment for bacteremia at time of PPS. • No blood samples taken for culture	15 (48) 10 (35) 3 (10) 2 (7)
Not identified in either system (n=1,926)	70 (58–80)	953:973	Hematology (n=107) ICU (n=76) Other departments (n=1743)		

NOTE. ICU, intensive care unit.

[a] As reported by PPSs.

SUPPLEMENTARY TABLE 1. Computer algorithm for HA-bacteraemia

Data preparation		
1	The initial extract from MiBa was based on the following MDS codes (Microbiological Diagnosis System)[35] for specimen material: • 10001 Whole blood; 10002 Whole blood from peripheral vein; 10003 Whole blood from catheter; 10160 Blood (blood culture bottle); 10164 Blood from umbilical cord (blood culture bottle); 10165 Blood from peripheral vein (blood culture bottle); 10166 Blood from catheter (blood culture bottle); 10167 Blood from artery (blood culture bottle).	MiBa
2	Relevant specimen were subsequently identified through the following MDS codes for the requested microbiological test: 10002 Aerobic culture (bacteria); 10003 Aerobic and anaerobic culture (bacteria); 10011 Culture and resistence; 10040 Anaerobic culture (bacteria); 10045 Aerobic and anaerobic culture in blood culture bottle; 10122 Staphylococcus aureus (MRSA) (culture); 10190 Listeria monocytogenes (culture); 10410 Actinomyces (culture); 12127 Staphylococcus aureus (MRSA) (DNA/RNA and culture); 17000 General bacterial investigation (=culture) and bacterial DNA/RNA; 20001 Culture (mould); 20010 Culture (yeast); 59015 Staphylococcus aureus (MRSA) (investigation for); 12129 and 12300 - not mapped in MiBa, but included not to miss important information.	MiBa
3	Records with an incorrect result in the field that indicates the microorganisms found in a blood culture were excluded.	MiBa
4	The date for the bacteraemia was determined, using the sampling date. • If the sampling date was missing, then the date of receipt in the Department of Clinical Microbiology was used. • If the sampling date was more than 7 days before the date of receipt then the date of receipt was used. • If the sampling date was after the date of receipt, the date of receipt was used.	MiBa
5	The time for bacteraemia was determined, using the time of sampling. • If the sampling time was not available, and the date of sampling and receipt were the same then the time of sampling was set to 4 hours (parameter) before receipt. • If the time of sampling was still missing, then it was set at 08:00.	MiBa
6	The number of samples with a sampling time at 08:00 was calculated by Department of Clinical Microbiology, but only for those that initially had information on the time of sampling. If there was an increase of >75% on one day, then those above 75% were set to 09:00, but only those that originally did not have information on the time of sampling.	MiBa
7	If there were more than one sample for the same person at the same time, then they were merged into one. Information on the microorganism(s) and the original laboratory identification numbers was kept.	MiBa
8	All observations with at least one pathogenic bacterium or fungus were marked as having bacteraemia. Pathogens were classified as all those **not** in the following list: • *Acinetobacter* spp., *Aerococcus* spp. (except *A. urinae*), *Bacillus* spp. (except *B. anthracis*, *B. cereus*), *Corynebacterium* spp. (except *C. diphtheriae*), *Lactobacillus* spp., *Lactococcus* spp, *Micrococcus* spp., *Moraxella* spp. (except *M. catarrhalis*), *Neisseria* spp. (except *N. meningitides, N. gonorrhoeae, N. elongate, N. animaloris*, *N. canis*, and *N. zoodegmatis*), *Propionibacterium acnes*, *Staphylococcus* spp. (except *S. aureus*, *S. saprophyticus*, *S. lugdunensis* and *S. schleiferi*). *Streptococcus* spp. and non-haemolytic streptococci.	MiBa

	Comment: *Streptococcus* spp. and non-haemolytic streptoccocci are usually determined on species level, especially in those situations where the microorganism is considered the etiological agent. Reporting at genus level is taken to be a sign that the Department of Clinical Microbiology did not consider the microorganism to be the etiological agent and such reports were therefore assessed as contaminants in our algorithm.	
9	Course of admission was determined using an algorithm that linked related records to each other (manuscript submitted).[26]	DNPR
10	For courses of admission the risk time was indicated (≥48 hours after admission up to 48 hours after discharge).	DNPR
11	14 days were marked before the admission to be able to identify blood cultures taken during this period, indicating that there was a (suspicion of) bacteraemia before admission.	DNPR
Constructing the algorithm		
12	A bacteraemia was counted on the date and time of sampling. A bacteraemia was counted as a new bacteraemia if the sample date and time was >14 days (in hours) after a previous one. If a positive blood culture was found ≤14 days after a previous one, a new 14-day window started during which no new bacteraemia was counted.	HAIBA
13	In order to calculate the prevalence, it was defined that each bacteraemia episode lasted for 14 days, starting from the date and time of sampling.	HAIBA
14	Data from MiBa were combined with data from DNPR if the CPR-number was the same and the sample date fell within the period of 14 days before admission and 48 hours after discharge.	HAIBA
15	A bacteraemia was counted as hospital-acquired if it occurred within the period between >48 hours after admission and 48 hours after discharge, and no positive blood culture was found during the 14 days before admission nor within the first 48 hours of admission.	HAIBA
16	For incidence calculations, only the first HA-bacteraemia per course of admission was counted. For prevalence calculations, also further bacteraemias within a course of admission were included.	HAIBA
17	The number of risk days for incidence calculation was calculated as the number of days in the period between 48 hours after admission and 48 hours after discharge.	HAIBA
18	The number of risk days for prevalence was calculated as the number of days in the period from >48 hours after admission until 48 hours after discharge.	HAIBA

Paper IV

An automated surveillance system for hospital-acquired urinary tract infections in Denmark.

