Summarizing discussion and future perspectives

SUMMARIZING DISCUSSION

In this thesis, epidemiological studies were conducted in order to understand, describe, and evaluate the dynamics between patients and microorganisms in a hospital environment. We focused on risk factors, transmission, and detection of transmission.

Healthcare-related pathogens: risk factors

By performing systematic reviews with meta-analyses, we identified the leading risk factors, the leading protective factors, important environmental sources and reservoirs, and effective infection prevention strategies for carbapenem-resistant Enterobacteriaceae (CRE) (**Chapter 2.1**) (1), carbapenem-resistant *Pseudomonas aeruginosa* (**Chapter 2.2**) (2), and extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella* species (**Chapter 2.3**) (3); all highly-resistant microorganisms (HRMO). Figure 1 shows a summary of all patient-related and environmental factors identified in chapters 2.1, 2.2 and 2.3 for acquiring and preventing acquisition of these HRMO.

We identified that the most reported environmental source for CRE, carbapenem-resistant *P. aeruginosa*, and ESBL-producing *Klebsiella* species was the sink (Figure 1) (1-3), although in many individual studies a source was not described, not identified, or not searched for. The sink flora is, next to the waterborne flora, determined by the flora of admitted patients and by its use, after which a biofilm forms (4). Unfortunately, there are no studies about design and materials in preventing contamination of sinks with bacteria. In other words, the best sink to use in a hospital environment has not been engineered yet. Transmission of microorganisms via de sink occurs through splashing of water, or if materials used for a patient are put in or near the sink (5). Since the sink plays such an important role in transmission of HRMO, it is questionable whether a sink in a hospital environment is necessary. A study conducted by Hopman *et al.* in the Netherlands and a study conducted by Shaw *et al.* in Spain concluded that removal of sinks and water-free patient care significantly reduced colonization with Gram-negative bacteria in patients (6, 7). However, as Hopman *et al.* state in the limitation section of the article, removal of sinks could interfere with the transmission of *Clostridium difficile* spores, norovirus, and several other non-enveloped viruses, because they are resistant to hand alcohol. In these cases, after having contact, hands must be washed. Additionally, if your hands are soiled (*e.g.* with blood) or small surgical procedures are performed in for example a room on an intensive care unit (ICU), there must be a facility to wash your hands. **We conclude** and recommend that a sink must be seen as an important but dangerous object in a patient room. Sinks should be considered dirty and an important source for transmission of bacteria. Healthcare workers (HCW) and patients must become aware of this risk and act accordingly.

We identified that the second most identified source was transmission by contaminated hands of healthcare workers (HCW). Meanwhile, the low compliance rate to hand hygiene by HCW is still a concern (8). Unfortunately, interventions to increase compliance are of varying success (9, 10). Factors that impact compliance to hand hygiene by HCW are: (i) motivational factors (*e.g.* social influences, acuity of patient care, self-protection), and (ii), perceptions of the work environment (*e.g.* resources, knowledge, organizational culture) (11). A study conducted in the Netherlands introduced a multicomponent intervention program in 10 hospitals. Hand hygiene compliance increased from 42.9% to 51.4%, a significant increase (12). Connected to that, as most effective infection prevention strategy reported for ESBL-producing *Klebsiella* species, and the fourth most reported effective strategy to control CRE was improving adherence to hand hygiene (Figure 1). Therefore, **we conclude** that efforts to improve hand hygiene compliance are still important and must be and/or remain a top priority in every hospital.

The most reported effective infection prevention strategy for control of CRE were barrier and contact precautions when identifying a patient with CRE, and the second most reported infection prevention strategy was transfer of identified patients to a

