IMPLEMENTING ANTIBIOTIC STEWARDSHIP: INVOLVING STAKEHOLDERS IN EHEALTH

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EURSAFETY HEALTH-NET

UNIVERSITY OF TWENTE.

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Table of contents

Chapter 1:
General introduction

General introduction

When Charles Darwin published his “The Origin of Species” in 1859, he introduced the scientific theory of evolution [1]. The famous phrase “survival of the fittest” [2] was coined by Herbert Spencer after reading Darwin’s book and was later also used by Darwin himself. Survival of the fittest means that organisms adapt to their environment in order to survive and some organisms are better at it than others. This idea of survival of the fittest is a nice analogy to quickly explain the two central topics in this thesis: antibiotic stewardship to curb antibiotic resistance, and, implementation research to implement eHealth interventions.

The discovery of penicillin in the late 1920s was a big advance in modern medicine. Soon, more antibiotics were discovered and a new era dawned in healthcare [3]. Antibiotics were used heavily to treat infections and with great results, however, the efficacy of the antibiotics soon started to wane. Certain infection-causing microorganisms adapted quickly to the exposure to antibiotics and developed defense mechanisms [4]. An initial response was to discover new antibiotics and use those instead, which started a “survival of the fittest”-arms race until microorganisms became resistant against those as well. However, over time the discovery of new antibiotics declined and the medical world has to cure infections with the current arsenal of antibiotics [5, 6]. This calls for new cross-border infection control strategies to curb antibiotic resistance. Antibiotic stewardship, a program that promotes prudent antibiotic use by prescribing physicians, is becoming important for hospitals [7]. These programs are fairly new, especially in the Netherlands, so teams tasked with implementing antibiotic stewardship can use extra guidance and support in how to implement antibiotic stewardship in their hospitals.

Survival of the fittest is also relevant in implementation research for eHealth. Implementation research is the study of methods to promote the uptake of research into practice to improve the quality and effectiveness of health services and care [8]. Implementation research in healthcare can be a complex task. Healthcare has many stakeholders with different interests; funding challenges; strict policies and regulations that can obstruct innovation; challenging (technical) infrastructures; hesitant status quo; absence of marketing for dissemination and business model innovation [9, 10]. eHealth should not only be seen as a technological product or a service alone, but as a holistic way to improve healthcare [11, 12]. Many eHealth technologies are based on a good idea, but in practice a lot of endeavors turn out unsuccessful [13-16]. In fact, so far, many implementations of eHealth technology show little to no substantial evidence that they are truly beneficial for outcomes or cost-effectiveness [14]. It is up to implementation researchers to co-create a fitting implementation for their eHealth technologies with the right, important stakeholders that ensures sustainability, efficacy and -to draw another parallel with Darwin's "survival".

In this thesis the two topics are combined. We used business modeling as the central research method for discovering implementation strategies for antibiotic stewardship and we develop eHealth technologies to facilitate the implementation of antibiotic stewardship. As ASP implementations rely mostly on expert guidelines and recommendations, we researched the implementation with business modeling to involve stakeholders in the implementation process to understand their values and needs from a bottom-up perspective. We developed eHealth technology to support the stakeholders with a supportive online implementation application based on the findings from the business modeling research.

The following paragraphs introduce the background of infectious diseases, the role of antibiotics, the challenges of antibiotic resistance and antibiotic stewardship. Next, implementation research is introduced, followed by an introduction to eHealth. What follows is an overview of the Center for eHealth research roadmap, which in this thesis is used for eHealth development, and business modeling is explained as our implementation method. Lastly, the general introduction concludes with the research questions that are addressed in this thesis and an outline of the chapters.

Infectious diseases

It is estimated that microorganisms, mainly bacteria, outnumber human cells in our body 10 to 1 and that around 10,000 different species of bacteria live inside every human being [17]. Many microorganisms that live inside the human body are harmless and are part of the normal flora inside every human being. Microorganisms and humans even have a symbiotic relationship where they both benefit from each other [18]. For example, our bowels are full of bacteria that help digestion [19], or the commonly accepted idea that occasionally getting into contact with bacteria is actually good for priming your immune system. Although most microorganisms are harmless, some do bring harm to their host. These microorganisms (then called pathogens) cause an infection in their host. Infectious diseases can be caused by many possible microorganisms like bacteria, viruses, protozoa, fungi, etc. [20]. Typical for these infectious diseases is that they easily spread via contact between infected and uninfected humans, usually by physical contact, air, food or other modes of transmission. The recent outbreak of Ebola in Africa is a textbook example of a life-threatening pathogen causing havoc due to its difficult curability, difficulties to maintain rigid hygienic protocols (e.g. mourning family members touching the deceased), and its dangerously effective ways of spreading.

Hospital-acquired infections

A global problem in healthcare is a special kind of infections, the hospital-acquired infections (HAIs) [21, 22]. HAIs are infections that are not present or incubating at the time of admission of a patient to a hospital [23]. That means patients acquire an infection in the hospital while receiving care for what they were hospitalized for. Around 8-12% of patients in Europe suffer from adverse events while receiving care in a hospital, with HAIs being the most prominent of them [24]. For example, methicillin-resistant Staphylococcus aureus (MRSA) is a common HAI worldwide [25]. MRSA can be carried by healthy people without ill effects, but patients with wounds (for example after surgery), invasive/implanted devices or weakened immune systems risk getting infected with MRSA, resulting in pneumonia, blood poisoning and in worst case death. The prevalence of MRSA differs greatly per country, for example the prevalence of MRSA is 10%-25% or even higher in most Southern European countries, whereas in the Netherlands and most Scandinavian countries the prevalence is 1% or lower [26, 27]. These differences between prevalence between countries are explained by (nationally) implemented guidelines concerning infection prevention and control measures and antibiotic policies [25].

Besides adverse effects to patients, HAIs are also a big societal problem as they cause four million infections and around 37,000 yearly deaths in Europe alone [21], subsequently resulting in estimated extra costs of 700 million Euros a year for the European Union [21]. These costs are incurred by increased antibiotic use, longer length of hospital stay, extra hygiene precautions, etc. International and national health agencies intend to increase the awareness of HAIs and started campaigns and guidelines to control HAIs [21, 28, 29]. As already said in the paragraph above, the prevalence of hospital-acquired infections is different per country, but it is also different per region or even per hospital or per hospital ward [27, 30, 31]. For example, at hospitals in rural areas like Twente, the prevalence of livestock-associated MRSA is higher than at hospitals in urban areas like Amsterdam.

Antibiotics

Antibiotic is derived from the Greek words ‘anti’ and ‘biotikos’ that, when combined, mean ‘against life’ [32]. An antibiotic is a substance produced by microorganisms to protect itself against other microorganisms. Before the 20th century, medicine relied on molds, soil and plants to cure bacterial infections. While most of these treatments were rooted on spiritual ideas, some were occasionally effective due to the active chemicals present in those substances. In 1928 a major medical breakthrough came as Alexander Fleming discovered that penicillin had antibacterial properties. Soon more antibiotics were discovered or developed. More and more infectious diseases, such as meningitis or pneumonia, that hitherto caused terrible inflammations or deaths could now be successfully treated and cured.

Note: Strictly speaking one has to use the word antimicrobials to include all agents (also synthetic), but for the sake of clarity when using the term 'antibiotic stewardship', we do not differentiate between the two when referring to antibiotics in this thesis. Some researchers prefer to call it 'antimicrobial stewardship' to differentiate but in guidelines in the Netherlands it is preferred to call it 'antibiotic stewardship'.

Aside from curing infections, antibiotics also play an important role in preventing infections. The preventive properties of antibiotics can be especially useful after surgery, called prophylaxis, which makes surgeries less dangerous and prevents complications. This is also why antibiotics are a commonly used medication in health care. As for today, about 30-40% of all patients in a hospital in the Netherlands are prescribed antibiotics [33].

Another notable application of antibiotics is in animals to prevent infections while farming them. It is out of the scope of this thesis to go into non-hospital applications of antibiotics, however, the use of antibiotics in other fields, such as livestock farming, can also cause resistant infections in patients too (via food chain or contact with animals) and is a factor of concern in the causes of antibiotic resistance [34].

Antibiotic resistance

Antibiotics as a miracle drug against infections sounds too good to be true, which brings us back to the concept of 'survival of the fittest'. Soon after the introduction of antibiotics, scientists discovered that the efficacy of antibiotics quickly waned [4]. They discovered that, when microorganisms are exposed to antibiotics, they adapt and reproduce themselves with defensive mechanisms [35]. For example, some bacteria evolved by adapting their cell membranes to simply no longer let antibiotics through or they created pumps on the membrane that pump antibiotics out of the cell. A problematic infection in many hospitals worldwide is methicillin-resistant Staphylococcus aureus (MRSA), which is a strain of Staphylococcus aureus that has developed resistance to beta-lactam antibiotics [24]. In a recent study it is even demonstrated that MRSA makes the infection worse when beta-lactam antibiotics are applied [36].
Initially, the emerging antibiotic resistance spurred an arms race. At that time, antibiotics were a fairly new area of research, so scientists discovered and developed many new antibiotics in the 1930s-1960s to keep up with the resistance-forming microorganisms [37]. Unfortunately, every time microorganisms were exposed to these new antibiotics, they developed resistance after a while. To speed up the resistance problems, the discovery and development of new antibiotics stagnated [6, 38]. Only two new classes of antibiotics were discovered in the last 30 years, and, to demonstrate the speed of resistance-forming, microorganisms got resistant to one class of antibiotic even before the antibiotic was officially approved for medical use [37]. Why antibiotic research and development has plummeted is mostly money related. Development of new medication is expensive and takes

many years of trials and test before approval to go to market. Antibiotics are not exactly a cash cow product for pharmaceuticals unlike chronic disease drugs like those to treat cholesterol, diabetes or cancer. Therefore, it is not worth the investment and drug companies withdrew from new antibiotic research and development [37].

Antibiotic resistance is still steadily rising [39]. This why the term 'post-antibiotic apocalypse' is uttered by several infection control scientists. If we do not act, the glory days of antibiotics will be over, and, for antibiotics to remain of use in health care, we are in dire need of change how antibiotics are used [35, 40].

Textbox 1: EurSafety Health-net

The European Union stimulates mobility of their citizens. Also in healthcare an increasing number of patients and healthcare professionals cross the borders and seek or offer healthcare services abroad. Especially in border regions, such as Euregio Enschede-Münsterland, cross-border healthcare is common and Dutch and German healthcare professionals learn from each other. Cross-border healthcare faces differences in healthcare systems and policies, subsequently differentiating the quality of care. A comparison between the Netherlands versus Nord-Rhein Westfalen showed that in 2010 the German region had 32-fold higher incidence of MRSA than the Netherlands [41]. This big difference was attributable to the Dutch Search-and-Destroy policy for MRSA whereas Germany did not have such a preventive screening policy [42]. The MRSA-net project was a cross-border project to take action against the incidence of MRSA in both the Netherlands and Germany [43]. After the MRSA-net project that resulted in a cross-border infrastructure of collaborating health care and research organizations to take action against MRSA, EurSafety started a follow-up project with the primary goal to scale these initiatives up and targeting wider than MRSA [44]. Dubbed "EurSafety Health-net", this project had the key ambition to improve patient safety in cross-border healthcare.

Our involvement in this project focused on developing an Internet-based platform for cross-border infection control [45]. In cross-border regions, even the slightest differences in antibiotic policies and infection control measures can cause numerous complications when healthcare professionals and/or patients cross the border. Aware of the fact that "infection control" is a wide field, our project focused on antibiotic prescription in hospitals -and later "antibiotic stewardship" specifically- as intervening antibiotic use can be a next step in curbing antibiotic resistance and hospital-acquired infections, and subsequently improving patient safety [46]. Our specific contribution to the project was developing persuasive eHealth technology for infection control and effectively implementing this technology using stakeholder-driven, participatory design and business modeling. During our research we worked closely in alliance with the local hospital in Enschede (Medisch Spectrum Twente), the microbiology laboratory Twente (LabMicta) and later also the academic hospital in Groningen (Universitair Medisch Centrum Groningen), academic hospital in Münster (Universitätsklinikum Münster) and Certe microbiology laboratory North-Netherlands.

The implementation of antibiotic stewardship and business modeling for eHealth subjects presented in this thesis was one of three PhD research tracks part of the research at University of Twente for EurSafety Health-net. My project colleagues, dr. M.J. Wentzel researched participatory development of eHealth interventions to support healthcare professionals with their information needs [47] and N. Beerlage-de Jong, MSc is researching the development of decision support interventions.

Antibiotic stewardship

The increasing antibiotic resistance is a global concern. Organizations like World Health Organization (WHO) and European Center for Disease Control (ECDC) call for a change in how antibiotics are used [48, 49]. It is pointed out in previous studies that up to 50% of all antibiotic prescriptions in hospitals are inappropriate or even unnecessary [50]. Improving the use of antibiotics in hospitals calls for a programmatic approach [51]. An antibiotic stewardship program (ASP) is such a program that aims to optimize antibiotic use. ASP ensures proper use of antibiotics with the best patient outcomes, lessen the risk of adverse effects, promote cost-effectiveness and reduce or stabilize levels of resistance [7]. This idea for a program that influences antibiotic use is not exactly new; the first acknowledged antimicrobial stewardship, or antibiotic stewardship program started in the 1970s in Hartford Hospital in the United States [52].

In the 2000s and 2010s worldwide more interest arose for implementing such antibiotic stewardship programs in hospitals. Expert guidelines recommend hospitals (how) to introduce ASPs, in particular the IDSA/SHEA guidelines [51] are commonly acknowledged as a helpful basis. Also in the Netherlands, the SWAB (Dutch working party for antibiotic policy) released a directive document [53] in 2013 stating that hospitals should start with ASP initiatives per January 2014 followed by workshops and a website for antibiotic stewardship teams [33]. Recent publications on antibiotic stewardship focus strongly on effect assessment of these programs as outcome assessments are necessary to determine whether and to what extent ASPs are effective [54]. Focusing on the effectiveness of interventions on antibiotic prescribing, Davey et al. concluded in their review that there is overall evidence that particular interventions have a positive effect on prescribing and resistance [55]. Also, Kaki et al. assessed the impact of ASPs specifically in intensive care units and also concluded the overall evidence suggests that ASPs improve antibiotic use in the intensive care unit, and, improve resistance and adverse events without compromising short-term clinical outcomes [56].
Despite a growing body of literature on interventions and the efficacy of these interventions for ASP, hardly any practical literature is available for hospitals to implement such programs. Not enough guidance is offered on the practical aspects of implementing ASPs and hospitals need to overcome implementation issues by accounting for their unique characteristics [57, 58]. In other words, antibiotic stewardship teams need to figure out themselves how to implement ASP. Related to the lack of practical literature, still little is understood about the effectiveness of individual interventions (and their interplay) that are part of comprehensive ASPs [59]. This may explain why there is no consistency between local implementations of ASPs [60].

Implementation

The other main topic in this thesis is implementation research. It is acknowledged that many health care innovations struggle with their implementation [9, 10, 14]. Also in regard of the implementation of antibiotic stewardship in hospitals, we can say that there are many implementation barriers to overcome as well [61].

But what exactly is "implementation"? The word "implementation" is a generally accepted word in society and used in all kinds of contexts. Even when one checks the dictionary, it remains a rather abstract term that seems to revolve around the idea of incorporating or embedding something. Implementation research is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care [8]. Implementation frameworks aim to improve the uptake (i.e. implementation and adoption of healthcare technologies) or the impact (i.e. effectiveness of eHealth technologies), and for an optimal implementation ideally both [12]. Factors that support the adoption and implementation of healthcare technology are often underestimated in research [9, 10].

There are not many methodologies available for healthcare technology that truly deal with encompassing implementation methodologies. In van Gemert et al, an overview was given of 16 frameworks that aim to bring about the widespread diffusion and adoption of eHealth technologies, the implementation of eHealth technologies, or the improvement of the performance and effectiveness of eHealth technologies [12]. Commonly used implementation frameworks in eHealth research, such as Normalisation Process Theory (NPT) [62], RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework [63], intervention mapping [64] or the STOF-model [65], focus on advising possible implementation factors that influence the implementation of eHealth. These frameworks are generally expert-driven approaches to implement healthcare technology. However, as of yet there is no framework that addresses the problems with diffusion, acceptance and adherence [66] combined with overcoming the uptake and impact barriers that eHealth technologies face [12]. We, therefore, advocated to obtain such factors directly from the stakeholders themselves. We are not saying the above expert-driven methods are not successful methods to find an implementation for eHealth technologies, but we believe that a bottom-up approach, where stakeholders themselves take an active role in determining the implementation helps the uptake and impact of eHealth [12]. Based on assessing the strengths and limitations of all these frameworks, we introduced the CeHRes roadmap that supports the development of eHealth technologies [12].

The following paragraphs introduce our approach for implementing eHealth. We explain what eHealth is, give a short description of the CeHRes roadmap and finally, introduce business modeling, which plays an important role in implementing eHealth using the roadmap.

eHealth

In the 2000s, research into blending technologies and healthcare increased, called consumer health informatics, telemedicine, Health 2.0 or eHealth. There is a plethora of terminologies and definitions in the academic world how to define eHealth and it is still a subject for discussion [67]. One of the leading eHealth researchers, Eysenbach, defined eHealth as “an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve health care locally, regionally, and worldwide by using information and communication technology” [11]. This definition states that eHealth should not only be seen as a technological product or service, but it is something more: eHealth is a way to improve healthcare. To expand on how eHealth can improve healthcare, Eysenbach explains how the “e” in eHealth not necessary stands for electronic, but also ten other important characterizations: efficiency, enhancing quality, evidence-based, empowerment, encouragement, education, enabling, extending, ethics and equity [11]. The strong points of eHealth are that it improves access to healthcare, can save resources, innovates health processes, empowers patients, can improve care quality, can offer just-in-time care and, finally, can improve outcomes and improve the effectiveness of care [68].

eHealth can be used for many technologies, such as web technology (e.g., portals, peer support sites, information sites), mobile technology (e.g., tracking apps, information apps), medical devices (e.g., domotics, robotics), data sharing networks (e.g., electronic patient records, personal health records), wearables (e.g., tracking apps, alerts), to name just a few possibilities. The choice of technology is also dependent on the context in which it will used. eHealth can support healthcare processes in telediagnostics, online triage, decision support, remote consultation, online therapy, remote monitoring, information/advice, E-learning, appointment management, health record management, procurement, etc. eHealth technologies can target different user groups. Usually the main users are patients or health professionals, or in some cases, both. This also means there can be different ways of user interaction, for example doctor-to-doctor, doctor-to-patient, patient-to-doctor, or patient-to-patient.

Even though eHealth sounds very promising, the innovation in healthcare with eHealth still faces obstacles that hinder the global uptake of eHealth. As said earlier in the introduction, many eHealth technologies struggle to be successful. Implementation of eHealth has almost universally proven to be more complex and time-consuming than anticipated [14]. The biggest cause is that there appears a strong emphasis on the design of the technology, but relatively little attention to the effect on roles and responsibilities, risk management, engaging professionals and transparency of potential benefits [69]. eHealth is an interesting, multidisciplinary field [70]. However, this multitude of disciplines also bring in a multitude of stakeholders and a multitude of stakes and interests. The healthcare technology and its implementation has to reflect these stakes in an optimal fit between users (and stakeholders), the organization and the technology [71]. A stronger focus on implementation research to discover how the eHealth technology can be embedded in its intended care setting, to ensure it is effective, is important.

CeHRes roadmap

The Center for eHealth research (CeHRes) roadmap originated from the idea to combine Human-Centered Design [72] with implementation research to develop eHealth that will reflect the needs of its users, but that also gets the right uptake and support from stakeholders in its embedding in organizations [12]. Before we introduced the roadmap, we noticed that most eHealth frameworks primarily focus on supporting design processes yet do not address the problems that need to be overcome with diffusion, acceptance and adherence [66]. The CeHRes roadmap introduces a holistic approach. Holism means that properties of individual elements in a complex system are determined by the relations they bear with the whole system [73], or, in a different healthcare-focused definition, that the holistic model 'deals with health problems in their physical, psychological, social, cultural, and existential dimensions' [74]. This means that developing eHealth is more than creating a nicely designed tool. It has to be a catalyst for innovation and encourage new infrastructures for knowledge dissemination, communication and organization of care [68].

Van Gemert et al provided five principles for eHealth development that are embodied within the CeHRes roadmap and these principles will also be central in our approach for business modeling [12, 68]:

- eHealth development is a participatory process;
- eHealth development creates an infrastructure for changing health and well-being;
- eHealth development is intertwined with implementation;
- eHealth development is coupled with Persuasive Design [75];
- eHealth development requires continuous formative and summative evaluation.

In short that means eHealth development requires the involvement of stakeholders in the design and implementation of the technology, that their needs determine an implementation and infrastructure and that the persuasive design of the eHealth technology reflects user and stakeholder needs. Paired with this is a continuous, formative evaluation which is key in improving the technology, as well as summative evaluation which is necessary to assess sustainability.

The first ideas for the CeHRes roadmap sparked at the beginning of the business modeling research introduced in this thesis. Originally it started as a simple iterative design process (Figure 1A) to streamline possible research instruments both for human-centered design as implementation in a phased structure. In Figure 1B we started to combine Human-Centered Design research instruments with business modeling research instruments to plan the research for our work packages in the EurSafety Health-net project. As the roadmap was deemed promising to use for eHealth development beyond the EurSafety Health-net project, the research of other eHealth research colleagues was added (Figure 1C). By then, the roadmap was complemented with methods to evaluate eHealth[66], design persuasive technology [76] and participatory development [47].

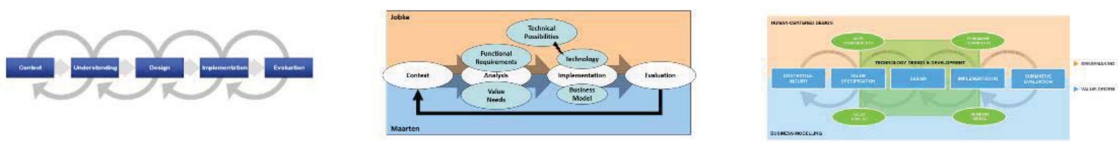

Figure 1: Conceptual stages of the roadmap

In the final stage of the roadmap (Figure 2) we decided to remove the differentiation in two colors between business modeling with the design of the technology, as well as the evaluation. eHealth development is an interwoven process and combines human-centered design instruments with business modeling instruments for a holistic, comprehensive approach to develop eHealth.

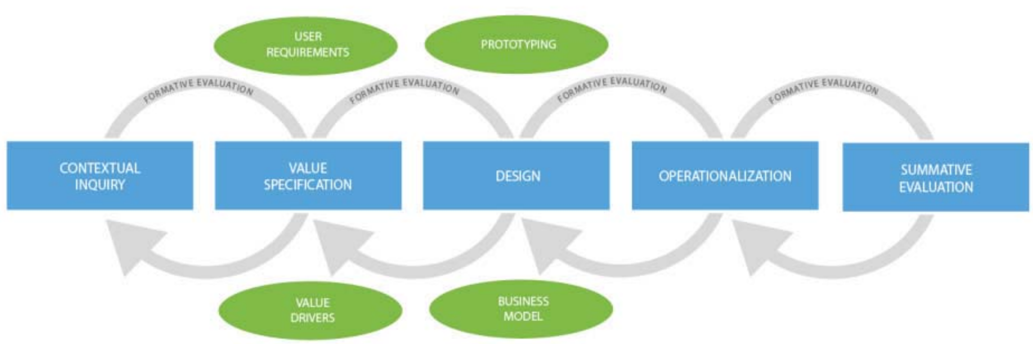

Figure 2: Center for eHealth research roadmap

In this thesis, we mostly focus on the implementation aspects of the roadmap, known as business modeling. Implementation is often seen as an ex-post activity, a step in the development process after the design of the eHealth technology is almost completed. This is prone to problems when trying to implement an already thoroughly designed technology. Making a good technology is not enough and suffers from the ‘Fields of dreams’-syndrome, named after the movie where the plot revolves around the idea that ‘if you make it, they will come’ [77]. Just because you make something that seems a great idea does not mean people will automagically show up and use it. Implementation research is necessary to actually discover what these people want, in order to make sure they will really consider the eHealth technology interesting and beneficial. Implementation of eHealth needs to start ab initio, right from the start.

Business modeling

To think ahead of implementation strategies and to avoid possible implementation problems, we introduced business modeling as a method to implement eHealth technology in chapters 2 and 3. Successful implementation of eHealth requires a deep understanding of current processes and an adaption of these processes to the technology [78]. ‘Business’ as a word may cause skepticism among some people in healthcare. These people should not be put off by the use of ‘business’ in business modeling. It is not about commercializing everything; it is about discovering value expectations. Throughout this thesis, business modeling is used as a method to implement eHealth by discovering the necessary conditions for the infrastructure surrounding an eHealth technology. With stakeholders we discuss what value they expect from the eHealth technology and the resulting business model acts as a blueprint for implementation. One of the key researchers in innovation management, Chesbrough, even says that a technology alone holds latent value, but requires infrastructural aspects around it, i.e. a business model, to yield its actual value [79].

Business modeling is based on the concept of business models. Business models recently gained increased attention, although one of the first acknowledged business model by The Gillette Company already dates from the late 1920s. Especially with the new opportunities from E-Commerce and globalization in the 2000s, business models became much more important for companies to understand how they can do commercially viable business [80]. Business models are mostly used in strategic management for high-level organizational planning that determines the commercial conduct of a firm. A currently popular business model approach is Business Model Generation by Osterwalder and Pigneur who analyzed many business models to design a generic business model suitable for many industries [81]. They define a business model as ‘the rationale of how an organization creates, delivers and captures value’. In short, that means the rationale describes the products and services the organization offers, how the organization can reach its customers and how customers pay in return for the products and services. The complete business model is a narrative for the rationale how to do business [82]. Likewise, a business model can be used to describe the rationale of an implementation of eHealth technology. A business model can be used to provide an overview of critical design issues [65] or critical success factors [83] that are crucial for the implementation.

In our business modeling approach, the focus is mostly on the modeling process. We use a business model as a framework or blueprint to structure the value analysis with stakeholders, in order to determine a possible implementation for eHealth. The business model is also used to present the results of the discussed values with stakeholders. It allows us to model the important aspects necessary to implement the researched eHealth project. The rationale is therefore less a rationale to describe a commercial 'business' (that is how it is used in strategic management for example) but rather a way to describe the conditions necessary for implementing an eHealth technology successfully, according to the involved stakeholders.

In chapters 2 and 3 we will introduce business modeling for eHealth in more detail as it was part of the research for this thesis. In short, business modeling aids to make implementation of eHealth a co-creative and value-driven process. Value may seem to have a commercial connotation, but it is more than that. Value can also be non-monetary aspects like, for example, the well-being of a patient, the improvement of quality of care, or even the reliability of the machines that run the eHealth technology. In earlier research for our roadmap, we defined value as 'an ideal or interest a stakeholder aspires to or has regarding the eHealth technology' [84]. These values can be gathered from stakeholders in value-driven dialogues, which brings us to another important aspect for implementation: stakeholder involvement. Stakeholders need to be involved in the entire development process of eHealth. A stakeholder is defined as anyone who affects or is affected by the project [85]. Business modeling helps identifying stakeholders and assessing which ones are important for the development process. This involvement of stakeholders fosters co-creation for the implementation of eHealth. Co-creation entails that basically the creators and users (and other stakeholders) collaborate in the creation of value [86].

The added value of business modeling is that: 1) it is a method to prepare an implementation for eHealth technology, 2) it is intertwined with design, so discovered important infrastructure aspects can influence the design of the technology and vice versa, 3) it is used to involve stakeholders to discover their value needs and co-create, so the technology reflects needs and fits its intended care setting, 4) it starts at the beginning of development, this is important as finding a fitting implementation is much more difficult ex post.

Implementing antibiotic stewardship

At the beginning of the research in this thesis, most Dutch hospitals were not involved with antibiotic stewardship at all. Some larger hospitals and some academic hospitals were beginning to experiment with antibiotic stewardship based on an increasing attention for the topic in international, academic literature. The implementation research gained traction when the SWAB (Dutch working party for antibiotic policy) released a document in 2013 stating that all Dutch hospitals should start with ASP initiatives per January 2014. Additionally, with our background in eHealth, we planned to use eHealth technology to present the results from the business modeling research, and thus provide the stakeholders in antibiotic stewardship with online tools on how ASP can be implemented.

ASP implementations rely mostly on expert guidelines and recommendations. In order to support the implementation of ASP, we decided to research the implementation with business modeling. Two perspectives are at play: on one hand, there are top-down expert guidelines, recommendations and directives that need to be considered. On the other hand, there are local stakeholders who need to give their input to a pragmatic implementation of ASP in their hospitals, which is a bottom-up perspective. Both perspectives are relevant for the effectiveness, success and uptake of the ASP implementation. With business modeling we look at both perspectives.

Research questions

The main research question in this thesis is:

How can business modeling be used to implement antibiotic stewardship with eHealth technology?

The above research question is divided in three sub-questions:

1) *How can business modeling be used as an implementation method?* (chapters 2, 3)
2) *What are current practices of antibiotic stewardship programs?* (chapters 4, 5)
3) *How to implement antibiotic stewardship?* (chapters 6, 7)

Outline of this thesis

The chapters in this thesis correspond with the chronology in which the research was done. To answer the first sub-question on business modeling, the implementation research started with a viewpoint paper that introduces business modeling as an approach to implement eHealth (chapter 2). This viewpoint paper gives a theoretical overview of business modeling as a method and its added-value to implementation research in eHealth. It also explains the connection of business modeling with the CeHRes roadmap. In chapter 3, we looked more pragmatically at business modeling and in this chapter we give an overview of methods that can be used for business modeling to identify and assess important stakeholders, methods to define the needs and value expectations relevant for implementation, and to compose a business model from these needs and value expectation.

In the next chapters we focus our implementation research towards the case study, antibiotic stewardship. The implementation focus funnels from an inquiring outlook of current practices of antibiotic stewardship on an international scale to a more pragmatic, local perspective, presenting a recommendation for a concrete implementation strategy for antibiotic stewardship using eHealth technology.
The second sub-question assesses current practices, so we looked at how ASPs are implemented. Antibiotic stewardship is often implemented as comprehensive programs, so in chapter 4 we performed a literature study into the characteristics of interventions of already implemented antibiotic stewardship programs. In this literature study, we found key interventions, a basic description of these key interventions, key stakeholders, and a possible way to measure the impact of an antibiotic stewardship program. In chapter 5 we focused more on the outcomes of these business modeling methods as delineated in the previous chapters and this is a first step towards a contextual inquiry for finding possible eHealth interventions for antibiotic stewardship.

The assessment of current practices gave us a good overview of implementation possibilities, but for our third sub-question we had to go deeper and more pragmatically into ASP implementations. With an antibiotic stewardship implementation maturity assessment, we further analyzed the progress with antibiotic stewardship initiatives at participating hospitals and found practical differences in implementation of key interventions relevant for Dutch hospitals (Chapter 6). As a follow-up, we organized interview sessions with antibiotic teams that are responsible for implementing antibiotic stewardship in their hospitals and used their input as case studies to design an eHealth technology that supports the implementation of antibiotic stewardship using a combination of our antibiotic stewardship implementation maturity assessment, expert guidelines and practical recommendations derived from the interviews (Chapter 7).

The thesis ends with a general discussion of the posed research questions, implications for future research and a final conclusion.

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Chapter 2:

Why business modeling is crucial in the development of eHealth technologies

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“Coming together is a beginning; keeping together is progress; working together is success.” - *Henry Ford*

Abstract

The impact and uptake of information and communication technologies that support health care are rather low. Current frameworks for eHealth development suffer from a lack of fitting infrastructures, inability to find funding, complications with scalability, and uncertainties regarding effectiveness and sustainability. These issues can be addressed by defining a better implementation strategy early in the development of eHealth technologies. A business model, and thus business modeling, help to determine such an implementation strategy by involving all important stakeholders in a value-driven dialogue on what the technology should accomplish. This idea also seems promising to eHealth, as it can contribute to the whole development of eHealth technology. We therefore suggest that business modeling can be used as an effective approach to supporting holistic development of eHealth technologies. The contribution of business modeling is elaborated in this paper through a literature review that covers the latest business model research, concepts from the latest eHealth and persuasive technology research, evaluation and insights from our prior eHealth research, as well as the review conducted in the first paper of this series. Business modeling focuses on generating a collaborative effort of value co-creation in which all stakeholders reflect on the value needs of the others. The resulting business model acts as the basis for implementation. The development of eHealth technology should focus more on the context by emphasizing what this technology should contribute in practice to the needs of all involved stakeholders. Incorporating the idea of business modeling helps to co-create and formulate a set of critical success factors that will influence the sustainability and effectiveness of eHealth technology.

Keywords

Business model; co-creation; collaboration; eHealth; implementation; multidisciplinary; stakeholder; sustainability; value creation

Introduction

Health care systems worldwide will face sustainability problems in the near future caused by a tension between an increasing demand for and a mismatch in the supply of health care services [1]. The growing demand for health care services is generally explained by an aging population and the rise in prevalence and incidence of chronic diseases and obesity. In addition, these increased demands imply increased complexity of treatments due to rapid advances in medical technology and increased comorbidity [1,2]. At the same time, the health care industry struggles with inefficiencies in procurement of supplies and inadequate use or lack of resources. In the United States, for example, the financial consequences of inefficiency are estimated to be in the range of 30% to 40% of total health care costs [3]. Without rapid action, health care services shall soon become less accessible and unaffordable and will deteriorate in quality.

In many industries, Web-based and mobile technologies have changed and are still changing conventional business activities to Internet-based activities such as Web 2.0 services or e-business [4,5]. In the health care industry, similar opportunities, often called eHealth, seem promising to help solve the aforementioned demand and supply problems in healthcare [6,7]. Indeed, eHealth technologies can contribute to improved communication and information sharing among health professionals, patients, and researchers and aim to improve quality and effectiveness of health care services [6,8,9]. However, eHealth technologies suffer from a range of recurring problems [3,10-16] as outlined in *Textbox 1*.

These problems can be attributed to insufficient attention to the development process and implementation of eHealth technologies. We believe that in order to tackle the aforementioned problems and to ensure a proper uptake, long-term sustainability, and effectiveness, new development frameworks are needed that make implementation an integral part of eHealth development. We see that implementation of eHealth technologies in practice is underestimated and overlooked in eHealth development approaches. Therefore, we proposed a new holistic approach in our paper, *"A Holistic Framework to Improve the Uptake and Impact of eHealth Technologies"* [17], which describes the entire development and is aimed at creating a fit between technology, humans, and organizations.

Textbox 1: Recurring problems of eHealth technologies

- Currently established financial structures slow down innovation.
- Necessary legislations for modernizing health care lag behind.
- Involved parties are reluctant and uptake remains low.
- eHealth development focuses too strongly on engineering-driven solutions.
- eHealth technologies are deployed in a fragmented fashion and have poor scalability.
- The number of stakeholders and dependencies cause complexity.
- There is a lack of cost-effectiveness studies.
- eHealth research tends to focus on finding clinical evidence in terms of health outcomes, yet the impact of eHealth technology does not rely solely on clinical evidence; there are more factors that determine the success of eHealth technology.

CeHRes Roadmap

The Center for eHealth Research and Disease Management (CeHRes) Roadmap (Figure 1), introduced in *"A Holistic Framework to Improve the Uptake and Impact of eHealth Technologies"* in this issue of the Journal of Medical Internet Research [17], offers a holistic approach to eHealth development. This roadmap guides the development of persuasive technology and business modeling as interwoven activities. This approach allows eHealth technologies to be designed according to the needs of its users and to fit with their behavior, but also, due to business modeling, it allows the development process to be value-driven. Stakeholders are involved in the development process and, based on their values, an eHealth technology can be designed matching with intended collaboration and co-creation, and eventually an implementation can be found.

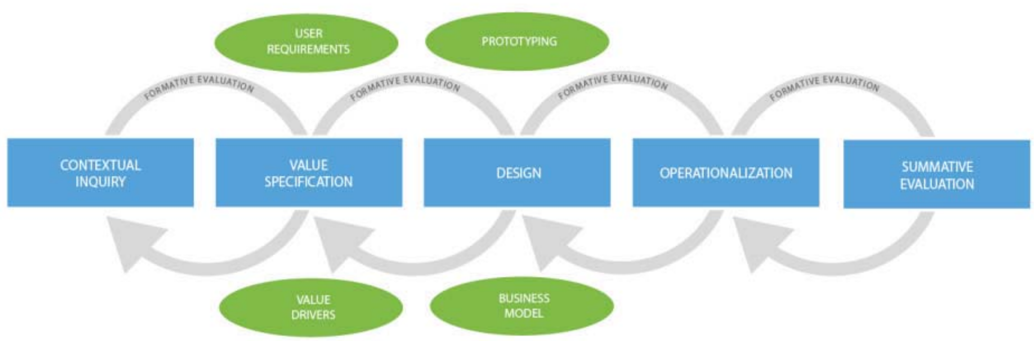

Figure 1: Center for eHealth research roadmap

In this paper we focus on business modeling and why it supports the development of eHealth technologies. Business modeling is interwoven with development to make both design and implementation value-driven. After all, it is futile to develop an eHealth technology that does not catch on because in practice it does not match demands or its intended purpose.

Why eHealth needs business modeling

Implementation must ensure that an eHealth technology will live up to its fullest potential in real-world conditions and circumstances. In order for eHealth technology to succeed, all organizations have to collaborate and interact, and some organizations have to maintain and perhaps fund the project. eHealth technology needs to fit in existing care infrastructures or, perhaps even more importantly, be a catalyst for new, innovative care infrastructures. In other words, eHealth development encompasses more than technical design. It requires additional research to determine an implementation strategy, that is, a plan to embed technology in its intended practice. Implementation starts with detecting and involving concerned parties and results in a business model that describes the value creation and acts as the basis for a care infrastructure for collaboration and co-creation, possibly with multiple organizations involved. To our knowledge, very few implementation rationales relating to eHealth technologies have been explained. Many of these eHealth technologies are developed with a "jump on the eHealth bandwagon" mentality without clear predetermined goals. Once an eHealth technology has been developed and it becomes apparent that goals are needed, the organization finally starts to think about an implementation strategy. So, current eHealth implementations are usually done post development rather than integrated in the development process.

Attention to implementation appears too late in the development, and we therefore point out that it is crucial to start preparing an implementation strategy early on. It is better to invest more time and money in researching how eHealth technology can be implemented in its intended care practice than to invest money in an eHealth technology that will not have a satisfying uptake. It happens too often that as soon as research funding stops, an eHealth technology cannot be implemented sustainably, mainly because there is neither support nor interest from other parties. Through business modeling, development of eHealth technologies can be guided with a value-driven evaluation of what is necessary and what is not. Often eHealth technologies are built as replacements for or copies of existing care services and are then fine-tuned for user requirements using user- or human-centered design principles. It is yet to be questioned whether this approach is effective and whether the choices made are really grounded. Business modeling introduces research activities before the start of the actual technical design that focus on the context of eHealth technology and provide value drivers that will ground choices of what to develop.

Starting with a context

An important early step in the development of eHealth technology is analyzing the relevant problem, that is, an eHealth technology is meant to improve a problem of inefficiency or a lack of information or communication. In order to take proper

action, the situation needs to be carefully assessed: this is known as sense making [18]. It is tempting, however, to rush toward thinking of technical solutions for a problem. Such fast solutions may lead to a solution that is technically state-of-the-art but poorly suited to the problem. By analyzing the problem at hand, eHealth technology will gain more context, and this increased understanding will contribute to all further choices that are required in the development process and the implementation. This is why the contextual inquiry in our business modeling approach is a crucial first step.
By discussing the problems with all concerned parties (so-called stakeholders, see next paragraph), it becomes clearer which parties will play an important role in the development process and which parties may come to play a role in the implementation of the eHealth technology. Also, this problem-oriented dialogue helps to make these parties more aware of each other's problems, as health care organizations often have limited knowledge of the processes and/or problems that go on at other organizations. In fact, during several of our workshops, it became apparent that people even within the same organization were unaware of each other's exact responsibilities and duties (see Textbox 2 as example).

Textbox 2: Example case: finding the problems with antibiotics prescription

Our intention was to understand and improve the behavior behind antibiotics prescription as part of the contextual inquiry for an eHealth technology that is in development. Based on a literature review and expert interviews, we identified the general problems with imprudent antibiotics prescription (causing a high risk of infections), the general prescription process, as well as key stakeholders. We organized a workshop with these key stakeholders within the first hospital ward where we had aimed to start our pilot. These key stakeholders discussed the problems they face daily based on patient scenarios validated by infection experts. This workshop not only enlightened the project management (that was us) to what problems and opportunities there were, but also created awareness among stakeholders as to what problems other stakeholders face and how the mutual problems also affected others. This awareness is vital for the collaboration of these key stakeholders and their future commitment to the project.

Stakeholder participation

Everyone who affects or is affected by a project is considered a stakeholder [19]. It is therefore critical for the success of eHealth technology to understand the value needs of each stakeholder [20]. Through participation of stakeholders in the development process of eHealth technologies, value needs can be retrieved and a mutually determined fit can be found. According to Pagliari, developing eHealth technologies is a multidisciplinary process [21]. Business modeling deepens this multidisciplinary development of eHealth as it brings multiple stakeholders together in the discussion of the necessary implementation. Business modeling also allows for an exploration of the value needs of stakeholders that determines both the design of the technology as well as the implementation.