Condell O, Gubbels S, Nielsen J, Espenhain L, Frimodt-Møller N, Engberg J, Møller JK, Ellermann-Eriksen S, Schønheyder HC, Voldstedlund M, Mølbak K, Kristensen B.

J Hosp Infect. 2016 Jul;93(3):290-296.
doi: 10.1016/j.jhin.2016.04.001. Epub 2016 Apr 19.

Corrigendum to 'An automated surveillance system for hospital-acquired urinary tract infections in Denmark'.

Condell O, Gubbels S, Nielsen J, Espenhain L, Frimodt-Møller N, Engberg J, Møller JK, Ellermann-Eriksen S, Schønheyder HC, Voldstedlund M, Mølbak K, Kristensen B.

J Hosp Infect. 2016 Dec;94(4):410.
doi: 10.1016/j.jhin.2016.09.001. Epub 2016 Sep 21.

Journal of Hospital Infection 93 (2016) 290–296

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Automated surveillance system for hospital-acquired urinary tract infections in Denmark

O. Condell [a,b], S. Gubbels [c,*], J. Nielsen [c], L. Espenhain [c], N. Frimodt-Møller [d], J. Engberg [e], J.K. Møller [f], S. Ellermann-Eriksen [g], H.C. Schønheyder [h,i], M. Voldstedlund [c], K. Mølbak [c], B. Kristensen [a]

[a] *Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen S, Denmark*
[b] *European Program for Public Health Microbiology Training, European Centre for Disease Prevention and Control, Stockholm, Sweden*
[c] *Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen S, Denmark*
[d] *Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark*
[e] *Department of Clinical Microbiology, Slagelse Hospital, Slagelse, Denmark*
[f] *Department of Clinical Microbiology, Vejle Hospital, Vejle, Denmark*
[g] *Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark*
[h] *Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark*
[i] *Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

ARTICLE INFO

Article history:
Received 16 September 2015
Accepted 5 April 2016
Available online 19 April 2016

Keywords:
Hospital-acquired
Urinary tract infection
Automated surveillance
Validation

SUMMARY

Background: The Danish Hospital-Acquired Infections Database (HAIBA) is an automated surveillance system using hospital administrative, microbiological, and antibiotic medication data.

Aim: To define and evaluate the case definition for hospital-acquired urinary tract infection (HA-UTI) and to describe surveillance data from 2010 to 2014.

Methods: The HA-UTI algorithm defined a laboratory-diagnosed UTI as a urine culture positive for no more than two micro-organisms with at least one at $\geq 10^4$ cfu/mL, and a probable UTI as a negative urine culture and a relevant diagnosis code or antibiotic treatment. UTI was considered hospital-acquired if a urine sample was collected $\geq$48 h after admission and $<$48 h post discharge. Incidence of HA-UTI was calculated per 10,000 risk-days. For validation, prevalence was calculated for each day and compared to point prevalence survey (PPS) data.

Findings: HAIBA detected a national incidence rate of 42.2 laboratory-diagnosed HA-UTI per 10,000 risk-days with an increasing trend. Compared to PPS the laboratory-diagnosed HA-UTI algorithm had a sensitivity of 50.0% (26/52) and a specificity of 94.2% (1842/1955). There were several reasons for discrepancies between HAIBA and PPS, including laboratory results being unavailable at the time of the survey, the results considered clinically irrelevant by the surveyor due to an indwelling urinary catheter or lack of clinical signs of infection, and UTIs being considered HA-UTI in PPS even though the first sample was taken within 48 h of admission.

* Corresponding author. Address: Department of Infectious Disease Epidemiology, Statens Serum Institut, DK-2300 Copenhagen S, Denmark. Tel.: +45 3268 8338.
E-mail address: GUB@ssi.dk (S. Gubbels).

http://dx.doi.org/10.1016/j.jhin.2016.04.001

Conclusion: The HAIBA algorithm was found to give valid and valuable information and has, among others, the advantages of covering the whole population and allowing continuous standardized monitoring of HA-UTI.