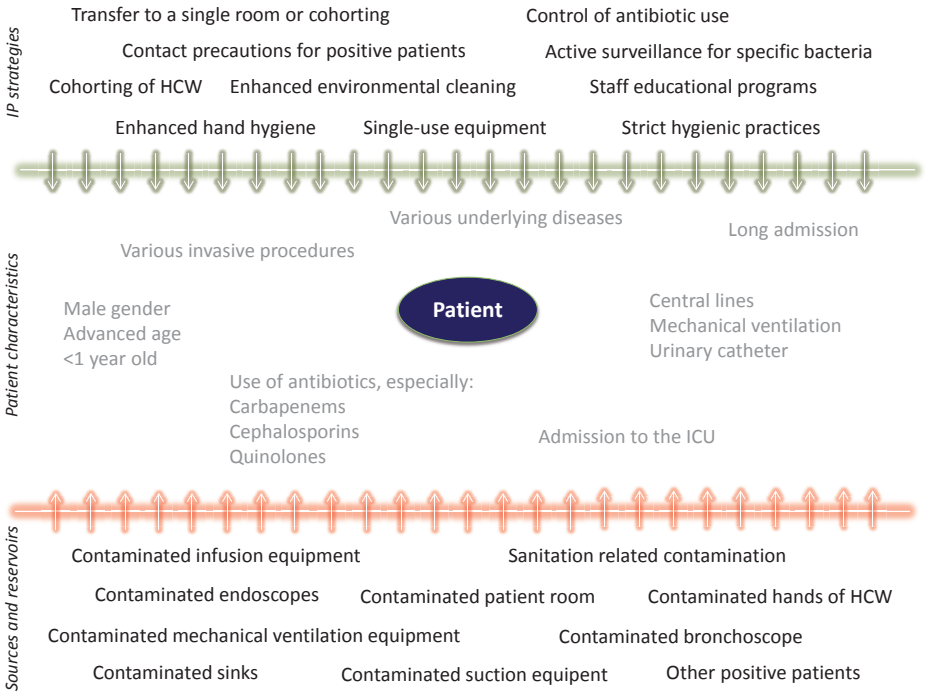

Figure 1. Infection prevention strategies, sources/reservoirs and patient-related risk factors for acquisition of highly-resistant microorganisms identified in chapters 2.1, 2.2 and 2.3.
Abbreviations: ICU; intensive care unit, HCW; healthcare workers, IP; infection prevention.

single-occupancy room, or cohorting of patients with the same microorganism (Figure 1). Concerning single-occupancy rooms, there is increasing evidence showing a relationship between hospital room design and infection control. A systematic review by Taylor *et al.* showed that there is moderately high evidence that single-occupancy rooms are an intervention for infection control, and a systematic review by Stiller *et al.* showed that single-occupancy rooms are beneficial for infection control (13, 14). Additionally, the 2018 USA guidelines for design and construction of hospitals and outpatient facilities states: "*The maximum number of beds per room in a medical/surgical patient care unit shall be one unless the necessity of a two-bed arrangement has been demonstrated* (15)." All other types of patient care units (*e.g.* oncology, intermediate care) mentioned in this guideline refer to this section (*i.e.* patient rooms shall comply with requirements of medical/surgical patient care unit – patient room) (15). Unfortunately, in the Netherlands no such guideline is available. Therefore, it is difficult for the Dutch infection control departments to demand only single-occupancy rooms. There are also other advantages of single-occupancy rooms; it was shown to improve patients' recovery because of increased privacy and increased patient support, to decrease length of hospital stay, to reduce patients' stress, to cause less medication errors and to increase doctor-nurse-family communication (16-19). However, opponents claim (i) that single-occupancy rooms are more expensive, (ii) that it may cause social isolation, (iii) that it affects the layout of the hospital (*e.g.* walking distances) which reduces quality of care, and (iv) that there is not enough evidence that proves that single-occupancy rooms reduce healthcare-related infections (16-19). The reason that only a few studies are performed on this topic is that it is difficult to perform RCTs with single-occupancy rooms as intervention. **We conclude** based on the results of chapter 2.1 that contact precautions need to be installed for patients identified with CRE, and that a single room is preferred above multi-occupancy rooms.

The risk factor we identified as having a high pooled odds ratio (OR) in all three systematic reviews in this thesis was use of antibiotics (Figure 1) (1-3). Additionally, as described by Paño Pardo *et al.* antibiotic use is likely the primary determinant for persistent CRE carriage (20). This urgently calls for reducing use, and also optimizing appropriate use of antibiotics (*i.e.* antibiotic stewardship) (21). A Cochrane systematic review by Davey *et al.* concluded that there is high-certainty evidence that interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment (22). They also identified that less use of antibiotics did not increase mortality, but reduced length of hospital stay (22). However, as described by Parsonage *et al.*, there are numerous ethical problems to be considered when reducing use of antibiotics (23). In short, authors discussed if you can deny helpful and even potentially lifesaving antibiotics to a patient because there is a potential lack of therapies for that patient in the future (23). Antibiotics are a risk factor for acquiring HRMO because broad-spectrum

antibiotics (*e.g.* carbapenems, cephalosporins and fluoroquinolones) influence the normal gut flora and effectively kill or suppress the susceptible microorganisms, thereby enabling resistant bacteria to emerge or adhere, survive, and proliferate (*i.e.* antibiotic selective pressure). **We conclude** in all three chapters that antibiotic use is associated with acquisition of HRMO, and use needs to be reduced as much as possible. Also, we describe that since many risk factors are identified (Figure 1), bundled interventions are needed, and these should include antibiotic stewardship.