There are many types of stakeholders associated with eHealth: patients, policymakers, vendors, insurers, health care organizations and providers, home care workers, and employers [22]. Therefore, every eHealth technology will have its unique stakeholder network (sometimes also referred to as an ecosystem) that determines potential customer segments and the infrastructure required for value co-creation for eHealth technology. Patients are often overlooked as stakeholders, yet they also have to participate in eHealth development. Patients often use or are subjected to the technology and have legal and social rights to be part of the development [8]. Patient empowerment does not stop at letting patients use eHealth technology; patients should be invited to participate in the development process of technology as well.

The level of engagement determines the salience of each stakeholder to the stakeholder network [23]. In our roadmap, we start by mapping the stakeholder network as part of the contextual inquiry process. As suggested by Sharp, it is best to start with baseline stakeholders (in our approach we start with project initiators) and let them suggest more stakeholders that may be relevant to the eHealth project [24] (see *Textbox 3* as an example). We base stakeholder salience on three variables: power, legitimacy, and the urgency of the stakeholder [25]. There are various ways to assess salience. This can be done either by asking experts to score the above variables or by asking the stakeholders to score each other. The next step is to start discussing value with stakeholders. The most salient stakeholders will eventually have a bigger influence on the value drivers than less salient ones.

Textbox 3: Example case: finding stakeholders through experts and by "snowball sampling"

In the early phases of any project, there are one or more initiators involved that can provide a list of baseline stakeholders. In one project, for example, a health information technology (IT) company wanted to develop a personal health record service. We spoke to several opinion leaders in health insurance, eHealth, and patient empowerment to form a stakeholder map specific for the Dutch health care system. In the interviews that followed, these stakeholders also provided more potential stakeholders that were relevant for the project, and so a specific stakeholder map appeared. Later on, this stakeholder map was used to report several business model opportunities to the management of the health IT company.

Co-creation

Co-creation in eHealth has already been introduced in disease management, for example, to streamline health care activities among multiple health care organizations. It also plays a role in patient empowerment, as patients are actively involved in their care [12]. Introduction of eHealth technology is often top-down, that is, technology is mainly determined by management. Obviously, management has an important say in whether or not a technology should be introduced, but in our view, a bottom-up approach is needed as well. This bottom-up approach can mean, for example, that a few specialists from a hospital ward also supply input on how they see technology adding value to their work. This is value specification that looks further than human-centered design, as it does not only look at the usability of the technology but much wider, that is, at the intended purpose of the technology and its fit in practice.

Participation of stakeholders in development also involves a political element, in that stakeholders feel they really contribute to the technology, and therefore, they feel more involved and positive toward it than when they are excluded. Dialogue is very important in co-creation [26]. Also, scalability problems can be tackled with business modeling by planning ahead through involving future stakeholders, particularly political or influential stakeholders, early in development to avoid eHealth technology becoming too localized and too narrowly focused.

Co-creation and dialogue with stakeholders requires a willingness to be open with each other. Openness is a way of thinking that is rooted in the opportunities of open source software and Web 2.0 that advocates operating with open systems for mutual benefits and transparency [5]. The open business model, as described by Chesbrough, combines this idea of openness with business models and promotes that organizations can embed co-creation and collaboration in their business models for shared benefits [27]. Classic success stories of open business models are the Philips Senseo coffee machine or the budget airline Ryanair. In the eHealth context, open systems are emerging too, such as interoperable electronic health records. Business modeling also pursues openness as multiple organizations co-create value of technology and share benefits. Regardless of the industry, traditional boundaries between organizations are becoming fuzzier and open business models pave the way for future collaborative success.

When co-creation is a goal, it will mean that eHealth technologies will be more intricate than one single organization carrying full responsibility, and it will require cooperation of multiple health care organizations. Inter-organizational dependencies can be very complex, so exploring benefits and value needs is a complex task that requires input from all involved stakeholders. To cooperate and balance these value needs, health care organizations need to extend beyond their traditional boundaries. This implies a different view of the development process of eHealth technology as well: it is not only an “apparatus” that is being created; there is a whole new underlying infrastructure for collaboration that has to be created as well (see *Textbox 4* as example).

Eysenbach [8] observes that social networks, collaboration, and active participation are key elements in today’s eHealth. When the opportunities of Web 2.0 technology are used for this collaboration in eHealth, this is often called Health 2.0 or Medicine 2.0. For co-creation and collaboration, an infrastructure such as a social network of organizations is needed as well [26]. Within this infrastructure, stakeholders have to interact to co-create value to eHealth technology. The stakeholder network that appears in the development process is also the basis for an infrastructure and will eventually become an infrastructure required for the collaboration and co-creation supporting the eHealth technology. This co-creation and collaboration is ongoing; therefore, it is imperative stakeholders all stay involved and interested in supporting and further developing the technology.

Textbox 4: Example case: a service model for teledermatology

In a teledermatology project, it became apparent that the stakeholders required more than just a technology for a fitting teledermatology solution, they also required a new infrastructure for a service delivery that, for example, would replace hospital care with home care. Via stakeholder meetings, the possibilities were identified, and scenarios were made that would allow co-creation and collaboration with third parties to implement the technology in practice. This resulted in a service model that described value co-creation between the engineers of the technology company and several health service companies, which was quite different to what the management initially had in mind during the early stages of the project.

Value drivers in eHealth

Chesbrough emphasizes the importance of an implementation by stating that "a mediocre product with a good business model yields more value than a good product with a mediocre business model" [27]. So, business modeling is crucial for the success of an eHealth technology. Through business modeling, the entire development becomes stakeholder-focused and value-driven. Stakeholders are asked early on what value drivers they expect regarding eHealth technology. These value drivers are relevant for both the design of technology as well as the design of the implementation strategy that will determine effectiveness and sustainability of eHealth technology.

Business modeling is a value-driven process and, as such, it is not simply a business model but an extensive process through which early opportunities for an eHealth technology are explored, assessment is made of what is required, a case-specific business model is developed, and the said technology is accordingly implemented. As part of the roadmap, we stress that development is a continuum and thus requires ongoing research activities that include design, evaluation, and redesign. Making a choice based on facts today can be improper a week later when new facts emerge. Web technology in particular is notorious for being relentlessly progressive; thus, adaptability is crucial. Over time, stakeholders can come and go or their value needs change, and the implementation needs to be reevaluated and redesigned. In terms of business models, this is called business model erosion [28], and due to this erosion, eHealth technology will be less sustainable and effective. So we need more sustainable methods to ground the eHealth development process and, for this, stakeholders need to be continuously involved in the development process and have their say in an implementation.

Our current approach to business modeling is to hold various workshops with relevant stakeholders to determine problems and opportunities in health care, which role technology can play, and which stakeholders are involved and what their importance is to the developed eHealth technology. Stakeholders at the workshops determine the role that the technology needs to fulfill in practice by forming an infrastructure and also determine what makes or breaks effectiveness and sustainability. All these elements are captured with a business model that can be detailed in a business case for further operationalization and deployment of the eHealth technology.

Value creation is central to business modeling. Obviously, in for-profit contexts, this value is mostly monetary, but other kinds of value drivers can be important too. Especially in the health care context, we often see extra attention paid to nonmonetary values, as health care is a special market. Intel's health care information technology (HIT) value model breaks down value into three levels: monetary value, quantifiable value, and benefits, the latter being, for example, social value or certain qualitative values that are considered beneficial but are hard to express in concrete figures [29]. In our business modeling approach, value drivers can be seen very broadly, that is, anything that a stakeholder considers critical to technology is a relevant value driver worthwhile to research. These values drivers form the basis for the development process and implementation.

Business modeling promotes a value-driven dialogue and promotes better understanding of what should be accomplished with eHealth technology [30]. This value-driven approach allows stakeholders in eHealth technologies to better discuss and reflect on the intended value that technology has to offer to the health care setting. Value drivers can also be initially counterproductive, as, for instance, when a certain stakeholder loses money or influence, this stakeholder will then criticize the technology. These negative value drivers then must be compensated for elsewhere. Also, by determining the overall expected value before designing begins, the assessment will be more profound whether or not eHealth technology is worth the investment. Nevertheless, value and value drivers remain complex concepts. During the value specification, many values will appear and many will also conflict; hence, dialogue is very important. It can be an extensive task to assess and to clarify to stakeholders what value eHealth technology can create, but without looking into value drivers, exact gains of eHealth investments remain unclear a priori, and it will be impossible to find a fitting implementation.

With business modeling, we aggregate all value needs bottom-up from the stakeholders, and, through dialogue, we try to co-create a fit between all the values that will become the overall expected value of the eHealth technology. Value becomes the focal point for technical design and also for the critical success factors [31] required for implementation. In our workshops, we use custom mapping software, to elicit these values from stakeholders and to rank scores to their importance according to the stakeholders. This ranking acts as a way to quantify and prioritize values. (A common method for this is called the analytic hierarchy process [32] that, in short, alters the initial scores given to the values by taking the hierarchy of these values into consideration.) These values are input for the design of an eHealth technology and are the basis for implementation. For example, if the value security is given a high score by multiple stakeholders, then during implementation, all security-related choices (e.g., collaboration with a good software security company) need to be given serious consideration; otherwise, certain stakeholders will not consider the technology valuable. This determination also influences the technology itself, that is, security-based features are apparently important, and thus designers and developers should thoroughly research what the security requirements are. *Textbox 5* provides another example.

Textbox 5: Example case: how value drivers can influence technical design

During the problem analysis in a teledermatology project, it was found that there were many additional problems in the whole teledermatology process that the initial design of device did not reflect. In general, the device had to offer support regarding how health care professionals in home care can take pictures of wounds so that wounds can be better diagnosed. Consensus arose among stakeholders that it was necessary to provide standardized guidelines for using the technology. We determined what value drivers were relevant to these guidelines, as without these standardized guidelines, the device would be less useful and thus less valuable to the stakeholders. This process also resulted in technical design additions.

Business models

As the term business modeling implies, its core output is a business model. A business model plays an important part in implementation: it acts as the basis for discussion of value drivers with stakeholders and becomes the basis for further operationalization where the business model is made more concrete through a business case, and, subsequently, the actual deployment of eHealth technology can happen.

Research in business models is relatively new, and, thus far, the term business model is still ambiguous in science and in practice [30]. Business models are quite often confused with business process models that are used on an operational level to describe detailed operational processes [33]. Also, some people associate business models with detailed financial prognoses, which are actually more characteristic of a business case. Osterwalder [34] defines a business model as “the rationale of how an organization creates, delivers, and captures value.” By this definition, business models act on a strategic level and can be the basis for more detailed business process models and business cases [35]. In our view, one needs to decide on a business model first in order to develop a business case. The business model can be created early on in the development process. The business case can gradually take shape and the details can be developed while the technology is being designed. Obviously, during the development process, a business model can also be refined or altered depending on unforeseen changes or new insights.

Business models became prominent in the late 1990s when the methods of doing business rapidly grew more complex and interdependent [36]. During that time, Internet-based activities became important assets in value creation and opened possibilities for new moneymaking activities and sped up globalization. Organizations had to change their existing strategies and develop new strategies. Yet, in order to achieve this transformation, organizations required something to plan ahead. This is when the term business model became widely adopted. A business model helps to relate all strategically defined critical success factors (critical elements in the achievement of successful value creation) into a working whole [37,38]. As such, they allow managers to understand, communicate, and evaluate the strategy for value creation and to conceptualize the strategy in a concise, modeled form [37]. In this period, numerous new business models emerged, and, coinciding with the popularity of the Internet, these were, in particular, business models that explored the potential of Web 2.0 [4].

A framework that is currently popular for defining a business model is the business model canvas by Osterwalder (depicted in *Figure 2*) [34]. It describes the whole rationale in nine building blocks. In the middle block is the value proposition, the eHealth technology in this case. The top three blocks on the left-hand side of the diagram deal with the required organizational aspects, that is, the key activities, resources, and partners. The top three blocks on the right-hand side deal with who the customers/users are and how to interact with them. At the bottom are the financial aspects. Creating and offering value generate costs, and a revenue model is necessary to capture value back to at least cover these costs. This canvas is an empty framework or blueprint that can be filled with critical success factors and choices to describe the implementation of an eHealth technology. The framework is useful as it describes the entire value creation logic and is a guide for making sure that all nine aspects necessary for value creation are addressed. The framework also helps to classify and group the components of a business model.

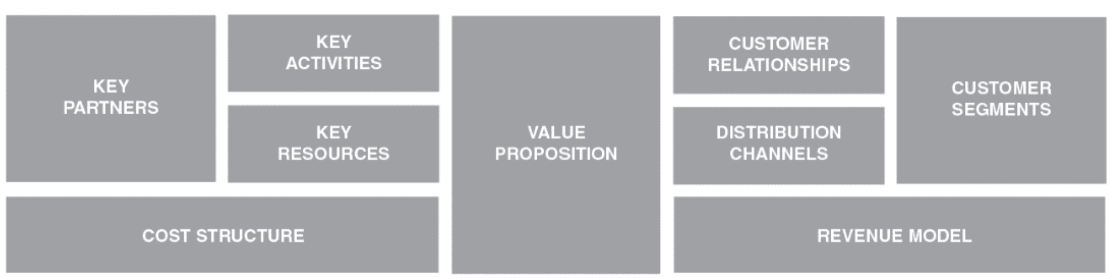

Figure 2: Business model canvas

However, the process behind filling this canvas determines the quality of the business model. In Osterwalder's book, Business Model Generation [34], a strong focus is on ideation, that is, thinking up innovative business models on a very high level of abstraction early on for new businesses. But the canvas can also be filled with value drivers based on the value specification that we apply in our business modeling approach. The chosen, important value drivers from the value specification become critical success factors, as they will determine the success of the implementation of the eHealth technology. We place these in the canvas to get an overview as well as to check if all building blocks received adequate attention from the stakeholders and/or researchers. It is also possible that multiple business models can be formed based on the value drivers gathered from the stakeholders, as the example in *Textbox 6* demonstrates.

Textbox 6: Example case: multiple business model opportunities for different scenarios

The aforementioned service model in the teledermatology example (Textbox 4) resulted in multiple possible business models with different service paths. These were:

- Keeping everything in-house
- Co-creation with third party organizations that would take care of the teledermatology infrastructure so that the technology company could focus on the technology
- A mix between providing a technology to third parties yet also providing additional technical services to third party organizations in return for a payment for each use

Each business model had its pros and cons, and it was up to the management to decide which of these models they found best fitting to the future of their company.

Business case

Having a business model alone is not enough. Once the desired business model is decided on and all stakeholders agree on the plans, the operationalization can be further determined by making a concrete business case based on the business model. A business case contains much more concrete information about the details of the implementation than a business model, but a business model is required to provide an idea of what the implementation should look like. In the business case, concrete descriptions of the necessary activities, resources, and costs can be written down. Usually business cases contain several financial prognoses based on estimated usage of the technology. These prognoses are based on multiple usage scenarios (low, projected, high usage) to gain a better understanding of the dynamics of the costs and potential revenues. *Textbox 7* demonstrates how a business case can be made early in a project to demonstrate financial benefits of an eHealth technology. Usually, a business case is continuously updated during the development.

Also in this stage, the required infrastructure that resulted from the stakeholder network and value specification can be further arranged more formally with contracts, formal agreements, and so forth.

Once these steps are taken and the technology is designed, it can be implemented in practice. However, the operationalization is not an endpoint; evaluation is necessary to track whether the technology and implementation still meet the intended goals and whether redesign iterations are necessary in the development.

Textbox 7: Example case: business case for implementing an antibiotic stewardship program

Changing antibiotic prescription can be beneficial. For example, patients can have a shorter length-of-stay or the prescriber can choose a quicker swap from intravenous to oral antibiotics. Through a calculation, we showed the hospital management that they could save up to a million euros a year on antibiotic costs alone. These financial prognoses convinced the management to start a pilot project for an antibiotic stewardship program.

Evaluation

Development of an eHealth technology starts with a variety of assumptions defined by time or budget constraints. Not everything in a business model can be understood *ab ovo* and requires reflection and progressive insight [39]. By spending more time investigating the exact value needs—even during usage of a technology—the technology and its implementation can be continually refined. As with any technology, eHealth technologies are subject to environmental and contextual changes. Technology never stands still, and most technologies are developed using iterative design approaches [21]. Just as technologies evolve over time, business models are also not static objects [40]. Therefore, summative and formative evaluation cannot be performed in an inert state but should be an action or a process (see *Textbox 8*). Business modeling makes sure technology and implementation keep reflecting on the current and future needs of the stakeholders for sustainability. It is imperative that an eHealth technology remains an object of study even after the technology has been implemented into practice; eHealth technology is not a "fire-and-forget" technology. The evaluation of its success needs to continue for further improvement and anticipation of changes in the health care environment. As a value-driven approach can project the critical success factors, the intended goals of the eHealth technology can be measured.

Textbox 8: Example case: summative evaluation of web-based infection control system for methicillin-resistant Staphylococcus aureus (MRSA)

In 2008, we launched a website that informs general audience and health care professionals about methicillin-resistant Staphylococcus aureus (MRSA). With server logs, we analyzed how the website has been used by visitors over the years and discovered that the chosen card-sort presentation of questions and answers, codesigned in 2008 with the intended users, was indeed effective and could be maintained. Additionally, we found a few ideas for improvements such as improving the search engine optimization, as the number of visitors via Google was significantly growing over the years.

Conclusion

Many eHealth technologies still fail in practice, and little or late attention is given to implementation. We believe preparing the implementation strategy is part of the development process and should start as early as possible in the development. In strategic management, business models are used to define the rationale behind value creation in terms of eHealth, which means the required rationale for implementing an eHealth technology in its care setting. We introduced business modeling as a vital part of our holistic approach for eHealth development in order to improve the uptake and sustainability of eHealth technologies. Business modeling, and our CeHRes Roadmap generally, have proven in multiple, different eHealth projects to be worthwhile in the development of eHealth technologies, helping us to find a better fit among humans, organizations, and technology with a value-driven and stakeholder-focused eHealth development. Business modeling fosters a ground for dialogue regarding the perceived value and purpose of an eHealth technology. An eHealth technology simply has a plethora of stakeholders and they all influence or are influenced by the eHealth technology. Implementation of eHealth technology depends on how well the value needs of stakeholders are met and how they partake in the infrastructure needed for the eHealth technology. Business modeling is a continual activity because the environmental conditions in eHealth are dynamic, so iterative development and anticipation to changes are important for sustainability and long-term success of the technology.

Health care organizations base their operations on century-old reimbursement business models [3]. Progress in medical and technological possibilities and many sociopolitical factors have altered the processes but left settled business models unchanged. Lagging legislation, financial complexity, and a status quo of roles and dependencies seem only to work in favor of perpetuating these inefficient health care processes. Evidential benefits from eHealth technologies remain unsure, as new technological possibilities often cause extra side processes rather than an efficient replacement for the processes that need to be improved. eHealth should not be an irrelevant remake of old processes. Innovative eHealth business models require that core conceptions, current roles, and processes are reevaluated and overhauled from complex organization-centered health care chains to efficient patient-centered health care networks in which multiple health care organizations collaborate to provide care.

eHealth projects need to research new business models. Both in practice as in academic context, a business model is often mentioned as a kind of panacea to improve the effectiveness and sustainability of eHealth technologies; however, the exact why and how are omitted from the arguments. Often generic business models from other industries (at the so-called taxonomy level) are mentioned as potential solutions which are per se unsuited, for example, taxonomies such as subscription-business models or pay-per-click-business models. These generic business models are excellent for classification, but for implementing an eHealth technology, this level-of-detail will not suffice. It is possible to inspire business models from other industries for eHealth, for example, in 2000. Parente described four e-commerce-inspired eHealth business models that were emerging at that time along with the growth of e-commerce generally [41]. E-commerce activities are probably easier to mimic from other industries than business models for health services and their complex value co-creation activities.

Not only are new business models for eHealth needed but also needed are the approaches for creating them. Admittedly, the lack of publications that discuss how business models can be created is not only a problem in eHealth. In general, few approaches to defining business models exist or remain cursory. Another barrier is the problem of introducing business-like thinking in health care. This continues to be a sensitive topic, as in the field of health care, the focus is the well-being of patients; thus, focusing on money is considered in a negative light because it is not patient-centered. However, with the emerging problems that health care is facing, business-like thinking could be pivotal in keeping quality health care affordable.

Future research

We have applied and are applying the CeHRes Roadmap in several of our eHealth projects, which are all quite varied and exist in different settings ranging in complexity and size, yet all of these projects are focused on providing some form of technology that supports disease management. A few example projects that have made or are currently making use of the roadmap and, therefore, also of business modeling are shown in *Textbox 9*.

Textbox 9: Examples of projects using the CeHRes roadmap

- Collaboration platform for cross-border infection prevention
- Setting up an antibiotic stewardship program
- Development of a teledermatology device
- Personal assistance website for diabetes care
- Prevention and quick warnings regarding the dangers of Lyme disease

All of these cases are useful for testing and improving the roadmap and are relevant to this paper. They are test cases for the current instruments for business modeling. We see that the roadmap and business modeling are applicable in all these different types of eHealth technologies, and we are working on adding instruments and evaluating current instruments. In a subsequent paper, we will give an introduction to these instruments and how they can support eHealth development. Our goal is to find robust instruments that are generic enough to be applicable for all eHealth technologies. Thus far, we have seen with our current focus groups and workshops as well as with our mapping tools that the extra effort of business modeling gives vital information not only for the implementation but also vital information with consequences for the design of the eHealth technology.

We also plan a systematic review to predetermine outcomes and effects of interventions in the antibiotic stewardship programs. After this review, we hope to assess how a literature review can be used as input for the start of the value specification by providing the outcomes and effects as general value drivers to discuss with the stakeholders.

The roadmap has been made public as a wiki (available at ehealthwiki.org). The goal is to provide a platform for anyone interested to collaborate on providing methods, ideas, and example cases for eHealth development as described by our roadmap. Obviously, we would also like to see contributions to the business modeling side of the roadmap.

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Chapter 3:

Business modeling to implement an eHealth portal for infection control: A reflection on co-creation with stakeholders

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"Design is not just what it looks like and feels like. Design is how it works." - Steve Jobs

Abstract

Background: It is acknowledged that the success and uptake of eHealth improve with the involvement of users and stakeholders to make technology reflect their needs. Involving stakeholders in implementation research is thus a crucial element in developing eHealth technology. Business modeling is an approach to guide implementation research for eHealth. Stakeholders are involved in business modeling by identifying relevant stakeholders, conducting value co-creation dialogs, and co-creating a business model. Because implementation activities are often underestimated as a crucial step while developing eHealth, comprehensive and applicable approaches geared toward business modeling in eHealth are scarce.
Objective: This paper demonstrates the potential of several stakeholder-oriented analysis methods and their practical application was demonstrated using Infectionmanager as an example case. In this paper, we aim to demonstrate how business modeling, with the focus on stakeholder involvement, is used to co-create an eHealth implementation.
Methods: We divided business modeling in 4 main research steps. As part of stakeholder identification, we performed literature scans, expert recommendations, and snowball sampling (Step 1). For stakeholder analyzes, we performed "basic stakeholder analysis," stakeholder salience, and ranking/analytic hierarchy process (Step 2). For value co-creation dialogs, we performed a process analysis and stakeholder interviews based on the business model canvas (Step 3). Finally, for business model generation, we combined all findings into the business model canvas (Step 4).
Results: Based on the applied methods, we synthesized a step-by-step guide for business modeling with stakeholder-oriented analysis methods that we consider suitable for implementing eHealth.
Conclusions: The step-by-step guide for business modeling with stakeholder involvement enables eHealth researchers to apply a systematic and multidisciplinary, co-creative approach for implementing eHealth. Business modeling becomes an active part in the entire development process of eHealth and starts an early focus on implementation, in which stakeholders help to co-create the basis necessary for a satisfying success and uptake of the eHealth technology.

Keywords

Business modeling; roadmap; value; co-creation; eHealth; implementation; stakeholder; guideline

Introduction

Implementation of eHealth

Implementation is necessary to promote the systematic uptake of research findings and other evidence-based practices into routine practice and to improve the quality and effectiveness of health services and care [1]. Attention for evaluating the implementation of eHealth has steadily grown in the last 5 years [2]. Despite this increased attention for implementation, little attention has been given to effects on roles and responsibilities, risk management, engagement of professionals, and transparency of potential benefits of eHealth [2]. Therefore, many implementations are not complete enough when technology "goes live" and its anticipated success is rather a lottery than an actually preplanned implementation. In fact, Black et al [3] concluded in their systematic review that many eHealth projects provide little evidence for actually improving outcomes or being cost effective. Implementation of eHealth has almost universally proven to be more complex and time consuming than anticipated [3]. In addition, many eHealth researchers assume that implementation is an ex-post activity and start preparing implementation when a technology is nearly finished [4]. Many eHealth projects suffer from the "field of dreams" syndrome with the expectation that users will show up as soon as the technology is made available, yet end up having little support, no plans for sustainability, poor uptake, and unknown added value to stakeholders [4,5]. The implementation should not be treated as an afterward necessity, nor treated subordinately to the design of eHealth technology. "Innovation is not just about technology anymore" [6], and therefore, a well-prepared implementation is just as important as a well-designed eHealth technology.

Business modeling

In a previous viewpoint paper, we had introduced business modeling as a possible approach to guide the development and implementation of eHealth [4]. Business modeling fosters a ground for dialog regarding the perceived added value and purpose of an eHealth technology [7]. The resulting business model depicts how an organization creates, delivers, and captures value [8]. Such a model can be used as a narrative to explain new ideas [9]. With business modeling, we use this narrative to discuss, plan, and operationalize an implementation of eHealth. Using stakeholder identification, stakeholder analysis, and value co-creation dialog, relevant values can be discussed and then modeled as a business model.

The Center for eHealth Research (CeHRes) road map (*Figure 1*) introduces eHealth development as a holistic approach integrating eHealth technology design with business modeling for implementation [4]. The road map consists of the following 5 phases: contextual inquiry, value specification, design, operationalization, and summative evaluation. The road map advises research activities that support eHealth research in each of these phases. This paper expands on this road map by demonstrating the research activities that we apply for business modeling.

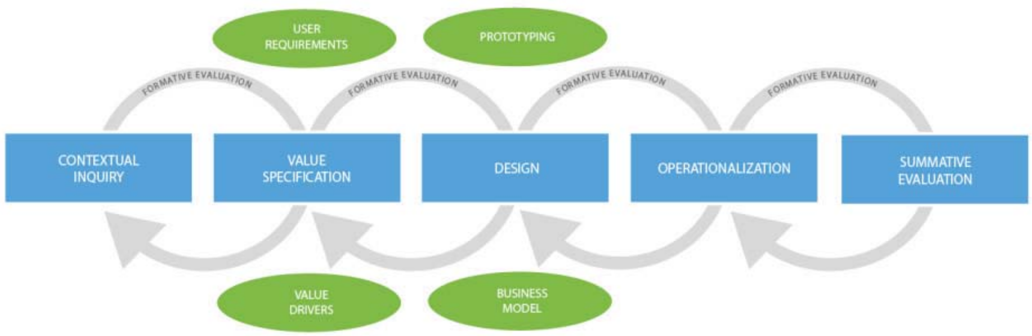

Figure 1: Center for eHealth research roadmap

Stakeholder involvement

Coiera [10] stressed the importance of sociotechnical design in health care. In his paper, he claimed that instead of technology, the social system surrounding that technology should be the central focus. Attention to sociotechnical factors is important to maximize the likelihood of successful implementation and adoption [3]. Academic interest in stakeholder theory started in the late 1970s in the fields of public policy making and business management. The most acknowledged definition for a "stakeholder" in stakeholder theory was established by Freeman as "everyone who affects or is affected by -in this case-the eHealth technology" [11]. A stakeholder analysis aims to evaluate and understand stakeholders from the perspective of an organization to determine their relevance to a project or policy [12]. In 2004, Bryson [13] reviewed 15 stakeholder methods to identify and analyze stakeholders. Although this review described step-by-step instructions for analysis techniques, these techniques focus strongly on expert-driven stakeholder classification without "true involvement" of stakeholders. To sum up, there is adequate information on expert-based stakeholder identification, yet methods or ideas on "how" to involve stakeholders (e.g., users, developers, suppliers) as active partakers in stakeholder analysis and further co-creation are less established. Likewise, in implementation research for eHealth, the involvement of stakeholders is still relatively unexplored.

Aim of this paper

This paper presents an approach for implementing eHealth with a strong accent on stakeholder involvement. We demonstrate our business modeling research and stakeholder-centered analysis methods in an example case, its added value to implementing eHealth, and conclude with a step-by-step guideline for stakeholder-centered business modeling for eHealth technology.

Methods

In a learning-by-doing approach to form our business modeling research, we applied various stakeholder-centered analysis methods in an example case study with a strong focus on discovering how stakeholders can best be involved in business modeling. These stakeholder-centered analysis methods are based on stakeholder theory, existing business modeling tools, and paradigms from human-centered design. In the "Methods" section, we present a theoretical overview for each stakeholder-centered analysis method followed by a practical application as an example and reflections on their application.

Example case: Infectionmanager

The European Union stimulates the mobility of their citizens. Similarly, in health care an increasing number of patients and health care professionals cross the borders and seek or offer health care services abroad. "EurSafety Health-net" has the primary goal to address patient safety in a cross-border context. The EurSafety Health-net consists of 5 "Euregios" or 38 geographical regions, totaling 19.2 million citizens. In these regions, 32 public health organizations and over 300 hospitals participate in the project. Our involvement in this project focuses on developing an Internet-based platform for cross-border infection prevention and control, called "Infectionmanager" (*Figure 2*). Infection prevention and control is a broad field, and therefore, our eHealth project mainly focuses on antibiotic prescription in hospitals. A change in prescription behavior is urgent, as up to 30-50% of the prescribed antibiotics are either inappropriate or even unnecessary and thereby harming the effectiveness of these antibiotics [14]. Intervening antibiotic use with antibiotic stewardship (ASP) interventions can be a step in curbing antibiotic resistance and hospital-acquired infections, and these can subsequently improve patient safety and reduce costs [15].

The Infectionmanager website is a platform designed to offer eHealth applications that support multiple crucial steps in the antibiotic therapy process and targets multiple, different users and stakeholders. The platform offers eHealth applications with information, decision support, and an overview of the ongoing research and development concerning the platform [16-18]. It targets stakeholders in infection control with currently a specific focus on stakeholders who deal with ASP in hospitals.

The Infectionmanager case is an example of a typical complex eHealth project. First, there is a multitude of stakeholders with diverse stakes, and therefore, an excellent opportunity to try methods for stakeholder involvement. Second, the development options were unlimited, allowing very open discussions with stakeholders to co-create possible eHealth applications and ideas for an implementation. Lastly, the complexity is influenced further by the novelty of ASP in the Netherlands and the novelty of exploring possible eHealth opportunities. Infectionmanager has been researched and developed according to the CeHRes road map [4].

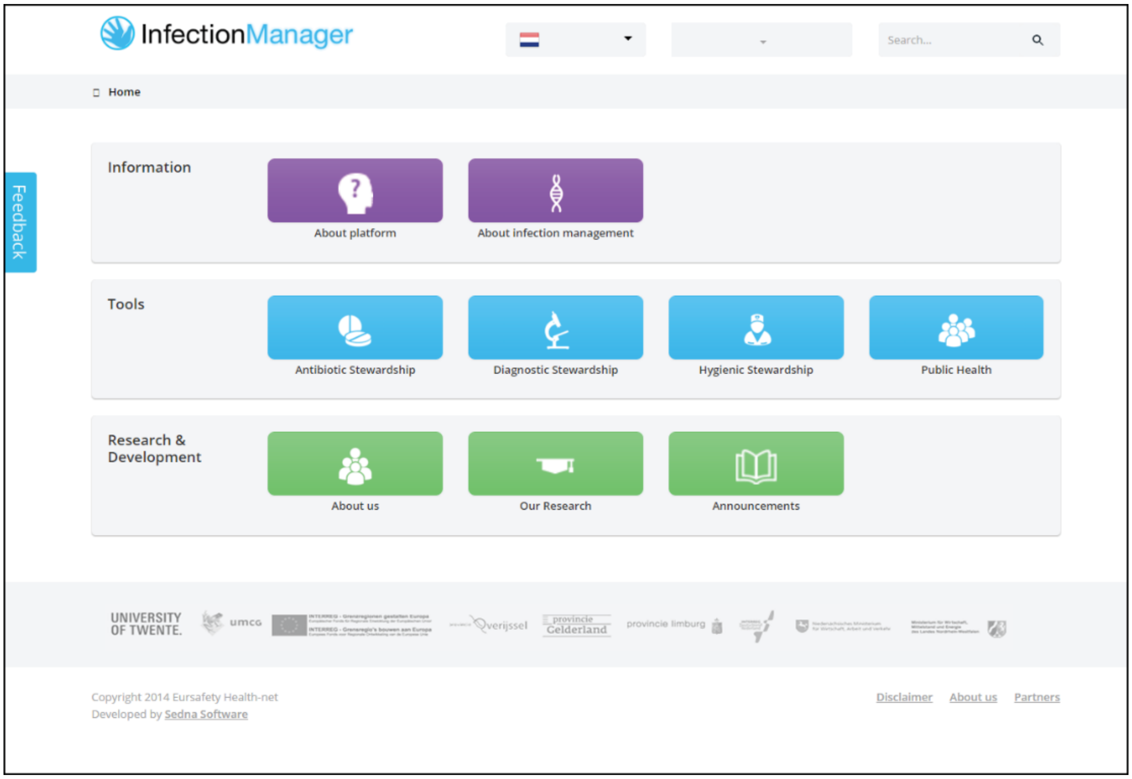

Figure 2: Homepage of Infectionmanager

Stakeholder-centered analysis methods

Involvement of stakeholders changes over time in the research process. In the beginning of an eHealth project, the analysis focuses on finding the right stakeholders and discussing global problems and opportunities, whereas in the later stages of the project, certain opportunities are combined into a possible eHealth technology and the implementation research moves on to value co-creation with topics that deal with added value, feasibility, sustainability, and costs-benefit issues.

In this section, we present each stakeholder-centered analysis method as listed below. First, we give a short summary of the theoretical background of used methods, followed by the practical application in our example case. We conclude each method with some gaps and lessons learned from use and experience.

Stakeholder identification

Every eHealth project will have its own unique stakeholder landscape that needs to be understood [4]. As a first step, before analysis of or with stakeholders can take place, all relevant stakeholders need to be identified. We noticed that stakeholder analysis methods focus more on classification and categorization than identification. Identifying a complete list of the right stakeholders is very crucial for all further analysis. Therefore, the identification step is very important and it is remarkable that it is not described in depth. Many authors consider stakeholders as a default product of a non-explained identification process [19].

We explored the following 3 approaches to identify stakeholders in an eHealth project: a literature scan/review, expert recommendations, and snowball sampling of stakeholders. These methods are not mutually exclusive and should be integrated as a mixed-method approach for optimal results.

Stakeholder identification method number 1: Literature scan/review

In Theory

There are 2 ways to identify stakeholders with literature:

- Identify stakeholders in stakeholder theory. This can result in a list of general types of stakeholders or stakeholders specifically in relation to eHealth.
- Identify stakeholders mentioned in literature on similar (eHealth) interventions.

Ballejos and Montagna [19] recommend starting with identifying stakeholder types [19]. These types of stakeholders can be very diverse, depending on the desired level of detail. *Table 1* lists some literature examples from stakeholder theory of possible different stakeholder types that can be relevant for eHealth research [19-26]:

Table 1: Overview of stakeholder types in literature related to eHealth

Study	Research focus/setting	Identified stakeholder types
Volere template [24]	Stakeholder roles in IT	Clients, customers, business/subject experts, future idea specialists, current system specialists, clerical users, technical users, potential users, sales specialists, marketing specialists, aesthetics specialists, graphics specialists, usability specialists, safety specialists, security specialists, cultural specialists, legal specialists, environmental specialists, maintenance specialists, packaging designers, manufacturers, product installers
Wolper [26]	Stakeholders in a typical, large hospital	Competitors, related healthcare organizations, government regulatory/licensing agencies, private accreditation associations, professional associations, unions, patients, third-party payers, hospital suppliers, media, financial community, special interest groups, religious organizations, local community, non-management medical staff, hospital board, parent companies/organizations, stockholders/taxpayers/contributors, management
Sharp et al [25]	Baseline stakeholders in requirements engineering	Users, developers, regulators, decision makers (with possible client, supplier and satellite stakeholders for each of the above baseline stakeholders)
Alexander [20]	Product-centric onion model	Developer, maintenance operator, operational support, normal operator, interfacing systems, sponsor or champion, functional beneficiary, purchaser, consultant, political beneficiary, financial beneficiary, negative stakeholders, regulators, the public
Mantzana et al [22]	Health care actors involved in the adoption of information systems	Acceptors, providers, supporters and controllers
Mettler et al [23]	A total of 4 key stakeholder types with subtypes for eHealth	Service customer, payer of service, responsible for referral, competitor, supplier of goods, supplier of services, supplier of information, government and community
Ballejos and Montagna [19]	Stakeholder roles (internal or external)	Beneficiaries (functional, financial, political, sponsors), negatives, responsibles, decision-makers, regulators, operators, experts, consultants, developers
Hyder et al [21]	Eleven stakeholder categories in healthcare	Beneficiaries, central government agencies, ministry of health, local governments, financiers, civil society organizations, health governing boards, provider organizations, professional organizations and health workers, unions, suppliers

Table 1 demonstrates that the stakeholder types can differ for each chosen focus and that multiple focuses can be used to be thorough in the stakeholder identification. Still, these stakeholders are only stakeholder types, and therefore, a researcher still has to identify which of these stakeholder types are present and more importantly, identify who the exact stakeholders are for each stakeholder type. For example, relevant stakeholder types can be “users” or “service customers,” but are they patients or specialists? What kind of patients? Which of these patients are included in research and which ones are not?

The second option is to identify stakeholders in the literature on similar interventions. These interventions do not have to be technology per se but are implemented in the same domains as the intended eHealth technology. In this case, very precisely defined stakeholders can be found by looking at the context [27]. This requires sufficient prior knowledge of the domains (medicine, policies, technological) and a clear idea of the goals of the intended eHealth technology. Literature can then be reviewed for mentioned stakeholders (usually professions or organizations); for example, by ranking their occurrence in each publication.

Example Case

When starting with Infectionmanager, our research team decided that ASP was a key intervention for infection control in hospitals and that our main interest was to start exploring eHealth possibilities. We conducted a quick scan literature review on ASP to list possible stakeholders who are relevant for ASP [28]. We performed a quick scan (so not a systematic review or similar strict methods) as this list would provide a general idea of stakeholders who should be involved in our ASP research. We ran a query on “antibiotic stewardship” and selected papers of most cited or key literature from that research domain. We scanned 12 key papers and noted every mentioned stakeholder in these papers. This resulted in a complete list of stakeholders in international hospitals based on the literature scan of ASP.

Textbox 1: List of antibiotic stewardship stakeholders identified in a hospital after a literature scan

(Clinical) pharmacists	Microbiologists
Epidemiologists	Nurse practitioners
Head of pharmacy department	Nurses
Infection control nurses	Pharmacologist experts
Infectious disease specialists	Physicians
Investigators	Psychologists
Medical executives	Software engineers
Medical students	

Gaps/Lessons Learned

- A (quick) literature scan is a good starting point to start with stakeholder identification. It is a fast way to draft a list of stakeholders who may be relevant for further stakeholder identification and later stakeholder analysis.

- An inventory of stakeholder types can be useful as an extra check to see if certain stakeholder types are missing on the stakeholder list or left out for a clear reason.
- Start with a manageable amount of key publications using a simple query in your research subject and list or tally mentioned stakeholders. With 10-20 publications, that stakeholders list will saturate.
- New, innovative health care interventions have limited available literature, especially in an academic context. In our example case, little literature was available for eHealth/health care technology in the field of prescribing antibiotics and stewardship.
- A potential danger with international literature is that it describes various different health care contexts and thus identified stakeholders may not be relevant for local health care systems. To illustrate with examples from our project: Microbiologists in Francophonic countries are called "bacteriologists," and thus, are not 2 different stakeholders; or "infectious disease physicians" do not exist as-is in the Dutch health care system and the closest comparable profession would be an infectologist, which we learnt afterward through validation of our stakeholder list with experts.
- Policies, (clinical) protocols, and documents are very relevant sources to take into consideration as literature for stakeholder analysis [29], especially when the eHealth intervention is targeted toward supporting tasks performed by health care professionals. Obtaining these protocols and documents requires access via experts or stakeholders who use them.

Stakeholder identification method number 2: Expert recommendations

In Theory

After exploring stakeholders from a theoretical perspective, the next step is to introduce a practical perspective. Most stakeholder analysis methodologies seem to prefer an expert-driven approach. According to Bryson [13], the "basic stakeholder analysis technique" suggests that the planning team (ie, the eHealth research team in eHealth context) brainstorms which stakeholders should be included for analysis. Depending on the composition of the planning team, one can also ask (external) field experts to nominate stakeholders [21]. The goal of this brainstorming session is to make a complete overview of relevant stakeholders to the eHealth project.

Example Case

We planned 2 brainstorming rounds. The first round started by using specific software that allowed to visualize stakeholder mapping. Our planning team consisted of eHealth researchers and infection control experts affiliated with our EurSafety Health-net project. We conducted 22-hour brainstorming sessions to visualize an overview of stakeholders relevant for infection control and subsequently Infectionmanager. In this early phase of our research, we looked at infection management, which had a broader scope than ASP specifically. We also categorized the stakeholders in stakeholder groups with the mapping software. The Infectionmanager was the central point of discussion, and so, the central question was "Which people or organizations have an influence on Infectionmanager?" And subsequently, "Which people or organizations are influenced by Infectionmanager?." Using these 2 questions, we brainstormed a stakeholder map. In this visual way of brainstorming, the network and relationships of stakeholders become clear. For example, the stakeholder "care recipients" can be categorized into 3 different types of care recipients with different roles toward Infectionmanager. Or, as another example, we listed possible commercial third parties, possible hospitals, and so on. The visualization aspect of this approach helps to draft a visual representation of the possible stakeholder map, which makes the brainstorming process less abstract and more comprehensive for all participants in the brainstorming team. A global overview of our stakeholder map can be seen in *Figure 3*.