Introduction

Hospital-acquired infections (HAIs) constitute a major public health concern. Such infections are associated with increased morbidity, mortality, extended hospital stays and increased financial burden on the healthcare system.[1,2] Urinary tract infections (UTIs) are among the most frequently occurring nosocomial infections in Europe, including Denmark.[3,4] Surveillance of such infections is an important step in reducing their occurrence, providing evidence for the implementation and monitoring of preventive interventions.[5]

In Denmark, a 1979 survey estimated the prevalence of hospital-acquired urinary tract infections (HA-UTIs) at 5.5%. Estimates from 1999 showed a reduction to 2.1%, although the study populations were different.[6] Since 2009, manual point-prevalence surveys (PPSs) have been carried out twice a year, estimating a prevalence for HA-UTI at 1.6–2.5%.[7,8] However, these PPSs are conducted on a voluntary basis and not all clinical departments or hospitals participate. The aim of PPSs is to determine the prevalence of HAI on a given day and the surveys are conducted through manual registration of infection by chart reviews.[9]

PPSs are associated with drawbacks and limitations. They are time-consuming, costly, and difficult to standardize. PPSs are subject to variation in classification between individual reviewers and are difficult to compare between hospitals or countries.[1] Several studies have shown that automated surveillance systems, based on electronically registered data such as patient records, antibiotic consumption documentation, and microbiological data, are more reliable and consistent than PPSs for detecting HAI.[1,10]

The Hospital-Acquired Infections Database (HAIBA) is a newly launched, automated surveillance system in Denmark, which combines continuously updated patient administrative data, microbiological laboratory results, and data on antimicrobial treatment.[11] The overall objective of HAIBA is to detect and monitor HAI continuously for all hospitals and clinical departments in Denmark. HAIBA aims to improve the evidence for reducing the incidence of preventable HAI through motivating and supporting hospital staff in evaluating effectiveness of preventive measures.[11] The system further aims to ensure that monitoring HAI in Denmark can be conducted without requiring time-consuming reporting from clinicians or nurses.

HAIBA became operational in March 2015 for HA-bacteraemia and *Clostridium difficile* infections. Data for HA-UTI were added in October 2015. This study outlines the case definition for HA-UTI and describes the surveillance data from 2010 to 2014. Second, this study compares a subset of the surveillance data with data from two PPSs in order to evaluate how the new surveillance system relates to the traditional method for monitoring HA-UTI.

Methods

Danish healthcare system

In Denmark, secondary and tertiary healthcare is mostly public. Healthcare-related policymaking and management occurs at the national level as well as in five Danish regions. A study describing dynamics in hospital admissions and outpatient contacts registered in the Danish National Patient Registry (DNPR) described 138 Danish hospitals between 2010 and 2014, of which 54 were public (S. Gubbels *et al.*, unpublished data). It was estimated that these 54 public hospitals accounted for 97.9% of inpatient contacts.

Data sources

Three data sources were linked together using the uniquely defined civil registry number (CPR) allotted to all Danish citizens and permanent residents at birth or immigration. First, patient administrative data were obtained from the DNPR.[12] Admission and discharge dates and diagnosis codes were extracted from DNPR. Coherent courses of admission were established taking into account transfers to other departments and hospitals (S. Gubbels *et al.*, unpublished data). Data on all submitted specimens coded as urine sample with a corresponding laboratory analysis code for cultivation were extracted from the Danish Microbiology Database.[13] For these samples, the following data were retrieved: sample collection date, date of receipt in the laboratory, and results of the laboratory cultivation analysis, i.e. type(s) of micro-organisms isolated and their quantification [numbers of colony-forming units (cfu)/mL]. Finally, data on antibiotic treatment were obtained from regional medicine modules of the Capital Region of Denmark and Region Zealand, which hold data on prescribed and administered antibiotics during hospital admission.

Case definition in HAIBA

The HAIBA case definition for HA-UTI specified criteria for classification as either laboratory-diagnosed or probable.

Laboratory-diagnosed UTI:

- At least one urine culture revealing no more than two micro-organisms, with at least one at $\geq 10^4$ cfu/mL of urine.

Probable UTI:

- A patient with at least one urine culture submitted to a department of clinical microbiology, but not fulfilling the criteria for laboratory-diagnosed UTI
  and

- The patient had at least one of the following:
  - a relevant course of antibiotic treatment within a relevant timeframe (Appendix A, Supplementary Table I)
  - a diagnosis code indicating UTI (Appendix A, Supplementary Table I).

The UTI (laboratory-diagnosed or probable) was considered hospital-acquired if the first urine culture was taken between ≥48 h after the admission time and <48 h after the discharge time.

Data from patients aged less than one year were excluded. A new infection could be acquired after 14 days, independent of the micro-organism. The infection was attributed to the department where the patient was admitted at the time the urine was collected.

Further details of the algorithm are provided in Appendix A, Supplementary Table I.

Incidence and prevalence data from HAIBA

Incidence was calculated for cases fulfilling the laboratory-diagnosed case definition, between 2010 and 2014. Only the first infection per course of admission was included. The denominator was the number of risk-days counted from 48 h after admission to 48 h after discharge or until HA-UTI occurred.

Prevalence data were calculated by day for the laboratory-diagnosed case definition and the laboratory-diagnosed case definition and probable case definition combined. Prevalence was defined as the number of patients who fulfilled the case definition for a given day divided by the total number of patients admitted to the relevant department on that day. For these calculations, patients were considered ill for 14 days, starting on the date of urine culture submission. Subsequent infections were included in the prevalence calculation.