Healthcare-related pathogens: sources and transmission

Transmission is defined as the process, the mechanisms and the determinants by which an infectious agent or an infectious disease is spread from a source or reservoir to another person or across communities and countries (24). Transmission can be (i) direct (*e.g.* from person to person), or (ii) indirect (*e.g.* vehicle borne, vector borne or airborne) (24). All hospitals deal with outbreaks every now and then, and our tertiary hospital is no exception; as LeBourdais stated in 1974: "*Hospitals are bacterial collectors and distributers.*" In **chapters 2.1-2.3**, we evaluated outbreaks and transmission of microorganisms in our tertiary hospital (*i.e.* for two specific microorganisms) and nationwide (*i.e.* for a specific route of transmission).

Chapter 3.1 showed that when dealing with a large hospital-wide outbreak by Verona-integron-encoded metallo-beta-lactamase (VIM)-positive *P. aeruginosa*, the entire ward should be seen as reservoir and as contaminated, and unidentified persistent sources in the innate environment play an important role in transmission dynamics (25). This means that surveillance and cleaning of the environment is of utmost importance. In 2017, the World Health Organization (WHO) published a guideline for the prevention and control of CRE, carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *P. aeruginosa* in healthcare facilities (26). Although a low quality of evidence, the panel recommended that environmental surveillance cultures for these microorganisms may be considered when epidemiologically indicated (26). Also, because environmental contamination is associated with increased rates of patient colonization and infection. We identified quinolone use, use of the selective digestive tract decontamination regimen (SDD) and having undergone a gastroscopy as robust risk factors (25). A risk factor was defined as "robust" when identified using two different groups of control patients. Regarding SDD, Sánchez-Ramírez *et al.* concluded that SDD was effective in an ICU setting with a high level of resistance and subsequent high level of clinical infections (27). Several Dutch studies concluded the same in ICU settings with low levels of resistance (28-31). Additionally, SDD appeared to be cost-effective, and there was no relation between the use of SDD and the development of resistance in microorganisms in patients in the ICU (32-35). We hypothesize that the reason why we identified SDD as a robust risk factor, despite the antibiotic colistin being present in

SDD, could be because (i) the sites of the patient's body where VIM-positive *P. aeruginosa* primarily adhered was not in the gastrointestinal tract so could not be reached by SDD, (ii) the SDD could not reach VIM-positive *P. aeruginosa* in the gut because of a paralytic ileus, or (iii) topical application of colistin is not sufficient enough. Because SDD does kill other bacteria present in the gut, VIM-positive *P. aeruginosa* may adhere and proliferate. This is supported by James Hurley, who concluded that the incidence of ventilator-associated pneumonia caused by *P. aeruginosa* stayed similar in patients who did and who did not receive SDD (36). Regarding having undergone a gastroscopy; complex endoscopes have a relatively high chance of inadequate reprocessing compared to non-complex endoscopes, such as gastroscopes. However, outbreaks with as source the gastroscope have been reported, and to date no study was performed to determine the prevalence of microbial contamination of patient-ready gastroscopes, or critically assessed the gastroscope reprocessing procedures (37-39). **We conclude** that when studying microorganisms using a case-control study design, investigators need to consider using different control groups, and reason in the method section of the article why certain control groups were chosen. Additionally, use of quinolones and SDD can make patients prone to carriage of VIM-positive *P. aeruginosa*, and gastroscopy could be considered as a high-risk procedure in patients with risk factors.