The second brainstorming round targeted "ASP" more specifically and was a continuation of the stakeholders found with the quick literature scan as described in the previous method. Our team of eHealth researchers asked an infection control expert working at a pilot hospital to help us transpose the theoretical list of (international) stakeholders to stakeholders present at a pulmonary ward. We chose this pulmonary ward, as these wards have a relatively high use of antibiotics and relatively low multimorbidity. In the focus group, we brainstormed about every stakeholder on the list and the stakeholder's possible role in ASP, Dutch analogous profession, and whether that stakeholder was available in the pulmonary ward. Later, for further stakeholder analysis, we organized a focus group with the following stakeholders [30]: clinical microbiologists, pharmacists, (chest) physicians, residents, nurses, nurse manager, ward manager, and staff members of management.

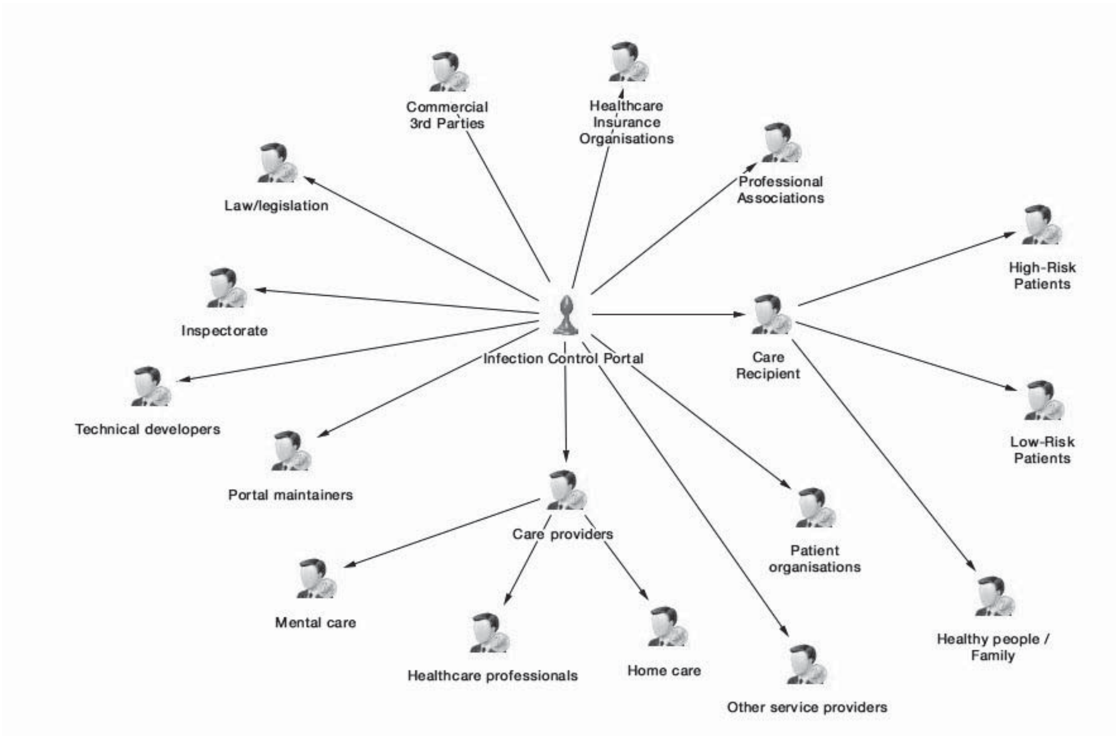

Figure 3: Stakeholder map relevant for infection control and subsequently infectionmanager.com

Gaps/Lessons Learned

- Brainstorming with experts is a useful method to bridge the theoretical list of stakeholders with the relevant practice. Experts are active in the field, so a researcher needs to make use of their firsthand knowledge.
- Visualization of the stakeholder map helps making the discussion of relevant stakeholders less abstract and fosters the collaboration and discussion. A map is quick to comprehend and easier to share than long lists, for example. It also visually structures the mentioned stakeholders.
- The more experts involved, the better. Experts are limited to their profession and background and may not know all parts of the stakeholder map. For example, a microbiologist knows all about the laboratory and microbiological diagnosis but has little insight into the daily routine of a nurse during ASP.
- Structure in the focus group is important. Prevent vociferous stakeholders who hijack the session for sharing their views only. Give every stakeholder adequate time and attention.
- Involving more experts also increases validation and paints a broader picture.
- Be open-minded to the stakeholders that experts suggest despite prior knowledge from the literature. In case of questionable or unclear

stakeholders, note them and ask why they are relevant and discuss/evaluate their relevance later with other experts.

Stakeholder identification method number 3: Snowball sampling with stakeholders

In Theory

Both literature and expert recommendations can still miss certain stakeholders who may be important to the project. A final step, once a list of stakeholders is ready, is to ask these stakeholders to complete the list. The added value of this step is to validate the list of stakeholders from a stakeholder's perspective and a last chance to identify missing stakeholders. Snowball sampling is a technique where existing participants recruit future participants among their acquaintances. In terms of stakeholder snowball sampling, stakeholders can be asked who the stakeholders are, or, in case of an already available list, which stakeholders are important and which ones are missing. Snowball sampling is one of the common methods used for stakeholder identification [31].

Example Case

In earlier brainstorm sessions (mentioned at the previous method), we drafted an initial list of stakeholders in infection control. These stakeholders were sent a questionnaire in which they could rank the importance of stakeholders on our stakeholders list and suggest missing stakeholders [32]. This eventually resulted in the stakeholder map of infection control as depicted in *Figure 4*. What is interesting is that this map contains some different stakeholders than the ones mentioned by experts and us but above all, it has a broader focus than the expert-based map in *Figure 3*. For example, our research mostly focused on stakeholders related to infection control in hospitals; yet, these stakeholders also pointed out that dental care and livestock industry deal with infections and antibiotics and are very relevant for infection control as a whole. Therefore, despite having a focus on hospitals (as outlined in *Figure 3*), there are a lot more other infection control stakeholders to involve in the stakeholder analysis.

As mentioned in the previous method, we further focused on ASP as a key intervention for infection control inside hospitals. Thus, we planned a focus group with stakeholders at a pulmonary ward [30]. We also applied snowball sampling to this focus group, and the existing stakeholders agreed that we should additionally contact dieticians, cleaning personnel, and a representative of the information technology department as they may have an influence on ASP.

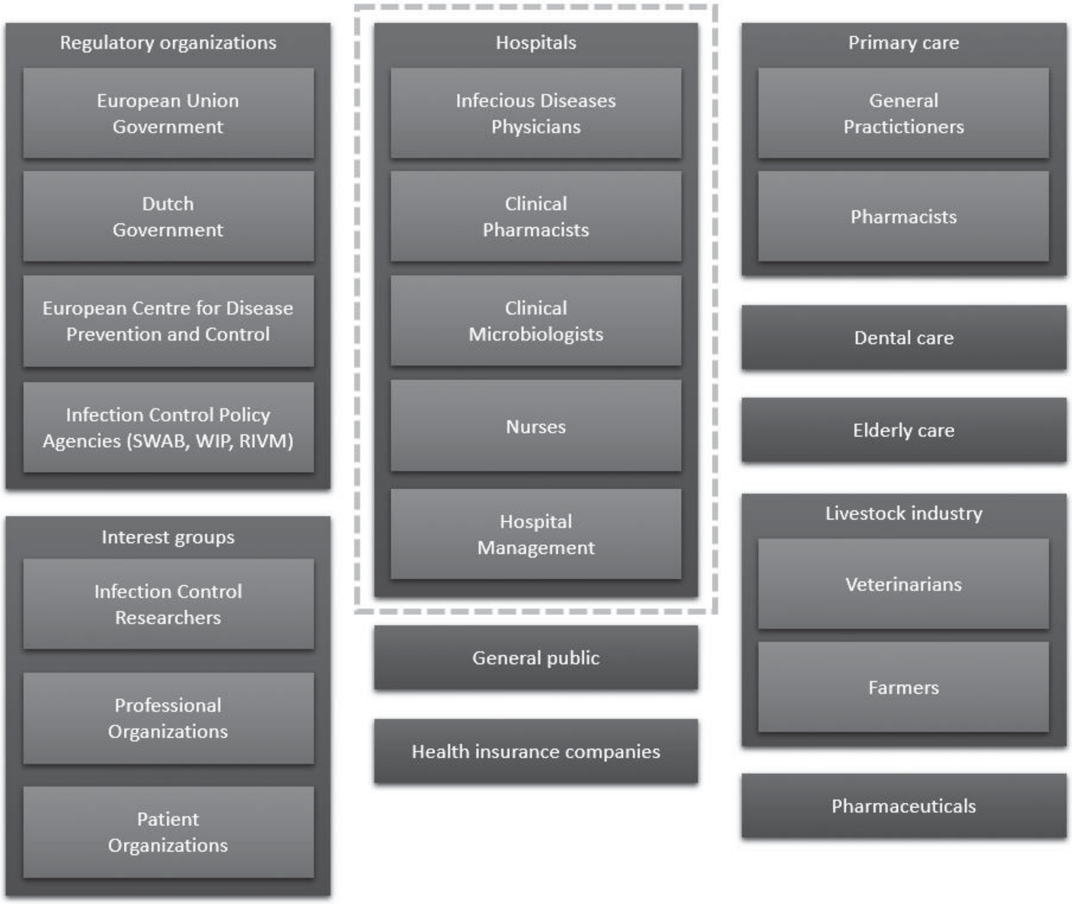

Figure 4: Example of all the stakeholders relevant for infection control

Gaps/Lessons Learned

- Stakeholders have the most direct firsthand experience within the subject domain and thus are crucial in stakeholder identification.
- Snowball sampling is suitable for identifying missing stakeholders. In our case, for example, we identified neither dieticians nor cleaning personnel as relevant stakeholders for ASP via literature.
- Questionnaires are the most convenient method for snowball sampling a complete list.
- Focus groups allow interaction with stakeholders, to iteratively assess conclusions from stakeholders and researchers. Yet, focus groups can be difficult to organize, especially when they consist of a high number of stakeholders. The focus group needs to have something for the stakeholders to be willing to schedule it.

Stakeholder analysis

After stakeholders are identified, they can take part in the stakeholder analysis. Not every identified stakeholder will be equally important to the implementation of the eHealth technology [4]. In addition, it takes time and resources to interact with every single stakeholder, and therefore, it is recommendable to work toward a selection of key stakeholders. Narrowing the list of stakeholders requires applying some acceptable and justifiable sorting criteria [33]. Again returning to the review by Bryson [13], there are a plethora of stakeholder analysis methodologies to classify stakeholders. In this paper, we demonstrate our application of the basic stakeholder analysis, stakeholder salience (Mitchell's classification), and ranking/analytic hierarchy process (AHP) method.

Stakeholder analysis method number 1: Basic stakeholder analysis

In Theory

The basic stakeholder analysis method involves brainstorming expert-based opinions on behalf of each stakeholder [13]. The research team and/or experts can give a global impression from the stakeholders' point of view about what the expectations can be for each possible stakeholder. The analysis aspect behind this method is that a stakeholder with many (important) expectations will most likely be important to the project throughout development. In terms of business modeling, these expectations are related to "values" that we will discuss more in depth later in this paper.

Looking from a research team stance, this overview of possible expectations also allows a first impression on the value proposition possibilities [34]. A value proposition is "the value created for users by the offering based on technology" [35]. In other words, it describes what added value a technology has to offer, as well as possible services around the technology. This value proposition will be the basis for the design and implementation of the eHealth technology.

Example Case

During our brainstorming sessions early on in our research, we examined with experts what possible values each stakeholder could express. We used the same stakeholder mapping software by Inpaqt again to make a value tree for every stakeholder. Value trees can be used to identify a hierarchy of values [36]. For each stakeholder, our project team discussed possible value expectations of Infectionmanager. The next step was to assign a level of importance to these value expectations. We assigned a number between 1 and 5 for each value and its attributes. Not only can this method prioritize stakeholders with many (high-ranking) value expectations, but it can also provide an overview of possible value needs and how these values and their attributes are linked with each other. In this example, providing information for high-risk patients with the Infectionmanager (the attribute "information") would not only affect the value "be informed" but also the values "feeling better," "empowerment," and "peace of mind".

In *Figure 5*, we show an example of a value tree with possible values (diamonds)—expectations of a high-risk patient group—as well as attributes (blue boxes) that detail these values.

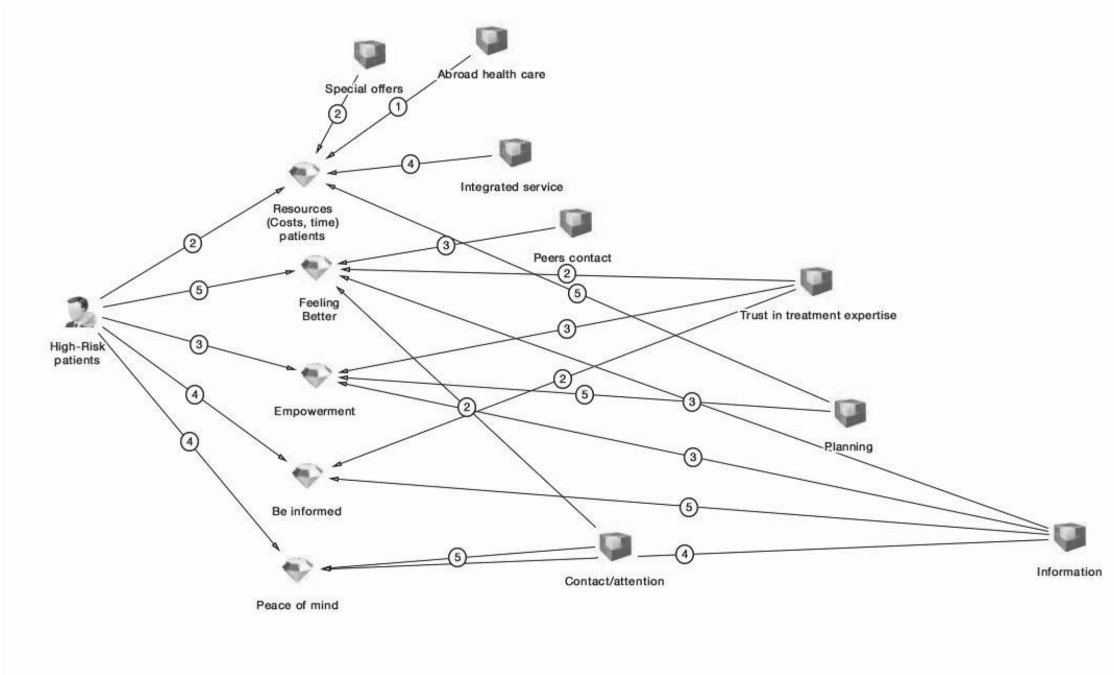

Figure 5: Example of value tree with possible values expectations and attributes for high-risk patients

Gaps/Lessons Learned

- This method is a start to understand who the possible important stakeholders are and to prepare a general impression on what to expect as value needs for the technology and implementation.
- It helps to understand the linkage of values. For example, the same values can be shared by multiple stakeholders or values can influence the technology on several places and vice versa.
- Theoretically, this "basic stakeholder analysis" method does not truly involve stakeholders because it is done by experts. To make this method less expert driven and more stakeholder driven, stakeholders can partake in the stakeholder analysis sessions as well.
- Doing this digitally can be a bit more difficult as during the brainstorming sessions a researcher has to real-time model while conducting the discussions, although this is very convenient for continuing and sharing the session results.

- The analysis remains subjective and rather high level or abstract as you try to draw an overall picture of all possible views of all possible stakeholders with experts.
- Experts only see their part of the process, and thus, their conceived values may be biased.

Stakeholder analysis method number 2: Stakeholder salience

In Theory

A popular method to determine the importance of stakeholders is the stakeholder salience approach proposed by Mitchell et al [33]. They defined stakeholder salience as the degree to which managers give priority to competing stakeholder claims. Salience is based on 3 attributes that can be classified, namely, power, legitimacy, and urgency (*Figure 6*). Power is defined as “a relationship among social actors in which one social actor, A, can get another social actor, B, to do something that B would not have otherwise done.” Legitimacy is defined as “a generalized perception or assumption that the actions of an entity are desirable, proper, or appropriate within some socially constructed system of norms, values, beliefs, and definitions.” Finally, urgency is defined as “the degree to which stakeholder claims call for immediate attention.” Based on the 3 attributes, Mitchell et al [33] defined 9 possible stakeholder classes for classification. It is out of the scope of this paper to elaborate on each class, but in short, stakeholders who score on all 3 attributes are definite stakeholders, and thus key stakeholders. Stakeholders who score 2 of 3 are relatively dominant, dependent, or dangerous stakeholders and should also be included. Stakeholders who only score 1 of 3 are dormant, discretionary, or demanding stakeholders.

Stakeholder salience can be determined by experts in the aforementioned expert brainstorm sessions or project meetings, or by stakeholders themselves using a questionnaire, one-on-one interviews, or a focus group.

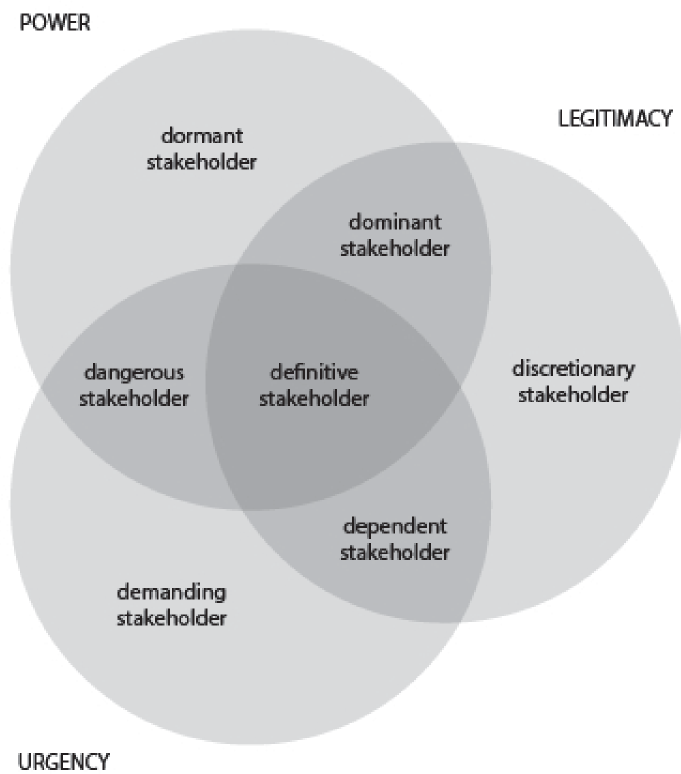

Figure 6: Stakeholder salience diagram according to Mitchell et al [34]

Example Case

We first arranged expert interviews to rate the infection control stakeholders, according to Mitchell's salience. We asked 2 infection control experts to rate stakeholders on whether they have power, legitimacy, and urgency. We then sent a questionnaire to stakeholders who according to experts were the "definite stakeholders" [32]. *Table 2* shows a fragment of our salience assessment.
Practically, we learnt that these 3 attributes of salience (i.e., power, urgency, and legitimacy) are difficult and had to be explained in more general, nonbusiness-specific terms to the experts and stakeholders: We explained power as "the level of influence a stakeholder has in infection control." Legitimacy was explained as "the level in which a stakeholder needs to be legally, morally, or contractually involved in infection control." And finally, urgency was "the priority or necessity of the stakeholder in infection control." It is crucial to keep these terminologies and definitions consistent [31].

After comparing the stakeholder salience expressed by stakeholders and by experts, we could validate and draw consensus in both results [32]. The differences were that experts mentioned the Ministry of Health as important and stakeholders did not, and stakeholders found the National Institute for Public Health and the

Environment, nurses, and veterinarians more salient. We added these 3 to our final definite stakeholders list.

Table 2: Example fragment of a classification of infection control stakeholders using Mitchell's stakeholder salience

Stakeholder	Power	Legitimacy	Urgency	Type
Medical specialist / physician	X	X	X	Definite
General practitioner (GP)	X	X	X	Definite
GP assistant	-	X	X	Dependent
Clinical microbiologist	X	X	X	Definite
Nurse		X	X	Dependent
Pharmacist	X	X	X	Definite
National Institute for Public Health and the Environment (RIVM)	-	-	X	Demanding
Dutch Working Group on Antibiotic Policy (SWAB)	X	X	X	Definite
Medicines Evaluation Board (MEB)	X	X	-	Dominant
Insurance companies	X	-	-	Dormant

Gaps/Lessons Learned

- This salience approach is the most commonly used method to assess the importance of stakeholders, and thus, can be seen as a widely acknowledged method. It is also a commonly used method for stakeholder assessment in eHealth research.
- Determining which stakeholders are definite stakeholders—in-turn important for implementation research—is feasible using Mitchell's stakeholder salience. This is especially true when it is necessary to bring the number of stakeholders down to a manageable number to actively involve them in the implementation research.
- The 3 salience attributes (i.e., power, legitimacy, and urgency) are difficult concepts. They might overlap and as they are explained in business terms, they are also complex to properly explain to stakeholders. The researchers have to be consistent in the explanation and make sure the stakeholders understand the difference.
- Subsequently, there is also a risk that stakeholders do not fully comprehend the attributes and give answers based on gut feelings or what they expect should answer. Therefore, as the researcher, one needs to be alert and ask for short elaborations.
- The stakeholders who score all 3 attributes of salience are important stakeholders to be involved in the project; however, with a high number of stakeholders, it is important that further analysis is carried out to identify those stakeholders who scored 2 (or maybe even 1) of 3 attributes and

include them in the list. This depends on the number of stakeholders and keeping it manageable for research purposes.

Stakeholder analysis method number 3: Ranking/analytical hierarchy process

In Theory

Another way to classify the importance of stakeholders is by attributing an importance score to stakeholders. This scoring or ranking can be done in several ways. In our research, we used a 5-point scale and a derivative of AHP [37] as 2 methods for ranking:

The 5-point scale is very straightforward. Hyder et al [21] proposed to articulate the power or importance of stakeholders using a 5-point scale. Experts or stakeholders themselves can assign 0 (not important) to 5 (very important) points to a list of stakeholders. Similar methods can deviate from the scale, eg, a 9-point scale [36] but different scales seem arbitrary.

A mathematically more sophisticated method for ranking is Saaty's AHP [37], which is also applied in health care research [38]. It is out of the scope of this paper to explain how AHP works in full detail. In short, AHP is frequently used in the analysis for decision making. In AHP, the hierarchic relation (an eigenvector approach) of stakeholders weights their relative importance. Saaty's AHP technique becomes especially interesting when the hierarchy expands by also mapping values and attributes to stakeholders (as seen in the value trees in *Figure 5*). Using a mathematical construction, the number of values and hierarchic relationships determine a weighted outcome for every stakeholder, value, and attribute. It is a sophisticated method, but in our experience the most thorough analysis currently available.

Example Case

The software tool we used for ranking the stakeholders also allowed for a 0-5-point scale to rate the importance of stakeholders. We applied a simple hierarchic calculus based on the value trees. For example, a value with 5 points from a stakeholder with 5 points would get 25 points, a value with 5 points from a stakeholder with 2 points would score 10 points. This is slightly different to Saaty's AHP method as we did not apply relative weights and eigenvectors to avoid overly complex calculations. We assigned the ranking in a brainstorm session with experts as can be seen in *Figure 7* and we did the same to values (as already shown in Figure 5). We did not rank stakeholder or values in an interactive session with stakeholders themselves in our example case, as it would be unfeasible to organize all stakeholders together.

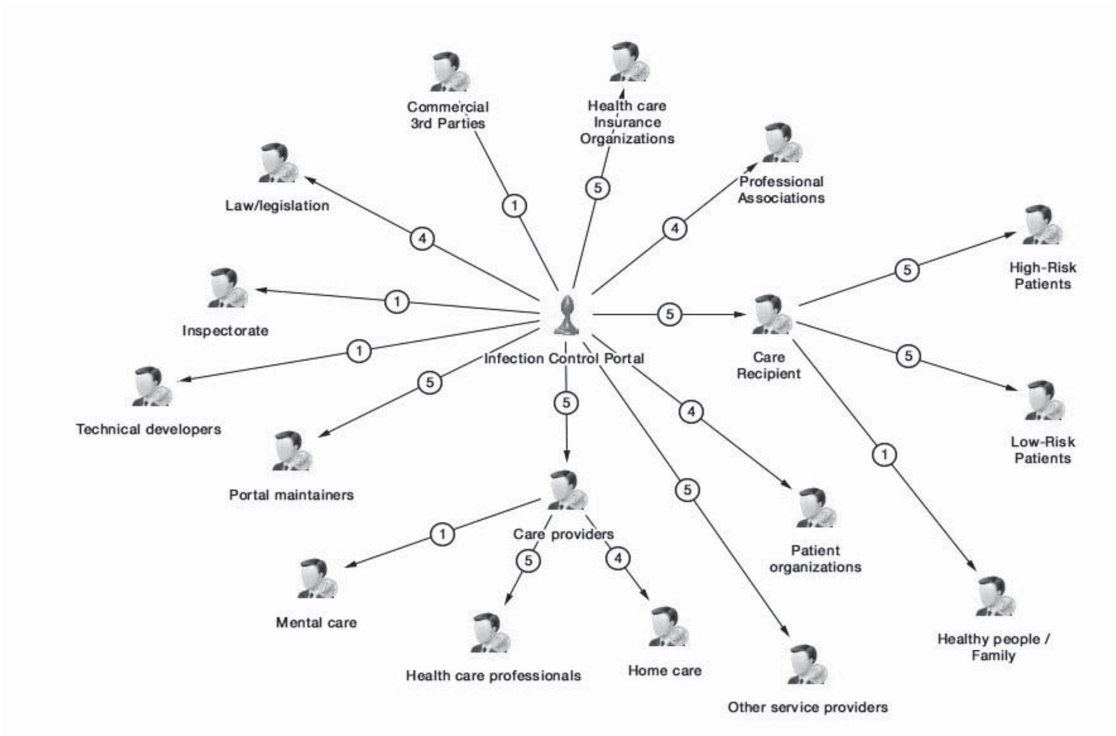

Figure 7: Expert-based stakeholder ranking for infection control portal

Gaps/Lessons Learned

- Ranking with numbers is a simple yet effective way to quantify and classify the importance of stakeholders.
- AHP can overkill and in practice a simpler calculation of [stakeholder× value × attribute] might be a good alternative.
- The 0-5-point scale is still an arbitrary quantification that is interpreted by stakeholders or experts. For example, what makes a stakeholder a 2 or a 3? The best way to get satisfying results is by validation by either asking multiple stakeholders to rank or to work toward a consensus.
- We did not choose to fully use AHP because it has to be done very thorough, as the hierarchy will determine the importance through eigenvectors. If 1 stakeholder or value is lacking, results may become counterintuitive [37]. More research is needed on this.

Value co-creation dialogs

After the stakeholders are analyzed and it is known whose input to the implementation of the eHealth technology is more important than others, it is time to start with value co-creation. We define a "value" as an ideal or interest a (future) end user or stakeholder aspires to or has [29]. These values can be further detailed into "attributes." An attribute is a summary of the need or wish that is spoken out by the (future) end user or stakeholder [29]. Still, "value" remains a difficult concept to concisely communicate as this can elicit philosophical debates on what is good and bad. The eventual eHealth technology and its surrounding services to embed it properly in its intended care setting all encompass the value of the eHealth technology.

Value co-creation is a joint activity involving customers to identify values from their perspective [39]. In other words, with co-creation, stakeholders get an active dialog and co-design the development process of eHealth. In addition, for most stakeholders, value is also a difficult business concept to grasp. One cannot simply ask, “Ok, what value do you expect?” In fact, in most cases the stakeholders cannot even grasp what the technology will be like, nor how it can be used. The researcher has to prepare relevant value co-creation questions and have a discussion with all key stakeholders about their value expectations.

We demonstrate 2 possibilities as to how we conducted these value co-creation dialogs: process analysis and stakeholder interviews using the business model canvas.

Value co-creation dialogs method number 1: Process analysis

In Theory

To co-create value, Prahalad and Ramaswamy [39] noted that a joint problem definition and problem solving are required. To facilitate this process, the authors recommend the DART method:

- have “dialogs” with stakeholders about their experiences;
- get “access” to information;
- assess “risks” and benefits with stakeholders; and
- be “transparent” with information.

We combined these 4 with ideas of the contextual inquiry of our road map that recommends performing interviews or focus groups using a scenario-based problem analysis. Focus groups offer an opportunity to obtain insights regarding the experiences, observations, and opinions of group members [40]. As Prahalad and Ramaswamy [39] point out, to understand the individual experiences for co-creation, the problem analysis, inspired by action research, sense making [41], and previous research [42], should encompass a general discussion of the entire process, including individual tasks, information, and communication needs, as well as the problems experienced and bottlenecks.

Example Case

We organized a workshop for a focus group in a pulmonary ward, inviting stakeholders relevant for ASP [30]. In this workshop, we asked stakeholders about the problems they experienced (general), process bottlenecks (coordination, communication), and information needs (communication, documentation). Stakeholder role playing (enact a situation or process) is mentioned as a possible way to determine importance and value needs of stakeholders [43]. Thus, we started a quick role play of "Who does what?" with the process behind antibiotic prescription for a complex patient. For each topic, we prepared a poster on which stakeholders could stick written Post-its with possible values, and group them in importance. The main problems that were mentioned were regarding the information flow of patient information and insufficient cooperation and consultation between the attending physician and microbiologists again due to inefficient information sharing as well as due to unstructured procedures for consultation. Some stakeholders also noted that an insufficient knowledge of (new) procedures or application of medication might cause problems [30]. An interesting find was that nurses could play a big role in ASP.

Gaps/Lessons Learned

- Value creation with a focus group approach allows for a discussion, and therefore, when talking about processes, problems, or tasks, stakeholders can directly respond to each other, allowing co-creation through agreement and consensus on possible positive and negative values.
- This discussion itself can already be an eye-opening experience for stakeholders. On several occasions, a stakeholder admitted, "I did not know that you were experiencing that (as a) problem," which suggests that discussions create more understanding for each other and willingness for improvement or change.
- Stakeholders might not express all problems or play them down due to the presence of other stakeholders.
- Through this approach, stakeholders will mostly discuss problems and opportunities to change these problems. They might not express them exactly as values but more as attributes. In that case, after recording the focus group sessions, researchers need to extract values from the transcript that are relevant to the technology and its implementation [29].
- In this step eHealth opportunities can also be discussed that can help ideating possible eHealth technology in collaboration with the (technical) design researchers.

Value co-creation dialogs method number 2: Business model building blocks

In Theory

For this approach, we started with a business model as a basis to discuss values. A business model mediates between technology development and its intended (economic) value creation [6,35]. In other words, it can be used to explain the value creation logic necessary to create a successful piece of technology. Likewise, a business model can explain the rationale behind implementing eHealth technology [4]. The most commonly used framework for making a business model is the business model canvas by Osterwalder and Pigneur [8]. Their business model consists of the following 9 building blocks: value propositions, customer relationships, channels, customers, key activities, key resources, key partners, cost structure, and revenue streams. These building blocks can guide questions regarding the necessary values for implementing eHealth. Although Osterwalder and Pigneur [8] proposed several questions for each building block, these are targeted toward high-level strategic management. The trick is to transpose these questions to the intended eHealth technology and ask which values are necessary for that eHealth technology to be successful.

Example Case

We took the building blocks of the business model canvas and organized them into 4 main topics for questions on necessary values for implementing ASP, taking the mentioned problems and bottlenecks during the focus group into consideration when preparing questions. *Table 3* presents some questions used. Each of the 4 topics has a central question that needs to be answered, with several sub-questions. We then organized 1-hour, one-on-one interviews with stakeholders and used this questionnaire as a basis for the interview.

Table 3: Example of topics based on business model components

Building blocks	**Central question**	**Explanation**
Value proposition (the technology and its services)	What value should an antibiotic stewardship program (ASP) offer?	The value proposition is basically the to-be-developed platform for ASP. We prepared concrete questions like “What value does ASP need to deliver to you, to your department, and to the hospital?,” “What problems does it help to solve?,” “What technology and services can we offer to you?,” and “What do you deem really necessary to be satisfied with ASP?
Customers, key resources and key partners (the stakeholders)	Who are the stakeholders?	Here we focused on all human interactions relevant for ASP. We asked which stakeholders (people or organizations the stakeholder interacted with, or should interact with for ASP). We made a list of stakeholders, described their role briefly, and ranked their importance. We also asked for external stakeholders who may be relevant for ASP as, in general, stakeholders tended to respond from their internal, hospital perspective.
Key resources and key activities (the infrastructure)	What is the required infrastructure?	We asked “How can ASP be integrated with your daily routine?” Regarding possible resources, we asked what tools, means, documents, sources, or people were necessary for ASP and their importance.

		We had to steer the stakeholder by asking specifically whether a certain technical infrastructure is needed, what technical medium, which data flows and connections or systems are relevant to assess the needs for eHealth technology. We also steered by asking what knowledge is further required, in terms of support from people or literature to have an ASP to assess what resources are specific to ASP.
Costs and revenues (the added values)	What are the success factors?	We avoided monetary discussions with stakeholders. Costs and revenues are always a difficult subject as there may be many benefits not directly linkable to 1 particular stakeholder. In the focus group we organized earlier, stakeholders stated there is a trade-off between quality and efficiency regarding ASP and that they should be balanced [30]. Therefore, we chose to ask for effects and success factors. We asked what the expected effects on patient outcomes (eg, length of stay, mortality, treatment duration, patient safety) would be and their relative importance and whether other quality aspects not directly related to the patient are relevant. We did the same for efficiency, and so, what are the important outcomes for efficiency (costs, less usage of antibiotics, fewer complications, etc) and their importance.

Gaps/Lessons Learned

- One-on-one interviews allow for in-depth analysis of possible values and critical success factors for implementing an eHealth technology and results in a deeper discussion and understanding of each stakeholder's value expectations. Not only are values expressed, but it is also elaborated why they are important.
- From our experience, we advise that the questions need to be concrete enough for stakeholders to give satisfying answers. If the questions are too abstract, the answers will be equally abstract and thus less useful.
- It is important that the interviewer focuses on what the technology should contribute, not design or requirements. It is not about how they want the eHealth solution to be, it is about the why.

Business model generation

As "business modeling" suggests, the eventual output is a business model. Exact visualizations of business models are diverse and there is no unanimous agreement on what they exactly should look like or the level of detail they should contain [7]. This is also why there is neither a dominant design nor many tools available for making business models. A popular method for visualizing a business model is the business model canvas [8]. Although this canvas is perfect at abstracting and visualizing key elements that should be in a business model, comprehensive step-by-step instructions on how to retrieve the detailed narrative for these key elements remain rather abstract and is therefore mostly targeted at high-level strategic management. However, existing templates or blueprints such as this business model canvas are useful to make a model representation of an implementation of health care technology [4]. We also used this business model canvas as our template for a business model.

Business model generation method: Business model canvas

In Theory

The business model canvas (*Figure 8*) consists of 9 building blocks that can describe the whole rationale of an implementation. In the middle block is the value proposition, the eHealth technology in this case. The top 3 blocks on the left-hand side of the model deal with the required organizational and infrastructural aspects, that is, the key activities, resources, and partners. The top 3 blocks on the right-hand side deal with who the customers/users are and how to interact with them. At the bottom are the financial aspects. Creating and offering values generate costs, and a revenue model is necessary to capture value back to at least cover these costs. This canvas can be used as an empty framework or blueprint to fill with critical success factors that describe the implementation of an eHealth technology.

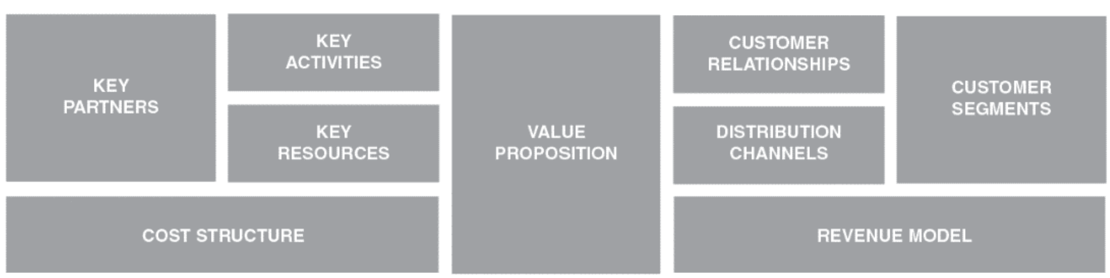

Figure 8: Business model canvas by Osterwalder and Pigneur [8]

Example Case

We made a business model (*Figure 9*) filled with the values that were concluded using the focus group and one-on-one interviews as delineated in the previously explained value co-creation methods. We listed critical success factors that are our translation of expressed values and attributes.

This business model in *Figure 9* gives an overview of relevant critical success factors that determine the success of ASP and what role Infectionmanager can play in ASP. It pinpoints critical values that the technology needs to offer to be valuable to stakeholders, critical values that need to be made available in the infrastructure to guarantee feasibility, uptake, and sustainability. This business model also gives an idea about financial opportunities that are available to make Infectionmanager self-sustainable. To sum it up, this business model provides a bird's-eye view of all critical success factors to implement our Infectionmanager.

Figure 9: Business model canvas filled with critical success factors

Gaps/Lessons Learned

- A business model can give an overview of the critical success factors for implementing an eHealth technology.
- The level of detail depends on the dialogs with stakeholders, and therefore, the completeness of the business model depends on the (successful) completion of those earlier research steps.
- This is still only a model that reflects a possible (maybe even multiple) implementation. It still needs to be explained to others and practically expanded on to put the eHealth technology "live."

Results

Stakeholder analysis and co-creating values for a business model with them is a progressive journey to understand the global context and problems and to gradually work toward an in-depth, individual dialog with stakeholders to understand what they find important to the technology and its implementation. By exploring several stakeholder-oriented methods as part of business modeling as delineated in the

“Methods” section, should we have to start implementation research anew from scratch, we would suggest the business modeling steps presented in *Textbox 2*.

Textbox 2: Step-by-step guideline for stakeholder involvement for business modeling in eHealth technology implementation

1. Start with a literature review on comparable interventions to get a feeling for the domains, jargon, and global issues and stakeholders.
2. Involve 1 or 2 domain experts in the research and development team to reflect future findings, ideally experts who have an affinity with technology and research processes.
3. Make an overview of all possible stakeholders based on literature on comparable interventions in the domain.
4. Assign stakeholder types to possible stakeholders, verify if certain types are missing and why.
5. Validate the entire overview by snowball sampling a complete stakeholder list with these key stakeholders.
6. Let experts select key stakeholders from the complete stakeholder list.
7. Organize a focus group with at least one in-person representative of each key stakeholder:
    a. Start with discussing each stakeholders’ role in the current processes.
    b. Let them complete the stakeholder list for missing stakeholders based on the process.
    c. Ask stakeholders to rank the importance of stakeholders, or alternatively let experts do it later.
    d. Discuss what bottlenecks are experienced.
    e. Discuss opportunities for improvement and opportunities for eHealth.
8. Summarize bottlenecks and opportunities and determine with the research team which opportunities are there for eHealth technology and whether these fit the project goals.
9. Ideate an eHealth technology (when possible, make mock-ups or a prototype of the ideas).
10. Plan interviews with stakeholders, or if possible, multiple stakeholders of the same stakeholder type, for value co-creation dialogs for the ideated eHealth technology.
11. Prepare the value co-creation dialog interview with questions that address all business model components (also prepare subquestions that propose possible ideas or values on each business model component to help the interview along. Focus on what the technology should contribute to their daily routines, not technical requirements).
12. Code transcripts of the focus groups and interviews, extract all implementation-related comments and combine all values and critical factors in the business model canvas.
13. Discuss the resultant business model with the research team.
14. (Optionally, for transparency and extra validation, explain the business model to stakeholders and let them reflect on it or write a document that explains the implementation strategy based on the business model as the model itself may be unclear to share with the relevant stakeholders.)

Gaps/Lessons Learned

- To further substantiate the guideline, we conclude the following main lessons from the gaps and lessons learned from our implementation research, for which the aforementioned guideline will help:
- Understanding the context beforehand is crucial to find the right stakeholders and to understand their problems and opportunities for

eHealth. As an eHealth researcher, you will have to familiarize yourself with the relevant domains. In our example case, we read up on antibiotics and microbiology literature. If the domain is not your core expertise, involving an expert from the domain is a must to help validating the research.

- Identifying stakeholders is easier than identifying their stakes. Stakeholder analysis is a complex task and needs to be done thoroughly to understand which stakeholders play a key role in the implementation of eHealth technology. Our advice is to discuss it with a group of stakeholder or combine multiple analyses so that outcomes can be compared.
- Co-creation requires incorporating multiple perspectives. Eventually, everything is joined in an implementation. When important stakeholders have different or even incompatible views on the implementation, this will become a huge problem for the technology. All effort should then go toward finding a consensus or a workable trade-off between values.
- Values are tough constructs. Business modeling is about discussing values, but stakeholders usually do not express their views in terms of "greater goods," but in to-the-point, pragmatic statements of what they want or what should be changed. It is up to the research team to interpret and combine these statements into high-level values.
- Business models are not all about money. Health care is a complex market in which, for example, quality of care or patient safety can be much more important than cost savings or maximized profits. Therefore, the values to discuss are truly "greater goods" and not only money flows.
- An implementation is never finished. Every environment is dynamic, so stakeholders change, business models change, technologies change, etc. The technology needs to be evaluated and when outcomes are getting unsatisfactory it may be worthwhile to redo the business modeling steps iteratively to see what has changed and how these changes can be anticipated.