Reference data for validation: PPSs

Point prevalence survey data were used to validate HAIBA, since PPSs provided the surveillance data in Denmark before HAIBA was developed. As such, they form the de-facto gold standard. Infection control units in participating hospitals and the Central Unit for Infection Control at Statens Serum Institut carried out manual PPSs in Denmark. The methodology and parameters have been described in detail elsewhere.[8] Briefly, each hospitalized patient in the ward/department under examination was registered as currently having or not having HA-UTI. The presence of indwelling devices such as urinary catheters was also recorded. The case definition for UTI was a Danish adaptation of that provided by the Centers for Disease Control and Prevention (CDC).[14,15] The definition gives criteria for a UTI based on a microbiological result (≥10^4 cfu/mL with at most two different micro-organisms) in combination with at least one clinical sign (fever >38°C, urge, pollakiuria, dysuria/stranguria, suprapubic soreness). In the absence of positive microbiological results, the definition required at least two clinical signs in combination with other signs of UTI including urine dipstick tests or a clinical diagnosis.

For the purposes of this comparative study, prevalence data were obtained from two PPSs, one conducted in autumn 2012 including 66 departments in 10 hospitals in the Capital Region of Denmark and Region Zealand, the second conducted in spring 2013 including 58 departments in eight hospitals in the same regions.

Comparison of the PPSs and HAIBA

Prevalence was calculated in HAIBA for patients who were reported in these PPSs. Data were linked using CPR numbers and PPS study dates.

The number of HA-UTIs concordant and discrepant between the two systems was determined. The reasons underlying discrepancies were analysed, including urine culture reports for samples submitted within 28 days prior to and on the date of the PPS. If no explanation for the discrepancy was apparent, we examined medical records covering the same period.

Analysis

Surveillance data generated by HAIBA were analysed for trends by Poisson regression. The number of HA-UTIs was the dependent variable and the model was adjusted for the number of risk-days as offset values. The annual increase was calculated using monthly time units.

Sensitivity and specificity were calculated for HAIBA data compared to the PPSs. A 95% confidence interval (CI) was given for frequencies assuming a binomial distribution.

Data analysis was carried out with SAS (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

HAIBA has permission from the Danish Data Protection Agency for surveillance purposes and for this validation study (j.nr. 2015-54-0942).

Results

HA-UTI incidence and trends

Between 2010 to 2014, we detected 69,628 laboratory-diagnosed HA-UTI with 16,484,141 risk-days. The incidence of HA-UTI was 42.2 (yearly range: 39.9–46.6) per 10,000 risk-days (Table I). The median daily prevalence was estimated at 4.9% (range between daily estimates: 4.0–6.1%).

There was overall a gradually increasing trend in the incidence of laboratory-diagnosed HA-UTI (Table I, Figure 1). When analysed separately there was a significant increasing trend in all regions (Table I, Figure 1). Trends in Capital Region and Region Zealand showed distinct shifts. In the Capital Region, a change in coding practice between April and August 2013 caused the incidence to decrease to a lower baseline. Trend analysis was done separately for the periods before and after this change, excluding April 1st to July 31st, 2013. In Region Zealand, the catchment area changed in March 2011, resulting in a higher baseline incidence. The trend analysis was performed separately for these periods. The baseline incidence per 10,000 risk-days of HA-UTI tended to differ between regions (Table I, Figure 1).

Validation and comparison with PPSs

Data from the PPS was obtained for 2007 records from 1980 patients: 1541 records from the Capital Region and 445 from

Table I
Numbers of laboratory-diagnosed hospital-acquired urinary tract infections (HA-UTIs), risk-days, incidence, prevalence, and trends in Denmark, by region for 2010 to 2014

Region	No. of primary laboratory-diagnosed HA-UTIs	No. of risk-days	Overall incidence per 10,000 (yearly range)	Median daily prevalence (range between daily estimates)[a]	Linear trend in incidence		
					Period	Annual change in incidence[b]	95% CIs
All regions	69,628	16,484,141	42.2 (39.9–46.6)	4.9 (4.0–6.1)	2010–2014	1.02	1.02–1.03
Capital Region of Denmark[c]	25,841	5,806,988	44.5 (42.3–46.4)	5.4 (4.1–7.3)	2010–Apr 2013	1.01	1.00–1.03
					Aug 2013–2014	1.06	1.00–1.13
North Denmark Region	5785	1,744,775	33.2 (30.6–35.7)	3.9 (2.2–5.9)	2010–2014	1.02	1.01–1.04
Central Denmark Region	12,987	3,212,751	40.4 (38.6–42.7)	4.8 (3.0–7.3)	2010–2014	1.03	1.02–1.04
Region Zealand[c]	9371	2,476,379	37.8 (27.0–43.9)	4.4 (2.1–6.6)	2010–Feb 2011	1.06	0.92–1.22
					Mar 2011–2014	1.04	1.02–1.06
Region of Southern Denmark	15,644	3,243,249	48.2 (46.2–50.3)	5.1 (3.4–6.8)	2010–2014	1.02	1.01–1.03

[a] Daily prevalence estimates for January 2010 were excluded, because these included outliers caused by the start-up phase of the data in the Danish Hospital-Acquired Infections Database (HAIBA).
[b] To test the null hypothesis that the coefficient (yearly incidence per 10,000, offset by risk-days) is equal to zero, meaning that there is no trend.
[c] For these regions, the linear trend was analysed for different periods, because of a shift in the incidence, as indicated in Figure 1.