In **Chapter 3.2**, we performed a nationwide cross-sectional study to assess the contamination rate of patient-ready duodenoscopes, after we proved and published in 2015 that these were a source for VIM-positive *P. aeruginosa* and the cause of an outbreak of this bacterium (40). Our study showed that 22% (33 duodenoscopes) of patient-ready duodenoscopes from 67 hospitals in the Netherlands were contaminated with ≥20 colony forming units (CFU), and 15% (23 duodenoscopes) were contaminated with gastrointestinal or oral bacteria, independent of CFU count (41). We also showed that this was not dependent on the duodenoscope manufacturer (*e.g.* Olympus, Pentax or Fujifilm), or duodenoscope type (41). This means that our study showed that patients are at risk. Since duodenoscopes are causally linked to outbreaks of CRE, and are difficult to clean and disinfect, it is a thin line between benefiting patients by the ERCP procedure and doing harm (41, 42). The different sampling conditions of the endoscopes and adherence to the strict sampling protocol could not be checked in our study, which is a limitation. **To conclude**, this study showed high prevalence rates of contaminated patient-ready duodenoscopes. This means that the current reprocessing and process control installed or the design of the endoscopes is not sufficient. This calls for further research and uniform guidelines and instructions, since they are currently lacking.

Third, **chapter 3.3** shows an outbreak of *C. difficile*; a microorganism first identified in 1935, causing infection, with as symptoms severe diarrhea and colitis (43). This outbreak was caused by a hypervirulent not-before published new *C. difficile* clone, and involved 5 patients (44). By constructing an epidemiological curve and by conducting molecu-

lar analyses transmission was confirmed. However, an environmental source was not identified. *C. difficile* can be hospital-acquired as well as community-acquired (45-47). Previously identified and known sources include (i) *C. difficile* colonized persons (*i.e.* in the absence of symptoms), as described by Crobach *et al.* in 2018: the most important unexplained reservoir for *C. difficile* transmission (48), (ii) animals, from wild animals to pets (49), and (iii), the environment, including water, plants and soil (49). With such a variety of sources successful infection prevention and control is difficult. In 2011, the burden of *C. difficile* infection (CDI) in the United States was estimated at almost 500,000 infections, and 29,000 deaths (47). In Europe, during a point prevalence survey during 2011-2012, 48% of all gastrointestinal infections registered were due to *C. difficile*, and most common in Hungary and UK-Wales (50). **We conclude** that new *C. difficile* ribotypes still emerge without a clear source. Therefore, ongoing surveillance as currently installed in the Netherlands needs to continue (51). In this way, outbreaks can be detected in an early phase and measures can be installed.

Overall, the conclusions from the studies presented in these three chapters show that bacteria are most often transmitted from an unidentified patient to the environment, object, or hands of HCW, to the next patient. Bacteria can remain on inanimate surfaces for months and therefore the hospital environment acts as a continuous source (52). Finally, outbreaks with HRMO happen, and close monitoring of high-risk environments and of high-risk patients is important to control transmission in an early phase.

Healthcare-related pathogens: detection of transmission

To detect local hospital outbreaks typing techniques are necessary. Therefore, we studied the then novel method Raman spectroscopy, a phenotypic typing method, in order to conclude whether or not to implement this technique in the diagnostic laboratory of our tertiary-care hospital. As described by Eberhardt *et al.*, advantages for diagnostic laboratories when using Raman spectroscopy are (i), minimal sample preparation, (ii), high specificity, (iii), label free, no dyes and toxic waste products, and (iv), non-destructive, non-invasive (wavelength and power dependent) (53). Disadvantages are (i) auto fluorescence (sample dependent), (ii) low sensitivity, (iii) long measurement times if weak Raman signal, and (iv) sophisticated data analysis are often necessary (53).

In **Chapter 4.1**, we evaluated Raman spectroscopy using SpectraCell*RA* analysis (RiverD International B.V., Rotterdam, The Netherlands) for a period of 43 months (54). We applied this typing method retrospectively and included patients identified with ESBL-producing *Klebsiella pneumoniae* or ESBL-producing *Klebsiella oxytoca*, and used it prospectively, also for patients identified with an ESBL-producing *K. pneumoniae* or ESBL-producing *K. oxytoca*. We could detect clonal outbreaks which were epidemiologically plausible, which could have possibly been prevented if instant prospective typing had been implemented in our hospital. However, we think that our results are the tip of

the iceberg, because we did not install routine admission screenings, and therefore have presumably missed a lot of unidentified carriers. For this study, we also developed definitions of epidemiological relatedness, and conducted a spatial analysis to combine this with the Raman data. The definitions were not only applicable to *Klebsiella* species, but we also applied them to ESBL-producing *Escherichia coli* (**chapter 4.2**), and VIM-positive *P. aeruginosa* (**chapter 3.1**) transmission events (25, 55). Our definitions could have been too strict. Therefore, it is possible that we misclassified or missed epidemiological relations that were present.