Discussion

Preliminary Findings

In this paper, we propose a guideline for business modeling with stakeholder-oriented analysis methods for implementing eHealth. The aim of this guideline is to co-create an implementation for eHealth together with stakeholders, by identifying and analyzing stakeholders, discussing co-creation of value with stakeholders, and determining a business model. Once all values are captured in a business model following the step-by-step guide, the model can be used as a basis to disseminate or further detail the design and implementation of the eHealth technology.

We saw that most applications of business models in eHealth (if applied that is) are usually based on generic, strategic models or concocted by experts without truly involving stakeholders in the process. In that regard, there is little to no co-creation with stakeholders. The proposed guideline may seem a lot of research and time consuming, but if it can avoid misaligned plans or expectations, lack of uptake, or even design mistakes, it should be worth to spend that time and effort in business modeling.

Because only few frameworks or guidelines are available for business modeling, we chose a pragmatic approach for determining a guideline that can be used in future implementation research. The CeHRes road map (*Figure 1*) originated in the search to combine "design research" with "implementation research" for a holistic approach for health care technology development. Design and implementation influence each other; hence, a holistic view that combines both is essential for the success of health care technology [4]. Health care technology development is a multidisciplinary process [44]. However, in the field of health care, a multidisciplinary and participatory approach toward development is novel as many of these projects are still expert or eminence driven. This causes problems, as experts also are biased in how they perceive the setting. Policymakers or management see the big picture and understand the global problems a technology needs to address, but still details necessary for implementation can only be understood by talking to those who are directly influenced by the technology.

Stakeholder analysis theory is less scarce than theory on business modeling. In fact, there are many methods in the academic field such as stakeholder theory, policy making, or requirements engineering. Yet, all these possible methods have to be combined in the context of eHealth development. eHealth brings multiple domains of research together; thus, it calls for experimenting with combinations of multidisciplinary research methods. We believe this guideline is a first step toward a very pragmatic approach to think about an implementation for eHealth technology with the essence that stakeholders should be involved in the entire process.

Whereas other implementation theories such as normalization process theory [45], service, technology, organization, and finance model [46], human, organization and technology-fit [47] focus on advising possible factors that influence eHealth implementation, we focused on obtaining such possible factors from stakeholders themselves. Although the aforementioned methods may be successful to find an implementation, we believe that the focus on stakeholders helps to make the technology fit their daily routines and environment in a bottom-up approach. It basically emulates the principles of user/human-centered design, by co-creating an implementation with stakeholders. Instead of a top-down approach in which experts work with a preset of possible critical factors, we apply a bottom-up approach by extracting possible critical factors from what stakeholders deem critical for implementation.

Considering the difficulties with implementation of eHealth as we laid out in the "Introduction" section, we found that describing a pragmatic approach for co-creating an implementation with stakeholders may spur others to be more transparent in how they did it. Instead of reinventing the wheel or repeating the same mistakes again, eHealth projects can learn from each other by giving more insights into the steps that were taken to implement the technology.

Limitations

The presented guideline also has some limitations. First, this paper only demonstrated one example case. We applied individual methods or parts from the guideline in parallel to eHealth research based on our CeHRes road map [4,42,48-50], yet further validation of its generic use as a complete framework for other eHealth projects is necessary. It is certainly worthwhile to test the guideline in different research settings as well as compare differences in the results of its methods to see what works best under different conditions.

Second, the proposed activities can be very thorough and time consuming. Going through them faster or being less thorough is an option when time or resources are limiting factors. This suggests opportunities for future research to determine which methods are crucial or which can be left out or possible quicker or discount variants on the methods to find a balance between investing minimal time and satisfactory results. For example, it would not make sense to spend a few years researching the possible relevant stakeholders in a quickly changing environment like eHealth and technology.

Finally, this paper was written over time while exploring all instruments for business modeling, and therefore, our choices for these instruments were based on our good and bad experiences and constraints posed by our projects.

Future Research

We applied the business modeling steps in our example case and also applied them in other projects to test whether they can be used in various projects. In future road map-related publications, we plan to further expand on the business modeling steps and their applications to other eHealth projects. At present, there is 1 eHealth project on zoonoses that is starting with the stakeholder identification and analysis steps. In another eHealth project on dermatology, our business modeling steps are also applied thoroughly and can be published as a second example case.

Conclusions

A successful, sustainable implementation of eHealth technologies is still a tough nut to crack for many eHealth projects and we believe that more involvement of stakeholders in the whole development process of eHealth, and not only designing the actual technology but also designing its implementation can improve the overall success of the eHealth project. Having a dialog with stakeholders about their value expectations will help researchers and developers—as well as all involved stakeholders—to understand what and why they are developing eHealth technologies. We hope we can spark others to work with our proposed guideline, or try stakeholder involvement and business modeling, to advance research in the implementation of eHealth.

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Chapter 4:

Scoping an implementation strategy for antibiotic stewardship

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Revised as thesis chapter

“When you translate a dream into reality, it's never a full implementation. It is easier to dream than to do” - Shai Agassi

Abstract

Suboptimal use of antibiotics has caused alarming worldwide problems with increasing microbial antibiotic resistance and treatment of hospital-acquired infections. As a response, antibiotic stewardship programs (ASP) are formed to advocate a more prudent use of antibiotics while increasing therapeutic outcome and patient safety. In order to develop and successfully implement such a program several critical factors, like organizational, behavioral and medical factors, have to be taken into account. The aim of this literature study is to scope implementations of antibiotic stewardship programs and to identify critical factors that have impact on the implementation. In the 28 included studies, we have evaluated the reported goals, identified important stakeholders and their respective roles, as well as which interventions were parts of the program, and how impact of a program is typically assessed. Most frequently reported components of ASPs were: 1) setting up an antibiotic team; 2) setting up antibiotic guidelines that provide a rationale for optimal, appropriate antibiotic use; 3) actual intervention(s) on prescription, which vary per ASP strategy; and 4) education. Based on these findings we synthesized a strategy with critical factors that can be used as a foundation for successfully implementing antibiotic stewardship programs in a hospital setting.

Keywords

Antibiotic stewardship; implementation; stakeholders; outcomes; assessment; hospital

Introduction

The suboptimal use of antibiotics has caused a worldwide epidemic of antimicrobial resistance among microbial pathogens causing nosocomial or hospital-acquired infections [1]. The burden of disease due to these resistant pathogens, for example methicillin-resistant Staphylococcus aureus (MRSA) or Extended-Spectrum Beta-Lactamases (ESBL)-producing Enterobacteriaceae results in serious threats to patient safety and quality of care in hospitals and other healthcare institutions, and increases morbidity, mortality and healthcare-associated costs [2-4]. The option to circumvent development of resistance by using new antibiotics/antimicrobials will soon run short as no new classes of agents are to be expected in the next 20 years [5]. With no new antibiotics in prospect, a change in prescription habits and antimicrobial use is required to curb the development of resistance. Various studies report that antibiotic prescribing is not optimal, for example, Owens and Ambrose pointed out that several surveys acknowledged about half of all prescribed antibiotics are either inappropriate or even unnecessary [6]. Thus, prudent antibiotic prescription will be a pivotal step in optimizing antibiotic use.

As part of infection control, antibiotic stewardship programs (ASP) - also referred to as antimicrobial stewardship (AMS) - are interventions that encourage optimal antibiotic use. An ASP focuses on ensuring the proper use of antimicrobials to provide the best patient outcomes, lessen the risk of adverse effects, promote cost-effectiveness, and reduce or at least stabilize levels of resistance [7]. Although definitions and terms vary, ASP generally refers to an overarching program [7], a collaboration of several stakeholders in infection control [8] and management, to influence antibiotic use at a healthcare institution [7]. As the term ‘program’ implies, it consists of multiple interventions. Hence they are sometimes referred to as ‘(care) bundles’ [9] which is a more common term used for a combination of interventions in healthcare institutions.

The first documented antibiotic stewardship initiatives started already back in the late 1970s at Hartford Hospital in the United States [10]. Especially in the last decade attention for ASPs intensified both in the appearance of such programs as well as in academic research. In 2007 the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) published guidelines to support the development of ASPs [11], which to this day is a leading document for guidance in setting up ASP initiatives in hospitals. Also in the Netherlands, the urgency for ASPs increased as the Dutch Working Party on Antibiotic Policy (SWAB) published a guideline stating that all hospitals need an antibiotic (stewardship) team as of January 2014 [12].
Recent publications about antibiotic stewardship focus strongly on assessing effects of these programs as outcome assessments are necessary to determine whether ASPs are effective and to what extent [13]. Focusing on the effectiveness of

interventions on antibiotic prescribing, Davey et al. concluded in their review that there is overall evidence that these interventions have a positive effect on prescribing and resistance [14]. More recently, Kaki et al. assessed the impact of ASPs specifically in intensive care units and also concluded the overall evidence suggests that ASPs are associated with improved antimicrobial utilization in the intensive care unit, with improvements in resistance and adverse events, and without compromising short-term clinical outcomes [15]. These studies reviewed ASPs from the perspective of medical experts, while ASPs influence the organization of a healthcare institution also on a socio-technical and organizational level.

The objective of this literature study is to perform a contextual inquiry into the currently available literature on implementations of ASPs. Based on the findings we can synthesize an implementation strategy based on existing knowledge and practical, actual implementations of ASPs in hospitals. This literature study applies a comprehensive perspective that includes a behavioral, socio-technical and organizational focus. By addressing these factors, we expand the focus beyond the 'classical' medical expert-driven development of ASPs. In this literature study we therefore look at intervention characteristics – and the role of technology herein -, stakeholders and their involvement and how the impact of these interventions is assessed aside from a medical evaluation of these outcomes. We postulate that the synthesized strategy will provide critical factors to assist implementations of ASPs.

Methods

We searched PubMed, Scopus, and Cochrane Library to identify all relevant studies (*Table 1*). We ran the queries on 7 September 2011 and while reviewing we ran the Scopus query again on 1 November 2012 to update our ongoing literature study. Inspired by the ASP definition in MacDougall et al. [7], we decided to specify our search terms to any form of antibiotic program, as long as it is clearly stated as a program or bundle and part of patient care in a hospital setting. We deliberately avoided specifying the search terms towards potential types of interventions or measures, as that would potentially bias the results. We used the following search queries:

Table 1: Search queries

Search syntax	Hits
Scopus	
TITLE-ABS-KEY((antibiotic* OR antimicrobial* OR antibacterial*) AND (patient OR patients) AND (hospital OR hospitals OR clinic OR clinics) AND (steward* OR program OR programs OR programme OR programmes OR bundle*)) AND (LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(SRCTYPE, "j")	2378
PubMed	
(antibiotic* OR antimicrobial* OR antibacterial*) AND (patient OR patients) AND (hospital OR hospitals OR clinic OR clinics) AND (steward* OR program OR programs OR programme OR programmes OR bundle*) *with limits activated: Type:[Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Case Reports, Classical Article, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Corrected and Republished Article, Evaluation Studies, Government Publications, Guideline, Historical Article, In Vitro, Journal Article, Multicenter Study, Overall, Patient Education Handout, Technical Report, Validation Studies] Language: [English]*	1843
Cochrane Library	
(antibiotic* OR antimicrobial* OR antibacterial*) AND (patient OR patients) AND (hospital OR hospitals OR clinic OR clinics) AND (steward* OR program OR programs OR programme OR programmes OR bundle*) *[Clinical Trials only]*	70
Total # of studies found	4291

Titles and abstracts had to match the following two inclusion criteria: a) mention a program or mention a combination of interventions, b) report study outcomes and/or effects. Exclusion criteria were: a) study focuses on one specific infection (including sexually transmitted diseases) or antibiotic (not overarching), b) study is specific for one intervention (no program or bundle focus), c) study focuses on clinical effects of antibiotics itself (e.g. drug tests, susceptibility testing, studies into adverse effects), d) study focuses on surveillance or prevalence, not prescription, e) study is done in a non-hospital situation (e.g. dental, home care or veterinary), f) study is out-patient therapy, g) study focuses on minimal resources or third world settings (too atypical for our focus).

Two reviewers independently examined the studies for inclusion in the literature study. Studies that did not contain a methodology, were a viewpoint paper or a review, or were without clear intervention/impact analysis, were omitted. We chose a qualitative review of the studies using a customized data extraction form based on our eHealth review guidelines [16], filled in independently by two reviewers and these forms were later compared.

Results

4,291 titles were extracted from all three databases and were screened using the inclusion and exclusion criteria. A resulting 407 abstracts were screened with the criteria. 100 studies were collected, screened and read in full-text. Eventually 28 studies were included in the literature study (see *Table 2*, placed at the end of the chapter). The included studies ranged from 1996-2012 and most studies were from the last decade.

Study designs

Of the 28 studies as listed in *Table 2*, 15/28 had an interrupted time series (ITS) design [17-31], 8/28 were before-and-after studies (BA) [32-39], 3/28 were randomized controlled trials (RCT)[40-42] and 2/28 articles performed a (clinical) trial between two interventions [43, 44].

Blinding was applied in two of the RCTs [40, 42] and one article with a clinical trial [43], in which prescribers were unaware being in the intervention group or control group. Only one study did a power analysis a priori [38]. One other study did mention a satisfying power a priori, however did not reach that quantity [41]. Significance levels and confidence intervals were overall used inconsistently for outcomes in the studies. None of the studies tested or validated their outcomes or explained why these outcomes were chosen to prove an impact. Most studies retrospectively measured ASP as a whole.

The common overall study duration (see *Table 2*) was three years, usually spread over a one-year baseline and two-years impact assessment after implementing the ASP. The majority of studies did not state whether ASPs were continued after research. In 11/28 studies we could clearly assume ASPs were continued [17-19, 25, 29, 31, 33, 34, 36, 42, 44]. In one study the ASP was stopped as apparently it was only performed as a temporary pilot on two wards [38].

Regular mentioned study design-related shortcomings were: 1) causality between ASP interventions and outcomes was often deemed difficult to determine due to the observational nature of the study; 2) use of a limited historic cohort; 3) presence of possible confounding or external factors; 4) effects on development of resistance could not be measured; 5) duration of ASP (and study) was short; 6) inability to measure employee time savings (and related costs).

Setting

Sixteen of 28 studies originated from the United States [19, 22-24, 26, 28, 31, 32, 34, 35, 38-43]. Canada [30, 36], France [18, 29], Japan [25, 37] and Taiwan [20, 33] were all represented with two studies and the remaining ones were from China [21], Hungary [27], Singapore [44] and the United Kingdom [17]. The majority of hospitals (if stated) were providing tertiary care and were usually university-affiliated or teaching hospitals. Other types of hospitals were: (big) medical centers, acute care referrals, public/community or rural. Ten of 28 studies reported their ASPs were implemented in the entire hospital [18-21, 26, 31, 32, 37, 42, 44], for an additional two we had to assume from context that their ASPs were implemented in the entire hospital as it was not explicitly stated [33, 43]. When ASP was implemented in specific wards, two types of wards stood out: surgical [17, 22, 28, 30, 38, 39] and medical wards [17, 22, 24, 28, 30, 38, 39], often in combination. In lesser frequency other wards such as intensive care, obstetrics, gynecology, oncology, or even psychiatry were also mentioned. Five of 28 studies did not clearly state wards or whether the whole hospital participated [23, 25, 29, 35, 41].

Implementing an Antibiotic Stewardship Program

Goals of ASP

We looked at the introduction of ASP to see what goals were expected of ASPs (*Table 3*, placed at the end of the chapter). In 14/28 studies, the primary goal of ASP was to influence antibiotic use. The expected influence was either to reduce use [19, 22, 36], improve use [28, 29, 34, 35, 38, 40], or to make antibiotic use more appropriate [17, 18, 25, 27, 30, 31, 33, 42]. Appropriate use meant that antibiotics are prescribed according to predetermined guidelines. Reducing costs related to antibiotics was mentioned as a goal in 5/28 studies [23, 28, 30, 36, 42]. Agwu et al. had as financial goal that the program would be cost-neutral [32]. Reducing antimicrobial resistance was mentioned only twice as an explicit goal of the ASP [28, 33]. Nine of 28 studies did not clearly state any goals, but usually provided an introductory/literature context of global problems with antibiotics [20, 21, 24, 26, 37, 39, 41, 43, 44].

Grounding of ASP

Nineteen of 28 studies (*Table 3*) provided literature to ground their ASP implementation [18, 19, 21-26, 28-30, 33, 36-44], of which 8/19 based their implementation on the IDSA/SHEA guidelines for developing an institutional program to enhance antimicrobial stewardship [26, 36-39, 41, 42, 44]. Four of 28 studies based their ASP on programs implemented prior to the study and the initiated ASP was an improvement of a local, already existing program [29, 32-34]. Five of 28 studies did not provide background information about the choice of their interventions [17, 20, 27, 31, 35].

Identified stakeholders

ASPs affect the prescribing process multidisciplinary, so they typically require collaboration between different stakeholders in the hospital. Two stakeholder types were most frequently mentioned in the reviewed studies (*Table 3*): Clinical or Infectious Diseases (ID) pharmacists were involved in 25/28 studies [17-26, 28-33, 36-44] and ID physicians in 22/28 studies [18-24, 26-29, 32, 33, 35-37, 39, 41-44]. These two stakeholders also had an active role in the ASP. Microbiologists were involved in 14/28 studies [18, 20, 21, 23, 25, 27-29, 31, 35, 37, 40, 44], either as part of the antibiotic team or in a diagnostic role. Substantially less actively involved was a member of hospital management, be it at ward or hospital level. Eight studies explicitly reported management was involved in the program [19, 28, 29, 31, 35, 39, 40, 44]. The same applies for nurses, as seven studies reported the involvement of nurses in their ASP [20, 21, 25, 30, 32, 36, 37]. The majority of these studies were from Asia and these nurses usually had a specialization in infection control.

Another important stakeholder is the attending physician or in other words, the actual prescriber. Their role in the prescription process is vital for an ASP as they de facto determine the actual antibiotic use. Attending physicians were mentioned in 18/28 studies [18-22, 24, 25, 27-32, 34, 35, 38, 40, 42]. In the other studies they were likely influenced by the program but not explicitly mentioned. Despite being mentioned often; they all seem passively subjected to the interventions with no say in the planning or implementation of the program.

Remaining stakeholders and their roles were too specific for local conditions to conclude key stakeholder types or to generalize their contribution to the implementation.

We were also interested in how stakeholders were identified. However, none of the studies performed a stakeholder analysis. A stakeholder analysis is an implementation activity for finding which individuals and organization affect or will be affected by the program and rank their relative impact on the program [45, 46].

Identified interventions

Three common strategy-independent classifications of interventions appeared, either for preparatory or supplementary purposes: team, guidelines (formulary, clinical pathways or practices) and education.

- The inception of an antibiotic (stewardship) team or antibiotic committee was reported by 19/28 studies [17, 18, 20, 21, 23, 25, 28, 29, 31, 33, 35-37, 39-44]. This team had to perform tasks within the program but also contributed to the inception and implementation of the program.
- (New) guidelines or antibiotic formulary were mentioned by 10/28 studies [17, 18, 23, 25, 28-30, 40, 43, 44]. This does not mean guidelines or an antibiotic formulary did not exist prior to the ASP, but the ASP interventions required antibiotic use policies to capture the rationale for antibiotic restriction, decision support, intravenous-to-oral switches, or clinical pathways for appropriate antibiotic therapy, as laid out in the goals of the ASP.

- Activities to educate participants of the program were reported by 13/28 studies. There were two common ways of education: providing recommendations with a rationale [23, 25, 35, 36, 38, 41] or general education about the program [17, 18, 23, 25, 28-30, 40, 44]. The general education served the purpose to train participants of the program for the new ASP interventions (usually as a meeting) or to raise awareness for the program.

As suggested in the IDSA/SHEA guidelines for developing an ASP, there are two primary strategies: 'restriction and authorization' (restrictive) or 'audit and feedback' (prospective) [11]. These strategies also re-appeared in this literature study (see Table 3): 8/28 studies applied the restriction and authorization strategy thus restricting all antibiotics, a selection of broad-spectrum antibiotics, often referred to as reserve antibiotics [20, 23, 27, 29, 30, 32, 33, 43]. 7/8 had interventions we classified as approval [20, 23, 27, 30, 32, 33, 43]. The exact approval intervention differed from a decision support application [32] or case-by-case approval [20, 23, 27, 30, 33, 43]. 3/8 studies did not apply an approval system and used a restricting policy or guidelines for de-escalated or streamlined therapies, meaning a more regulatory, passive control on the prescriptions [23, 29, 43].

16/28 studies had a program involving the 'audit and feedback'-strategy, suggesting this is the most preferable strategy. This strategy avoids taking away the prescribing physician's autonomy by making recommendations non-committable or even voluntary [7]. In this strategy antibiotic prescriptions are prospectively audited and when needed a corrective recommendation is given as feedback [17-19, 21, 24-26, 31, 34, 36-41, 44]. The chosen feedback interventions were either a note in the patient records [18, 21, 26, 37, 39, 41] or bedside assistance on the wards [21, 24, 25, 31]. One study performed prospective audits and gave indirect feedback through educational meetings [38].

4/28 studies applied a combination of both strategies, i.e. combined a form of restriction with prospective audits [22, 28, 35, 42]. These studies restricted or controlled the use of (certain/high-risk) antibiotics and only performed audits on these restricted or controlled antibiotics.

A regularly reported shortcoming regarding interventions was poor portability of interventions in the program. Especially technology copes with this problem as three studies claimed their technology is institute-specific and should therefore be difficult to transpose to other institutes. One study also pointed out having had difficulties transposing protocols from one ward to another [29]. Another shortcoming reported twice was the inability to determine the contribution of each intervention individually.

Technology

We also assessed the role of technology in ASPs. Three studies developed a decision support tool [32, 34, 42] and one study used teleconferencing for a remote ID physician [31]. Two studies used existing electronic records as a medium for their alerts [36, 37]. Other mentions of used technology were present before the program and were not directly influenced by the goals of ASP, therefore we did not classify these as relevant technologies and information systems. E.g. it is likely that pharmacy data systems or electronic patient records existed in more studies and even were used for data collection for the reported outcomes, but were not directly related to ASP.

Measuring the impact of antibiotic stewardship program after implementation

Costs

Costs (*Table 4*, placed at the end of the chapter) were reported by 22/28 studies [17-23, 25, 26, 28-32, 34-37, 39, 41-43]. Our classification showed two types of costs are typically reported: (Total) antibiotic costs [17, 18, 20-23, 25, 28-30, 34, 36, 37, 39, 42, 43], and (total) antibiotics acquisition costs [19, 26, 28, 30-32, 35]. Other costs, such as utilization costs (costs related to change in e.g. hospital stay or using resources) [34, 37, 41, 43], or intervention costs (costs made for the program) were hardly reported [17, 43], therefore it remained unclear in many studies whether their ASP was cost-effective.

Acquisition costs were calculated with a fixed acquisition or purchase price multiplied with usage figures. The fixed acquisition price was used to avoid biases due to price fluctuations over time. Total antibiotic costs were obtained from financial reports and thus may contain such biases. Niwa et al. reported a reduction in 'medical expenses' that may have covered indirect costs [37]. Next to that, two other costs types (total treatment costs [41] and total hospitalization costs [34]) were also reported that may reflect indirect costs as well. One study reported "total hospital cost after approval call" [43] and was very thorough in describing how these costs were determined compared to the other studies. The authors composed an economic model including costs for hospitalization, consultation, salary for all involved team members, etc.

In summary, all 22 studies reported a beneficial effect on reducing antibiotics-related costs.

Several studies mentioned the difficulty in monetizing certain types of costs, such as time-related costs (employee time savings or productivity loss) or the wider (societal) impact. A commonly mentioned shortcoming is that reported cost savings are not necessarily generalizable for other wards or other health care institutions.

Antibiotic Use

As shown in *Table 5* (placed at the end of the chapter), a total of 20/28 studies report antibiotic use to measure impact of the ASP [17-23, 25-28, 30, 32-34, 36, 37, 39, 41, 44], 18 of which used Daily Defined Doses (DDDs, "the assumed average dose per day used on its main indication in adults") as defined by the World Health Organization (WHO) as a reference standard [17-23, 25-28, 33, 34, 36, 37, 39, 41, 44]. Two studies referred to antibiotic “dose” but did not apply the formal DDDs measure [30, 32].

The reported use varied whether it targeted total antibiotics or a selection of targeted antibiotics, depending on the characteristics of the intervention of prescription. All 20 studies reported positive effects on antibiotic use, i.e. an overall reduction in either total antibiotic use or of the targeted antibiotics. When a certain selection of antibiotics was restricted or controlled, it was possible that use of substitute antibiotics (e.g. narrower spectrum or less expensive alternatives) increased.

Reported shortcomings suggest that authors wished to establish a better evaluation of the associated benefits of reduced antibiotic use, which cannot be evaluated due to lack of data or lack of understanding causal connections.

Length-of-Stay

Length-of-stay (LoS) was reported by 14/28 studies [22, 23, 25-27, 32-35, 37, 38, 40, 42, 44], 12/14 studies reported it as length-of-stay [22, 23, 25-27, 33-35, 37, 38, 40, 44], though also ‘hospital stay’ [32, 34, 37] as well as ‘hospitalization’ [33, 42] was used.

As can be seen in in *Table 6* (placed at the end of the chapter), in 4/14 studies LoS was <10 days [22, 23, 32, 40], in another 4/14 studies >10 days [25, 34, 37, 44]. In overall, the result on LoS suggests a positive (thus reduction) effect. 6/14 studies did not report the actual number of days [26, 27, 33, 35, 38, 42], all of which did not mention a (significant) reduction either.

Generally, how LoS was determined was not reported, so we assume these studies interpret LoS as the time between admission and discharge of a patient. One study also defined LoS as time between intervention (a recommendation) and discharge [44].

One shortcoming was pointed out twice: the direct effects of influencing antibiotic use on outcomes, such as LoS, are hard to determine.

Mortality

Mortality was reported by 14/28 studies (see *Table 7*, placed at the end of the chapter) [20-22, 26, 27, 33-36, 38, 40-42, 44]. Mortality remained stable in all studies except one. One study did find a significant reduction in mortality, however the writers stated the effect could not be directly related to ASP [35]. In summary, no study reported adverse effects of an ASP on mortality.

Mortality was not used as a clearly-defined outcome, as no studies provided a clear definition or explanation. Mortality can be defined differently, and some studies used the term 'in-patient mortality' or 'crude mortality rates', 'survival', etc. One study reported infection-related mortality [44], i.e. mortality that can be associated directly with patients dying from infections. The timeframes to determine mortality could differentiate between 28 days and 90 days. In conclusion, if provided, the mortality figures cannot be safely compared between studies.

One reported shortcoming was that it remained unclear whether or not ASP influenced the outcomes.

Compliance and acceptance

Compliance and acceptance was used analogous in the studies, as they both meant the level in which recommendations were followed-up by the prescriber. Nine of 28 studies reported compliance [18, 19, 21, 24, 28, 30, 38, 43]. In *Table 8* (placed at the end of the chapter) we coded this compliance either to recommendations [19, 21, 24, 30, 39] or to guidelines [18, 28, 38, 43]. This division depended on the choice of the primary strategy for the program. Not all studies reported a trend in the compliance rates. Due to the before-after study design they did not offer additional measure points while the program was intervening. Thus the studies could report a (high) compliance rate. Four studies reported a high compliance with ASP in the range of 70-95% [21, 24, 28, 39] and four reported an increasing compliance [18, 19, 30, 38]. Both groups showed that the program had a positive effect on compliance.

Acceptance was reported by 8/28 studies [18, 22, 28, 36-38, 41, 44]. Five studies showed that acceptance was between 75%-100% [22, 28, 36, 38, 41, 44], two studies showed an improvement in acceptance [18, 37]. One study had a rather low acceptance rate of 60%, but also a low number of interventions where this acceptance rate was based on [41].

No shortcomings were reported regarding compliance or acceptance.

Unevaluated measures

Remaining reported measures were: days of therapy [25, 32, 38, 41, 44], re-admission [26, 33, 35, 41, 44], severity-of-illness/morbidity [23, 32, 36, 39, 41], errors [24, 43]. They were mentioned not frequently enough to perform a generalizing impact assessment.

Microbiological outcomes, such as changes in bacterial susceptibility, surveillance of antimicrobial resistant pathogens, occurrence of Clostridium difficile infection associated with antibiotic use or other adverse effects, were reported conform local relevance. We decided not to fully review and evaluate these outcomes in our implementation focus as they are beyond the scope of directly critical factors for implementation. Certainly, they could indirectly influence factors we did evaluate, e.g. less necessary infection control interventions in case of reduced incidence of resistant microorganisms. Also, microbiological outcomes are important as clinical evidence for the effectiveness of ASP as they help drawing medical conclusions about the effectiveness of antibiotics and their effects but these outcomes are difficult to generalize towards a (generic) implementation strategy.

Discussion

Overall the included studies provided evidence that ASPs can be associated with a beneficial decrease in antibiotic use and related costs and – if reported - evidence that this occurred without compromising patient safety. ASPs in the studies have not been active for a long time, so it was not possible to estimate their long-term effectiveness or find comprehensive evidence which initiatives really work sustainably, and which do not. The intended impact (goals) of ASPs was not so straight-forwardly clear in the studies we reviewed. Influencing antibiotic use, either by reducing it or optimizing it, seemed to be the main priority of the programs, based on the frequency these were mentioned. However, what exactly was deemed ‘optimal’ or ‘appropriate’ was not really defined in the studies.

There is an expert-driven approach in how ASPs are implemented. Stakeholders involved in the implementation of an ASP appear to be strongly influenced by interventions suggested in expert guidelines and hardly explore local practices and attitudes towards ASP. Hence we could not identify any stakeholder identification activities in the reviewed studies. ID physicians and (ID) pharmacists are the most frequently mentioned key stakeholders in the studies. These two groups of stakeholders were also stated as ‘should be minimally present’ in expert guidelines [11]. A “problem” we face with the usefulness of these stakeholder types is that they are based on the American healthcare system and thus are not necessarily directly transferable to other settings. For example, in the Netherlands, smaller hospitals hardly have ID physicians in service, and hence a clinical microbiologist often takes care of the ID physician duties as described in the guidelines [47]. Clinical microbiologists are only mentioned in half of the reviewed studies. We believe the role of microbiology and diagnostics is essential in susceptibility testing for local guidelines and in day-2 bundles / definite therapy. Implementation of ASPs will influence multiple professionals in a hospital and the way they work. It is therefore noteworthy to see how uncommon it was that prescribing physicians were involved in planning and implementing the programs in the studies included in this literature study. We consider it imperative that targeted stakeholders (e.g. prescribing physicians or nurses) are involved in the early stages of development of interventions [48]. Hulscher et al. described many social and behavioral aspects that influence prescribing habits [49]. This bottom-up and stakeholder-participative approach in implementing ASP might result in different tasks and responsibilities in an ASP than suggested by top-down implemented expert guidelines. It should therefore help to increase participation of physicians (and possibly more stakeholders who will be subsequently influenced by the program) in the early stages of determining ASP interventions that affect their prescribing habits.

In our literature study, we focused on the characteristics of hospital-based programs and found that they often consist of four components or key-interventions: 1) setting up an antibiotic team; 2) setting up antibiotic guidelines that provide a rationale for optimal, appropriate antibiotic use; 3) actual intervention(s) on prescription, which vary per ASP strategy; and 4) education. Regarding the actual intervention on prescription, we found a preference for the 'audit and feedback'-strategy with either the choice to deliver feedback directly via bedside rounds, or more passively via a memo in records. The choice for these interventions was usually based on other literature and in particular the IDSA/SHEA guidelines for ASP [11]. This correlation might also be due to the fact that the majority of the included studies were derived from US hospitals. To establish the best implementation strategy, it is important to further specify characteristics of these four interventions with the aforementioned stakeholders and determine which form of audit and feedback fits the stakeholder needs best.

We also looked at the role technology played in ASPs, but it was minimal. In focus groups held with stakeholders in a local hospital, Wentzel et al. concluded technical opportunities for eHealth for various stakeholders in various stages of the program [50]. Possible eHealth interventions such as decision support could improve information sharing and provide advice for optimal or appropriate treatment. For example, something simple like dosage correction for a patient's weight and kidney function, a notification system that a patient should not drink milk for breakfast, or something more advanced like empiric guidelines that real-time adjust to susceptibility patterns or medical history of the patient.

ASP interventions can be implemented in the entire hospital or in a selection of 'high-risk' or 'heavy use' wards. The latter might even be favorable as it is probably not always necessary to implement ASPs in the entire hospital. This also reflected in the studies, two of such higher risk wards really stood out, medical and surgical wards, and also ICUs but in lesser frequency in our selected pool of studies.

Our impact assessment of the reviewed ASPs remained less clear. Outcomes and how outcomes were measured were rather unclear and methods of impact assessment were often not explained in detail. All studies reported they found a (beneficial) impact of the ASP, but can conclude this only in a local context, i.e. with locally relevant data and definitions. Standardized measures are a must to adequately assess and compare ASPs at a higher, macro-level. Various initiatives are started to determine standardized measures, e.g. the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) initiative by ECDC [51], or with expert panels [52].

Reduced costs are mostly not explicitly mentioned as a goal but were the most measured effect in the included studies. According to McGowan Jr this is because costs are traditionally used to demonstrate effects of ASPs [13]. In most cases costs were determined by using acquisition costs or total antibiotics expenditure. We found that a lot of hidden cost savings were not analyzed, e.g., an earlier switch to oral antibiotics that would allow that a patient can be earlier discharged and can result in reducing many additional patient-related costs. Also, as costs for all ASP activities and resources were usually not given, it is unproven whether these programs are cost-effective or even cost-neutral.

Measuring antibiotic use was also a very frequently used method for impact assessment and the most consistent one as most investigators used DDDs as indicator to evaluate changes in use of antibiotics. However, it has to be noted that DDDs are not 100% unanimously accepted as a proper indicator for use and it is debated whether prescribed daily doses (PDDs) reflect actual antibiotic use better [53]. Reduced DDD of an antibiotic is not necessary beneficial and may only prove to be a virtual improvement, e.g. due to 'squeezing the balloon' where prescribers shift to other antibiotics which are not targeted by ASPs [54]. We found half of the reviewed studies used a limited set of clinical outcomes to assess patient safety: in fourteen studies length-of-stay and mortality rates were reported. An important point to make for these outcomes is to specify them with regard to critical patients, where optimal antibiotic use can make a larger difference than in the general patient population. Most included studies reported mortality being stable as they reported hospital-wide mortality rates. In that situation the (beneficial) effect of ASP on mortality washes away with the sheer number of patients. Also, consequences of other programs/bundles or other medication can be confounded in these clinical outcomes.

Acceptance and compliance were used analogous in the studies, as they both reflect the level in which recommendations were followed up. It has to be noted that in behavioral sciences these terms have different meanings, but either way, they (have to) demonstrate the uptake of the intervention on prescription.

Additional impact parameters that could be taken into account are microbiological results that we deliberately left out of our analysis. Having adequate diagnostics and surveillance is a must for an ASP – or effectively functioning infection control in general. Measuring Clostridium difficile was most commonly performed as it is an adverse effect directly related to antibiotic (mis)use. Other (resistant) pathogens in hospitals differed on those relevant for their ecology and antibiotics.

Based on reported outcomes and measures, we advise to report the use of antibiotics (in e.g. DDDs or other clearly defined and adapted standard doses), a complete as possible overview of costs, including costs for the intervention and a thorough cost savings estimation, monitoring compliance of the uptake of interventions, and length-of-stay and in-hospital mortality, ideally specifically for (critical) patients receiving antibiotics. Apart from unstandardized measures, the methodologies of included studies were not strong either, as claimed before in other reviews [15, 55]. Overall, the impact assessments were not strong. Reductions in antibiotic use could be demonstrated, but it remains to be seen whether the programs were cost-effective and patient safety was truly not harmed. Shortcomings also suggest possible problems with causality of the ASP interventions due to the study designs and possibility of confounding factors. Furthermore, the duration of the ASPs was short so conclusions are made on limited historic cohort data and limited data collection during the ASP.

Future in ASP research

We looked at the studies from an implementation science and organizational perspective to determine critical factors for implementing ASPs. This perspective aims at taking into account all factors related to implement innovation in healthcare to overcome non-compliance and to set the right conditions for changing work processes and behavior in a hospital setting [48]. Further research is needed to develop a guideline for the implementation of ASPs fitting the Dutch and German context of our project. The identified critical factors can be used as a basis to determine further which stakeholders need to be involved in the ASP initiatives, which intervention options they can choose from and what effects these stakeholders can expect or wish to see. Through stakeholder identification and value specification with these stakeholders using the critical factors as input, the implementation strategy should be further detailed into an online dashboard for ASP.

Limitations

Over half of included studies were situated in the US so a bias towards the American healthcare model might be present. This was for example evident in the stakeholder types, and may also explain the high frequency of references to the IDSA/SHEA guidelines on how to develop an institutional program to enhance antimicrobial stewardship. A publication bias may also be present as most hospitals were academic or teaching hospitals. An opportunity for future research may lie in looking at ASPs in non-academic hospitals. We intended to publish this study as a systematic review - to identify implementation characteristics – but our findings were only answered half-satisfactory due to the lack of details of the implementation, lack of standardization and lack of details in outcomes. We did not use a validated extraction form, as formal tools like e.g. EPOC or ORION were not suitable enough for our extraction. In the update of articles, we only queried Scopus; we believe Scopus was sufficient as 90% of the included studies in the prior query were all retrieved through Scopus.

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Appendix for chapter 4

Table 2: Overview of included studies and study designs

Author (Year)	Study design	Main study entity (N if avail)	Randomized	Blinding	Power	Group evaluation	Baseline	Over	Duration	Type of hospital Setting	Shortcomings regarding study design
Agwu (2008)	Before-and-after (+ Survey)[1]	N/A	NO	NO	NO	NO	YES	Whole ASP	1yr(pre) 1yr(inv)	- Tertiary - size: 175 beds **Implemented in:** Entire hospital	- Limitations of this study include a lack of specific knowledge about time savings (i.e., the actual reduction in the time that pharmacists spent fielding antimicrobial-related telephone calls). We did not investigate the potential impact of decreased antimicrobial use on resistance rates.
Ansari (2003)	Interrupted time series	Pharmacy data (N=N/A)	NO	NO	NO	NO	YES	Whole ASP	2yr(pre) 2yr(inv)	- Tertiary, university - size: N/A **Implemented in:** Medical, surgical[N/A]	- Measurement of hospital antibiotic use needs to be supported by more detailed analysis of indications for use and outcomes. - Quality indicators require consensus about evidence-based clinical standards and about the information that must be recorded in order to evaluate compliance with standards.
Bevilacqua (2011)	Interrupted Time Series	Prescriptions (N=55,000)	NO	NO	NO	NO	YES	Whole ASP	12yr(pre) 3yr(inv)	- Teaching - size: n/a **Implemented in:** Entire hospital	- Observational, non-experimental aspect of the study does not claim the evolution of antibiotic consumption, but causal link is very likely
Camins (2009)	Randomized controlled trial	Prescriptions (N=784)	YES	YES	NO	YES	NO	Whole ASP	10mth(inv)	- Urban, teaching - size: 953 beds **Implemented in:** Internal medicine[N/A]	- Potential for "cross-contamination" between the intervention and control groups during the trial. - Conducted among internal medicine ward teams and did not include teams working in

											intensive care units and on other medical subspecialties - In control group twice as many patients started on antibiotics for asymptomatic bacteriuria compared to the intervention group (p=0.02) which may potentially create bias away from the null in results. - Unable to measure the effect that our intervention had on the development of antimicrobial resistance
Carling (2003)	Interrupted Time Series [trend formula]	N/A	NO	NO	NO	NO	NO	Whol e ASP	7yr(inv)	- Teaching - size: n/a [“medium”] **Implemented in:** Entire hospital[5]	- The main limitation of this study is that it was not randomized and instead relied on historical controls. - The authors cannot be certain that other, unrecognized changes did not contribute to the decrease. The authors did not examine these possibilities and cannot exclude them - The nosocomial C. difficile rates, ceftazidime-resistant nosocomial infections, and vancomycin-resistant enterococci rates might have had confounding variables that explain the beneficial rates.
Chan (2011)	Interrupted Time Series	N/A	NO	NO	NO	NO	YE S	Whol e ASP	2yr(pre) 5yr(inv)	- Medical center, university - size: 3500 beds **Implemented in:** Entire hospital	- Lack of external controls whether changes are associated with or independent of the system
Chang (2006)	Before-and-after	Patients (N=5046 (b) & 5054(a))	NO	NO	NO	YE S	YE S	Whol e ASP	3mth(pre) 3mth(inv)	- Medical center - size: 921 beds **Implemented in:** [#Entire hospital]	- It was a short-term study, and therefore lacks information on the severity of patient’s diseases, as well as the consumption of oral antibiotics

Cheng (2009)	Interrupted Time Series	Prescriptions (N=?(b)[2] & 4432(a))	NO	NO	NO	NO	YES	Whole ASP	1yr(pre) 2yr(inv)	- Tertiary, university - size: 1500 beds **Implemented in:** Entire hospital[5]	- The baseline observation and post intervention period were relatively short, so that a segmental regression analysis could not be applied. - The possibility of Hawthorne effect could not be ruled out, with the regular education sessions alone
Cook (2004)	Interrupted Time Series	Inpatient AB dispensing data N=N/A	NO	NO	NO	NO	YES	Whole ASP	1.5yr(pre) 1.5yr(inv)	- Tertiary, teaching - size: 731 beds **Implemented in:** Adult medical, surgical services[N/A]	N/A
Danaher (2009)	Randomized controlled trial	Patients (N=73)	YES	NO	NO	YES	NO	Whole ASP	6mth(inv)	- Military, teaching - size: N/A **Implemented in:** N/A	- Financial savings and cost not analysed - Nor productivity lost at ID physician and clinical pharmacist for being involved in ASP [# - Small sample size]
Evans (1998)	Before-and-after	Patients (N=766(b) & 398(a))	NO	NO	NO	NO	YES	Whole ASP	2yr(pre) 1yr(inv)	- Private, acute care referral, teaching -size: 520 beds **Implemented in:** Respiratory tract ICU[n/a]	- No single measure of quality with respect to anti-infective therapy is likely to be sufficient.
Frank (1997)	Interrupted Time Series	N/A	NO	NO	NO	NO	YES	Whole ASP	1yr(pre) 1yr(trans) 1yr(inv)	- Primary & tertiary, university - size: 365 beds **Implemented in:** N/A	- Retrospective nature of evaluation and use of historical control periods makes it difficult to determine causality.