Region Zealand. For 52 patients a HA-UTI was reported, a prevalence of 2.6%. The HAIBA laboratory-diagnosed algorithm detected 139 HA-UTIs among the same patients (prevalence 6.9%), whereas the laboratory-diagnosed and probable algorithm detected 161 HA-UTIs (prevalence 8.0%).

Comparison between the laboratory-diagnosed algorithm for HAIBA and the PPS revealed 26 UTIs recorded in both surveillance systems; 113 were found only in HAIBA, and 26 were found only in the PPS. Compared to PPSs the laboratory-diagnosed case definition had a sensitivity of 50.0% (26/52; 95% CI: 33.2–60.8) and a specificity of 94.2% (1842/1955; 95% CI: 94.6–96.4).

Examination of laboratory results and medical records shed more light on the 113 patients found positive by HAIBA but not by PPS. The reasons are categorized in Table II. The largest category (36.3%) represented patients who would probably have been reported in the PPS had their laboratory result been available on the day of the PPS. The second largest category comprised patients who had a positive urine culture and an indwelling catheter. In the cases where the urine sample was collected through the catheter (7.1%), this may have been the reason for discarding them in the PPS. In the other cases (9.7%), it was specifically indicated in the laboratory results or medical records that the urine culture could not be considered as positive. Another group of seven patients (6.2%) had a positive urine culture, but did not meet the PPS clinical criteria as no clinical symptoms were recorded. Most of these patients were elderly with neurological disorders, for whom it was difficult to establish symptoms because of aphasia, dementia and/or already present incontinence.

Reasons for the discrepancy of the 26 cases detected by the PPS but not by HAIBA are also given in Table II. In 14 cases (53.8%), HAIBA detected them as having UTI, but not as HA-UTI, as the first sample was taken within 48 h of admission. In three of these cases, at the time of the PPS a second urine culture had shown infection with another micro-organism. Six cases remained unexplained; the medical records could not be accessed for five, whereas the remaining case had negative laboratory results and no clinical signs of UTI noted in the medical records.

The application of the HAIBA probable case definition detected an additional 22 HA-UTIs. Only one of these patients was classified as having HA-UTI by the PPS.

Discussion

This study analysed data for monitoring of HA-UTI as part of a newly launched automated surveillance system for HAI in Denmark: HAIBA. The aim of this work was to describe the case definition for HA-UTI and to compare it with the traditional manual system of PPSs.

The majority of discrepancies between the two systems could be explained and a number of benefits and limitations of HAIBA were disclosed. Our work validated the HA-UTI case definition. However, this validation study was based on a small subset of all cases captured by HAIBA and was geographically skewed, as access to PPS data was for the Capital Region of Denmark and Region Zealand only. Further studies covering the entire surveillance population are required. It would also be useful to study how the sensitivity and specificity of HAIBA develop over time. In addition, it should be noted, owing to its drawbacks and limitations, that we do not consider the PPS as a gold standard for measuring HAI but we rather used it for comparative purposes as it remains the system used in Denmark.

This study has shown that HAIBA detected more HA-UTIs than the current PPS approach. About a third of the laboratory-confirmed HA-UTIs detected by HAIBA but not by the PPSs were potentially missed by the PPSs because the positive result of a urine culture was not available at the time of the survey. This is in line with other studies demonstrating that electronic hospital surveillance systems detect a larger number of HAIs than traditional manual methods.[16,17] Our study also highlights the benefits of a system based on continuous monitoring. The point in time when the PPS is carried out may not represent the prevalence at other points in