In **Chapter 4.2**, we studied if High-Throughput Multilocus Sequence Typing (HiMLST) and Raman spectroscopy could detect ESBL-producing *E. coli* healthcare-related transmission events, using four different models (55). We concluded that we did identify genetically and phenotypically defined clusters, however; patients in all four models were not epidemiologically related. This can be explained by (i), missing links (*i.e.* unidentified carriers), and/or (ii), the high community carriage rates of ESBL-producing *E. coli* sequence type (ST) 131. To solve this problem, we concluded that more sensitive typing techniques (*e.g.* whole genome sequencing or wgMLST) and admission screening are needed.

We conclude that epidemiological plausible clusters for ESBL-producing *Klebsiella* species; however, this could not be concluded for ESBL-producing *E. coli*. Additionally, epidemiological relatedness is often described in publications; however, definitions are almost never published in such a way that they are directly applicable to your own research. With our table of epidemiological relatedness, applied to three different scenarios, we hope to contribute to epidemiological research on transmission of bacteria. Raman spectroscopy had advantages and disadvantages. Eventually, Raman spectroscopy was not implemented as a routine typing technique in our hospital. This was mainly due to the software instabilities and the sudden unavailability of the method at that time.

FUTURE PERSPECTIVES

Healthcare-related pathogens: risk factors

The literature studies in chapters 2.1, 2.2, and 2.3 may serve as a basis and provide knowledge for observational or experimental research on HRMO. We feel that especially **(i)**, future research should not only focus on developing new antibiotics, but also on novel therapeutic strategies since resistance to all biologic antimicrobials will ultimately develop (23). **(ii)** Future studies should reconsider the design of the hospital sink, including the faucet, faucet aerator, sink tap, grating, plughole, and siphon because of biofilm formation of bacteria in these areas. **(iii)** More research is needed about single-

patient rooms and the effect on acquisition of HRMO. On May 18, 2018, the Erasmus MC University Medical Center, Rotterdam, the Netherlands (Erasmus MC), moved to a new building, with only single-occupancy rooms. This event provided a unique opportunity to perform such a study. Hundreds of patients that were housed in multiple-occupancy rooms in the old building, and hundreds of patients that are housed in the new building were and continue to be included. From these patients, admission and discharge cultures (perianal swab) were and continue to be performed. Additionally, the hospital environment was and continuous to be thoroughly sampled in both buildings. Hopefully, this study will add to the existing knowledge about changes in environment and in patients when moving from multiple-occupancy rooms to only single-occupancy rooms. **(iv)** It is not known whether there is a relationship between HRMO infection prevention policy and the prevalence of HRMO. Therefore, future studies should assess the cost-effectiveness of infection prevention strategies to prevent transmission and acquisition of HRMO and compare policies in settings with a high prevalence of HRMO to settings with a low prevalence of HRMO.

Healthcare-related pathogens: sources and transmission

P. aeruginosa can survive in environments with low and high availability of nutrients, can grow at temperatures between 10^0C and 42^0C, and forms biofilms (56). Therefore, this microorganism is difficult to remove from the environment. **(i)** The most optimal cleaning agent for *P. aeruginosa* environmental cleaning protocols has not yet been defined. This can be investigated by future studies. **(ii)** We identified use of SDD as a risk factor for acquiring VIM-positive *P. aeruginosa*; in future research a subgroup analysis of all patients with SDD could be performed to unravel any unidentified important patient characteristics. Additionally, future studies should determine if SDD can be optimized in settings were this microorganism is present. **(iii)** Since gastroscopy was identified as a high-risk procedure, future studies should investigate the prevalence of bacterial contamination of gastroscopes, and should assess the gastroscope reprocessing process.

Regarding contamination of duodenoscopes, future studies should **(i)** investigate the effect of other confounding factors, such as age and number of procedures of the duodenoscope and the time component (*i.e.* considering the warnings by for example the U.S. Food and Drug Administration and newly developed guidelines) on contamination levels of duodenoscopes. **(ii)** Since the reprocessing of duodenoscopes is not optimal, future studies should investigate different and novel cleaning and drying methods. **(iii)** A cross-sectional study design is useful when wanting to know a prevalence; however, follow-up data of duodenoscopes is needed to study persistence of colonization and to study the effects of interventions on contamination rates. This can be investigated by future studies.