Gentry (2000)	Before-and-after	N/A	NO	NO	NO	YES	YES	Whole ASP	2yr(pre) 2yr(inv)	- Medical center, teaching - size: N/A **Implemented in:** N/A	- Impossible to determine effect of ACP on LOS or improvement of mortality - ICD-9-CM is not without problems, but generally accepted. Impossible to determine community acquired vs nosomocial infections due to ICD-9-CM - Severity score such as Apache II could not be used for the baseline period because many patients lacked certain data.
Gross (2001)	Clinical trial	Logged calls (N=180)	NO	YES	NO	YES	NO	Per intervention	1mth(inv)	- Tertiary, university - size: 772 beds **Implemented in:** [#Entire hospital]	- It's no RCT, so confounding variables couldn't be tested. - Times of operation of the 2 groups were mutually exclusive, unable to control for time of day as a factor. - The limitations of the economic model include the fact that the "societal perspective" was not the focus. Moreover, we assessed only incremental costs incurred. Thus, the economic results may not be generalizable to settings in which no ID approval service is present.
Kravitz (2005)	Interrupted Time Series	AB prescription errors (N=671)	NO	NO	NO	NO	NO	Whole ASP	2yr(inv)	- Private, nonteaching - size: 410 beds **Implemented in:** Medicine care unit, oncology[n/a]	- We did not attempt to measure any changes in antibiotic resistance within our institution during the period of study. - Because of changes in our pharmacy accounting system initiated contemporaneously with our study, we were unable to quantify antibiotic cost savings. - Because of lack of a control group, we were unable to measure any effects on patient outcomes.
Leung (2011)	Before-and-after	N/A	NO	NO	NO	NO	YES	Whole ASP	3mth(pre) 3mth(inv) 3mth(inv)	- Community, teaching - size: 490 beds	- Short timeframe - Effects on resistance unknown - Observational in nature so potential biases

										Implemented in: ICU[12]	- Potential Hawthorne effect, staff in the ICU were aware of the intervention.
Liew (2012)	Clinical trial	Prescription data (N=N/A)	NO	NO	NO	YES	NO	Whole ASP	2yr(inv)	- Acute, tertiary - size: 1559 beds **Implemented in:** Entire hospital	- Retrospective observational nature could perhaps not recognize differences that could exist between the two groups
McGregor (2006)	Randomized controlled trial	Medical records (N=2237 & 2270)	YES	YES	NO	YES	NO	Per intervention	6mth(inv)	- Tertiary, medical center, university - size: 628 beds **Implemented in:** Entire hospital[5]	- Another limitation to this study is that the antimicrobial management team could not be blinded as to the randomization status of the patients and thus there remains the potential for bias.
Miyawaki (2010)	Interrupted Time Series	N/A	NO	NO	NO	NO	NO	Whole ASP	7yr(inv)	- "Advanced treatment", university - size: 1076 beds **Implemented in:** N/a	N/A
Niwa (2012)	Before-and-after	Patients receiving IV AB (N=6251 (b) & 6348(a) & 6507(a)[3])	NO	NO	NO	NO	YES	Whole ASP	1yr(pre) 1yr(trans) 1yr(inv)	- University - size: 606 beds **Implemented in:** Entire hospital	N/A
Nowak (2012)	Interrupted Time Series	N/A	NO	NO	NO	YES	YES	Whole ASP	4yr(pre) 2mth(trans)[4] 3.5yr(inv)	- Medical center, tertiary - size: 583 beds **Implemented in:** Entire hospital	- No definite causality due to quasi-experimental design - Other system changes could have influenced

Peto (2008)	Interrupted time series	Records (N=N/A)	NO	NO	NO	NO	YES	Whole ASP	2yr(pre) 2yr(inv)	- Tertiary, university - size: n/a **Implemented in:** ICU[6]	- This was a single-centered study where only quantitative but not qualitative data on antibiotic use was collated. - Other possible confounding factors (e.g. other than bloodstream infections, nursing habits) were not explored - It cannot be ignored that ICU patient turnover increased during the course of the analysis
Philmon (2006)	Interrupted Time Series	Targeted AB requests (N=1426)	NO	NO	NO	YES	YES	Whole ASP	1yr(pre) 1.5yr(inv)	- Community, general - size: 900 beds **Implemented in:** Medicine, surgery, obstetrics-gynecology, psychiatry[n/a]	- We failed to include any methodology at the outset to determine improvements in length of hospital stay. - We also did not include a method to formally determine whether any adverse outcomes occurred because of our program.
Saizy-Callaert (2003)	Interrupted Time Series	Patients (receiving AB)	NO	NO	NO	NO	YES	Whole ASP	3yr(inv)	- N/a - size: 600 beds **Implemented in:** 5 teaching departments[n/a]	- Follow-up data based on resistance rates are difficult to interpret.
Salama (1996)	Interrupted Time Series	N/A	NO	NO	NO	NO	YES	Whole ASP	1yr(pre) 1yr(trans) 1yr(inv)	- Tertiary, university - size: 465 beds **Implemented in:** General medicine, surgery, oncology, obstetrics-gynecology, orthopedic	N/A

										prosthetic surgery[n/a]	
Storey (2012)	Before-and-after	N/A	NO	NO	NO	YES	YES	Whole ASP	8mth(pre) 16mth(inv)	- Community hospital - size: 100 beds **Implemented in:** Medical-surgical unit[43]	- Additional interventions may have had impact
Toth (2010)	Before-and-after	Patients (N=80(b) & 80(a))	NO	NO	YES	YES	YES	Whole ASP	3mth(pre) 3mth(inv)	- Tertiary - size: 903 beds **Implemented in:** Interal medicine, surgery[n/a]	- Simple institution populations, therefore impact may vary on institution/provider acceptance - Possible confounding factors that were not detected (due to quasi-experimental design) - Study not designed to find difference in patient outcomes
Yam (2012)	Interrupted Time Series	N/A	NO	NO	NO	NO	YES	Whole ASP	4mth(pre) 1mth(trans) 14mth(inv)	- Rural hospital - size: 141 beds **Implemented in:** Entire hospital	N/A

[1]) survey for finding improvements for the existing ASP.
[2]) baseline N was not clearly specified.
[3]) study measured two years as after study.
[4]) additionally, 3 months prior to implementation apparently unmeasured.
[5]) some wards were excluded.

Table 3: Overview of goals, stakeholders and interventions

Author (Year)	**Goals** **Grounding**	**Mentioned stakeholders**	**Strategy** **Classified interventions**	**Description of interventions**	**Shortcomings regarding goals, stakeholders and interventions**
Agwu (2008)	Reduce redundancy and workload, would improve communication and user	- ID fellow - 2x pharmacist - Nursing units - Prescriber	**Restriction & authorization** - Technology	- WWW-based app with automatic reports/information, reminders, approval	- The authors acknowledge that the use of a PIDF in decision making may provide less standardized decision making and may limit the system's

	satisfaction, and would be cost neutral. **Grounding: Prior**		- Decision Support - Approval - Education	system and clinical decision support. - Approval via PIDF - Education how to use it	portability to institutions where this service is not available.
Ansari (2003)	Reduce inappropriate use of key antibiotics because they should be reserved for infections caused by organisms that are resistant to first line antimicrobials. **Grounding: N/A**	- Surgeon - Junior staff - Clinical teams - Local opinion leaders - Clinical pharmacists - Attending physician	**Audit & feedback** - Team - Guidelines - Education - Audit - Feedback	- Antibiotic subcommittee - Disseminated policy - Immediate Concurrent Feedback	- Need to expand to cover all antibiotics in order to assess which reduced use of Alert Antibiotics is associated with increased use of other drugs
Bevilacqua (2011)	Sensitize prescribers to the need of changing prescription habits. **Grounding: Theory**	- ID specialists - Referent physician - ICU physician - Bacteriologists - Pharmacist - Pharmacy intern	**Audit & feedback** - Team - Guidelines - Audit - Education - Feedback	- Commission - Antibioguide - Pharmacist's analysis on nominative prescription form - Education - Referent physicians for advice	N/A
Camins (2009)	Using a antimicrobial utilization team (AUT) as mechanism to improve antimicrobial use (3 targeted drugs). **Grounding: Theory**	- Faculty attending physician - Senior resident - Junior residents - Medical students - ID physician - ID clinical pharmacist - Clinical pharmacist - Director - Microbiology personnel	**Audit & feedback** - Team - Guidelines - Feedback	- Antibiotic utilization team - pocketcards with guidelines - feedback - audit using mb data - assessment of appropriateness	N/A
Carling (2003)	Anticipating the trend toward increasing use of expanded-spectrum cephalosporins and aztreonam. **Grounding: Theory**	- Members of pharmacy committee - Members of infection control committee - ID clinical - ID physician - physician caregivers - resident - staff physicians	**Audit & feedback** - Audit - Feedback	- Joint assessment - Recommendations	N/A

Chan (2011)	N/A **Grounding: N/A**	- ID physician - Prescriber - Pharmacy - Clinical microbiologists - IC nurses	**Restriction & authorization** - Team - Approval - Feedback	- AB Subcommittee - Restriction of certain antibiotics - Review + approval by ID physician (based on provided supportive data) - Consultation if necessary	N/A
Chang (2006)	Enforce the appropriate use of antimicrobials for inpatients, and to further reduce antimicrobial resistance. **Grounding: Prior**	- ID physicians - IC professional - Clinical pharmacist - Other medical specialists	**Restriction & authorization** - Team - Approval - Education	- AB Team - approval by team - educational campaigns	N/A
Cheng (2009)	N/A **Grounding: Theory**	- IC nurses - Clinical microbiologists - ID physicians - Clinical pharmacists - Prescribing doctor	**Audit & feedback** - Team - Audit - Feedback	- Antimicrobial team - Review of daily generated lists from pharmacy system - Memo for inappropriate prescriptions - Bed-size assistance for difficult cases	N/A
Cook (2004)	Reduce use of broad-spectrum antibiotics by monitoring the use of these agents, and providing recommendations for streamlining or discontinuing antibiotics once culture data and diagnostic studies were available for review. **Grounding: Theory**	- Clinical pharmacist - ID physician - ID staff - ID practitioner - Pharmacy - Attending physician - House staff	**Both** - [Team] - Approval - Audit - Feedback	- [Committee (but already founded pre-ASP)] - Classification of restricted / controlled / unrestricted antibiotics - Approval for restricted - Review of controlled antibiotics by pharmacist - Review of appropriateness of treatment after 2 days based on patient charts for controlled and restricted. - If needed, recommendation	N/A
Danaher (2009)	Optimize clinical outcomes by making evidence-based, case-	- ID physician - Clinical pharmacist	**Audit & feedback**	- AB Team was set up	- Lack of verbal interaction with provider at the time a treatment

	specific suggestions, which reduced total per-patient exposure to antibiotics. **Grounding: Theory**	- Physician	- Team - Audit - Feedback - Education	- ad-hoc pharmacy reports for patient receiving broad-spectrum antibiotics 3+ days - Data collection - note card with recommendations and rationale	decision was being made. [written suggestions might be ignored due to lack of trust and context]
Evans (1998)	Improve the use of anti-infective drugs for prophylaxis in patients undergoing surgery, for empirical therapy, and for the treatment of microbiologically confirmed infections. **Grounding: Prior**	- Physicians	**Audit & feedback** - Technology - Decision Support - Feedback	- Computerized decision support program [that gives patient specific recommendations]	- Measuring the quality of anti-infective treatment is more problematic than assessing the acceptance and efficiency of the computer program itself - Because this evaluation was conducted in an institution with advanced computerized medical information systems that were operative even in the pre-intervention period, our results may not adequately reflect the benefits of the computerized tool for ordering anti-infective agents in other health care settings
Frank (1997)	To control antimicrobial expenditures and improve antimicrobial prescribing. **Grounding: Theory**	- ID physicians - Clinical pharmacists - Microbiologist - Hospital epidemiologist	**Restriction & authorization** - Team - Guidelines - Approval - Education	- AB Subcommittee - use criteria in formulary (restricted, controlled) - case-by-case approval by subcommittee - additional provision of educational information	N/A
Gentry (2000)	Optimize AB use by altering the approval process for restricted and non-formulary antimicrobials. **Grounding: N/A**	- ID physicians - Microbiology laboratory director - Clinical specialist - Primary team/physicians - Chief of staff	**Both** - Team - Guideline - Approval - Audit - Education - Feedback	- AB advisory group - Formulary - Approval of restricted antibiotics - Review after 24 hours - Recommendation for stop-order - Case-by-case education	- Not possible to determine contribution of individual program components

				- Complex cases required consultation of clinical specialist upon request	
Gross (2001)	Improve the quality of patient care by ensuring the effectiveness of treatment regimens and to compare the effectiveness of the AMT with that of the ID fellows with respect to antimicrobial recommendations and clinical and economic outcomes. **Grounding: Theory**	- Residents - ID fellows - Clinical pharmacist - ID physician	**Restriction & authorization** - Team - Guidelines - Approval	- Antimicrobial management team - renewed formulary - handbook - approval by beeper	N/A
Kravitz (2005)	Provide concurrent review of the use of antibiotics and identify and correct errors in antibiotic prescription. **Grounding: Theory**	- ID physician - Doctors of pharmacy / pharmacists - Attending physician	**Audit & feedback** - Team - Approval - Audit - Feedback	- AB Team that did rounds over the wards - Review of patient charts - Correction of prescription errors	N/A
Leung (2011)	Reduce the use, expenditures and rates of nosocomially acquired C. difficile infections. **Grounding: Theory**	- ID physician - Nursing - AMS pharmacist - Pharmacy staff - ICU care team - ICU pharmacist	**Audit & feedback** - Education - Team - Audit - Feedback - Technology	- Educational material for awareness - in-service education sessions - ID team does prospective audit and feedback - Alerts via electronic medication administration / order entry	- This institution uses computerized physician order entry and electronic medication administration records; however, it has yet to develop an automated method of extracting data for DDDs per 100 patient-days or days of therapy according to the doses administered to patients.
Liew (2012)	N/A [evaluate impact on patient safety] **Grounding: Theory**	- ID physician - Clinical microbiologist - Clinical pharmacists - Pharmacy and therapeutics Committee - Medical Board	**Audit & feedback** - Team - Guidelines - Education - Audit - Feedback	- ASP team - Guidelines for antibiotics - Switch-algorithm - Education on guidelines + algorithm - Audit with recommendations	

McGregor (2006)	Reduce antimicrobial expenditures and improve the appropriateness of antimicrobial utilization, by facilitating appropriate treatment choice, dosing, and duration. **Grounding: Theory**	- ID attending physician - Clinical pharmacist - Member of the admitting or primary team	**Both** - Team - Audit - Feedback - Technology	- Antimicrobial management team - two interventions side-by-side: * list of restricted abs, based on patient charts if necessary a recommendation * application with alerts, review with app. Recommendation with printed form from app.	- A limitation to the generalizability of this study was that it was conducted at a single institution and the effectiveness of an informatics intervention, such as the computerized clinical decision support system we have evaluated, may vary between institutions since the system cannot be evaluated independently of the system's users
Miyawaki (2010)	Promotion of appropriate use of broad-spec antibiotics and anti-MRSA agents. **Grounding: Theory**	- Physicians - Nurses - Pharmacists - Clinical laboratory technologists - Medical Cleric Employees	**Audit & feedback** - Team - Guidelines - Feedback - Audit	- Infectious control team - Guidelines were set up - Supporting consultation as education - Surveillance in Excel	- Couldn't distinguish the effect of either the 'active' ASP or the education activities.
Niwa (2012)	N/A [to optimize AB use] **Grounding: Theory**	- IC physician - Clinical pharmacist - Medical/microbiological technologist - IC nurse	**Audit & feedback** - Team - Audit - Feedback - Technology	- infection control team (ICT) - Alerts via digital records - Daily review of all antibiotic prescriptions - Contact via phone	
Nowak (2012)	N/A **Grounding: Theory**	- Residency-trained physicians - Pharmacist - ID physician [external]	**Audit & feedback** - Audit - Feedback - Technology	- Automatic datamined reports - 1st Review by pharmacist - 2nd Review by ID physician - Recommendation form	
Peto (2008)	Achieve a more considered antibiotic prescribing practice, a new antibiotic policy. **Grounding: N/A**	- ID specialist - Microbiologist) - Surgeons	**Restriction & authorization** - Feedback - Approval	- Consultation service by infectious diseases specialist - Restricted authorization to prescribe antibiotics	N/A
Philmon (2006)	Improve the overall use of antibiotics, prevent and/or slow	- Chief of the Department of Infectious Diseases	**Both**	- AB Team as part of program	N/A

	the emergence of resistant organisms, improve patient outcomes and to decrease healthcare costs. **Grounding: Theory**	- Clinical pharmacists - Microbiologist - Physician - ID physician	- Team - Guidelines - Approval - [Audit] - Feedback	- Policy (switch, discontinuation, restricted use of selection of antibiotics) - Notes and reminders to recommend change [who audits or how is quite unclear]	
Saizy-Callaert (2003)	Rationalize antibiotic usage, based on a participatory approach and aimed at obtaining a durable change in prescribing practices. **Grounding: Prior**	- Pharmacist - Bacteriologist - Clinical ID specialist - Representative of assessment board - Drugs committee - Senior hospital physician	**Restriction & authorization** - Team - Guidelines - Audit - Education	- Multidisciplinary steering committee - local consensus in pocked-sized prescribing guide - restricted prescribing policy - regular assessment of prescriptions - institutional training and information for prescribers	- Follow-up indicators, although simple, raise many problems: they are time-consuming and require sustained mobilization of health professionals. During the four-year study period, two of the eight planned audits could not be carried out. - The broad diversity of clinical indications for antibiotic prescription. Despite the large number of protocols developed during our programme (182 clinical situations), the number of situations not covered by a local consensus increased as the audit was extended to all the hospital departments
Salama (1996)	Cutting costs and reducing inappropriate antimicrobial use. **Grounding: Theory**	- Physicians - Pharmacists - Nurses - Administrative personnel - ID service	**Restriction & authorization** - Guidelines - Education - Approval	- Streamlining of formulary - Automatic stop order for reassessment - Stickers to remind oral switch - Approval - Extensive education program	N/A
Storey (2012)	N/A **Grounding: Theory**	- ID physician - clinical pharmacy supervisor - Pharmacy director	**Audit & feedback** - Team - Audit	- ASP team - Audit of records of prescribed antibiotics - Non-binding recommendation form	

		- Pharmacy team members	- Feedback		
Toth (2010)	Improve the quality of antibiotic use and improve outcomes of patients receiving ABs. **Grounding: Theory**	- Trained stewardship pharmacist - Medical team	**Audit & feedback** - Audit - Education	- Prospective audits - Educational inservice programs on antibiograms	- Team not fully multidisciplinary. No ID physician involved. - Not always follow-up culture data available.
Yam (2012)	Following IDSA/SHEA guidelines while addressing major gaps in resources. **Grounding: N/A**	- Chief medical officer - Director of pharmacy - Pharmacy practice residency director - Pharmacy practice residents - Pharmacists - Clinical microbiologist - Staff members involving QI and IC activities - Remote ID physician - In-house physicians	**Audit & feedback** - Team - Audit - Feedback - Education - Technology	- Roles for each team member - Reports by pharmacy dept - Teleconferencing "rounds" by remote ID physician - Direct contact with remote ID physician if necessary - Education by pharmacy dept	

Table 4: Overview of costs

Author(Year)	Classification and measures	Reported effects and overall effect	Measuring method	Shortcomings
Agwu (2008)	**- Acquisition costs** (Costs of restricted and unrestricted AMs)	- Annual costs of restricted AMs decreased $370,069 (decrease of 21.6%) - *Unrestricted stayed similar (~$570,000)* **Overall effect:+**	- From financial database - Data included purchase costs, but not administration costs, of the restricted antimicrobials	- Several reasons for the reduced number of doses and associated cost savings are possible, but direct cause and effect is not determined - Lack of specific knowledge about time savings (i.e., the actual reduction in the time that pharmacists spent fielding antimicrobial-related telephone calls).

Ansari (2003)	**- Intervention costs** (Total costs of intervention) **- Antibiotic costs (restricted)** (Average price of Alert Antibiotics)	- The total cost of the intervention over the 2 years (£15 143 + £4990) was therefore well below the most conservative estimate of the reduction in cost of Alert Antibiotics (£133 296 / based on lowest boundary of CI * 24 months) - Assuming that the cost of Alert Antibiotics would have continued to increase without the intervention, the cost of Alert Antibiotics was estimated to have decreased by an average of £23 852 per month (95% CI £18 154–£29 549, $P<0.0001$) (maximum estimate of reduction) **Overall effect:+**	- Measuring the time required for consultation, completing the records, data entry and interpretation. The time required for additional meetings of the Antibiotic Policy Committee was quantified and additional consumable materials were recorded. Time was costed using the average hourly rate for each grade in each of the years of the intervention, including employer's contributions and national insurance - Average price of each dosage form (£/bed-days/month) also, using average bed occupancy (used to reduce fluctuation in cost estimation above)	N/A
Bevilacqua (2011)	**- Antibiotic costs** ("Expenditures") [# of AB]	- 3,1m(1995); 3,8m(2000); 3.8m(2005); 3.7m(2006); 3.3m(2007); 2.5m(2006) - Drop of 34% between 2005-2008 **Overall effect:+**	- In euros calculated by using the costs of ABs in 2007 to neutralize effects in price variation	N/A
Carling (2003)	**- Acquisition costs** (Acquisition costs)	- Acquisition costs fell by almost 20% - Cost of antibiotic acquisition per 1,000 patient-days during 1990 with subsequent costs indicated that there had been a savings in acquisition costs of $200,000 to 250,000 per year after deduction of expenditures for support of the program of approximately $43,000 per year ($860 per 1,000 patient-days)	- The acquisition cost per gram for each antibiotic was developed using a 1994 catalogue of prescription drug costs. Both use and expenditures were adjusted for patient volume by calculating DDD/1,000 patient-days using a computerized spreadsheet program.	N/A

		Overall effect:+		
Chan (2011)	**- Antibiotic costs** **(**Ratio of AB in drugs expenditure)	- 49%, 42%, 43%, 42%, 40%, 43%, 45% (2003-2009) **Overall effect:±**	N/A	N/A
Cheng (2009)	**- Antibiotic costs (restricted)** (Antibiotic expenditure)	- An overall reduction in both the broad-spectrum intravenous antibiotic and total antibiotic consumption. *- The drug expenditure of meropenem increased by more than 50% between 2004 and 2007 in both the Medical and Surgical Departments.* **Overall effect:+**	- Cost multiplied by the Defined Daily Doses [# with WHO DEF]	N/A
Cook (2004)	**- Antibiotic costs** (Total costs of antimicrobials)	- Antimicrobial costs decreased in the first year of the programme and have continued to decrease slightly since that time. Resulting in a 20% decrease in monthly antimicrobial costs ($340 591 in 2000 to $274 030 in 2003, P= 0.024) *- Percentage of the hospital pharmacy budget that includes antimicrobial agents decreased from 23.8% in 2000 to 15.3% in 2003 (P< 0.0001)* *- No significant changes in individual drug acquisition costs* **Overall effect:+**	- Total costs of antimicrobials were determined over a 5 year period	N/A
Danaher (2009)	**- Utilization costs** (Total costs of antibiotic treatment)	- Did not significantly differ ($78.20±107.90 vs $136.87±199.64, p>0.05)	N/A	- Financial savings and cost not analysed (nor productivity lost at ID physician and clinical pharmacist for being involved in ASP)

		Overall effect:± (no sig.)		
Evans (1998)	**- Antibiotic costs** (Costs of anti-infective agents) **- Utilization costs** (Total costs of hospitalization)	- Average decrease of $81 in the cost of anti-infective agents (P<0.079) - Costs of hospitalization decreased from 40,290±42,928 to 29,515±24,965 (except when computer regimen was overridden, then an increase: 50,515±50,956) P<0.001 **Overall effect:+**	- Hospitalization -> medical care component of the consumer price index to adjust the costs of hospitalization	N/A
Frank (1997)	**- Acquisition costs** (Expenditures)	- *Overall annual AB expenditures decreased $785 380 between 1992 and 1994, reversing the increases seen in previous years.* - *partially ($116 858) due to contract purchase prices* - *Also due to decrease in # of admitted patients, shorter lengths of stay costs reduction of $278 708* - So adjusted with the above, cost savings (on overall annual AB expenditures) due to program: $389 814 in 1994 **Overall effect:+**	- Changes in expenditures due to change in price for each agent. Difference of contract purchase price was multiplied by the amount used in 1994 to see include in expenditure due to price change. Then summed. - Also adjusted similarly towards census days	N/A
Gentry (2000)	**- Acquisition costs** (Total acquisition costs (IV / average annual)) *(Inpatient pharmacy costs)*	- Total acquisition costs of IV ABs for 2nd baseline year was $473,133. In 1st program year $350,888 and in 2nd $303,453 - so average annual cost reduction of 30.8% and total cost saving of $291,885	- Tabulated and compared between 2nd year and entire program period, outpatient included	N/A

		- *Inpatient pharmacy costs decreased minimally (5.7%) over program compared to baseline.* *[# for comparing IV to overall trend]* **Overall effect:+**		
Gross (2001)	**- Intervention costs** (Cost of AMT) **- Utilization costs** **(**Cost of the hospitalization from the time of the call until discharge) **- Antibiotic costs** (Costs of agents) **- Infection costs** (Cost attributable to infection)	- *The cost of the AMT included the salary and benefits of the pharmacist and the portion of the salary and benefits of the director of the Antimicrobial Management Program* - demonstrated lower costs for the AMT group than for the ID fellows group both in total hospital costs and in costs attributable to infection (however, not significant) [# from table:] - Total hospital cost after approval call AMT: $6468 ID: $7864 ($1396) P=.08 - Cost of antimicrobial agents AMT:$79 ID:$122 ($43) P=.09 - Cost attributable to infection AMT: $3510 ID: $4205 ($695) P= .10 **Overall effect:± (no sig.)**	- Using financial data from data warehouse - Charges: accuracy of the data was confirmed by matching the length of stay with the sum of days for which there were room charges for the hospitalization. The charges were converted to costs using the ratio of costs to charges for 1993 - Model: acquisition cost of the antimicrobial agent(s),room costs during treatment, microbiology laboratory costs, and ID consultation costs (if such a consultation occurred after the approval call). Costs for administration of a second course of antimicrobial agents if the initial regimen failed were also included. The cost of the personnel of the AMT was included only for calls to the AMT. The ID fellows' work was covered by training funds, supported by the hospital. - Wholesale price to calculate costs for the antimicrobial agents. Costs of administration were not included. The mean cost per culture was assessed equally for all specimens.	- The limitations of the economic model include the fact that the "societal perspective" was not the focus. Moreover, we assessed only incremental costs incurred. Thus, the economic results may not be generalizable to settings in which no ID approval service is present.

			This was determined to be $6 per culture and included wholesale costs of reagents and technician time. ID consultation costs were calculated using the Health Care Financing Administration National Physician Fee Schedule's relative value for an inpatient consultation, adjusted for the Metropolitan Philadelphia Geographic Practice Cost and converted to 1993 dollars.	
Leung (2011)	**- Antibiotic costs** **(**- Absolute reduction) (Average antimicrobial cost per patient-day)	- Absolute reduction of $27917 - Average AM cost/patient day decreased 15.45 (36.2%; $42.64 to $27.18) - Post-pilot the avg AM cost/patient day was $18.31. - Average AM costs decreased sig. due to ASP (p=0.024) **Overall effect:+**	N/A	- Unpredictable fluctuations in drug acquisition costs
McGregor (2006)	**- Acquisition costs (restricted & total)** (Antimicrobial costs) (Savings per patient)	- Intervention arm spent less on antimicrobials than control arm in 3 months period. ($285,812 vs $370,006, savings of $84,194 (22.8%)) - Average savings per patient of $37.64 per patient in intervention arm - Less costs made on restricted AMs ($131,660 vs. $191,948 savings of $60,288 (31%)) - Less total wholesale cost of antimicrobials. ($4,841,474 vs.	- The cost data were measured using the hospital's pharmacy purchase prices, which are assessed per unit dose.	N/A

		$5,758,788 savings of $917,314 (15.9%)) **Overall effect:+**		
Miyawaki (2010)	**- Acquisition costs** (Drug Costs of specific antimicrobials) (Overall AB costs)	- Drugs cost specific ABs increased from 124mY (2001) to 138mY(2004) but decreased to 85mY (2007) - Overall AB costs from 379mY to 262mY. **Overall effect:+**	- Pharmaceutical prices * amounts used	N/A
Niwa (2012)	**- Antibiotic costs** (Saving of cost for AM injections) **- Utilization costs** **(**medical expenses)	- annual cost of AB injection was reduced from $2.02m to $2.00m in period 2 to $1.86m in period 3. - injection costs per patient were $324, $315, $286 in those periods. Resulting in a saving of 11.7% in period 3. - reduction in medical expenses due to hospital stay was estimated to be $1.95m in period 2 and $3.92m in period 3. **Overall effect:+**	- Annual cost of antibiotic injection - Costs of antibiotic injections/patient - Reduction in medical expenses to due hospital stay	N/A
Nowak (2012)	**- Acquisition costs** **(**Acquisition costs) **(**antimicrobial dollar per patient day) (actual cost savings)	- "ADPD" was rising, but decreased after ASP with 9.7% in first year, remained steady for two years and then slightly increased (due to increased use of linezolid) - year-to-year slope differed significantly (p=0.0086) - actual cost savings ranged between $234377 and $179088) - estimated cumulative cost savings suggest a cost saving of more than $1.7m	- Acquisition costs of all iv, oral antimicrobial, antifungal and antiviral agents over 8 years. Current acq. Prices were used for comparison. - "ADPD" = antimicrobial dollar per patient day) - actual savings (relating ADPD to ADPD in 2006 (baseline))	N/A

		Overall effect:+		
Philmon (2006)	- **Antibiotic costs** (Antimicrobial drug costs per patient-day) - **Acquisition costs** **(**Total acquisition costs)	- Antimicrobial drug costs per patient-day decreased $13.67 to $9.41 - Costs savings on total acquisition costs were $1,841,203 for the 3-year period **Overall effect:+**	- Data on the annual antimicrobial doses charged to patient accounts, annual antimicrobial acquisition costs, and patient-days - Based on antimicrobial acquisition cost alone and does not include mixing costs, administration costs, tubing costs, or nursing and pharmacy time.	N/A
Saizy-Callaert (2003)	- **Antibiotic costs** (AB budget as portion of global drug expenditure) (Mean cost of AB per patient)	- Consistent reduction in AB budget as proportion of global drug expenditure from 25% in 1997 to 12% in 2000 [due partly to a major increase in the cost of other drug classes (cancer meds)] - Mean cost of AB/patient falling from $13.8 in 1997 to $11in 2000(P<0.001) **Overall effect:+**	- Changes in the global cost of antimicrobials * proportion of total drug expenditure in the hospital * mean daily cost of antimicrobials per hospital patient, relative to the hospital's global activity.	- Likewise [# referring to shortcoming of difficulties with expanding protocols over wards], it is difficult to assess the cost impact of these programmes, and cost savings are difficult to measure.
Salama (1996)	- **Acquisition costs** **(**Annual total acquisition costs) - **Antibiotic costs** (AM budget) (Mean monthly savings) (Mean cost per dose per patient day) *(Monthly cost savings of restricted ABs)*	- Annual total acquisition costs were $3,6M (41,6% was AB) in 1994 annual costs $3,2M (28.2% was AB) - AM budget dropped 620k(40% decrease) - mean monthly cost savings were $6.810 in 1992, $11.480 in 1993 and $27.590 in 1994 - Mean costs per dose per patient day dropped from $11.88 to $10.16	N/A	N/A

		[# - various monthly cost savings on specific ABs attributable to the 3 strategies, omitted here] **Overall effect:+**		
Storey (2012)	**- Antibiotic costs** (Antimicrobial cost)	- 32% reduction in cost per admission (P= .013) in comparison to the baseline period - 25% reduction in cost per patient-day (P= .022) **Overall effect:+**	- "cost" [no explanation] - Per admissions - Per patient day	N/A
Yam (2012)	**- Acquisition costs** **(**Purchase costs)	- AB purchase costs decreased \$13,521 to \$9,756 per 1000PD in 2010 and \$6,583 in 2011 **Overall effect:+**	Total AMS-related costs expressed as percentage change per 1000PDs *[# tho, expressed in purchase costs]*	N/A

Table 5: Overview of antibiotic use

Author(Year)	Classification and measures	Reported effects and overall effect	Measuring method	Shortcomings
Agwu (2008)	**- Dose** **(**Dose of restricted AMs dispended and antibiotic days)	- The number of doses of restricted and unrestricted antimicrobials dispensed decreased with 11% (from 125.8 to 111.8 doses per day) - 12% reduction in the number of doses of unrestricted antimicrobials dispensed, from 227.5 to 201.0 doses per day **Overall effect:+**	- Number of dispensed doses per day	- Several reasons for the reduced number of doses and associated cost savings are possible, but direct cause and effect is not determined. - The impact of limiting excessive antimicrobial use or of limitation of pro-longed administration of broad spectrum antimicrobials on patient outcomes, as well as the potential limitation of antimicrobial resistance, must be considered.
Ansari (2003)	**- DDDs** ("DDDs")	- Overall use of all Alert Antibiotics decreased by 0.27 DDD/100 bed-days per month (95% CI 0.19–0.34, P< 0.0001)	- The DDD was adjusted for bed occupancy and is presented as DDD/100 bed-days.	- Need to expand to cover all antibiotics in order to assess which reduced use of Alert Antibiotics is associated with increased use of other drugs

		- There were also significant decreases in slope for amphotericin, ciprofloxacin, piperacillin–tazobactam, teicoplanin, and vancomycin - Slope of ceftriaxone usage increased significantly but there were no significant changes in slope for use of ceftazidime, meropenem or cefotaxime - The average reduction in use was greatest for teicoplanin (1.02 DDD/100 bed-days per month), piperacillin–tazobactam (0.80), and vancomycin (0.78) - Estimate that the Alert Antibiotic Policy reduced use by an average of 4.03 DDD/100 bed-days per month - Conservative estimate was a decrease in total use by 1.60 DDD/100 bed-days/month (95% CI 1.9–2.1, P<0.0001) **Overall effect:+**		- Measurement of hospital antibiotic use needs to be supported by more detailed analysis of indications for use and outcomes.
Bevilacqua (2011)	**- DDDs (**Consumption in DDDs)	- 844.2(1995); 981,4(2000); 701.4(2005); 653.3(2006); 739.3(2007); 634.8(2008) - Global consumption dropped 10% - Drop by antibiotic family ranged between 8% (penicillins) and 15% (glycopeptides) and was observed for all classes except aminosides (+8%)	- daily defined dose for 1000 patient days	N/A

		- Teicoplanin decreased 50% between 2005-2008 and vancomycin 10% - Fluoroquinolones accounted for 56% of prescriptions in 2005 and 41% in 2008 (P<0.03) **Overall effect:+**		
Carling (2003)	**-DDDs** ("DDDs")	- Use of third-generation cephalosporins and aztreonam, which had increased steadily by 1991 (from 7.2 to 24.7 DDD/1,000 patient-days), decreased rapidly and significantly during the next 6 years (to 6.2 DDD/1,000 patient-days; P< .0001) [# but: increased use of second-generation cephalosporins and, to a lesser degree, aminoglycosides and clindamycin] - The defined dose days for several parenteral antibiotics remained stable, including oxacillin / cefazolin (mean, 117 DDD/1,000 patient-days; standard deviation [SD], ± 9.2), cefuroxime (mean, 63 DDD/1,000 patient-days; SD, ±10.8), all aminoglycosides (mean, 37 DDD/1,000 patient-days; SD, ±9.8), ciprofloxacin (mean, 1.8 DDD/1,000 patient-days; SD, ±1.1), imipenem / cilastin (mean, 1.25 DDD/1,000 patient-days; SD, ±0.8), clindamycin (mean, 11.6 DDD/1,000 patient-days; SD, ±1.5), and ampicillin / sulbactam (mean, 11.6 DDD/1,000 patient-days; SD, ±1.5)	DDD/1,000 patient-days	- The authors cannot be certain that other, unrecognized changes did not contribute to the decrease. The authors did not examine these possibilities and cannot exclude them.