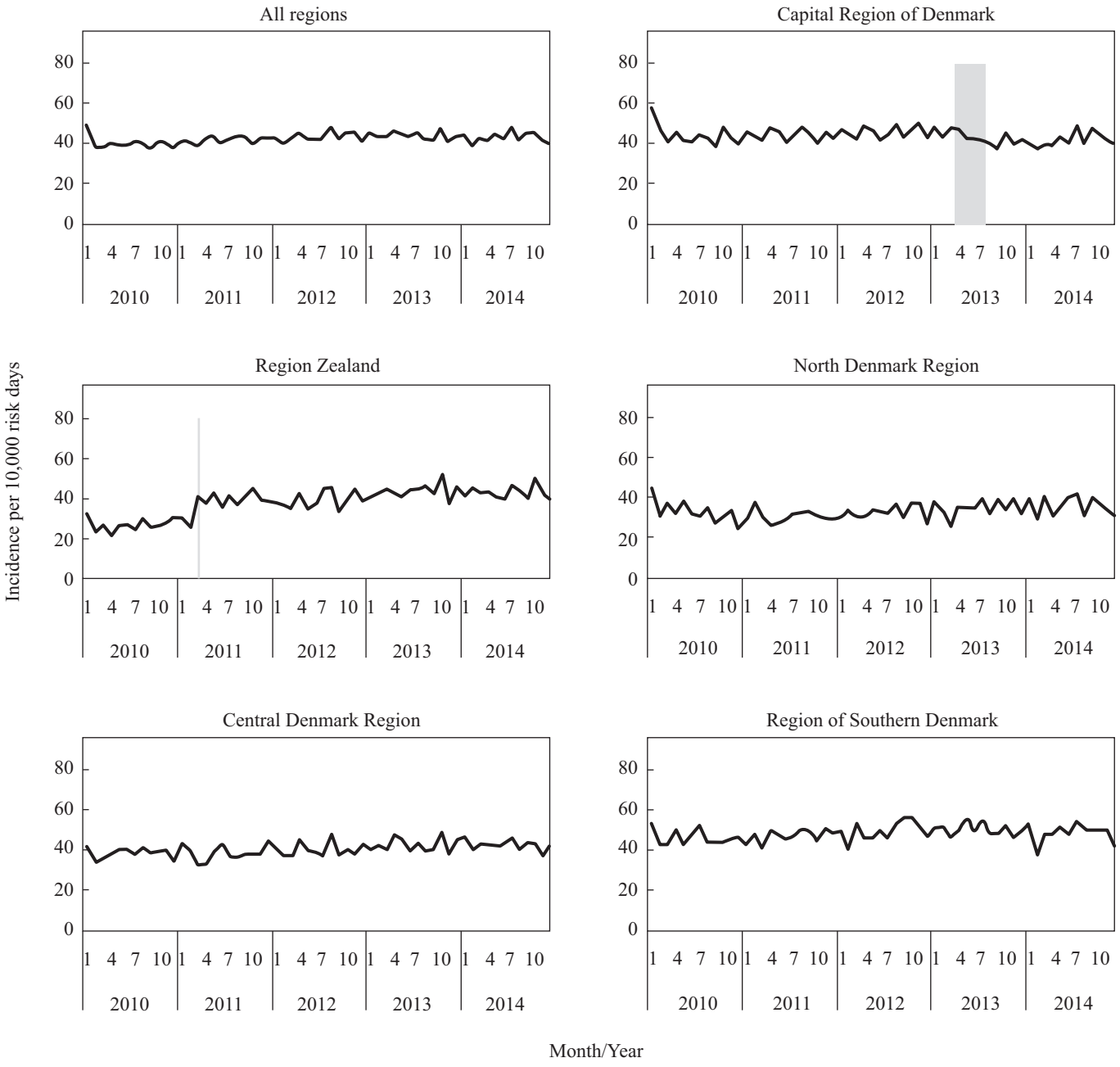


Figure 1. Incidence of hospital-acquired laboratory-diagnosed urinary tract infections from 2010 to 2014, per 10,000 risk-days, by region in Denmark.[1] An alteration occurred in the coding of sample material between March and August 2013.[2] In March 2011, there was a change in the catchment area and correspondingly in the surveillance population for the Zealand Region.

time or true prevalence at that time, if relevant indicators are not yet available.[17] By contrast, the collection of data by an automated system allows for the continuous monitoring of infection trends. In that respect, our observations that the HAIBA HA-UTI algorithm could detect trends in HA-UTI during the five-year period is reassuring. In addition, HAIBA may detect more infections due to its ability to correct retrospectively, when new information becomes available. Moreover, the inclusion of HAIs in recently discharged patients (up to 48 h after discharge) is a strength, especially in hospital systems with a general trend toward shorter hospital stays and more ambulatory contacts (S. Gubbels *et al.*, unpublished data).

In some HA-UTIs detected by HAIBA but not by the PPS, the PPS did not classify these patients as having infections because the patients had indwelling urinary catheters and/or did not have clinical signs of infection. Asymptomatic bacteriuria is common, especially in the elderly population, and is associated with the presence and duration of catheterization.[18,19] However, it may be difficult to assess symptoms in this population, due to neurological illnesses and/or incontinence, and symptomatic infections may be missed. Currently, clinical information on symptoms and presence of catheters is not consistently reported in any of the data sources available to HAIBA and thus not appropriate for inclusion in the automated

Table II
Summary of the explanations for the discrepancies between the detection of hospital-acquired urinary tract infections by HAIBA and the point prevalence survey, as apparent from laboratory reports and medical records