Finally, our newly identified ribotype 826 *C. difficile* was not identified in databases of human collections, and animal collections are lacking. Therefore, we strongly support the development of a global database or national reference laboratory for animal-associated *C. difficile* infections can be realized.

Healthcare-related pathogens: detection of transmission

Considering the different typing methods in combination with epidemiological relatedness, it is **(i)** important that there are as less as unidentified carriers as possible. Therefore, future studies about transmission dynamics should assess in a setting with admission cultures of all patients if molecular relationships can be explained epidemiologically. **(ii)** In chapter 4.2, we did not find any epidemiological relationships between patients with phenotypically identical ESBL-producing *E. coli*. If admission cultures are installed, the different relationships should be studied again for this microorganism. Since literature on the effect and necessity of infection prevention measures for patients identified with ESBL-producing *E. coli* is contradictory, these data could be helpful. **(iii)** In chapters 4.1 and 4.2, we studied ESBL-producing *K. pneumoniae*, ESBL-producing *K. oxytoca* and ESBL-producing *E. coli*; future studies should investigate other HRMO. **(iv)** Transmission dynamics of HRMO should be studied in different settings; for example university compared to non-academic hospitals, or hospitals in countries with a high HRMO prevalence compared to hospitals in countries with a low HRMO prevalence. Additionally, network analyses should be performed to further understand transmission dynamics. To fully understand transmission dynamics, the network analyses should not only include movements of patients in one hospital, but also movements of patients between different hospitals. Furthermore, not only movements in and between hospitals should be included, but also for example admissions to nursing homes and rehabilitation clinics. Finally, **(v)** future studies should keep evaluating novel promising typing methods, as speed and accuracy can always be improved, and are important in fast, efficient and effective infection prevention and control.

FINAL NOTES

Epidemiology is the study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems (24). Study includes: (i) surveillance, (ii) observation, (iii) screening, (iv) hypothesis testing, (v) analytic research, (vi) experiments, and (vii) prediction (24). In this thesis, epidemiological studies were conducted in order to understand, describe, and evaluate the dynamics between patients and microorganisms in a hospital environment.

Study designs

Back in 1904, summarizing and pooling of data in review articles was introduced (57). Currently, systematic reviews are well established studies to summarize all available evidence about a specific subject. Because of the possible high impact of results of systematic reviews on decision making in healthcare, the quality of reporting of meta-analyses (QUOROM) statement was introduced in 1996 (officially published in 1999) (58, 59). This statement aimed at enhancing quality of systematic reviews of randomized controlled trials (RCTs) (58). In 2009, the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was introduced as an update of the QUOROM statement (www.prisma-statement.org) (60). Currently, in 2018, an update of the 2009 statement is under development. In addition, in 2018, the PRISMA statement checklist is mandatory to add as supplemental material when submitting a systematic review to over 180 journals. Hence, we also need to consider the limitations of systematic reviews. A first limitation that needs to be considered is the between study heterogeneity. This means that there are underlying differences among the included studies. This may be caused by (i) the selection of patients, (ii) differences in study setting, (iii) patient characteristics, (iv) measurements, and/or (v) methodological study differences (61). One can reason if heterogeneity between studies is present or not, or use the I^2 statistic (61, 62). The I^2 statistic is easily available, easy to apply, and easy interpretations are available (62). However, the I^2 statistic is often used inappropriately (63). Only the statistic itself can give wrong information, as for example a meta-analysis with an I^2 value of 80% can correspond with less variance than a meta-analysis with an I^2 value of 20%. Therefore, it should always be used together with the forest plot. However, still when using a forest plot, the I^2 statistic only shows you the extent to which confidence intervals from the different studies overlap with each other, nothing about the actual study to study dispersion in effects (63). In chapters 2.1, 2.2 and 2.3, heterogeneity between studies was present when using the I^2 statistic in combination with the forest plot. Therefore, in all these three studies, a random effects model was fitted in all meta-analyses. A random effects model allows for differences from study to study, and is therefore a good statistical option if heterogeneity between studies is present (64). A second limitation of systematic reviews is publication bias. Publication bias means that the research that is available differs in its results from the results of all the research that has been done (65). Often, studies with a non-significant result or negative results are not published. Publication bias was also present in almost all meta-analyses present in this thesis, as indicated by funnel plots (*i.e.* visual inspection) or by bias indicators by Egger *et al*, and Begg and Mazumdar (66, 67). It is possible to correct for publication bias by imputing the apparent missing values in funnel plots; however, this is not always preferable.