		- Vancomycin use remained stable at 23 DDD/1,000 patient-days (SD, ±3.2) **Overall effect:± (variable)**		
Chan (2011)	**- DDDs** (Antimicrobial consumption in DDDs) *(Ratio of AB vs medication items)*	- 3rd/4th gen cephalosporin, fluoroquinolones and glycopeptides decreased significantly - carbapenems increased significantly - increase in front-line consumption (sign according to table) - *ratio AB of am medication item 1,3%; 1,2%; 1,2%, 1,2%, 1.1%, 1.0%, 1.0%* **Overall effect:± (variable)**	- In DDDs - Gradient DDD/1000 patient days vs. time - ratio of AB prescribed to hospitalized patients vs all medication items	N/A
Chang (2006)	**-DDDs** (“DDDs”)	- Reduction in parenteral antibiotic-prescribed cases of 4.2% (583 cases). - Total reduction in parenteral antibiotic usage (DDD/100 PDs) was 13.2%, with intervention resulting in a 3.9% reduction in the average number of parenteral antibiotics prescriptions per patient day: First-line 47.0 41.6 PD Second-line 16.2 14.5 PD Third-line 8.0 5.8 PD … Total consumption 71.2 61.8 PD [# but:] Three types of antibiotics which revealed increased consumption; these were the macrolides (100%; erythromycin),	- No. of Antibiotics used (vials) x Antibiotic Strength (g/vial) x 100] / [DDD(g) x No. of patient-days - Number of DDDs was calculated from the prescribed antimicrobial dosage per patient admission	- It was a short-term study, and therefore lacks information on the severity of patient’s diseases, as well as the consumption of oral antibiotics

		penicillins (19.2%), and quinolones (13.3%) **Overall effect:+**		
Cheng (2009)	**- DDDs** ("Usage Density" [# in DDDs])	- An overall reduction broad-spectrum intravenous antibiotics from 73.06 (2004) to 64.01 P/BDO (2007) - Increased in the department of Medicine despite the implementation of ASP, but dropped in 2007 when specific AB guideline was issued to Hematology - Dropped in Department of Surgery in 2004 to 2005, and increased again in 2007 - In Department of Orthopedic Surgery, there was a consistent drop each year - Piperacillin-tazobactam decreased from 34 P/BDO(2004) to 22 P/BDO(2007). ceftazidime decreased from 6 P/BDO(2004) to 3 P/BDO(2007). cefepime decreased from 11 P/BDO(2004) to 4 P/BDO(2007). meropenem increased from 11 P/BDO(2004) to 21 P/BDO(2007) [P/BDO=1,000 patient bed-day-occupancy] **Overall effect:+**	- The total amount of each antimicrobial agent used in grams divided by the number of grams per defined daily dose for the specific antimicrobial agent, which was then further divided by the total number of patients-days and multiplied by 1,000	N/A
Cook (2004)	**- DDDs** ("DDDs")	- The average quarterly broad-spectrum antibiotic use decreased by	- The defined daily dose/1000 PD (DDD/1000 PD)	N/A

		28% (693 DDD/1000 PD to 502 DDD/1000PD, P= 0.003) - Total antibiotic consumption, which included all intravenous and oral antibiotics dispensed from the pharmacy, decreased by 27% (1461 DDD/1000 PD to 1069 DDD/1000 PD (P= 0.0007) - Use of other drugs not considered broad-spectrum antibiotics also decreased. - Metronidazole use decreased by 54% (29.5 DDD/1000 PD to 13.6 DDD/1000 PD, P= 0.0003) - No significant change in the use of vancomycin, clindamycin or tobramycin - Trend toward less fluconazole use (P= 0.10) - Total antifungal agent use decreased by 28% (144 DDD/1000 PD to 103 DDD/1000 PD, P= 0.02) **Overall effect:+**	- Total grams of individual antibiotics dispensed to inpatients for all routes of administration are used along with total patient days (PD) for the period of interest	
Danaher (2009)	**- DDDs** "DDDs"	- DDDs per patient treatment course lower in invention (6.7±7.6 vs. 12.9±16.3. p=0.05) **Overall effect:+**	*DDDs per patient treatment course*	N/A
Evans (1998)	**- DDDs** ("Dose of anti-infective agents", received and	- Decrease in DDDs (11.4 vs. 23.6 and 27.6, respectively; P<0.001)	- DDDs per 100 bed-days	N/A

	excessive [# in DDDs])	- Linear regression showed that during the intervention period patients received an average of 4.7 fewer doses of anti-infective agents (P=0.042) - Decrease in excessive doses days for an average of 2.9 fewer days (P=0.001) **Overall effect:+**	- 'All patients' renal function was calculated on a daily basis, and each day that a patient received a dose of an anti-infective agent that was excessive in relation to his or her corresponding renal function was counted as a day of excessive anti-infective dosage'	
Frank (1997)	**- DDDs** ("DDDs")	- The total antimicrobial use (total DDD declined by 13.1% between 1992 and 1994. [reported that broad-spec and b-lactams decreased, where other small-spec antimicrobials increased] - The total antimicrobial use per admission also decreased from 11.2 to 9.8 DDD, a drop of 12.5%. **Overall effect:+**	- Per agent, then summed	N/A
Leung (2011)	**- DDDs** ("Utilization" [# expressed in DDDs]	- utilization of broad-spec antipseudomonal AMs was 38.59 DDDs/100PDs, a reduction of 24.57 (38,9%) compared to 63.16 DDDs/100PDs in baseline - Postpilot the utilization creeped up a bit to 28.47 DDDs/100PDs - Significant decreases in use of gentamicin, piperacillin-tazobactam, meropenem, moxifloxacin and antipseudomonal AMs. **Overall effect:+**	- DDDs/100PDs	N/A
Liew (2012)	**- DDDs** ("Total audited antibiotic	- consumption showed an increasing trend ($p<0.05$) largely contributed by meropenem and TZP.	- DDDs/100 inpatient days	N/A

	consumption" in DDDs")	- sign. declining trends for IV ciprofloxacin and cefepime. - ertapenem (p=0.46) and imipenem (p=0.79) remained stable **Overall effect:± (variable)**		
Miyawaki (2010)	**- DDDs** ("Injectable antimicrobial consumption" *[# in DDDs])* **- AUDs** ("Administrative period of antimicrobial agent" *[# as AUD (antimicrobial use density)]*	-Consumption of carbapenem antibiotics slightly decreased (8.5%, 10.4%, 9.9%, 11.0%, 10.7%, 9.4% and 7.1) *[# trend however suggests curve!]* - Consumption of penicillin antibiotics increased since 2004. - AUD of specific antimicrobials decreased since 2005. In contrast, AUD of penicillins and first-generation cephalosporins increased. - Number of patients receiving the specific ABs decreased from 1214 to 871(carb), 780 to 340 (4^{th}), 569 to 483(anti-MRSA) **Overall effect:± (variable)**	- DDDs (=WHO) - AUD = (DDDs*1000 / patient days) [Patient days = day of discharge - Day of admission (day cases are zero)]	N/A
Niwa (2012)	**- DDDs** ("Total antimicrobial consumption" in DDDs)	- prolonged use decreased from 5.2% to 4.1% [p=0.007) and 2.9% in period 3 (p<0.001) - no sign difference in total AM consumption between periods (210.3 vs 209.3) - total AM consumption was sign. lower in period 3 (p=0.003) - use of 2^{nd} gen cephalosporins, carbapenems, amino-glycosides also lower in period 3 **Overall effect:+**	- prolonged use of antibiotics exceeding two weeks - total antimicrobial consumption in DDDS/1000 PDa	N/A

Nowak (2012)	**- DDDs** ("Antimicrobial consumption" in DDDs)	Rising pre-ASP, but declined during ASP. DDDs values differed sign. pre-post. (0.0057) - Notably average total quinolone use fell 44% (159.3 to 114.9) - Vancomycin fell 28% (105.8 to 76.1) [but due to moving to linezolid] - Also carbapenems, piperacillin-tazobactam trended downwards. First-line AMs (cefazolin, ceftriaxone, metronidazole, doxycycline remained stable or increased slightly - Notable that linezolid rose strong (5.5 to 21.7) **Overall effect:+ (overall OK, yet variable)**	- DDDs per 1000 PDs	N/A
Peto (2008)	**- DDDs** (AB consumption data from pharmacy in DDDs)	- The estimated mean antibiotic consumption decreased significantly to 101.3 DDD per 100 patient-days (95% CI: 100.7–102.0) from 162.9 DDD per 100 patient-days (95% CI: 158.3–167.6) after the introduction - Change in slope of 1.5 DDD per 100 patient days per month - Significant drop in the consumption of quinolones, aminoglycosides, glycopeptides, metronidazole, and carbepenems - Third generation cephalosporin use was halved (11.0 vs 6.1 DDD per 100 patient-days) whilst an increase in the usage of second generation	- Calculated according to the 2005 version of the World Health Organization (WHO) anatomical–therapeutic–chemical (ATC) defined daily doses (DDD) methodology, and expressed as DDD per 100 patient-days - 'The monthly number of antibacterial packages dispensed to the intensive care unit were obtained from the Central Pharmacy'	- The lack of patient-level antibiotic use data also limited our ability to stratify antibiotic use data by prescriber (surgeon or ICU specialist) - It cannot be ignored that ICU patient turnover increased during the course of the analysis

		cephalosporins was detected (29.5 vs 39.1 DDD per 100 patient-days). - Cefuroxime was the most commonly used antibiotic in both periods - Oral products were used only marginally on the unit in both periods (6.9% vs 4.4%). **Overall effect:+**		
Philmon (2006)	**- DDDs** (DDDs)	- Statistically significant decrease in the daily defined doses per 1,000 patient-days for cefepime, ceftazidime, and imipenem - Use of vancomycin and linezolid increased [despite efforts] - Significant [positive] impact on the number of antibiotic doses used for surgical prophylaxis. - Use of cefazolin decreased significantly **Overall effect:+**	- Mean daily defined dose (DDD) per 1,000 patient-days	N/A
Salama (1996)	**- Dose** (Actual number of AM doses dispensed in patient days)	- Mean nr of AM doses dispensed per month fell from 9299 in 1991 to 8151 in 1994 - Mean nr of doses/patient day stayed the same (0.66) [!] [- Average Patient days per month declined 14.005 to 11.669] **Overall effect:+**	- Mean number of AM doses dispensed per month [- Avg Patient days / month]	N/A

Storey (2012)	**- DDDs** (“Mean monthly antimicrobial use” in DDDs)	- 22% reduction in mean monthly use per 100 admissions (p=0.006) - 16% reduction in mean monthly use per 1000 PDs (p=0.13) - sign. reduction in anti-pseudomonal carbapenems (imipenem and meropenem), clindamycin, levofloxacin, linezolid, trimethroprim-sulfa-methoxazole, antibacterials and antifungals using either metric denominator; - sign. increase from baseline in the use of cefazolin. **Overall effect:+**	- Mean monthly use of all ABs in DDDs - Per 100 admissions - Per 1000 patient days	N/A

Table 6: Overview of Length-of-Stay

Author(Year)	Classification and measures	Reported effects and overall effect	Measuring method	Shortcomings
Agwu (2008)	**- Hospital stay** (Duration of hospital stay)	- Mean duration of hospital stay (patient hospital days) stayed similar. (6.78±14.3 patient-hospital days vs. patient-hospital days; 6.67±14.1 P=.65). **Overall effect:± (no sig.)**	N/A	- The impact of limiting excessive antimicrobial use or of limitation of pro-longed administration of broad spectrum antimicrobials on patient outcomes, as well as the potential limitation of antimicrobial resistance, must be considered
Camins (2009)	**- LoS** (Median Length of Stay)	- 7 days (1–50) vs. 8 days (2–86); P= 0.03 [sign. reduction of 1 day] **Overall effect:+**	N/A	N/A
Chang (2006)	**- Hospitalization** (Number of hospitalization days) **- LoS** (“Clinical outcomes”)	- Hospital activity, in terms of the number of admissions, consultations and bed-days, remained stable. - [also:] No statistical differences in clinical outcomes, which included the length of stay in the medical center	N/A	N/A

		Overall effect:± (stable, no sig.)		
Cook (2004)	**- LoS** **(**Length-of-Stay)	- Essentially unchanged (1999, 5.7 days; 2000, 5.8 days; 2001, 5.8 days; 2002, 5.7 days; 2003, 5.8 days) **Overall effect:± (stable)**	N/A	N/A
Evans (1998)	**- LoS** (Length of stay in ICU) **- Hospital stay** Total length of hospital stay [admission to discharge]	- Total LoS 10.0 vs. 12.9 and 16.7 days, P <0.001 - Significant LoS in ICU decrease, 6.3±9.7 vs 3.3±3.7 and (when not followed:)9.8±10.3 - Hospital stay: 14.1 vs. 9.7 and 17.9 days **Overall effect:+**	N/A	N/A
Frank (1997)	**- LoS** **(**Mean / average LoS)	- Mean length-of-stay 7.3 to 6.6 (entire hospital) - Average ICU length of stay decreased from 9.3 to 7.2 days **Overall effect:+**	N/A	N/A
Gentry (2000)	**- LoS** **(**Mean LoS for program period) (Overall LoS in institute)	- Mean LoS for the program period patients decreased 18% - Overall LoS at the institution decreased only 4%. - LoS in ICU decreased, LoS in non ICU decreased significantly. **Overall effect:+**	N/A	- Impossible to determine effect of ACP on LOS or improvement of mortality
Liew (2012)	**-LoS** **(**LOS overall)	- LOS sign shorter between accepted (19.4±19.9 days) and rejected (24.2±24.2) recommendation groups	- LOS overall - LOS between intervention and discharge	N/A

	(LOS between intervention and discharge)	- LOS between inv and discharge also sign shorter between accepted (10.2±18.6 days) and rejected (16.6±21.6) **Overall effect:+ (trial)**		
McGregor (2006)	- **Hospitalization** **(**Length of hospitalization)	- No sign. difference between the two study arms (p = 0.38). **Overall effect:± (no sig.)**	- "Admission to discharge"	
Miyawaki (2010)	- **LoS** **(**Average length of stay)	- Is averagely 19.9 days - Mean length of stay decreased by 11.5 days **Overall effect:+**	N/A	N/A
Niwa (2012)	- **LoS** - **"Hospital stay"** (length of hospital stay) (length of hospital stay for patient receiving IV)	- Median LoS was sign. shortened from 12.0 days to 11.0 in period 2 (p=0.0005) and 11.0 days in period 3 (p=0.0001). - mean LoS of patients receiving IV was 20.5, 19.3 and 17.5 days respectively. **Overall effect:+**	- median length of hospital stay - mean length of hospital stay for patients receiving IV	N/A
Nowak (2012)	- **Los** (Length-of-Stay)	- LOS did not sign differ **Overall effect:± (no sig.)**	N/A	N/A
Peto (2008)	- **LoS** **(**Length-of-Stay)	- Length of stay showed a moderate, but statistically insignificant decrease. **Overall effect:± (no sig.)**	N/A	N/A

Toth (2010)	**- LoS** **(**Length-of-Stay)	- No statistical difference **Overall effect:± (no sig.)**	N/A	N/A

Table 7: Overview of mortality

Author(Year)	**Classification and measures**	**Reported effects and overall effect**	**Measuring method**	**Shortcomings**
Camins (2009)	**- Mortality** (Mortality)	- 11/390 (3%) vs. 18/194 (5%) control; P= 0.18. No sig. difference **Overall effect:± (no sig.)**	N/A	N/A
Chan (2012)	**- Mortality** (Inpatient mortality rates)	- 3,45%; 3.53%; 3.41%, 3.30%; 3.28%; 3.27%; 3.23% (2003-2009) (sig. unknown) **Overall effect:? (positive, but unknown sig)**	N/A	N/A
Chang (2006)	**- Mortality** (Mortality rates)	- No sig. differences in clinical outcomes [which encompasses mortality] **Overall effect:± (no sig.)**	N/A	N/A
Cheng (2009)	**- Mortality** (Crude mortality rates)	- Ranged between 1.79 and 2.51 during the study period, which was similar to the baseline data (1.82–2.56) **Overall effect:± (stable)**	- Crude mortality data throughout the study - Period was obtained from the hospital record office	N/A
Cook (2004)	**- Mortality** (Mortality rates)	- Mortality rates were also not significantly altered (1999, 5.65/100 discharges; 2000, 3.96/100 discharges; 2001, 3.97/100	N/A	N/A

		discharges; 2002, 3.72/100 discharges; 2003, 3.98/100 discharges) **Overall effect:± (no sig.)**		
Danaher (2009)	**- Mortality** (Mortality)	- No sig. Difference [from table: 4 vs 0; p>0.05] **Overall effect:± (no sig.)**	N/A	N/A
Evans (1998)	**- Mortality** (Mortality)	- (22% to 18% and 27%) (sign. unknown) **Overall effect:± (variable)**	N/A	N/A
Gentry (2000)	**- Mortality** (Mortality)	- Significant decrease in non-ICU setting (7.13% to 4.87% P=0.0002) - Similar in ICU (16.6% vs 16.4% P=0.95) **Overall effect:+ (but not necessarily effect of program)**	- Dead or alive	- Impossible to determine effect of ACP on LOS or improvement of mortality
Leung (2011)	**- Mortality** (Mortality rate)	- No adverse effects on patient mortality. 14.6% in baseline, 14.5% in intervention. **Overall effect:± (no sig.)**	N/A	N/A
Liew (2012)	**- Mortality** (Mortality) (Infection-rated mortality)	- no sig. difference between accepted and rejected group for both - in accepted 90.5% (4.3% died due to infection) survived, in rejected 86,7% (11.5% died due to infection) **Overall effect:± (no sig.)**	- Overall mortality - Infection-rated mortality	N/A

McGregor (2006)	**- Mortality** (Patient mortality)	- No sig. difference between patients assigned to the intervention and the control arms (p = 0.55), or between patients in the intervention arm with system alerts and patients in the control arm who would have received alerts (p= 0.52) **Overall effect:± (no sig.)**	N/A	N/A
Nowak (2012)	**- Mortality** ("Survival")	- Survival did not sig. differ **Overall effect:± (no sig.)**	Survival	N/A
Peto (2008)	**- Mortality** (ICU mortality rate)	- No sig. difference **Overall effect:± (no sig.)**	- Based on patient data	N/A
Toth (2010)	**- Mortality** (Mortality)	- No statistical difference **Overall effect:± (no sig.)**	N/A	N/A

Table 8: Overview of compliance and acceptance

Author(Year)	**Classification and measures**	**Reported effects and overall effect**	**Measuring method**	**Shortcomings**
Belvilaqua (2011)	**- Compliance to Guidelines** (prescriptions conform guidelines) **- Acceptance** (accepted interventions)	Conform: 76%;78%;91% Proposed: 7%;86%;82% Accept: 62%;82%;78% **Overall effect:± (conformance rose, acceptance variable)**	- % of prescriptions conform to guidelines Number of interventions made by the OTID - % of proposed prescription modifications - % of accepted interventions	N/A
Carling (2003)	**- Compliance to recommendations** (Compliance)	- Exceeded 85% of interventions within 6 months and reached 98% by 1993.	- Compliance to recommendations	N/A

		[… suggesting use of paternal AB appropriateness had improved as well] - Unchanged afterwards **Overall effect:+**		
Cheng (2009)	**- Compliance to recommendations** (Conformance rate to AB prescription) (Compliance rate)	- Conformance rate to the antibiotic prescription guideline was 79.4% - Non-conformed prescriptions, the overall compliance to the ICF was 83.8% - When "physician ICF" was implemented in the third quarter of 2005, the conformance rate was consistently higher than that of ICF **Overall effect:±**	- The compliance to ICF and " physician ICF " , antibiotics usage density measured by expenditure and defined daily doses (DDD) were recorded and analyzed before and after the ASP.	N/A
Cook (2004)	**- Acceptance** (Acceptance of recommendation)	Partial (12%) or complete(80%) acceptance of the recommendations occurred in 92% of cases **Overall effect:±**	Recommendations to streamline or discontinue antimicrobials were made based on results of available microbiology data, radiography studies, as well as the working diagnosis at the time of review. The charts were reviewed again on the following day to assess acceptance or rejection of the recommendations.	N/A
Danaher (2009)	**- Acceptance of recommendation** (Acceptance of recommendation)	40% not accepted of 10 recommendations. **Overall effect:-**	recommendations made by the AST	N/A
Gross (2001)	**- Compliance to Guidelines** (Adherence)	- AMT always adhered to the guidelines (25 [100%] of 25),	N/A	N/A

		whereas those of the ID fellows sometimes did not (6 [75%] of 8) **Overall effect:±**		
Kravitz (2005)	**- Compliance to recommendations** (Compliance to corrective recommendations)	- Compliance 94% over first 7 months to corrective recommendations **Overall effect:±**	N/A	N/A
Leung (2011)	**- Acceptance** (Acceptance rate)	- 142 recommendations, for which the overall acceptance rate was 94% **Overall effect:±**	N/A	N/A
Liew (2012)	**- Acceptance** (Accepted recommendations)	1256 recommendations, of which 743 potentially influencial on patient safety - Accepted: 77.8% (578/743) - Rejected: 22.2% (165/743) - no sign differences between those two groups **Overall effect:±**	N/A	N/A
Niwa (2012)	**- Acceptance** (Accepted proposals)	- of proposals, accepted: 93 (91%) and 186 (93%) **Overall effect:±**	- based on number of inquiries (40-50 a month during the program)	N/A
Philmon (2006)	**- Acceptance** (overall acceptance rate) **- Compliance to Guidelines** (compliance)	- overall acceptance rate of 76% - Compliance near 100% for IV->PO and # of interventions dropped over time	- To evaluate compliance with the components, a report using the pharmacy computer system was generated daily to identify patients receiving the targeted antimicrobials	N/A

		- Compliance for prophylaxis fluctuated, also # of interventions dropped over time. - Compliance for restricted use high and fairly stable **Overall effect:±**		
Salama (1996)	**- Compliance to recommendations** (compliance)	- At first compliance low later 75% when pharmacist actively monitored. [to possible switch IV->PO] **Overall effect:+**	N/A	N/A
Storey (2012)	**- Compliance to recommendations** (Implemented recommendations)	- 75% recommendation via audits implemented **Overall effect:±**	- Audits of unique patient records [from table: about 35% were discontinuation, 20% de-escalation, 15% no change]	N/A
Toth (2010)	**- Acceptance** (Acceptance rate) **- Compliance to Guidelines** (Compliance with care bundle, quality indicators)	- acceptance rate of 91%. - Compliance with the care bundle improved after implementation - Compliance with all quality indicators rose from 16% to 54% ($p=0.001$), - Prescriber documentation for the indication for therapy improved - Significant increase in de-escalation for therapy **Overall effect:+**	- Quality indicators. '(1) documentation of treatment rationale, (2) collection of appropriate culture specimens according to national and institutional guidelines (3) appropriate empirical selection of antibiotics according to national and institutional guidelines, alla at the initiation of antibiotic therapy,l and (4) appropriate deescalation' [Rationale for appropriateness based on: Demographics, infection characteristics, AM therapy, patient outcomes, (mortality, LoS, eradication, superinfection with Cdiff.)]	N/A

Chapter 5:

Co-creating with stakeholders: eHealth applications to support antibiotic stewardship in hospitals

Based on: M. van Limburg, MSc, H.C. Ossebaard, M.J. Wentzel, J.E.W.C. van Gemert-Pijnen. 2015. Co-creating with stakeholders: ideating eHealth applications to support antibiotic stewardship in hospitals.

Submitted

“Implementation of technological change must involve critics as well as advocates” - *Andy Hargreaves*

Abstract

Background: Inappropriate prescription of antibiotics can lead to complications with hospital infections and increased antimicrobial resistance. Antibiotic stewardship programs have been developed to influence antibiotic prescription behavior in hospitals at a multidisciplinary level. Antibiotic stewardship can be resource consuming, hence opportunity arises to implement eHealth applications that play a supportive, unburdening role in antibiotic stewardship interventions.

Methods: This paper focuses on stakeholder co-creation to analyze the antibiotic therapy process, ideate supportive eHealth applications, and co-create an implementation strategy for this online platform that fits the needs of all relevant stakeholders. The necessary business modeling steps are delineated using tools such as stakeholder mapping, problem analysis, ideation and value mapping for a focus group and individual interviews in a piloting hospital.

Results: We developed an online platform with multiple eHealth applications tailored to the roles and needs of hospital personnel who work with antibiotics. By analyzing the entire process of antibiotic therapy through these value-driven dialogues with all stakeholders, we ideated seven supportive eHealth applications that stakeholders find valuable in their daily practices with antibiotics. We also conclude an implementation strategy as a basis for further design and develop these ideated eHealth applications with end-users. This strategy can be used as a basis for a sustainable implementation of eHealth applications that support antibiotic stewardship in hospitals.

Conclusions: Most opportunities for eHealth arise in supporting information finding and sharing during antibiotic therapy. Overall, application of eHealth in ASP remains scarce. This article provides several opportunities for eHealth applications as well as a possible implementation strategy to introduce them sustainably into a hospital. We would encourage more awareness and use of eHealth as we believe it can support

Keywords

eHealth; antibiotic stewardship; implementation; stakeholders; business modeling; co-creation.

Background

Increasing antimicrobial resistance threatens the health and safety of patients and citizens and is a major concern for public health authorities [1]. Hospital-acquired infections that have become resistant to antibiotics such as the methicillin-resistant Staphylococcus aureus (MRSA) or the vancomycin-resistant Enterococcus (VRE) yearly cause an estimated 4 million infections in Europe, resulting in around 37,000 deaths per year [2, 3]. Few new classes of antibiotics are expected to be introduced over the coming decades the current arsenal is needed to cure infectious diseases or prevent aggravation [4]. Since up to 50% of all prescribed antibiotics is reported inappropriately prescribed, and overused, a change in prescription behavior is imperative [5]. Healthcare professionals and infection control experts have developed antibiotic stewardship programs (ASP) or antimicrobial stewardship interventions (AMS) to ensure prudent use of antibiotics for better patient outcomes, lower risk of adverse effects, promotion of cost-effectiveness and reduction of resistance levels [6]. These programs consist of a combination of several interventions that support healthcare professionals to optimize antibiotic therapy. Overall, ASPs show significant beneficial effects on reducing antibiotic use and costs [7]. ASPs should change current habits with antibiotics of healthcare professionals, for this, persuasive interventions could be embedded in social and behavioral approaches to behavior change [8] combined with innovative implementation strategies as well [9-12].

The antibiotic therapy process consists of various stages; in short, it entails primary (empirical) diagnosis, prescription, administration, and evaluation. In each of these stages, multiple stakeholders interact with different tasks, roles and urgencies. Stakeholders are here defined as all people or organizations that are influenced by or influence the eHealth technology used to reinforce antibiotic stewardship [13]. eHealth technology is not solely a technical development but refers to a way of thinking on how to improve healthcare and how technology can support this [11]. As part of EurSafety Health-net project (www.eursafety.eu) we co-created an online infection control platform called infectionmanager.com with constant stakeholder involvement (*Figure 1*). Its purpose is to provide a platform with several eHealth technologies that support ASP and implementation advice for all stakeholders involved with infection prevention and control and antibiotic therapy. The content of this platform follows three layers: information, tools and research and development [14, 15]. Each specific eHealth technology is developed to support a set of stakeholders in delivering antibiotic therapy while fitting requirements of several technical devices (desktops, tablets, Computer-on-Wheels) and providing user-tailored content that meets information needs and clinical authority/autonomy of each stakeholder.

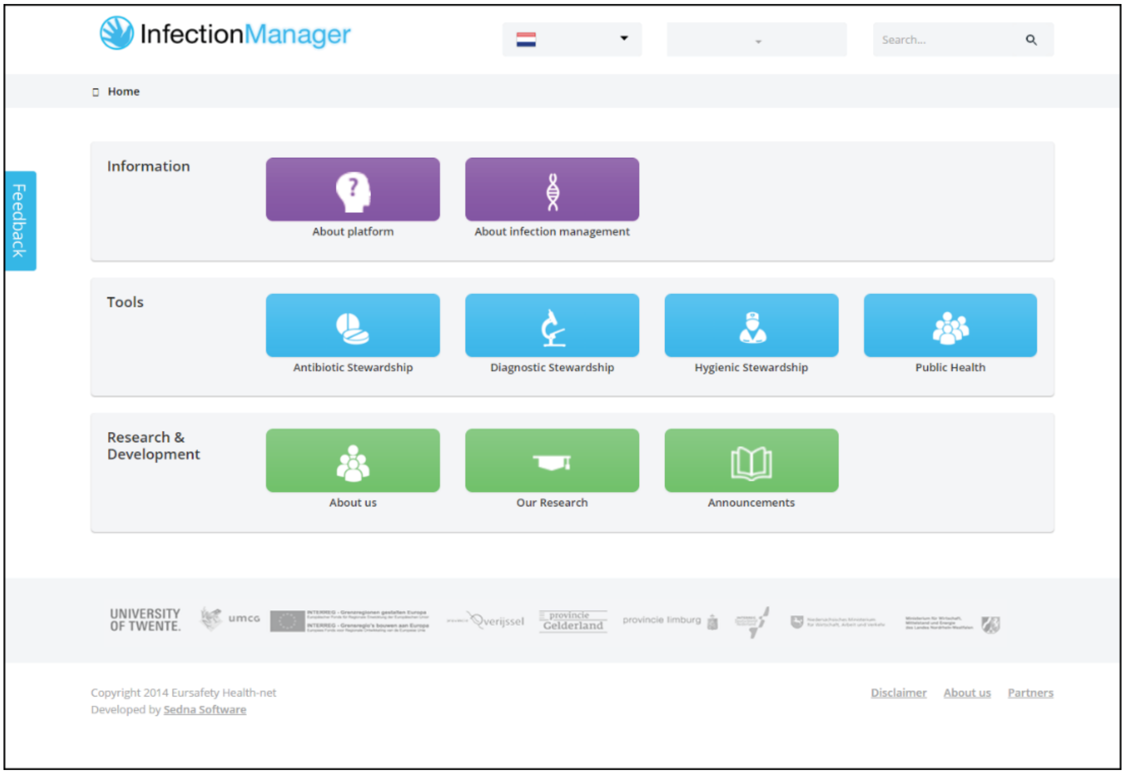

Figure 1: Screenshot of www.infectionmanager.com

Many eHealth technologies floundered because they failed to involve the intended users [11]. In the last two decades, more attention has been devoted to involving end-users in the design process of eHealth technology. Approaches are proposed such as e.g. socio-technical design [16], human-centered design [17] or co-creation [18] where end-users are actively involved in determining the product or technology. This co-creation should not only be part of the design, but also part of implementing eHealth [11, 12]. Health care is a hard and complex environment for innovation [19], thus requires a thorough understanding by involving stakeholders who are part of this complex environment. Stakeholders need to be involved ab initio in designing eHealth technology and participate in its implementation [12]. Stakeholder interaction, stakeholder relationships and added value(s) offered through the eHealth technology need to be understood for determining an implementation that fits their environment. When stakeholders deem a technology valuable for their daily practices, the more likely they will use or endorse it, thus improving the uptake and chances of success. Business modeling can be used as a value-driven approach to involving stakeholders in implementation research of eHealth [12].

Little literature is available on the opportunities of eHealth in ASP. This paper focuses on co-creating eHealth opportunities inferred from values found in co-creation research with stakeholders using business modeling [20]. Based on a value-driven dialogue with stakeholders, we ideated a list of possible eHealth applications that can support ASP. These eHealth applications are strategic opportunities to be embedded in the infectionmanager.com platform as part of persuading healthcare professionals to optimize the prescription and use of antibiotics in antibiotic therapy.

This study was structured in the following objectives:

- Understanding the antibiotic therapy process from stakeholder-perspective;
- Understanding which stakeholders are most influential in co-creating eHealth applications to support ASP;
- Understanding problems that stakeholders encounter in the antibiotic therapy process;
- Identifying which improvements and opportunities stakeholders see in this process;
- Ideating what eHealth applications are required;
- Designing an implementation strategy for a platform with eHealth applications to support ASP.

These objectives are concrete questions that follow the research process as introduced with the CeHRes Roadmap presented in the methods. We shall also present the results paragraphs one by one structured with these objectives.

Methods

CeHRes Roadmap

Central to our research is the CeHRes Roadmap (*Figure 2*). It supports researchers to develop, design and implement eHealth technologies using a holistic approach that combines human-centered design principles and business modeling principles [11]. Human-centered design allows researchers to design eHealth technology that reflects the needs of its end-users [17], whereas business modeling allows researchers to determine a fitting implementation for the technology [11]. Our Roadmap consists of five phases: contextual inquiry, value specification, design, operationalization and summative evaluation. The Roadmap contains specific research activities that support eHealth research for each of these phases. In this article, we focus primarily on its business modeling research activities delineated in the next paragraph.

Collaboratively determining the added-value of eHealth technology is central in business modeling [11, 12]. This added-value is the foundation for an implementation strategy for the technology. If added-value for stakeholders is lacking the odds for a successful implementation are low. By arranging value-driven dialogues with stakeholders, researchers can discuss and understand value needs. We define a value as any ideal or interest a stakeholder aspires with regard to an eHealth technology [21]. Value-driven dialogues are important for:

- Eliciting all relevant values from stakeholders' perspectives;
- Finding a consensus in these values with stakeholders;
- Co-creating the design and business model of the technology.

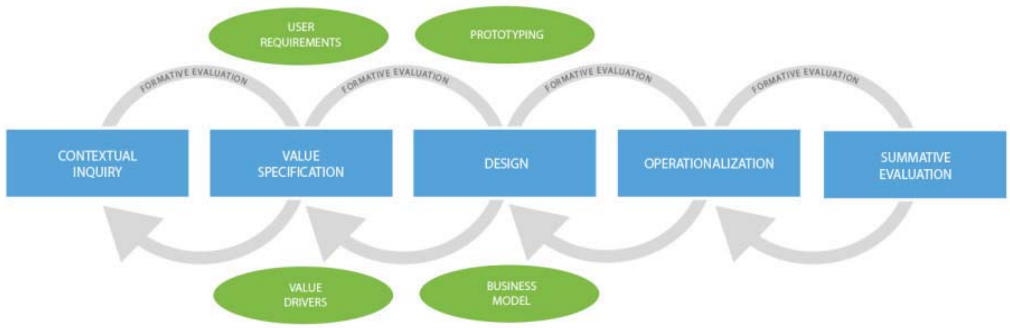

Figure 2: Center for eHealth Research Roadmap

Business modeling tools

A business model explains the rationale for creating, delivering and capturing value [22]. It is often used in management to strategically describe how a company makes its profits with their products. For example, the business model of Google or Facebook shows how they make a profit by placing advertisement on their free services or the business model of PayPal shows they profit from charging small processing fees for money transfers. A business model can also be used to create a comprehensive overview of the expected added-value for an eHealth technology, or 'how it is profitable in the eyes of its eHealth stakeholders'. The profit here does not have to mean money per se, in fact, especially in healthcare there are non-monetary values like ethics, care quality, etc., that are influential.

The commonly used business model canvas introduced by Osterwalder et al, depicts a business model in nine essential components that describe value propositions, customers and customer interaction, key activities and key resources and the involved finances [22]. These components can be used as topics in value-driven dialogues with stakeholders to discuss and prepare an implementation of an eHealth technology [11].

Business modeling is the process behind preparing a business model and subsequently all activities needed to find an implementation for the developed eHealth technology [11]. In this paper, we used business modeling tools that are part of the CeHRes Roadmap, to co-create and ideate possible interventions based on value needs of stakeholders. In *Table 1* we provide a short overview and description of the business modeling tools we used: stakeholder mapping, problem analysis, ideation and value mapping. While this paper aims to present the results of these tools, in another paper we discuss the methods behind these business modeling tools more in-depth with examples and discussion on how they can best be applied [20].

Table 1: Business modeling tools

Tool	Description of tool
Stakeholder Mapping	All stakeholders need to be mapped to present a complete overview of possible stakeholders. This starts with a comprehensive list of possible stakeholders but when analyzing the problems and the roles of each of them, a smaller, definite stakeholder map can be made. Not every stakeholder needs to be involved equally in the development. The group of stakeholders having high importance for involvement can be seen as the definite or key stakeholders [12, 23].
Problem Analysis	The problem analysis is based on 'sense making' [24]. In organizational sense making, the experiences, interests and perspectives of the different individuals are subject of research. By discussing roles, interactions, problems and ideas for improvement with stakeholders, the process can be understood. Various problem analysis techniques exist, such as cause and effect analysis, fishbone analysis, force fields, prioritization, etc. Also, problems can originate from many different contexts: processes, technical, people, culture, resources, policies, etc. Proposing alternative viewpoints or having adversary stakeholders can also help nuancing all problems. The clearer problems are defined in the beginning, the better for future choices in design and implementation. Time spent on this activity can pay off later.
Ideation	When discussing problems, one cannot really avoid discussing solutions too. Stakeholders sometimes find it easier to come up with solutions they find valuable to their processes than to pinpoint the deeper underlying problems that need solving. It is good to collect these solutions and ideas and moderately detail them. These ideas will be helpful to researchers to ideate and 'visualize' solutions for themselves and stakeholders. It is useful for prototyping the technology as well as its implementation.
Value Mapping	Value-driven dialogues with stakeholders are the heart of the co-creation [11, 18]. Stakeholders have to express their views on the added-value of the eHealth technology. These values can be mapped per stakeholder and later combined based on priority, stakeholder salience, value ranking, hierarchic, costs or other possible ranking systems. All these values will result in a business model and subsequently critical success factors needed for implementation and value propositions for the eHealth technology (used as input in design).

Stakeholder mapping and problem analysis were used to understand the antibiotic therapy process from a stakeholder's perspective and to understand which stakeholders are most influential in the antibiotic therapy process and thus have an important voice in co-creating eHealth applications to support ASP. The problem analysis also is used to analyze roles, interactions and problems that stakeholders face in the antibiotic therapy process, we use these problems and bottlenecks as starting point for value-driven dialogues. Discussing improvements and opportunities and possible eHealth applications to support ASP are required are part of ideation. We performed the value mapping part by having one-on-one interviews with key stakeholders to discuss value needs and to organize these needs in a business model.

Data collection via focus group

We used focus groups as the starting research instrument for stakeholder collaboration [25]. We organized a focus group with stakeholders in a pilot hospital participating in the EurSafety Health-net project [14]. We selected healthcare professionals from the pulmonary ward. This is one of the wards with a high risk of infections and a relatively high use of antibiotics. Stakeholders were selected based on healthcare professionals mentioned in key literature on ASP and were further specified to a list of healthcare professionals by an ASP expert working at the pilot hospital [14, 26]. *Table 2* contains the definite list of stakeholders we invited for the focus group.

Table 2: Invited stakeholders at the pulmonary ward for focus group

Clinical microbiologist	Clinical pharmacist (2x)
Chest physician (2x)	Residents (2x)
Nurse	Ward manager
Nurse manager	Quality manager

For the focus group, we prepared a ‘role-play’ for the antibiotic therapy process, known as scenario-based testing [14, 25]. We prepared a complex scenario with a fictive patient to invoke discussion over the exact choice of antibiotic therapy. In the focus group, we discussed the specific roles of respective stakeholder in this scenario. We also discussed which interactions, communication and information needs are present at different moments in time and the critical issues in this scenario or in similar daily practices. We focused on discussing problems as the main topic to understand value needs our stakeholders have.

Data collection via interviews

After organizing a focus group, it is common practice to organize follow-up interviews to deeper discuss the findings [25]. We organized semi-structured one-on-one interviews of one hour with a resident, a clinical microbiologist, a nurse manager and two infection control experts to further specify their views on the added-value of ASP and eHealth for a more in-depth understanding of the needs and ideas of each stakeholder. Based on business model components as introduced in the business model canvas [22], we addressed the following topics to discuss possible value needs: value propositions (what should the added value of the interventions be?), customers and interaction (who need ASP and how can they be involved?), key activities and resources (what is required in terms of infrastructure and resources?) and finally costs and benefits (who pay for ASP and what are its benefits?). After transcribing the interviews, we coded the texts into business model building blocks and finally combined these in the business model canvas for each interviewed stakeholder.

Results

Understanding the antibiotic therapy process from stakeholder-perspective

The focus group concluded the primary stakeholders in every form of therapy are the physician, the patient, and the nurse. The physician prescribes medication and the nurse usually administer all medication. In case of prescribing antibiotics, a clinical microbiologist may be consulted by the physician or resident for interpreting laboratory results or advice with non-routine antibiotic therapy. Clinical pharmacists check all prescribed medications, including antibiotics. They also occasionally give extra advice to physicians or nurses or provide background information on medication. Nurses use this information regularly when administering antibiotics. Other stakeholders in the focus group stated they play a more facilitating role and do not directly influence antibiotic therapy. They, however, support the primary stakeholders in terms of organizational aspects, resources and protocols.

The focus group was also asked whether stakeholders were missing. An infectious diseases physician who is not per se present in every Dutch hospital or at every ward and a dietician were mentioned as additional stakeholders.
Another important point the focus group agreed on is that it is important to keep the number of stakeholders involved in ASP low for optimal collaboration.

Understanding which stakeholders are most influential in co-creating eHealth interventions for ASP

Looking at the above analysis with stakeholders, the key stakeholders for the infectionmanager.com and possible users of specific ASP applications are physicians, clinical microbiologists, clinical pharmacists and nurses. This list of key stakeholders is comparable with the ASP stakeholders suggested by experts in literature [6, 27].

Based on the discussed antibiotic therapy process (as delineated above), we defined five essential interactions for these key stakeholders regarding antibiotic therapy (*Table 3*). Each of these interactions has a potential for developing specific eHealth applications to support the process and information flows in these interactions.

Table 3: Stakeholder interactions in antibiotic therapy

From	To	Main interaction
Clinical microbiologist	Physician	Share laboratory results
Physician	Clinical microbiologist	Consult antibiotic therapy
Physician	Nurse	Transfer of daily patient care
Pharmacist	Physician	Share medication details
Pharmacist	Nurse	Share antibiotic delivery information

Understanding problems that stakeholders face in the antibiotic therapy process

We report the results from the problem analysis in three topics: communication, information/documentation, and critical moments/bottlenecks during the process.

Communication during antibiotic therapy

There are two important moments of communication (see *Table 4*), one is the communication between the physician and microbiologist. This communication usually takes place per phone. A physician contacts a microbiologist for advice in complex situations or a microbiologist phones a physician to interpret and share laboratory results. The other important communication happens between physician and nurses. Nurses administer the prescribed antibiotics and may require extra information. These two important moments of communication were deemed worthwhile by the stakeholders to support with possible eHealth technology to streamline the communication and avoid miscommunication or forgotten information sharing.

A common communication problem expressed by the focus group is that communication by phone that information gets 'lost in translation'. As many patient details are shared verbally, also many are not. A microbiologist said that actually seeing a patient too for clinical assessment would improve his advice and could improve the appropriateness of the antibiotic therapy in some cases.

Table 4: Crucial moments in antibiotic therapy

Communication	- Physicians need information from the clinical microbiologist or clinical pharmacist. Usually, this communication occurs per phone, initiated by either the physician (for advice) or microbiologist (for interpreting and sharing laboratory results) or clinical pharmacist (while reviewing receipts). Contact with a microbiologist or pharmacist should be 24/7 possible; - Nurses take daily care of patients and frequently need patient-specific instructions from a physician. They also administer prescribed antibiotics and with less common therapies might need additional information or delivery advice –usually details concerning intravenous delivery- from protocols, a physician or a resident (face-to-face), or a clinical pharmacist (phone).
Information and documentation	- Finding the right information can be problematic due to multiple and different information sources. Some forms of information require research (e.g. state-of-the-art articles on pneumonia and pregnancy) and this information is difficult to generalize and centralize. But particularly information needs of nurses (and in a lesser way residents) about antibiotic administration can be improved by putting information from several existing sources together in one place; - The patient information system is not directly accessible by the microbiologist as the laboratory is an external facility thus microbiologists rely on patient information shared verbally by the physician. - Another important form of information is culture exchange and laboratory results on the cultures. The faster this information is available, the faster antibiotics can be de-escalated (adjusted), yet in practice this information flow is prone for delays.
Process bottlenecks	- Antibiotics should be stocked and available (either at the pharmacy or at the ward); - (Too) many diverse information sources for protocols, information, etc.; - Delays in sending cultures and communication of laboratory results cause prolonged antibiotic therapy that may be unnecessary; - Laboratory results are sent to the physician/resident who requested them, which is not ideal when physicians/residents share the care of patients and the one who requested the results is not available or present. It is also not ideal for patient care transfers as the data does not transfer along; - There is a focus on efficiency; which means available resources, time and personnel are limited and a balance has to be found in improving quality with ASP and efficiency; - Communication per phone can have a negative effect on quality of antibiotic therapy if not all information is shared. The more informed the decision making for therapy is, the better.

Information/documentation during antibiotic therapy

All stakeholders required information sources and documents. They reported information comes in mixed forms, either digitally in intranet information systems or hardcopy in folders or pocket cards. Each stakeholder has their own preference and selection of information sources and documents, which also causes problems due to information being distributed over various sources (see *Table 4*). Patient specific information is logged but not easily accessible by all stakeholders. Also, stakeholders stressed that the speed of information sharing, particularly on laboratory results is crucial for successful antibiotic stewardship as it can speed up the adjustment of (empiric) therapy and thus optimize antibiotic use.

Critical moments/bottlenecks during antibiotic therapy

The most important critical moments regarding patients' health are reported to be during the therapy process itself (diagnostics, prescription, administration), in the communication of laboratory results (correctness and timeliness) and the physical responses of the patient on the therapy (timely adjustment of medication). Stakeholders also expressed critical issues apart from patient-related ones (see *Table 4*). In general, there appear to be complications with the logistics to and from the laboratory, as it is an external facility, resulting in preventable delays. Avoiding or minimizing these delays will again speed up information sharing and possible adjustment of antibiotics and subsequently improve antibiotic stewardship.