Discrepancy	Explanation for discrepant result	No. (%) of discrepant cases
Laboratory-diagnosed HA-UTI in HAIBA, not detected by the PPS ($N = 113$)	– Laboratory results were not yet available to the survey team on the day of the PPS.	41 (36.3%)
	– Urine sample taken from an indwelling catheter.	
	– It was stated in either the laboratory results or the medical records that colony counts should be considered too low for the patient to be classified as having UTI.	11 (9.7%)
	– No further information from laboratory results or medical records available.	8 (7.1%)
	– No clinical signs to indicate the presence of UTI.	
	– No clinical signs stated in the medical records; patients did not fulfil the PPS HA-UTI case definition.	7 (6.2%)
	– Notes in the medical records that infection had cleared and had lasted less than the HAIBA-defined duration of 14 days.	4 (3.5%)
	– There was a subsequent negative urine culture before the date of the PPS – the PPS team may have considered the infection cleared.	7 (6.2%)
	– The urine sample was contaminated and explained with a free text note in the laboratory results – a comment that cannot be taken into account with the HAIBA computer algorithm.	1 (0.9%)
	– Urine sample taken 48 h after admission but symptoms began before admission	1 (0.9%)
	– The UTI was considered not HA.	
	– Indication in laboratory results of chronic cystitis.	1 (0.9%)
	– No clear explanation.	
	– Positive urine culture and symptoms of UTI infection described in the medical records.	5 (4.4%)
	– No clear explanation; medical records could not be accessed.	27 (23.9%)
HA-UTI in the PPS but not detected by HAIBA ($N = 26$)	– UTI in HAIBA, but not considered hospital-acquired.	
	– The first positive urine culture was taken within 48 h of admission.	11 (42.3%)
	– First positive urine culture was taken within 48 h of admission. At the time of the prevalence study another urine culture was positive for another micro-organism.	3 (11.5%)
	– The first positive urine culture was taken three days before admission.	1 (3.8%)
	– The urine culture was taken >14 days before the date of the prevalence study; patients were elderly and the duration of clinical signs of infection went beyond the HAIBA-defined illness duration of 14 days	3 (11.5%)
	– No urine culture was submitted; PPS diagnosis based on clinical diagnosis alone.	1 (3.8%)
	– Case had a negative urine culture, but biochemical laboratory testing (leucocyte count, urine dipstick) results and clinical signs indicated infection, as noted in the medical records.	1 (3.8%)
	– No explanation.	
	– Medical records could not be accessed.	5 (19.2%)
	– No clinical symptoms recorded in medical records.	1 (3.8%)

HAIBA, Danish Hospital-Acquired Infections Database; HA-UTI, hospital-acquired urinary tract infection; PPS, point prevalence survey.

system. HAIBA may therefore classify patients with catheters as falsely having HA-UTI. However, when the quality of recording improves, this issue may be addressed through revision of the HAIBA algorithm.

The low sensitivity of 50% was for a large part explained by discordant cases that had a first urine sample taken in the first 48 h of admission. The manual evaluation of a PPS has the benefit that it can use more information to judge whether an infection is hospital-acquired. However, it may be very labour intensive to evaluate the full history over several weeks preceding the PPS date, and in several cases it was likely to be a wrong judgement by the PPS. In three specific cases, the HAIBA algorithm could be improved by taking into account that their second urine culture showed a different micro-organism, suggesting an actual HA-UTI. The lack of clinical information in HAIBA in the absence of a positive culture may explain the other discordant cases.

In this study, no added benefit from the probable case definition was apparent; however, its advantages and disadvantages will be reassessed in future validation studies.

Subjectivity must be reckoned with manual PPSs, as reported previously.[20] Subjective judgements may potentially

introduce variation across institutions participating in surveillance schemes and between different surveyors. Such studies are therefore deemed unsuitable for detailed comparisons.[6,20]

Considering the concordant cases, the reasons for discrepancies, and the subjectivity of PPSs, we found that HAIBA yielded valid and valuable information that was consistent and objective. The prevalence as measured by HAIBA is higher than with the PPSs, suggesting that the burden of HA-UTI may be higher in Denmark than previously reported.

The HAIBA system could detect HA-UTIs and calculate HA-UTI incidence rates, trends, and differences between regions. However, there are variations in hospital practices and between regions as well as between hospitals and departments in the same region that impact incidence calculations and therefore limit the utility of such comparisons. For example, differences in urine culture practices and coding of sample material may impact the overall numbers of infections detected at a particular hospital or region. Different procedures in antibiotic administration and urinary catheter usage may also be reflected in the variations of UTI incidence calculated by HAIBA. More research is needed on the underlying reasons for differences between regions and hospitals. Despite these limitations, HAIBA can detect HA-UTIs in a standardized way and allow for monitoring in a continuous and timely manner without added workload for the clinical staff. HAIBA provides stakeholders with information that may allow them to monitor their own performance and to make preventive measures aimed at lowering the occurrence of HA-UTIs in Denmark.

Acknowledgements

The authors would like to thank the Departments of Clinical Microbiology and the Infection Control Units, the HAIBA Advisory Forum, C.S. Jensen (Department of Microbiology and Infection control, SSI), M. Chaine (Department of Infectious Disease Epidemiology, SSI) and A. Jasir (ECDC, EUPHEM supervisor).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jhin.2016.04.001.

Conflict of interest statement
None declared.

Funding sources
None.