From chapter 3.1 we learned that the approach of using two different groups as controls showed that results you obtain from case-control studies highly depend on

the choice of the control patients. As described by Feinstein and Horwitz in 1983, the different choices of control patients suggest either that (i) the perfect control group does not exist, or (ii) that just no specific standards have been established in order to decide which controls to use (68). Additionally, described by Grimes and Schulz in 2005, poor choice of controls can lead to both wrong results and possible medical harm (69).

With a cross-sectional study as used in chapter 3.2, data is collected at a given point in time. Making causal inferences is not possible with this type of study, unless the exposure, in this case contamination, is stable over time (70). Kraemer *et al.* states that limitations of cross-sectional studies are acknowledged, however understated (71). To assess the validity of observational studies, including cross-sectional studies, a Cochrane systematic review by Anglemyer *et al.* included reviews, and investigated healthcare-outcomes assessed with observational study designs compared with those assessed by RCTs (72). They concluded that when conducting a review on a specific topic, on average there is little difference between results obtained from RCTs and results obtained from observational studies (72). However, unfortunately a direct comparison between cross-sectional studies and RCTs was not possible, because of lack of identified studies (72).

The future of hospital epidemiology

An epidemiologist is a professional who strives to study and control the factors that influence the occurrence of disease or other health-related conditions and events in defined populations and societies, has an expertise in population thinking and epidemiological methods, and is knowledgeable about public health and causal inferences in health (24). A healthcare epidemiologist should have knowledge about (i) disease exposure and transmission, (ii) an understanding of measures of incidence and prevalence, and (iii) basic knowledge of microbiology, bacteriology, virology and mycology (73). As described by Bryant *et al*, having at least one dedicated full-time healthcare epidemiologist, next to infection preventionists and clinical microbiologists, is a requirement for an effective infection prevention and control/healthcare epidemiology program in a healthcare institution (74). In the future, I hope we can accomplish this in every Dutch hospital; both academic and non-academic.

In this thesis, we described three topics, all about healthcare-related pathogens; (i) risk factors, (ii) sources and transmission, and (iii) detection of transmission. In my opinion, the three topics in this thesis are connected. We need to learn from other outbreaks and studies about infection prevention and microorganisms, we need to learn from our own outbreaks and gain deep understanding how and why it happened, and we need to constantly evaluate existing and new typing methods to quickly learn if isolates from patients are related or not. There are also four different levels within the three topics (Figure 2): (i) healthcare at individual hospital level, (ii) healthcare at regional level, (iii) healthcare at national level, and (iv) healthcare at international level.

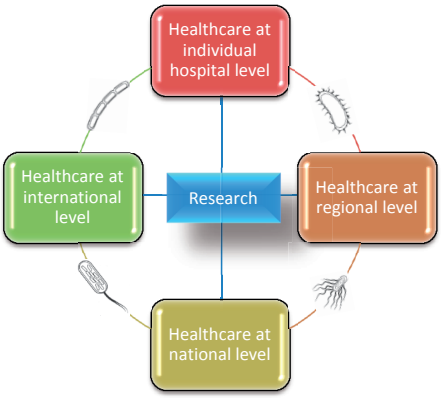

Figure 2. Connections of hospitals concerning risk factors, sources and transmission, and detection of transmission of microorganisms.

These levels are also connected. Concerning the individual hospital level, data collection and data connection can happen without any problems. However, when collecting and connecting regional, national or international patient data in order to epidemiologically interpret the results of molecular genotypic or phenotypic typing, problems of data ownership and patient privacy arise, especially when a website-based database is used. Therefore, agreements between institutes need to be signed and the patient privacy must be adequately protected. In the future, I hope we can develop first national guidelines, and then followed by international guidelines about data ownership and patient privacy. National and international collaborations are in my opinion the key. Overall, research is the connecting factor, which needs to be executed at each level, about every topic possible. Share information about infection prevention, share data, share research. In this way we can combat antimicrobial resistance and combat spread more effectively and efficiently, because transmission happens, and often through unidentified sources and/or reservoirs.

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