Identifying which improvements and opportunities stakeholders see in this process

Stakeholders mentioned the following improvements and opportunities how the antibiotic therapy process can be improved. There were three important interventions mentioned that would be interesting for their antibiotic stewardship initiatives, that would also be relevant to our eHealth research (see *Table 5*). A bed-side audit, which would technology that delivers need on-the-spot information tailored to physicians or microbiologists, maybe pharmacists even too. An eHealth technology that would offer information, protocols, pharmacy/medication information, etc. in a uniform and integrated way. Finally, there is an opportunity for eLearning to teach those involved with antibiotics about antibiotic stewardship or new protocols, etc.

We excluded the technical problems with currently existing IT infrastructure as we did not plan to overhaul their systems as it would be not feasible within the scope of the project and pilot ward (it would affect the entire hospital) and our research planned to expand the developed eHealth technologies to other hospitals after the pilot. Changing their IT infrastructure would be too hospital-specific.

Table 5: Possible improvements and opportunities for antibiotic therapy

Relevant for new eHealth technologies	- A bed-side audit consisting of a physician and microbiologist would improve clinical assessment for appropriate antibiotic therapy. Clinical pharmacists would also benefit from joining this bed-side audit to assist with prescription details. A bed-side audit is not needed at every prescription, yet with complex treatments it might be beneficial to visit the patient as a team; - Looking for uniformity in protocols and provided information can also be beneficial for antibiotic therapy. In fact, a resident stated many available protocols could be replaced with a solid uniform one; - Education to disseminate new protocols, changes in protocols or generally news regarding antibiotics could improve knowledge and awareness of ASP.
Out of scope	- Improvement in timely logistics with the microbiology laboratory, by adequately sending cultures to the laboratory and getting timely results might be needed; - Current IT systems require better data connectivity and information sharing.

Ideating what eHealth applications are required

Based on the antibiotic therapy process, problem analysis we ideated the following eHealth opportunities for the infectionmanager.com based on what stakeholders said in the focus groups and interviews. The following paragraphs provide an overview of opportunities for eHealth technologies based on what stakeholders deem helpful in the antibiotic therapy process translated into a short, general description of each eHealth technology.

Information tool to support antibiotic prescription

An important step is the start of this therapy, known as empiric therapy. A good start with empiric therapy is already a big step towards better stewardship, according to the clinical microbiologist. For common infections or antibiotics, the physician can rely on his/her experience, yet in some situations extra information may be needed to verify the right antibiotic, dose and duration. Physicians and residents usually use an antibiotic formulary that contains most of this information. Additionally, there are national guidelines and local guidelines and protocols that can be used as well. According to stakeholders, these guidelines are usually adequately covered by the formulary.

An antibiotic prescription information application can bring all these sources of information together in one place so that physicians have to search less. Another strong point of this application is that it can fulfill the need for uniformity in protocols and information if all content of the application has a consistent presentation.

Interactive antibiotic prescription decision support

In the pilot hospital, another intervention was on-going called 'Surviving sepsis'. This is a little pocket card to help physicians and residents signal life-threatening infections by scoring a few parameters in a checklist. A possibility for eHealth is to replicate an interactive variant of this pocket card with an antibiotic prescription decision support that can make this checklist go more in-depth towards e.g. suggesting possible infections and possible therapies. This application can be an expansion of the antibiotic prescription information application.

Information tool to support antibiotic administration

Nurses administer antibiotics to patients. With common antibiotics, the delivery is done on experience, yet for uncommon antibiotics, information is needed regarding the delivery. For example, the exact flow rate of an intravenous antibiotic or if an antibiotic needs to be given before or after dinner. Nurses - and occasionally also physicians and residents - check an information system of the pharmacy or national guidelines and local guidelines and protocols. Digital sources can be accessed via the Computer-on-Wheels, but some protocols are available as printed copies.

The antibiotic delivery/administration information application can bring all these sources of information together in one place. That way nurses, physicians, and residents do not have to search in multiple sources. Also, this application can fulfill the need for uniformity in protocols and information if all content of the application has a consistent presentation.

Information tool to transfer patient care

The care of patients is transferred multidisciplinary. Physicians transfer the care to nurses or physicians can transfer among each other or residents, or, patients can transfer from one ward to another. An opportunity for an application can be to provide an infection-specific or antibiotic-specific checklist of important therapy details that need to be shared during such patient transfers. A nurse gave as an example that he sometimes had to verify with the attending physician or resident when to stop therapy or that therapy was continued longer than officially stated in protocols.

Tool to facilitate the team doing audits

A possible ASP application is a bed-side assistance application to quickly access information:

- Patient information (primary parameters (age/weight), history, allergies);
- Antibiotic medication information (antibiotic formulary, guidelines);
- Laboratory results.

This bed-side assistance application can be useful for microbiologists, infectious disease physicians (‘infectiologists’), pharmacists and physicians (depending on the ASP team formation) to obtain information while doing audit rounds. Providing antibiotic medication information is easiest to manage as the technology and content will have much in common with the information applications described in eHealth applications #1 and #3. Patient information and laboratory results require connectivity with existing IT systems or some manual preparation beforehand.

Alerts/notifications

Within the antibiotic therapy process there are a few critical moments where an alert or notification application can be helpful:

- In the reviewing process done by clinical pharmacists, an alert or messaging system for important messages per receipt can be used to notify physicians to re-evaluate therapy or to provide patient-specific information such as conflicting medications. This can be combined with a restriction-approval strategy as suggested as a possible ASP strategy in IDSA/SHEA guidelines for implementing antibiotic stewardship programs in hospitals [27];
- When laboratory results are available for a certain patient, the currently attending physician or resident can be notified in addition to sending results directly to the physician or resident who requested them;
- When an antibiotic is prescribed and administered, after a certain time a re-evaluation is in order. This is described as a day-3 bundle that after two or three days the effectiveness of antibiotic therapy can be assessed [28]. At that point, the prescribed antibiotic can be continued, adjusted or even stopped. An eHealth opportunity here is to give an alert or notification when the re-evaluation should take place or co-create an application providing a daily list of antibiotic therapies to re-evaluate.

Education via E-Learning

In the focus group, it became apparent that education is important. Also in ASP guidelines education is an important supplementary strategy in implementing ASP interventions [27]. For every educational element of ASP, there is an eHealth possibility to provide that education using E-Learning applications. The following educational activities were deemed interesting when implementing ASP applications:

- All personnel need to be informed about the importance of ASP to gain awareness and understanding;
- All personnel need to be informed why a team is performing audits;
- Physicians, residents, nurses, microbiologists, infectious disease physicians and pharmacists should stay up-to-date with new information, guidelines, protocols, etc.;
- Training in using other eHealth applications implemented for ASP.

Ideating an implementation strategy for a platform with ASP applications

In the follow-up interviews, we discussed with stakeholders and two ASP experts what the added value of the platform and eHealth applications should be. All stakeholders unanimously agreed on that the most important benefit from optimized antibiotic therapy will be a reduction in length-of-stay. The length-of-stay of patients will reduce when they have optimal therapy, can go home sooner with oral antibiotics, and have less risk of complications with infections. This has beneficial consequences for the quality of care as well as less antibiotic use and thus less antibiotic costs.

All stakeholders also agreed that hospital management needs to be convinced that ASP and subsequently using the infectionmanager.com platform and its eHealth applications is beneficial. There is supportive evidence in the literature of already existing ASPs that they are beneficial [7], however, the role of technology in ASP is rather limited. Using eHealth applications as part of an ASP in the hospital, may lead to improvements when integrated with ASP initiatives within the hospital. Proving the beneficial effects of individual parts of a program is difficult as results are always reported over a program consisting of multiple interventions. Therefore, the platform can be implemented as part of (starting) ASP initiatives, but requires these existing ASP initiatives as a prerequisite. It can be part of a program and the team can choose which eHealth applications they want to embed in the ASP in their hospital. Nonetheless, the platform can also improve its own value by providing information how to set ASP initiatives up using the platform and its eHealth applications to facilitate teams with the introduction of the eHealth applications in their program.

Based on the above, the strongest business case for the hospital management is that this reduced length-of-stay can reduce costs and improve patient safety. One interviewee said the hospital management needs to understand that “investing at the beginning will pay off at the end”. The investment mostly requires making extra FTEs and financial resources available for stakeholders to prepare and perform ASP activities on a permanent basis. Also for the platform and eHealth applications the costs can be minimal for hospital-specific content creation and general maintenance. The revenue is in cost reductions: all costs related to length-of-stay can be reduced but also when speedier interventions in antibiotic therapy can be made, complications can also be reduced and thus reduce costs and negative effects for the patient [29].

Discussion

Using business modeling we established an understanding for the process, problems and opportunities to improve the antibiotic therapy from a stakeholder perspective. Key stakeholders for ASP are physicians, clinical microbiologists, clinical pharmacists and nurses. We also thoroughly discussed and analyzed the processes around antibiotic therapy to highlight current processes and bottlenecks that raise opportunities for eHealth. The processes can be improved mostly concerning finding information and information sharing. This analysis was used to further discuss eHealth opportunities relevant for ASP with these stakeholders in one-on-one interviews. In these interviews, we established through co-creation value-driven eHealth opportunities that fit the needs and daily practices of the included stakeholders. In this article, we ideated seven applications that are worthwhile to implement to support antibiotic therapy in a hospital. In sum, these applications mostly need to provide therapy or patient specific information to assure optimal therapy.

With a growing body of literature of expert recommendations on antibiotic stewardship [5, 6, 27, 30, 31] in combination with evaluations of existing programs [7, 32], the knowledge which interventions work best for ASP is expanding. Nonetheless, these expert recommendations still need to be implemented locally in every hospital. Despite guidelines, these local implementations are still diverse [33]. Patel et al pose that little guidance is offered on the practical aspects of implementing ASPs and that e.g. non-academic hospitals in the US need to overcome implementation issues by accounting for unique characteristics of their institutions [34]. To understand these ‘unique characteristics’ in a local context, we involved stakeholders in the implementation process of ASP with co-creation. Instead of putting existing expert-based interventions central, we put this stakeholders’ perspective central, by discussing their problems and needs with antibiotic therapy and what role ASP and eHealth can play therein. This way of co-creation allows us to understand not what experts find relevant for ASP, but what stakeholders need to improve the processes. By combining these value-driven dialogues with expert recommendations, we do not only implement expert-based interventions, but also implement them in a way that they are supported by the stakeholders, thus improving the uptake and (local) relevance of the interventions.

ASPs can be very comprehensive programs and containing multiple interventions for basically any process where antibiotics are involved. We decided to focus on primary care processes in the hospital and specifically the antibiotic therapy process as a first focus to implement possible interventions for ASP as one of the key pillars of antibiotic stewardship is more optimal prescription of antibiotics.

When we looked for the use of eHealth in ASP in literature, we noticed eHealth technology is rarely mentioned or used [35]. Some ASPs make use of existing software systems like electronic prescribing, electronic patient records, but few technological tools specifically designed for ASP were present. eHealth is attributed to help efficiency [36] and thus can be a helpful to optimize efforts and resources for ASP. Especially as manpower and (financial) resources are most attributed barriers that hinder ASP implementation [6].

Limitations

Limitations in this research are that we held a focus group in one ward in one hospital, who offered to participate in our research. Although some problems may be local and hospital-specific, we decided to provide generic tools that focus on the structure of presenting information and knowledge. The content of these eHealth applications can be hospital-specific and altered as hospital professionals see fit. As we also included experts in our EurSafety Health-net research from outside this specific hospital, later, we also expanded our research to multiple other hospitals to implement the applications elsewhere as there was interest in trying the applications in other ASPs. Based on this expansion we can test whether the structures are robust and how the content changes.

When we started our ASP research, very few hospitals were active with ASP. That was also a main reason why we collaborated with the pulmonary ward as they offered to be part of our pilot. Later when interest in ASP arose at other hospitals, mainly due to new guidelines in The Netherlands, we got more interest in our eHealth applications as well. In future research, we expand our research to other hospitals and research the necessary components for ASP to help hospitals with their implementation of ASP and the eHealth applications available via infectionmanager.com. For designing these applications, we used the principles of the CeHRes roadmap, human-centered design for requirements engineering and designing the technology for end-users and business modeling for stakeholder-based value-creation to embed the eHealth applications in ASP [11, 21].

Future research

Currently, there are three information applications in development. An antibiotic delivery/administration information application for nurses (app #3) finished its pilot with nurses at the pulmonary ward and is implemented in other participating hospitals [37]. Residents saw this application and asked whether they could have a spin-off information application. We also developed a similar information application called the antimicrobial therapy information application (app #1), containing German antibiotic therapy information tested in three German hospitals. Preparatory research for an antibiotic prescription decision support application (app #2) is in progress [38]. The research and development of the other remaining possible ASP applications is still to be planned.

The eHealth applications available via infectionmanager.com need to be part of a larger, more comprehensive ASP. Commonly these ASPs require an ASP team, surveillance/benchmarking of antibiotic use and infections, local guidelines, education and interventions that can intervene inappropriate prescription (usually audits) [6, 27]. The implementation strategy for the infectionmanager.com has to align with starting ASP initiatives. Helpful would be to add implementation advice inside the infectionmanager.com how to embed eHealth applications to support starting ASP initiatives. We are working on an additional implementation tool to help implementing these apps in a comprehensive ASP [39].

The added-value of the infectionmanager.com depends on the implementation of these ASP initiatives, but its strong point is that it eHealth applications can support processes in an efficient way when available manpower or resources are critical. We can offer our infectionmanager.com to ASP teams in return for collaboration on its content generation and subsequent research.

Conclusions

This example case of infectionmanager.com shows how we used business modeling to establish an implementation strategy early in the development of eHealth technology. We argue for more awareness among researchers who design and develop technologies targeted for healthcare that they should not only focus on designing great eHealth technology, but also designing great implementations. This infectionmanager.com example case demonstrated that “implementation” is not an ex-post development activity as how it is usually seen in eHealth projects. And that analyzing the implementation of technology early on the in any eHealth technology development process contributes to the understanding of what the added-value of this technology should be. Instead of following expert-recommended interventions (that also hardly deal with eHealth) for antibiotic stewardship, we asked stakeholders what role eHealth could have in these processes. These applications are worthwhile to develop, as the stakeholders already expressed their value.

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Chapter 6:

Evaluation of early implementations of antibiotic stewardship program initiatives in nine Dutch hospitals

van Limburg M, Sinha B, Lo-Ten-Foe JR, van Gemert-Pijnen JEWC

Antimicrobial Resistance and Infection Control (ARIC 2014, 3:33)

“What do you give a man who has everything? -Antibiotics” - *Unknown, a medical joke.*

Abstract

Background: Antibiotic resistance is a global threat to patient safety and care. In response, hospitals start antibiotic stewardship programs to optimise antibiotic use. Expert-based guidelines recommend strategies to implement such programs, but local implementations may differ per hospital. Earlier published assessments determine maturity of antibiotic stewardship programs based on expert-based structure indicators, but they disregard that there may be valid deviations from these expert-based programs.

Methods: An online questionnaire based on published guidelines and recommendations, conducted with seven clinical microbiologists, seven infectious disease physicians and five clinical pharmacists at nine Dutch hospitals.

Results: Results show local differences in antibiotic stewardship programs and the uptake of interventions in hospitals. Antibiotic guidelines and antibiotic teams are the most extensively implemented interventions. Education, decision support and audit-feedback are deemed important interventions and they are either piloted in implementations at academic hospitals or in preparation for application in non-academic hospitals. Other interventions that are recommended in guidelines - benchmarking, restriction and antibiotic formulary - appear to have a lower priority. Automatic stop-order, pre-authorization, automatic substitution, antibiotic cycling are not deemed to be worthwhile according to respondents.

Conclusion: There are extensive local differences in the implementation of antibiotic stewardship interventions. These differences suggest a need to further explore the rationale behind the choice of interventions in antibiotic stewardship programs. Rather than reporting this rationale, this study reports where rationale can play a key role in the implementation of antibiotic stewardship programs. A one-size-fits-all solution is unfeasible as there may be barriers or valid reasons for local experts to deviate from expert-based guidelines. Local experts can be supported with a toolkit containing advice based on possible barriers and considerations. These parameters can be used to customise an implementation of antibiotic stewardship programs to local needs (while retaining its expert-based foundation).

Keywords

Evaluation, Implementation, Antibiotic stewardship programs, Maturity, Hospital infections

Background

Antibiotic resistance is an increasing worldwide threat to patient safety and quality of care [1,2]. A correlation between antibiotic (over) use and increasing antibiotic resistance is widely acknowledged [3]. Hospitals can influence antibiotic use with improved, prudent antibiotic prescription, as up to 50% of prescribed antibiotics may be inappropriate or even unnecessary [4]. To curb the increasing resistance, hospitals started antibiotic stewardship programs (ASPs) as quality initiatives for infection prevention and control. An ASP ensures proper use of antibiotics with the best patient outcomes, less risk of adverse effects, optimal cost-effectiveness and to reduce or stabilise levels of resistance [5]. Guidelines from professional societies, such as the Infectious Diseases Society of America / Society for Healthcare Epidemiology of America (IDSA/SHEA) recommend expert-based strategies and interventions to implement ASPs in hospitals [6-8]. In the Netherlands, the Dutch Working Party on Antibiotic Policy (SWAB) is responsible for guideline development, education and surveillance for optimal antibiotic use. This organisation recently published a vision document, stressing the need for Dutch hospitals to form an ASP team and start planning future ASP initiatives as per January 2014 [9].

There is no consistent approach in local implementations of ASP in hospitals [10]. Hospitals combine expert-based strategies and subsequent ASP interventions in many different variations [4]. In a prior systematic review, neither a consistent implementation strategy nor a sufficiently described implementation rationale could be identified in international ASP studies (see chapter 4). To understand how these local implementations of ASP take form it is important to use a bottom-up analysis from within hospitals. In this approach, we involve the relevant local stakeholders in the hospitals we aim to assist with implementing ASP, as opposed to an expert-driven or authoritative top-down approach.

Progression in implementation can be assessed with the concept of ‘maturity’. Maturity models were first coined by Paulk et al [11] and are used in many disciplines to model or evaluate improvement of organisations and processes [12]. Maturity models describe a levelled progress of how, in this case, an ASP implementation gradually improves from an ad-hoc state to a structured and managed state and eventually to a measurable and self-optimizing state [11].

Maturity assessments are already used in the context of ASP. Earlier maturity assessments of ASPs were done by the Antibiotic Strategy International group who introduced a comprehensive list of potential structure indicators to assess maturity of ASP in hospitals in several European countries [13]. In short, this means that maturity of ASP depends on the number of expert-based structure indicators that are implemented as part of ASP in a hospital.

This study does not attempt to assess maturity by scoring a completeness of an ideal program, but analyses differences in local implementations of ASP interventions that are recommended in guidelines. Our aim is not primarily to identify which interventions are or should be implemented, but more importantly, to identify where rationale plays a role in implementing ASP interventions and what the consequences are for expert-based ASP strategies. The present study is the first step in our bottom-up assessment with local ASP experts to give an overview of which recommended interventions are implemented, or are being developed, combined with an importance analysis of these interventions. Incongruent responses from stakeholders show where possible difficulties or barriers surface when implementing ASP conform currently available expert guidelines and indicate possibilities for decision support. A follow-up study is required to understand the deeper rationale behind these differences and barriers and how local experts can be assisted with relevant implementation advice.

Methods

An online questionnaire using LimeSurvey was made available from August to November 2013. Clinical microbiologists, clinical pharmacists and infectious disease physicians were approached as these expert types are identified as being key-stakeholders in ASP (see chapter 4). Ethical approval was given after revision by an internal representative of the ethical board (reference: BCE14039) and no further ethical review procedures were deemed necessary. We sent a questionnaire invitation to known infection control experts recruited in earlier research projects. These experts represented academic and non-academic hospitals in the Dutch eastern border region and they were asked to distribute the questionnaire among clinical microbiologists, clinical pharmacists and infectious disease physicians tasked with ASP in their hospitals. As at the time of the questionnaire ASP teams were not necessarily formed at the hospitals yet, we chose to approach key stakeholders rather than teams directly. We also analysed the response of key stakeholders individually (not clustered per hospital) as stakeholders may have possible differences in views on ASP interventions (even within hospitals).
The questionnaire was structured around ten implementation topics based on a literature review (see *Table 1*, placed at the end of the chapter). The topics that were addressed involved ASP program initiatives, presence and importance of commonly used interventions and their possible characteristics, and possible outcomes and effects relevant for assessing evidence for the effectiveness of ASP. The extraction of implementation topics concerning ASP maturity or implementation assessments, attitude or opinion surveys towards ASP or practical implementation toolkits for ASP are presented in detail in *Table 1*.

The final questionnaire was adapted for the Dutch healthcare context, reduced and validated by microbiologists to have a final scope of 47 questions for an acceptable answering duration of 15–20 minutes. A literal English translation of the Dutch questionnaire can be found in as additional file at the end of the chapter for reference.

Responses were imported into SPSS21 for statistical analysis. Incomplete responses were excluded. Frequency cross-tables of responses stratified by hospital type (academic/non-academic) were used for reporting all results, as we anticipated differences between the two hospital types [10].

Results

Response

A total of 27 responses were collected. Eight respondents started answering the first few questions but did not complete the questionnaire and had to be excluded from the results. Based on the first questions we could identify that these were three clinical microbiologists, one infectious disease physician and four clinical pharmacists. Nineteen respondents completed the questionnaire, and the final sample consists of seven clinical microbiologists, seven infectious disease physicians and five clinical pharmacists from three academic hospitals and six non-academic (general tertiary care) hospitals.

Antibiotic stewardship program initiatives

The three included academic hospitals have implemented an ASP. At the non-academic hospitals, ASP initiatives are in development at five hospitals while one hospital has implemented an ASP. Almost all ASP initiatives were started from 2012 onwards.

Respondents from academic hospitals seemed more satisfied with current mandate from hospital management, available budgets and assigned full-time equivalents (FTEs) than their non-academic peers. No consensus was found in their opinions regarding satisfaction with the level of formalisation of ASP with, for example, documentation or task descriptions.

Academic hospitals targeted multiple wards in their ASP implementations, but the type of wards varied. Generally, these were all wards with high risk of infections and with relatively high antibiotic use. Most non-academic hospitals did not yet implement ASP. There, however, is a strong consensus that eventually ASPs should be implemented throughout the entire hospital.

Implementation of ASP interventions

Table 2 provides an overview of the maturity assessment as to whether common ASP interventions were already implemented, in development, considered necessary or considered unnecessary. The following paragraphs discuss the interventions in more detail.

Table 2: Maturity of ASP interventions in academic and non-academic hospitals

	Academic hospitals					**Non-academic hospitals**				
	Impl	In dev	Need	Un-need	N/A *	Impl	In dev	Need	Unneed	N/A *
Antibiotic team	6 (75%)	2 (25%)	-	-	-	6 (55%)	5 (45%)	-	-	-
(Local) antibiotic guidelines	7 (88%)	1 (12%)	-	-	-	9 (82%)	2 (18%)	-	-	-
Antibiotic formulary	7 (88%)	1 (13%)	-	-	-	8 (73%)	2 (18%)	1 (9%)	-	-
Audit-and-feedback	3 (38%)	2 (25%)	2 (25%)	-	1 (13%)	-	4 (36%)	6 (55%)	1 (9%)	-
Education	4 (50%)	4 (50%)	-	-	-	2 (18%)	8 (73%)	1 (9%)	-	-
Information systems for ASP	2 (25%)	1 (13%)	5 (63%)	-	-	2 (18%)	4 (36%)	3 (27%)	-	2 (18%)
Benchmarking	4 (50%)	3 (38%)	-	1 (13%)	-	1 (9%)	7 (64%)	2 (18%)	-	1 (9%)
Restriction	2 (25%)	4 (50%)	1 (13%)	1 (13%)			5 (45%)	3 (27%)	1 (9%)	2 (18%)
Academic detailing	1 (13%)	3 (38%)	3 (38%)	-	1 (13%)	2 (18%)	2 (18%)	4 (36%)	-	3 (27%)
Automatic stop-order	-	1 (13%)	4 (50%)	2 (25%)	1 (13%)	-	4 (36%)	3 (27%)	2 (18%)	2 (18%)

Pre-authorization	1 (13%)	1 (13%)	3 (38%)	1 (13%)	2 (25%)	-	2 (18%)	3 (27%)	1 (9%)	5 (45%)
Automatic substitution	-	1 (13%)	2 (25%)	5 (63%)		-	1 (9%)	3 (27%)	2 (18%)	5 (45%)
Antibiotic cycling	-	1 (13%)	1 (13%)	4 (50%)	2 (25%)	-	-	5 (45%)	2 (18%)	4 (36%)

**) Impl: implemented; in dev: in development; need: are needed; unneed: are unneeded; N/A: no answer or not applicable.*

Antibiotic team

In the early stages of ASP implementation, an antibiotic team (usually called A-team for obvious reasons) is mostly responsible for preparing an ASP. Subsequently, their tasks change to monitoring ASP effectiveness and performing important tasks that are part of the program. Based on the response, we can assume antibiotic teams were either already formed or in preparation.

Table 3 shows the composition of these teams. In both types of hospitals, the antibiotic teams consist of at least infectious disease physicians, clinical microbiologists and clinical pharmacists. These are also the stakeholders recommended to be at least present according to the national guidelines endorsed by SWAB [9]. Other stakeholders are involved in different team configurations but there is no consensus on which of these other stakeholders should be definite members of the antibiotic team. In both types of hospitals, it is clear that management and attending physicians have no active role in the team.

In non-academic hospitals, the frequency of infectious disease physicians in the teams is lower compared to academic hospitals. This can be explained by the probability that non-academic hospitals have no or too few (e.g. shared with other local hospitals) infectious disease physicians available, hence they cannot take part in their antibiotic team.

Table 3: Composition of antibiotic team in academic and non-academic hospitals

	Academic hospitals					Non-academic hospitals				
	Impl	In dev	Need	Unneed	N/A*	Impl	In dev	Need	Unneed	N/A*
Clinical microbiologist	8 (100%)	X		-	-	9 (82%)	X	1 (9%)	-	1 (9%)
Infectious disease physician	8 (100%)	X		-	-	5 (45%)	X	-	1 (9%)	5 (45%)
Clinical pharmacist	7 (88%)	X		1 (13%)	-	9 (82%)	X	1 (9%)	-	1 (9%)
Member of antibiotic committee	5 (63%)	X	1 (13%)	-	2 (25%)	4 (36%)	X	3 (27%)	1 (9%)	3 (27%)
Prescribing physician	4 (50%)	X	-	3 (38%)	1 (13%)	-	X	4 (36%)	3 (27%)	4 (36%)
Hygienist	1 (13%)	X	3 (38%)	3 (38%)	1 (13%)	1 (9%)	X	3 (27%)	4 (36%)	3 (27%)
IT specialist	-	X	3 (38%)	4 (50%)	1 (13%)	-	X	4 (36%)	5 (45%)	2 (18%)
Nurse	-	X	3 (38%)	3 (38%)	2 (25%)	-	X	2 (18%)	5 (45%)	4 (36%)
Epidemiologist	1 (13%)	X	4 (50%)	1 (13%)	2 (25%)	-	X	1 (9%)	4 (36%)	6 (55%)
Management	-	X	-	6 (75%)	1 (13%)	-	X	2 (18%)	6 (55%)	2 (18%)
Supervising physician	1 (13%)	X	1 (13%)	5 (63%)	1 (13%)	-	X	1 (9%)	6 (55%)	4 (36%)

(Local) Antibiotic guidelines

There are national antibiotic guidelines to which Dutch hospitals have to comply, based on evidence or expert-based guidelines and policies established in academic hospitals (e.g. available at www.swabid.nl). Hospitals are at liberty to use these national guidelines in full or adapt them slightly into local antibiotic guidelines.

Table 4 shows that academic hospitals have most common types of antibiotic guidelines locally implemented and overall, respondents were satisfied with currently available antibiotic guidelines in their hospitals. They responded that guidelines for intravenous-per os switches and for de-escalation are not yet available, but needed.

Table 4: Status of antibiotic guidelines in academic and non-academic hospitals

	Academic hospitals					**Non-academic hospitals**				
	Impl	In dev	Need	Unneed	N/A*	Impl	In dev	Need	Unneed	N/A*
Diagnosis of infections	8 (100%)	-	-	-	-	4 (36%)	-	3 (27%)	-	4 (36%)
Treatment of infections	8 (100%)	-	-	-	-	7 (64%)	2 (18%)	-	-	2 (18%)
Antibiotic therapy	8 (100%)	-	-	-	-	10 (91%)	1 (9%)	-	-	-
Duration of therapy	7 (88%)	-	1 (13%)	-	-	5 (45%)	2 (18%)	3 (27%)	-	-
Prophylaxis	8 (100%)	-	-	-	-	10 (91%)	1 (9%)	-	-	-
IV-PO switches	5 (63%)	-	3 (38%)	-	-	3 (27%)	4 (36%)	4 (36%)	-	-
De-escalation/streamlining	3 (38%)	1 (13%)	4 (50%)	-	-	1 (9%)	4 (36%)	5 (45%)	-	-

The situation in non-academic hospitals is different. Guidelines for treatment of infections, antibiotic therapy and prophylaxis are implemented (these are all available as national antibiotic guidelines). However, other antibiotic guidelines are incomplete and not as available when compared to academic hospitals. Respondents from non-academic hospitals agree that additional antibiotic guidelines are needed. It is interesting to see that exactly those guidelines that academic hospitals expressed as being needed (intravenous-per os switches and de-escalation) are in development at non-academic hospitals.

Antibiotic formulary

An antibiotic formulary contains an overview of indications and favourable antibiotic treatment (s). In the Netherlands, these formularies are usually introduced and maintained by the clinical microbiologists. Overall, an antibiotic formulary is present in both types of hospitals.

Audit-and-feedback

Audits are interactions with prescribers to influence the way they prescribe for antibiotic therapy. These audits can be prospective, thus directly influence therapy with feedback at patient level, or retrospective where the prescribed antibiotics are assessed and reported back to prescribers.

The response (see *Table 2*) from respondents at academic hospitals is diverse and suggests audits are performed but still as a pilot in only a few wards. As *Figure 1* depicts, there is no clear preference for bedside or remote consults as form of audit, but retrospective feedback seems less preferred. At non-academic hospitals audits do not yet take place but are in either in development or considered necessary. Compared to academic hospitals the respondents of non-academic hospitals have a slightly stronger preference for bedside audits over remote audits via phone or email as can be seen in *Figure 1*. All respondents stated audit-and-feedback was the preferred strategy for ASP.

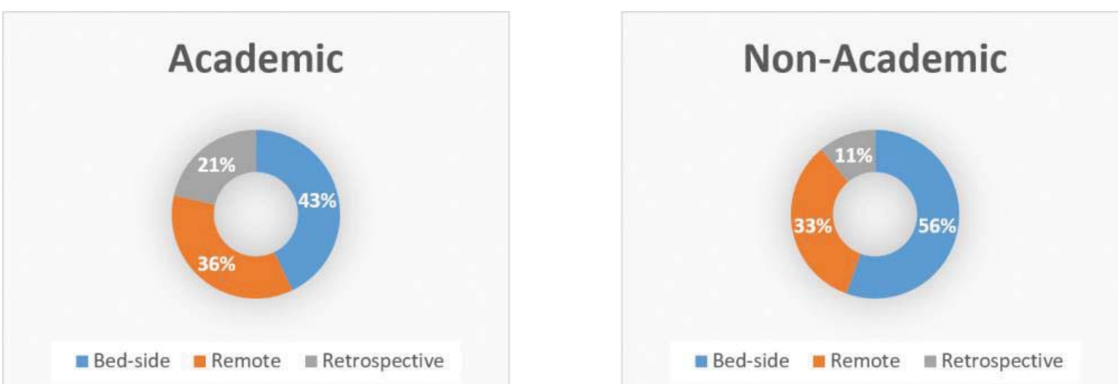

Figure 1: Preferences for audit

Education

Educational activities are needed to disseminate the goals and interventions of ASP among prescribers and other possible stakeholders for ASP. At academic hospitals, educational activities implemented or in development relatively equally, suggesting it this is something that is being piloted and still taking shape. Non-academic hospitals have progressed less with implementing education and hence educational activities are still contemplated or in development. Respondents of both types of hospitals have a strong preference for workshops as means of education (*Figure 2*).

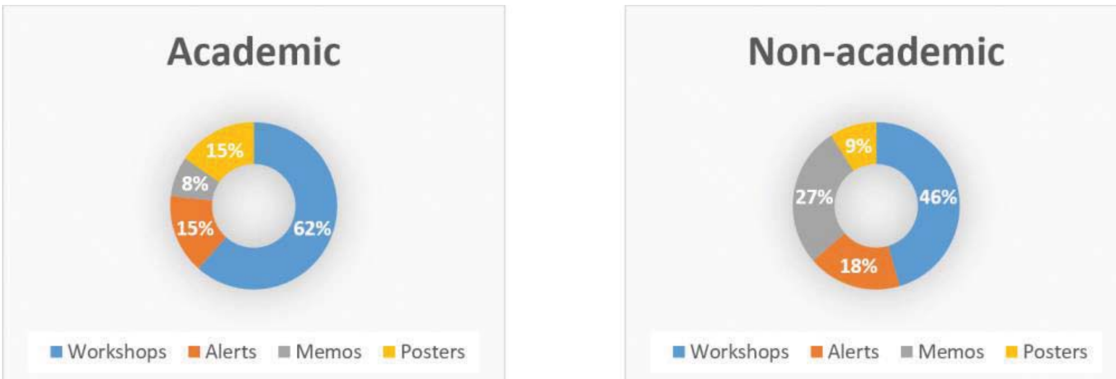

Figure 2: Preference for education

Information systems for ASP

Specific information systems (information technology or software) that can be used in ASP were present at academic hospitals, except for information systems to evaluate prescriptions and decision support tools, e.g. for information while performing audits.

At non-academic hospitals, the presence of information systems was more divided than at their academic peers and not generalizable, but information systems for ASP are mostly in development (*Table 5*).

Table 5: Status of information systems for ASP in academic and non-academic hospitals

	Academic hospitals					**Non-academic hospitals**				
	Impl	In dev	Need	Unneed	N/A*	Impl	In dev	Need	Unneed	N/A*
Electronic health records	5 (63%)	2 (25%)	1 (13%)	-	-	9 (82%)	2 (18%)	-	-	-
Digital laboratory data	6 (75%)	1 (13%)	1 (13%)	-	-	6 (55%)	1 (9%)	3 (27%)	-	1 (9%)
Digital antibiotic use data	7 (88%)	-	-	-	1 (13%)	4 (36%)	3 (27%)	2 (18%)	-	2 (18%)
Digital precribing	8 (100%)	-	-	-	-	7 (64%)	3 (27%)	1 (9%)	-	-
Evaluation of prescription	2 (25%)	4 (50%)	2 (25%)	-	-	1 (9%)	2 (18%)	5 (45%)	-	3 (27%)
Decision support systems	1 (13%)	2 (25%)	3 (38%)	-	2 (25%)	1 (9%)	4 (36%)	4 (36%)	1 (9%)	1 (9%)
Surveillance	6 (75%)	1 (13%)		-	1 (13%)	3 (27%)	4 (36%)	4 (36%)	-	-

Benchmarking

Benchmarking or monitoring antibiotic use related outcomes is necessary to assess changes caused by ASP. Such data can be compared internally (e.g. over time, between wards, between prescribers, etc.) and externally (e.g. between hospitals, nationally, internationally, etc.). Antibiotic teams at academic hospitals that benchmark or have it in development have access to common data sources for benchmarking. In non-academic hospitals benchmarking is less present and still in development, hence most data sources are not (yet) available either to the antibiotic team. Figure 3 gives an overview of the available (or in case of non-academic hospitals, in development) data sources. The figure suggests that daily defined doses and antibiotic costs are relatively the most used data types for benchmarking and monitoring antibiotic use.

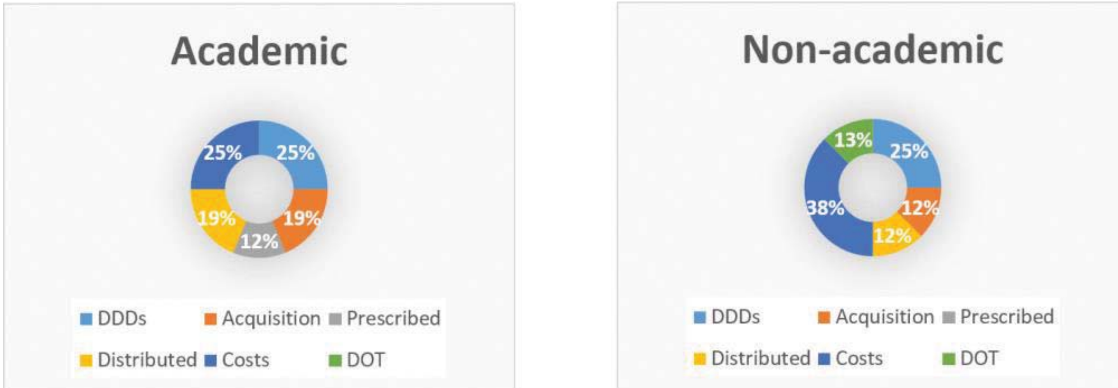

Figure 3: Preference for data types for benchmarking
**) DDDs: daily defined doses; DOT: days of therapy.*

Restriction

Restriction of antibiotics means prescription of some or all antibiotics requires validation by a member of the antibiotic team. This intervention is not commonly present in academic hospitals, but stated as being in development. Current and future application of restrictive measures is more common in non-academic hospitals. None of the respondents indicated that restriction and (pre)-approval were identified as key strategies for ASP.

Academic detailing

Academic detailing means that prescribers are influenced with structural evidence-based feedback, where the academic evidence plays an important role in the feedback as a form of education. This is hardly used in both types of hospitals but respondents stated this intervention is in either development or needed in the longer term. Currently there can be some ad-hoc academic explanation in feedback, but 'academic detailing' as a structural intervention that structurally provides prescribers with evidence-based feedback, is not seen as an important, urgent intervention according to our respondents.

Automatic stop-order, pre-authorisation, automatic substitution and antibiotic cycling

Respondents of non-academic hospitals stated that these four interventions are all in development or needed. Academic hospitals appear to be only interested in developing automatic stop-orders or pre-authorisation as automatic substitution and antibiotic cycling were often stated as being unnecessary.

Importance of ASP interventions

Respondents were asked in the questionnaire to rank ASP interventions. The list contained thirteen ASP interventions respondents could rank in order of importance to their ASP with a 1 to 13 score. Final scores in Figure 4 were averaged per type of hospital and overall average. The median of 7 was plotted to emphasize the perceived relative importance of interventions.

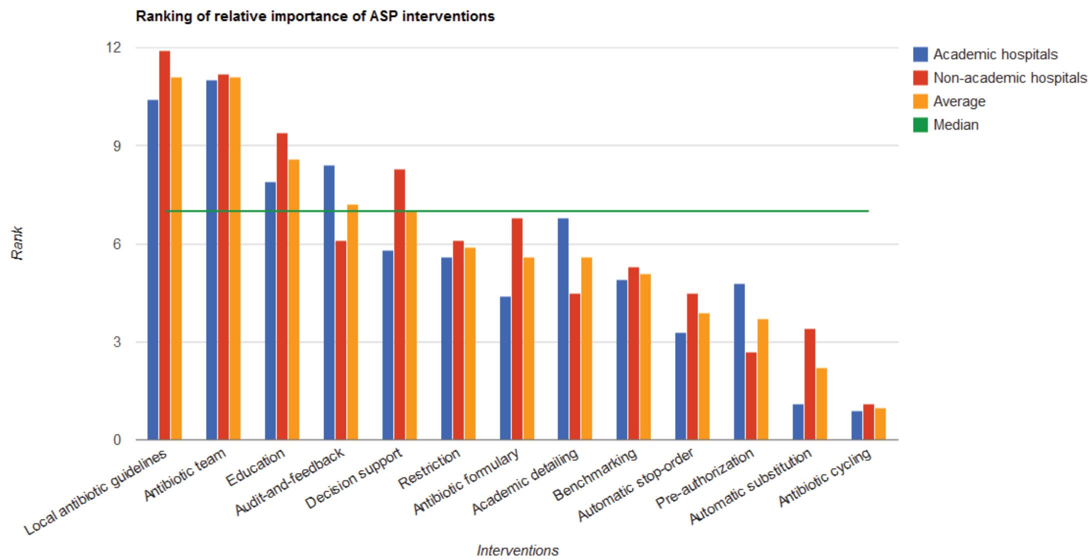

Figure 4: Ranking of relative importance of ASP interventions

Local antibiotic guidelines and an antibiotic team are scored as the two currently most important interventions for implementing ASP in both types of hospitals. Education and audit-and-feedback scored relatively high as well, and in combination with earlier data in Table 2, they can be seen as part of a primary ASP bundle. Decision support systems receive more attention in non-academic hospitals than in academic hospitals. A possible explanation for this is the higher preference for bedside audits in non-academic hospitals (see Table 2) since for audits such decision support systems are particularly helpful. Less direct attention is needed for restrictive measures, an antibiotic formulary, academic detailing and benchmarking. We think an explanation for the low score for antibiotic formularies is that most Dutch hospitals already have such formularies in place and as such they are not directly seen as a specific, important intervention of ASP. The remaining interventions, automatic stop-order, pre-authorisation, automatic substitution, and antibiotic cycling score relative low on importance and it is questionable whether these are interesting interventions for ASP.

Discussion

Both academic hospitals and non-academic hospitals in the Dutch border region are busy with antibiotic stewardship initiatives. When assessing local implementations of ASPs, a clear difference in academic and non-academic hospitals can be seen. Generally, academic hospitals are experimenting with comprehensive programs of recommended interventions in pilot ASPs. Non-academic hospitals have implemented interventions that are required by national guidelines and are expanding the program with other important interventions for a comprehensive ASP. Obviously the academic nature and larger size of academic hospitals support a more experimental, comprehensive approach, whereas non-academic hospitals seem to take a more practical approach by focusing on easily obtained gains first. Some existing processes can be reused as many activities that are now under the ASP umbrella are not necessarily new. For example, many hospitals have had remote consults with microbiologists in place for years. Also, this difference between academic and non-academic hospitals is strengthened by the fact that non-academic hospitals seem to have more difficulties in securing adequate resources for ASP.