References

1. Leth RA, Møller JK. Surveillance of hospital-acquired infections based on electronic hospital registries. *J Hosp Infect* 2006;**62**:71—79.
2. Stone PW, Braccia D, Larson E. Systematic review of economic analyses of health care-associated infections. *Am J Infect Control* 2005;**33**:501—509.
3. Zarb P, Coignard B, Griskeviciene J, *et al*. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveill* 2012;**17**(46). pii: 20316.
4. Petersen MH, Holm MO, Pedersen SS, Lassen AT, Pedersen C. Incidence and prevalence of hospital-acquired infections in a cohort of patients admitted to medical departments. *Dan Med Bull* 2010;**57**:A4210.
5. Scheckler WE, Brimhall D, Buck AS, *et al*. Requirements for infrastructure and essential activities of infection control and epidemiology in hospitals: a consensus panel report. Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 1998;**19**:114—124.
6. Christensen M, Jepsen OB. Reduced rates of hospital-acquired UTI in medical patients. Prevalence surveys indicate effect of active infection control programmes. *J Hosp Infect* 2001;**47**:36—40.
7. Central Enhed for Infektionshygiejne, Statens Serum Institut. Data fra Landsprævalensundersøgelser. Available at: http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Overvaagning/Praevalensundersogelser/Data%20fra%20Praevalensundersogelser.aspx [last accessed April 2016].
8. Central Enhed for Infektionshygiejne, Statens Serum Institut. Prævalensundersøgelser. Available at: http://www.ssi.dk/Smitteberedskab/Infektionshygiejne/Overvaagning/Praevalensundersogelser.aspx [last accessed April 2016].
9. World Health Organization. *Prevention of hospital-acquired infections, a practical guide*. Geneva: WHO; 2001.
10. Redder JD, Leth RA, Møller JK. Incidence rates of hospital-acquired urinary tract and bloodstream infections generated by automated compilation of electronically available healthcare data. *J Hosp Infect* 2015;**91**:231—236.
11. Gubbels S, Nielsen J, Voldstedlund M, *et al*. HAIBA-Hospital-Acquired Infections Database. EPI-NEWS — Statens Serum Institut 2015;(9).
12. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449—490.
13. Voldstedlund M, Haarh M, Molbak K. MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. *Euro Surveill* 2014;**19**(1).
14. Central Enhed for Infektionshygiejne, Statens Serum Institut. *Definitioner på de fire hyppigste infektioner til brug ved Prævalensundersøgelser, Modificeret efter CDC's definitioner til danske forhold* [not dated].
15. Centers for Disease Control and Prevention, National Healthcare Safety Network. *CDC/NHSN Surveillance Definitions for Specific Types of Infections* [not dated].
16. Pokorny L, Rovira A, Martín-Baranera M, Gimeno C, Alonso-Tarrés C, Vilarasau J. Automatic detection of patients with nosocomial infection by a computer-based surveillance system: a validation study in a general hospital. *Infect Control Hosp Epidemiol* 2006;**27**:500—503.
17. Tinoco A, Evans RS, Staes CJ, Lloyd JF, Rothschild JM, Haug PJ. Comparison of computerized surveillance and manual chart review for adverse events. *J Am Med Inform Assoc* 2011;**18**:491—497.
18. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis Mon DM* 2003;**49**:53—70.
19. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Archs Intern Med* 2000;**160**:678—682.
20. Trick WE, Zagorski BM, Tokars JI, *et al*. Computer algorithms to detect bloodstream infections. *Emerg Infect Dis* 2004;**10**:1612—1620.

Journal of Hospital Infection 94 (2016) 410

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Corrigendum

Corrigendum to 'Automated surveillance system for hospital-acquired urinary tract infections in Denmark' [Journal of Hospital Infection 93 (2016) 290–296]

O. Condell [a,b], S. Gubbels [c,*], J. Nielsen [c], L. Espenhain [c], N. Frimodt-Møller [d], J. Engberg [e], J.K. Møller [f], S. Ellermann-Eriksen [g], H.C. Schønheyder [h,i], M. Voldstedlund [c], K. Mølbak [c], B. Kristensen [a]

[a] *Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen S, Denmark*
[b] *European Program for Public Health Microbiology Training, European Centre for Disease Prevention and Control, Stockholm, Sweden*
[c] *Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen S, Denmark*
[d] *Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark*
[e] *Department of Clinical Microbiology, Slagelse Hospital, Slagelse, Denmark*
[f] *Department of Clinical Microbiology, Vejle Hospital, Vejle, Denmark*
[g] *Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark*
[h] *Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark*
[i] *Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

The authors regret that there is an error in the 95% confidence intervals presented. The correct 95% confidence intervals are as follows:

50.0% sensitivity (95% CI 37.4–64.6) and 94.2% specificity (95% CI 93.2–95.3).

The authors would like to apologise for any inconvenience caused.

DOI of original article: http://dx.doi.org/10.1016/j.jhin.2016.04.001.

* Corresponding author. Address: Department of Infectious Disease Epidemiology, Statens Serum Institut, DK-2300 Copenhagen S, Denmark. Tel.: +45 3268 8338.

E-mail address: GUB@ssi.dk (S. Gubbels).

http://dx.doi.org/10.1016/j.jhin.2016.09.001