When we combine maturity modelling with the findings of the current progress in ASP in hospitals included in our questionnaire, a number of conclusions can be drawn:

In the state before ASP really starts, the null or m0 state of a maturity model, most Dutch hospitals already have a comprehensive antibiotic formulary and at least guidelines for treatment of infections, antibiotic therapy and prophylaxis. This is helpful as it can be a head start for implementing ASPs. In many other countries such an antibiotic formulary did not yet exist and is usually an important first ASP activity of the antibiotic team (see chapter 4).

- In the first stage of maturity, the initial phase, processes are ad-hoc and unorganised [11]. We found that hospitals are triggered by the SWAB vision document [9] and data from the questionnaire suggests that stakeholders are busy with a primary bundle of interventions that constitute an ASP. An antibiotic team, adequate local antibiotic guidelines for ASP, educational activities and an audit-and-feedback intervention receive early attention and seem to be the first interventions to be implemented when hospitals start with ASP. However, it seems each intervention is implemented quite differently, according to local contexts and readily available means. In other words, interventions are implemented with a slight variation between them. For example, an intervention that seems rather straight-forward is an antibiotic team, however, the composition of an antibiotic team is already quite different in each hospital, depending on the available staff, and care focuses (children, trauma, etc.) in that hospital.
- The second stage of maturity, a managed state, is what regulatory documents aim for. There is a risk that the current proliferation of local ASPs and local variations between interventions in hospitals are unstandardized and will therefore be difficult to regulate, compare and manage. For example, how does a team with an ID physician relate to a team without? Timely guidelines that help standardisation are necessary.

From a regulatory perspective, two scenarios are possible: a) allow proliferation and wait until a dominant design emerges – assuming that over time current ASPs will evolve into comparable programs or b) interact with hospitals and understand the local differences and anticipate with the regulations.

- Further stages of maturity, which is a measured and self-optimising state, is difficult to achieve for ASPs in their current state. Standardisation in processes and measurements are necessary to evaluate ASPs both internally and externally. We found that data collection for benchmarking can be done; however, as ASPs are currently novel and diverse between hospitals, this would be like comparing apples and oranges. Also, although there is evidence that ASPs show positive effects on antibiotic use and antibiotic resistance [14,15], there is little or no standardisation in how effectiveness of ASPs is measured in terms of standardised outcomes or even methodologies [16,17]. That is also causing difficulties to compare (different) programs.

The assessment of the implementation of ASP can be expanded further by understanding the rationale and considerations local experts have based on expert-based recommendations in available regulatory documents. Patel et al. concluded that little guidance is offered on the practical aspects of implementing ASPs and that non-academic hospitals in the US need to overcome implementation issues by accounting for unique characteristics of their institutions [18]. Understanding these issues combined with these unique characteristics can eventually be used for parameters to customise local implementations of expert-based recommendations.

Earlier maturity assessments identified a set of structure indicators or characteristics that need to be present [13,19]. Prudence should be shown to assess the maturity of ASP implementation when using these structure indicators, as local experts may have valid reasons to deviate from expert recommendations. For example, a non-academic hospital may not have infectious disease physicians but a clinical microbiologist performing similar tasks. If available maturity assessments are strictly observed, this example hospital is missing an important structure indicator, while in practice the ASP was implemented differently from the ideal program as proposed and assessed by experts. Therefore, tallying whether expert-recommended interventions are present is not enough to capture the progress and maturity of ASP implementations.

By applying convenience sampling, we contacted respondents indirectly via infection control experts in the Dutch eastern border region and we depended on their willingness and involvement with ASP to find and persuade colleagues to partake. Due to the novelty of ASP, some experts declined participation as they claimed they were not sufficiently progressed with ASP initiatives yet. As a result, this study assessed only nineteen stakeholders from nine hospitals in the Dutch border region. Conclusions of this study do not reflect the entirety of Dutch hospitals. However, this was not the primary goal of the study, as we wanted to assess the implementation process of early ASP initiatives, for which the sample size sufficed. Another limitation was that by reducing the number of questions, not every intervention was assessed in high detail. We also omitted questions regarding microbiological diagnostics, infrastructure or tests and policy forming to keep the questionnaire at an acceptable length.

To keep the momentum going of ASP implementations and to improve the chances of success of these implementations, future research is necessary to obtain further insights into the rationale and issues that local experts consider during local implementations. What considerations did they have and why? At academic hospitals it would be interesting to assess what was learned with experimentation in pilot implementations. How did they arrive at the interventions as used in pilots and how will these pilots be scaled up? Case studies of these pilots can lead to concrete examples of potential and different implementations that can be used for advising other hospitals various configuration possibilities of ASPs. At non-academic hospitals, future research will be more focused on practical issues in implementing ASP. What do local experts in non-academic hospitals consider in practice when implementing ASP? What are easily obtainable gains? What are barriers?

These different case studies, potential issues and rationale behind characteristics between interventions can be used as parameters that influence the configuration of to-be implemented ASPs. By inventorying all these parameters, local experts can be supported in customising and implementing an ASP that fits their hospital. Eventually, these parameters could be used to synthesise an implementation maturity toolkit. We plan to design a decision aid for experts in academic and non-academic hospitals that will generate a customised implementation advice for ASP fit for their local conditions.

Conclusion

Advising an ASP implementation is not straightforward. Experts who are tasked to introduce ASPs in their hospitals use expert-driven guidelines but need to transpose these guidelines to locally implemented interventions. This transposition leaves leeway for experimentation and considerations and leads to local differences in implemented intervention and ASPs. Progress can be made by assisting local experts with implementing ASPs in their hospitals. This assistance, however, needs to take into account that local conditions need to be translated into practical implementation advice and that a ‘one-ASP-for-all’ advice does not meet the needs of local experts. A bottom-up assessment with local experts can find parameters that influence local implementations of ASPs. These parameters can be used as input for a decision aid that generates a customised advice for a local implementation of an ASP.

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Appendix for chapter 6

Table 1: Overview of literature scan and extracted implementation topics

#	Author(s)	Year	Title	Study description	Extracted implementation topics
1	Bannan, Buono, McLaws, Gottlieb	2009	Survey of medical staff attitudes to an antibiotic approval and stewardship program	Design: Questionnaire with 40 questions focused on restriction and approval Interest: Attitude	- restriction as intervention - authorization as intervention - advice as communication - education as intervention - stop-order (withholding pharmacy) as intervention - costs, appropriate use, resistance, time as outcomes - pager as communication - possible stakeholders in team
2	Barlam, DiVall	2006	Antibiotic-stewardship practices at top academic centers throughout the united states and at hospitals throughout Massachusetts	Design: Two surveys Interest: ASP components	- multifaceted programs - time of start with ASP - funding / financial support - (formulary) restriction as intervention - solicited input from ID as communication - costs, improved use, adverse effects, resistance, compliance, DDDs, clinical outcomes as outcomes - aiming prophylaxis - aiming only targeted antibiotics - aiming antibiotic therapy at order - aiming initial therapy - recommendations as intervention (day 3 bundle) - culture data as communication - possible stakeholders in team - approval as intervention - review as communication - consult as communication - computerized order entry as communication - stop-order as intervention - IV-PO switch as intervention - clinical practical guidelines as intervention - evaluation as intervention (benchmarking) - support and time needed from physicians - rounds, didactics, program, consults/feedback as education
3*	Burgmann, Janata, Allerberger, Frank	2008	Hospital antibiotic management in Austria – results of the ABS maturity survey of the ABS International group	Design: Survey Interest: 5 categories of maturity	- data evaluation as intervention (benchmarking) - AB consumption data as outcomes - hospital/department/ward levels of benchmarking - feedback of benchmarking as communication - possible stakeholders in team - guidelines for dosage, drug costs, IV-PO switch

					- guidelines for antibiotic treatment - guidelines for prophylaxis - education as intervention (seminars, literature) - financial resources - cooperation with other hospitals
4	Buyle, Metz-Gercek, Mechtler, Kern, Robays, Vogelaers, Struelens	2013	Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals	Design: Expert panel + validation survey Interest: Potential structure indicators for ASP	- bedside advice as communication - rounds as intervention - frequency of team meetings - audit as intervention - possible stakeholders in team - formulary as intervention - updating formulary - stop order as intervention - guidelines for microbiological documented therapy, empirical therapy, prophylaxis, iv-po switches - updating guidelines - clinical decision aid as IT - mandate from management - FTEs - Education as interventions - passive methods, interactive methods as education - evaluation as intervention - resistance data, consumption data, - hospital/department/ward levels of benchmarking - total DDDs, # of infections as outcomes
5	Cooke, Alexander, Charani, Hand, Hills, Howard, Jamieson, Lawson, Richardson, Wade	2010	Antimicrobial stewardship: an evidence-based, antimicrobial self-assessment toolkit (ASAT) for acute hospitals	Design: ASAT toolkit (checklist) Interest: Levels of antimicrobial stewardship	- guidelines as intervention - formulary as intervention - restriction as intervention - IV-PO switches as intervention - guidelines for prophylaxis as intervention - adherence as outcome - education as intervention - training as education - information systems as IT - digital prescribing as IT - possible stakeholders in team
6	Dumartin, Rogues, Amadeo, Pefau, Venier, Parneix, Maurain	2011	Antibiotic stewardship programmes: legal framework and structure and process indicator in Southwestern French hospitals, 2005–2008	Design: Survey Interest: Checking whether legal framework is present	- frequency in meetings - available human resources - digital prescription, pharmaceutical analysis, dispensation, digital link between lab, pharm, wards as IT - restriction as intervention - stop order as intervention - first-line, prophylaxis as guidelines - audits as intervention/communication - evaluation feedback as communication - education as intervention - Formulary as intervention - ab consumption as benchmarking - DDDs, resistance as outcomes (and communication) - possible stakeholders in team

7	van Gastel, Costers, Peetermans, Struelens	2010	Nationwide implementation of antibiotic management teams in Belgian hospitals: a self-reporting survey	Design: Questionnaire Interest: Level of AMT activities	- Possible stakeholders in team - consultation per phone, email, intranet, face-to-face, staff meetings as communication - formulary as intervention - guidelines for empirical and prophylaxis - updates of formulary and guidelines - restriction as intervention - approval/review as intervention - concurrent review/audit as intervention - de-escalation as intervention - stop order as intervention - order forms as intervention - IV-PO switch as intervention - consumption and resistance as outcomes - by hospital/unit or by antibiotic type - feedback of outcomes
8	Greater New York Hospital Association	2011	Antimicrobial stewardship toolkit	Design: Best practice Interest: Implementation toolkit	- benchmark and review antibiotic use (patterns) - review resistance - IT infrastructure - possible stakeholders in team - aim for common infections, pathogens, agents - rollout: hospital vs. ward - available resources - strategy: - guidelines for diagnosis, treatment, duration, dose optimization, IV-PO, streamlining/de-escalation - formulary as intervention - restriction as intervention - education as intervention - prospective review as intervention - stickers, notes, face-to-face as communication - data collection (benchmarking) - usage, clinical, microbiologic, costs as data
9	Hulscher, Grol, van der Meer	2010	Antibiotic prescribing in hospitals: a social and behavioral scientific approach	Design: Review Interest: socio-cultural factors of ASP	- formulary as intervention - order form as intervention - restriction as intervention - stop orders as intervention - infection control committee - guidelines as intervention - review as intervention - rounds as intervention - telephone advice as intervention - improve infrastructure - education as intervention - conferences, seminars, skill training programs as education - individual instructions (outreach, academic detailing) - feedback of outcomes - decision support via IT

10	Nault, Beaudoin, Thirion, Gosselin, Cossette, Valiquette	2008	Antimicrobial stewardship in acute care centres: survey of 68 hospitals in Quebec	Design: Questionnaire Interest: Proportion and nature of programs	- Duration of ASP or busy setting up - distributed units, DDDs, acquisition costs as benchmarking data - direct interaction as intervention (written or phone) - education as intervention - stop orders as intervention - auto substitution - formulary restriction as interventions - local guidelines as intervention - preauthorization as intervention - antibiotic cycling as intervention - decision support systems as intervention - possible stakeholders in team
11	Pulcini, Williams, Molinari, Davey, Nathwani	2011	Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland	Design: Survey Interest: Perception and prescribing practice	- local guidelines as intervention - presence of team- - approval as intervention - IV-PO switch protocol - advice from ID physician, senior, microbiologist, pharmacist or team as intervention - face-to-face, phone, consult upon request as communication - lectures, workshops, informal education, web-based learning, self-directed learning as education - possible stakeholders in team - computer aided prescribing as IT - resistance data availability
12	Thern	2013	Selection of hospital antimicrobial prescribing quality indicators: a consensus among German antibiotic stewardship (ABS) networkers	Design: Review+ questionnaire Interest: Indicators for quality of AB prescribing	- possible stakeholders in team - frequency of meetings - mandate - drug use, resistance rates as data - formulary as intervention - updating formulary - restriction/approval as intervention - guidelines for empiric therapy, IV-PO, dosing, prophylaxis, - rounds as intervention - education as intervention - guidance or assisted decision analysis via IT
13	Trivedi, Rosenberg	2013	The state of antimicrobial stewardship programs in California	Design: Survey Interest: State of ASP	- implemented or planned ASP - time of start with ASP - possible stakeholders in team - FTE availability - funding - benchmarking as intervention - DDDs, DOTs, costs, acceptance of recommendations, improved susceptibility patterns as data - use of IT in ASP - electronic health record, digital prescription, electronic medication administration records as IT - formulary restriction as intervention - ID physician consult as intervention - audit as intervention

					- prior approval as intervention - auto stop orders as intervention - verbal approval as intervention - pre-authorization as intervention - education as intervention - guidelines as intervention - IV-PO switch as intervention - streamlining/de-escalation as intervention - order forms as intervention

**) DDDs: daily defined doses; DOT: days of therapy; FTE: full-time equivalent; ID: infectious diseases; IV-PO: intravenous-per os; IT: information technology.*

English translation of online questionnaire "Maturity assessment of antibiotic stewardship programs"

Introduction		
1	What is your profession?	Clinical pharmacist|clinical microbiologist|"infectioloog"
2	Are there initiatives for antibiotic stewardship in your hospital?	Yes|in dev|no|N/A
3	Since what year?	XXXX
Topic #1: **ASP initiatives**		
4	Pick an answer on the following statements: - There is management mandate for ASP - There is a budget available for ASP - This budget is sufficient - Tasks are formally documented for ASP - There are FTEs available for ASP - These FTEs are sufficient - ASP can contribute substantially to infection prevention in my hospital	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #2: **Antibiotic team**		
5	Does your hospital have an antibiotic team	Yes|in dev|no|N/A
6	How often does this team assemble?	Daily|weekly|monthly|semiyearly|yearly|N/A
7	Who are part of this antibiotic team? - Clinical microbiologist - "Infectioloog"/ID physician - Clinical pharmacist - Management representative - Internist - Nurse	In our team|Should be in a team|Should not be in a team|N/A

	- Antibiotic committee representative - Ward/supervising physician - (Prescribing) physician - Epidemiologist - Hygienist - IT specialist	
8	Are any disciplines missing in this list?	Open answer
9	A-teams play a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #3: **(Local) antibiotic guidelines**		
10	Your hospital has guidelines for: - Diagnosis of infections - Treatment of infections - Duration of treatment of infections - Antibiotic therapy - IV-PO switches - Streamlining/de-escalation of antibiotics - Antibiotic cycling - Peri-operative prophylaxis	Implemented|In development|Are needed|Are not needed|N/A
11	Antibiotic guidelines play a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #4: **Antibiotic formulary**		
12	Does your hospital have an antibiotic formulary?	Yes|in dev|no|N/A
13	Is this formulary based on local resistance patterns?	Yes|no|N/A
14	How often is checked if prescription reflects antibiotic formulary?	Always|often|occassionally|rarely|never|N/A
15	Antibiotic formulary plays a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #5: **Audit-and-feedback**		
16	Does your hospital perform audits?	Yes|in dev|no|N/A Other -> open answer to "Please elaborate how your hospital reviews antibiotic therapy"
17	Who is performing these audits?	Clinical pharmacist|clinical microbiologist|"infectioloog"|other…
18	Which forms do these audits or should these audits have?	Bedside consult|remote consult(email/phone)|retrospective feedback(not during therapy)|other…|N/A
19	The person doing the audit takes action when a prescription is not conform guidelines	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown Other -> open answer to "Please elaborate how the audit process is or should be"

20	Audits play a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #6: **Education**		
21	Are there educational activities in your hospital for ASP?	Yes|in dev|no|N/A
22	Which forms of education?	Workshops|lectures|posters|memos|alerts|other…
23	Current educational activities are sufficient to improve prescription behavior	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
24	Education plays a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #7: **Information systems**		
25	Are there IT/software systems dedicated to ASP available in your hospital?	Yes|in dev|no|N/A
26	Please provide the current status of these IT/software systems in your hospital - Electronic Health Record - Decision support tools - Tracking antibiotic use - Surveillance - Sharing laboratory results - Digital prescribing - Evaluation of prescriptions - Digital patient file/"status"	Implemented|In development|Needed|Not needed|N/A
27	IT play a crucial role in ASP implementations	Strongly agree|agree|indifferent|disagree|strongly disagree|N/A|unknown
Topic #8: **Benchmarking**		
28	Does your hospital update resistance figures every year?	Yes|No, but we should|No, not necessary|N/A
29	Does your hospital benchmark antibiotic usage periodically?	Yes|No, but we should|No, not necessary|N/A
30	How often?	Daily|weekly|monthly|semiyearly|yearly|N/A
31	Benchmarked on which level?	Ward|hospital|N/A|other…
32	This data is used for trend analyses	Yes|No, but we should|No, not necessary|N/A
33	This data is presented to prescribing physicians	Yes|No, but we should|No, not necessary|N/A
34	Please select in which measures this data is available.	DDDs|PDDs|DOT|acquisition quantities|distributed quanitities|antibiotic costs|other…
Topic #9: **Implementation of ASP**		
35	On which level is ASP is implemented in your hospital?	Entire hospital|most wards|few wards|one ward|nowhere|N/A|unknown In case of 1 or more wards open anwer to "Please specify which wards"
36	ASP should be implemented on which level?	Entire hospital|most wards|few wards|one ward|nowhere|N/A|unknown
37	The implementation of an ASP should be detailed on which level?	Hospital wide|per ward|Combination of both|N/A
38	Does your hospital collaborate with other hospitals in terms of ASP?	Yes|no|N/A
39	Please rank the following ASP interventions in order of importance for your hospital	[RANKING 1-13]

	- Antibiotic team - Academic detailing (evidence-based education) - Pre-authorization of antibiotics - Audit-feedback - Restriction on (reserve) antibiotics - (Automatic) stop-order - Antibiotic cycling - (Automatic) substitution - Antibiotic formulary - Education - Guidelines - Decision support tools - Benchmarking	
40	Please provide the current status of these ASP interventions in your hospital - Antibiotic team - Academic detailing (evidence-based education) - Pre-authorization of antibiotics - Audit-feedback - Restriction on (reserve) antibiotics - (Automatic) stop-order - Antibiotic cycling - (Automatic) substitution - Antibiotic formulary - Education - Guidelines - Decision support tools - Benchmarking	Implemented|In development|Needed|Not needed|N/A
41	Are interventions missing in the list we provided in the above two questions?	Open answer

Topic #10: **Important outcomes to assess ASP**		
42	Please rank the following ASP outcomes in order of importance for your hospital - Antibiotic use - Length-of-stay - Prevalence rates - Cure/eradication rates - Days of therapy - Mortality - Morbidity - Resistance rates - Compliance rates - Costs - Re-admissions - Number of errors - Time spent per patient	[RANKING 1-13]
43	Are outcomes missing in the list we provided in the above question?	Open answer
Questions for questionnaire administration		
44	What is the name of your hospital	Open answer
45	Do you want feedback of the results of this questionnaire?	Yes|no
46	Can we contact you for further research?	Yes|no Yes->Open answer to “Please provide us your email address”
47	Any questions, advice or other remarks you want to share with us?	Open answer

Chapter 7:

Developing technology to support the implementation of antibiotic stewardship programs

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Submitted

“A person is wise if he listens to millions of advice and doesn't implement any of it.” - Michael Bassey Johnson

Abstract

Background: Antibiotic (or also antimicrobial) stewardship programs are currently being implemented in hospitals based on expert advice and guidelines. Despite the presence of these expert guidelines, antibiotic stewardship teams in hospitals still have to make decisions to adapt the implementation of stewardship interventions in their local context, considering e.g. available personnel, resources, etc. Especially non-academic, general hospitals can use extra guidance in implementing stewardship interventions as they lack time and resources to fully explore what is best for their local context.

Methods: We conducted interviews with antibiotic teams at participating hospitals to discuss the progress and plans of their antibiotic stewardship programs and implementing its stewardship interventions.

Results: The teams shared the progress and implementation issues of their implementation of antibiotic stewardship based on expert guidelines. The differences in progress and interesting issues were discussed. All hospitals had antibiotic stewardship teams implemented and were busy implementing intravenous-to-oral switches and a reserve list. The teams were planning their audits, however plans for how and where were quite different. Other important interventions such as education and benchmarking will take more time and possible more guidance to fully take off.

Conclusion: Based on our previously published antibiotic stewardship maturity assessment combined with the implementation issues from the current interviews and the concept of maturity modeling, we design a technology that can support antibiotic teams more practically in implementing antibiotic stewardship. This technology can assess the current state of implementation, show possible areas for improvements, and present a more tailored and practical advice based on expert guidelines and other team experiences.

Keywords

Implementation; Antibiotic stewardship programs; Guidelines; Maturity; Assessment; Tool

Background

Antibiotic stewardship programs (ASPs) are seen as one of the key pillars in infection prevention and control to curb antimicrobial resistance and provide optimal patient care [1]. ASPs are a programmatic, multi-interventional approach to ensure proper use of antimicrobials with the best patient outcomes, less risk of adverse effects, optimal cost-effectiveness and to reduce or stabilize levels of resistance [2]. Put short, in practice an antibiotic stewardship team (A-team) is made responsible for evaluating antimicrobial use and support health care professionals to optimize their antimicrobials prescriptions. Expert societies, both internationally as nationally, advise hospitals to implement ASPs [3, 4]. Despite the presence of guidelines, teams in these hospitals have to figure out themselves how to implement the necessary interventions of ASPs considering their local conditions. This may be a complex and time-consuming task, especially for general hospitals, thus we suggest that supporting these teams may be helpful to advance the implementation of ASP.

Implementations of antibiotic stewardship

Expert guidelines advise and describe possible coordinated interventions designed to protect antimicrobials from overuse and misuse [5-8]. In the Netherlands, most hospitals base their ASP plans on a provisional guideline published by the SWAB (Dutch Working Party on Antibiotic Policy) that is paired with workshops to detail the plans in more concrete steps with the participating hospitals [4, 6, 9]. It is acknowledged that there is no consistent approach in local implementations of ASP in hospitals [10]. This inconsistency in local implementations can be explained by the different embedding of ASPs in existing infection control measures, existing routines, available personnel, available (IT) systems, available budget, etc. [10, 11]. Based on an earlier maturity assessment with hospitals affiliated with the EurSafety project in late 2013, we concluded academic hospitals were experimenting with quite different (in comparison) pilot ASPs, whereas non-academic, general hospitals were just starting their ASP initiatives [12]. The assessment also showed inconsistencies in the opinions on the importance and characteristics of stewardship interventions for their ASPs.

These different local implementations may indicate that hospitals can benefit from additional support - besides expert guidelines - to implement an ASP that satisfactory meets the local conditions. While each hospital needs to tailor its ASP to its unique staffing, resources, culture, and existing practices and relationships, there are common lessons to guide implementation across hospitals [11]. Patel et al concluded that little guidance is offered on the practical aspects of implementing ASPs and that general hospitals in the United States need to overcome implementation issues by accounting for unique characteristics of their institutions [13]. There is a substantial body of evidence for interventions fit for ASP that reduce excessive antimicrobial prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions that increase effective prescribing can improve clinical outcomes [14-17]. However thus far, many stewardship interventions are implemented and evaluated towards one type of infection or at one ward, making it unclear whether successful interventions are equally successful in a different setting, such as other wards or other hospitals [10, 17].

Supporting the implementation of antibiotic stewardship

To support the implementation of ASPs, we propose the use of maturity modeling to gradually implement an ASP in steps. Maturity models are instruments to model or evaluate improvement of organizations or processes [18]. Expert guidelines usually describe comprehensive, 'ideal' programs with a plethora of reciprocal dependent interventions that can be quite overwhelming from an implementation perspective. Using maturity modeling for implementing ASP helps to introduce stewardship interventions in manageable steps to gradually expand and improve an ASP to meet its ultimate goals. For example, important interventions that provide the basis for ASP, such as an A-team or an antibiotic formulary, are the first key stewardship interventions to implement. Once these interventions are implemented satisfactory and thus matured, then next interventions such as an audit can be implemented to reach a higher level of maturity of the ASP. This way, hospitals can start with 'low-hanging fruits' and continue from there towards a comprehensive ASP.

Aim

The aim in this study was to identify implementation issues and possible deviations from expert guidelines that A-teams face when implementing ASP. For this article, we interviewed A-teams about the progress with implementing ASP as a whole and its common stewardship interventions and the A-teams expressed several implementation issues. Combining our antibiotic stewardship maturity assessment with these implementation issues and the concept of maturity modeling, we designed a structure for technology can support A-teams more practically in implementing antibiotic stewardship. This support tool needs to be based on existing expert guidelines but bridge the gap between these guidelines and the implementation issues that influence how ASPs are implemented locally and in practice.

Methods

Study design

Due to the early stages and novel nature of ASP implementations in Dutch hospitals, we chose for an exploratory qualitative design using semi-structured interviews to openly discuss prepared topics concerning implementation of ASP and its interventions [19].

Definitions

For defining ASP and stewardship interventions in this study the definitions are based on the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines [5]. We also used these definitions to clarify the interventions during interviews when one of the participants asked for clarification. ASP is a program consisting of different interventions all to promote optimal antimicrobial treatment within a hospital setting. Key interventions consist mostly of an antibiotic stewardship team that provides protocols, guidelines and/or an antimicrobial formulary; gives education; and performs audits and feedback all to promote correct use of antimicrobials. Ultimately this should lead to lower antimicrobial resistance rates thereby improving patient safety. In Table 1 the definitions of the individual antibiotic stewardship interventions are given.

Participants

As this research followed up on an earlier survey [12], we contacted these infection control experts again to help us plan interviews with the A-team in their hospitals. We interviewed A-teams of two academic hospitals and five general hospitals. The representation differed per team but they minimally consisted of two persons. A-teams were visited at their hospitals in the period of February-May 2014 during one of their planned meetings.

Interviews

The interviews were semi-structured based on the importance of stewardship interventions as identified in the earlier maturity assessment [12] and ASP literature [2, 5] (see *Table 1*). 1½-hour interview sessions were planned in which we discussed the on-going activities and progress concerning the ASP implementation and subsequently the individual stewardship interventions with representatives of the A-team. An English translation of the prepared sheet of interview questions can be found in the *additional file* (at the end of the chapter). Every interview was recorded with a voice recorder for transcription and data analysis.

Table 1: List of antibiotic stewardship interventions used as topics in the interviews

Classification of stewardship interventions	**Interventions**	**Definitions**
Key stewardship interventions	Protocols / guidelines / clinical paths / formulary	Multidisciplinary developed evidence-based practice guidelines incorporating local microbiology and resistance patterns that improve antimicrobial utilization
	Team	A multidisciplinary antimicrobial stewardship team include an infectious diseases physician, clinical microbiologist and clinical pharmacist with infectious diseases training[1]
	Education	Education to influence prescribing behavior and can provide a foundation of knowledge that will enhance and increase the acceptance of stewardship strategies
	Audit	Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an infectious diseases physician or a clinical pharmacist with infectious diseases training
Supportive stewardship interventions	Decision support	Health care information technology that improve antimicrobial decisions through the incorporation of patient-specific data
	IV-PO switch	Parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient's condition allows it
	(Point)-prevalence / Surveillance / benchmarking	Computer-based surveillance can facilitate good stewardship by more efficient targeting of antimicrobial interventions, tracking of antimicrobial resistance patterns, and identification of nosocomial infections and adverse drug events
Remaining Stewardship Interventions[2]	Reserve antibiotics / restriction[3]	(Formulary) restriction and preauthorization to limit the use of selected antimicrobials
	Academic detailing	One-on-one education by a clinical specialist on a patient-specific basis
	Automatic stop-order	Order forms with automatic discontinuation

	Automatic substitution	Substituting one antimicrobial for another may transiently decrease selection pressure and reduce resistance to the chosen agent
	Antibiotic cycling	Substituting one antimicrobial for another may transiently decrease selection pressure and reduce resistance to the restricted agent

1) *The IDSA/SHEA guidelines do not specifically mention a clinical microbiologist, but we added it to the definition as they are an important stakeholder in ASP in other guidelines and in Dutch hospitals.*
2) *In our earlier maturity assessment, the infection control experts considered these not per se part of ASP but rather part of bigger infection control measures, or, unproven or not interesting.*
3) *In our interviews we noticed that a reserve list for antibiotics is however deemed interesting, yet more rigid restriction policies are not favored. For example, a pharmacist said: 'just don't offer these antibiotics to wards that don't need them, or slightly complicate the process of prescribing them so prescribers will think twice'.*

Data analysis

The interviews were transcribed verbatim into Excel. An overview table was made with summarized statements from each A-team combined and structured conform the structure and questions in the interview sheet. Authors MVL, JWD, JRL went through this overview table in two discussion sessions and discussed whether there were patterns or interesting aspects in the responses to each interview question. The conclusions from these two discussion sessions were noted down and are presented in the results section of this study.

Ethics

Ethical approval for our maturity assessment and interviews with A-teams was given after revision by an internal representative of the ethical board (reference: BCE14039) at the University of Twente who stated no further ethical review procedures were required. All participants consented and the interview data was anonymized in the presentation of results.

Results

Antibiotic stewardship programs

Academic hospitals were already experimenting with their own ASP pilots before the Dutch provisional guideline was published yet general hospitals began with ASP initiatives based on the guideline. An A-team member said: *'The Inspectorate requires us to have ASP so that was a motive to really start with it. There were already early initiatives in the hospital community so a general idea for a plan of action was already there'*. Due to this higher level pressure to start with ASP, all A-teams stated there was adequate mandate from the board and management. At general hospitals the progress relied strongly on the workshops organized by SWAB for A-teams. These workshops were the main source of inspiration for implementation at general hospitals. At the time of our interviews, most general hospitals were not as far in the implementation of stewardship interventions as academic hospitals and were planning to start with audits, conform the progress in the workshops. The (planned) implementation progress were discussed according to an agenda and usually documented in plans of actions.

The person responsible for coordinating ASP was in most cases a clinical microbiologist. The stewardship tasks were done on top of the regular daily practices of the team members. Some hospitals did have (small) compensation for stewardship duties or tools, e.g. one team stated*: 'our ASP team members have 2 hours a week for ASP and we have some resources for tools and secretarial support'*. In a later phase where structural stewardship interventions are in place, for example, a daily audit, the tasks will become more time consuming and thus would require extra FTEs. However, these exact tasks were at the time of the interviews still in a speculative state and not estimated or budgeted in current plans.

Key stewardship interventions

Protocols, guidelines and formulary

All participating hospitals had an antibiotic formulary. Antibiotic formularies were already quite commonly used in Dutch hospitals and also recently the SWAB released a national antibiotic formulary that many hospitals used or want to use as a basis for an antibiotic formulary used for stewardship interventions. All hospitals were updating their antibiotic formulary to prepare it for antibiotic stewardship. Other protocols to support antibiotic therapy were quite diverse and depends on what additional protocols were deemed important or what was deemed missing, undetailed or different in the (national) antibiotic formulary.

Antibiotic stewardship team

All participating hospitals had an active antibiotic stewardship team. The primary tasks of this A-team is to prepare, plan and implement an ASP and in a later stage also play an active role in the implemented program itself. Most hospitals formed this A-team based on the specifications in Dutch provisional guideline that minimally a clinical microbiologist, clinical pharmacist and infectious diseases physician should be part of the team. However, hospitals with a small bed-size noted that they have no infectious diseases physician (the Dutch equivalent of an infectious disease physician) and in some cased not even a full-time clinical microbiologist which means their roles in ASP cannot be implemented as described in the Dutch guideline or international academic literature. The compositions of these teams were also variable. Some hospitals had really large teams, for example, a general hospital had a team consisting of: a clinical pharmacist, two clinical microbiologists, a pediatrician, an intensivist, a hygienist and residents for contact with the wards, while other hospitals had a small team of a clinical microbiologist, clinical pharmacist and internist/infectious diseases physician, to meet the minimally required team.

All teams were initiated from the medical microbiology department, so in the Netherlands clinical microbiologists seem to take the first step towards ASP. The division of tasks are still very conceptual but it is clear that the central task of the team should be optimizing antimicrobial therapy. The reach of the team inside the hospital depends on the intervention, a team member said: *'An intervention like an IV-PO switch can be implemented in the entire hospital, but bed-side audits, for example, are not necessary at every ward'*. This choice is also influenced by the amount of available time and resources, so teams prefer to approach the wards that are jokily referred to as 'heavy antibiotic users' first.

Education

Education specifically to disseminate ASP to prescribers had not really started at the participating hospitals. The academic hospitals had several infection control related courses, but no specific ASP courses yet. When asked whether education was important, most A-teams agreed it is and that it is the task of the team to set it up. However, ideas about the modality of education (e.g. lectures, online courses or portfolios) also differed. A team member explained: *'Education can be adjusted towards medical specialty. It can be useful to start with a few specialties and work up from there. Certain specialists also have to deal more often with complex infections, so these specialists may require a more in-depth form of education, whereas other specialists can just work with some basic knowledge, e.g. effectively applying the formulary'*. Most A-teams agreed that periodical workshops or trainings for groups of specialisms would work best as education for raising awareness of ASP and basic knowledge of infections and antimicrobials.

Education is also important in the stewardship interventions themselves. Two A-teams said that a bed-side audit can also be a way to educate prescribers. An additional educational tactic is also to educate how to use (new) interventions. An A-team explained: *'Best would be that all new residents and new specialists hear that they should respect our guidelines and get training why they are important and where to find them'*.

Audit

At the time of the interviews, most A-teams were still in a speculative state what these audit should exactly comprise. In the Dutch guideline, there were no further directives for audits and hospitals were therefore looking at possibilities. When asked why the progress is slow in starting audits, the most commonly mentioned barrier was the lack of resources regarding man-hours, time, capacity, etc. A team member said: *'When manpower is critical, one has to think properly where you will invest your time. You should not overdo things beyond your goals'*. Another barrier is the challenge in the necessary data for audits. A team stated: *'Setting up the data gathering, for example a point prevalence according to a standard. How can you do that efficiently? Also, how can you use this to prove the effects of ASP?'*. There seemed to be consensus at what wards should be audited, as internal medicine, and in lesser degree, also surgery were mentioned as the important wards to start as there are relatively many antimicrobials used in those wards. ICUs are treated special and were visited on a frequent (often daily) basis by clinical microbiologists already prior to any ASP initiatives.

An interesting observation is that there seems to be two different approaches to these audits: 1) a prospective audit, these are the bed-side, clinical audits where per patient the therapy is evaluated, or, 2) retrospective audit, where antimicrobial use is monitored and the A-team intervenes on patterns of misuse. Most teams state that before starting with ASP that ad-hoc prospective audits are not uncommon as the clinical microbiologist gets a call or calls a physician when something is 'not standard'. As a team member said: *'in the past clinical microbiologists already did a lot of what an ASP describes we must do, it is just that they formalize it now, they place a label on it to call it antibiotic stewardship'*.

Supportive stewardship interventions

Decision support

Decision support can entail two things: supporting the A-team in their ASP tasks or supporting prescribers in selecting the right therapy and antimicrobials, or even a combination of both. In the previous maturity assessment, decision support was deemed important but there appeared to be little concrete ideas yet. Several teams would prefer if several sources of information (e.g. patient records, lab results, and formulary) would be integrated in one place. Or, for supporting prescribers, that tailored advice is offered based on clinical rules and protocols. However, in both cases, teams acknowledged that (lacking) technology is still a large barrier to implement such decision support.

IV-PO switch

An IV-PO switch (intravenous to oral) seems one of the first stewardship interventions most teams want to start with as it is seen as one of the 'low-hanging fruits'. In fact, some hospitals even had a switch already prior to ASP initiatives. A team member *said 'I (clinical pharmacist) am implementing clinical rules for certain medication and so we implemented the IV-PO switch as a clinical rule in our system that's also used by our pharmacy. We will test this for the coming weeks to see how it works'*. It is preferably implemented throughout the entire hospital via the pharmacy (systems). An IV-PO switch is important for prevention of line-associated complications, patient comfort, length of stay and costs. Despite its popularity to implement, it scored fairly low importance in the maturity assessment as its impact on resistance prevention is still ambiguous. If applied incorrectly, e.g. structurally low dosing, it can even drive resistance rather than preventing it.

(Point-)Prevalence/benchmarking

The hospitals were exploring the possibilities for a point-prevalence measurement necessary for ASP. Central in this measurement is to make antibiotic use transparent. The data can then be used for multiple purposes: 1) to figure out at what wards/patient groups ASP can be interesting, 2) filtering out the right patients relevant for patient-centered stewardship interventions, 3) analyzing and reporting data and effects internally (e.g. proving that ASP effective) and 4) benchmarking to make antibiotic use transparent externally (e.g. national reports on incidences or antimicrobial use). Most teams were still mulling over how to exactly organize the data collection and how to do an effective point-prevalence measurement for ASP. One A-team said: *'For our annual reports - to PREZIES, a national hospital infections surveillance program - we use an approach for collecting fairly similar data: an infection specialist visits a ward to collect the necessary data and is supported by a nurse. Maybe we can use something similar because the good thing about this is that you visit the wards, the people at the ward understand it, and it has a level of standardization'*. Also, depending on how detailed this data is, it can also be used as important trigger for stewardship interventions, e.g. as a way of surveillance or analyzing adherence to guidelines.

Remaining interventions

Reserve antibiotics / restriction, academic detailing, automatic stop-order, automatic substitution, antibiotic cycling

The remaining interventions for ASP, that scored a very low importance and low impact on ASP were only briefly discussed at the end of the interview. In short, the main conclusions are: Restriction of antimicrobials and subsequently restriction with (pre-)authorization were debatable stewardship interventions. Most hospitals do have a small list of reserve antibiotics where either the prescriber has to provide extra information why these antibiotics are prescribed or they need to call in advance whether the antibiotic can be prescribed in the particular patient case. Most teams agreed that this is as far as restriction should go. As a team member said: *'you can use restriction by imposing some conditions onto a small list of antibiotics, as long as that list is small it is manageable like this. In fact, we recently added a new antibiotic to this list and we immediately noticed some muttering'*. Academic detailing seemed uninteresting, as most teams agreed that the academic aspect is adequately covered by the formulary, guidelines and otherwise the advice from the team. Automatic stop-order and automatic substitution are prone to cause errors because of the automation and therefore are not preferable. Finally, all teams agreed antibiotic cycling has unproven effects and is not feasible from a practical stance.

Discussion

Evaluations of the effectiveness of antibiotic stewardship interventions are a topic of interest in recent years [14, 16, 17, 20]. However, these evaluations focus mainly on reviewing published research that describe and evaluate stewardship interventions. Expert guidelines also base their advices on the conclusions from these international reviews. While doing our systematic review for finding implementation details for ASP (see chapter 4), we noticed two important drawbacks with this review approach: 1) there is a strong bias towards academic hospitals, 2) even though there is an evident diversity in chosen ASP interventions there are no detailed rationales supplied, 3) there is a lack of details and hands-on information that describe the practical aspects of implementing ASP. So, in our attempt to extract possible implementation details for ASP from literature, we found very little practical considerations. Without practical advice, it still requires effort from A-teams in the hospitals to apply expert guidelines in their local context and make practical considerations. In this article we therefore focused from the other perspective, a bottom-up analysis, by discussing the progress of implementing ASP with these teams to hear from them where the mismatches are between these guidelines and their ideas of feasible interventions. These considerations can be input to improve expert guidelines to let them better reflect practical considerations.

Primary findings regarding the progress in ASP implementation

For Dutch hospitals, antibiotic stewardship is not per se all new. Many activities that are considered part of antibiotic stewardship were already performed at hospitals in an ad-hoc, non-programmatic way. The A-teams acknowledged the added value of ASP and saw it, as one of the interviewed clinical microbiologists said, as a *'formalization of earlier practiced clinical microbiology processes'*. Academic hospitals started slightly ahead of the national initiative of SWAB and already piloted prospective and retrospective audits. This is also why ASP in academic hospitals may slightly deviate from the SWAB guidelines. The experimentation with ASP is explainable as academic hospitals have more leeway in time, people, and interest and resources for research activities concerning ASP than general, non-academic hospitals. This is consistent with the prominence of academic hospitals in ASP literature [14, 16, 21]. General hospitals seemed more focused on 'low-hanging fruits', most likely inspired by the publication of Goff et al [22]. They prefer to start a renewed formulary and an IV-PO switch before starting with audits. A-teams explained in the interviews that their biggest interest lays in effective stewardship interventions that are implementable with minor efforts and that meet the requirements as expected of them by the Health Care Inspectorate.

While in academic hospitals there has been comprehensive pilots with antibiotic stewardship interventions, it is safe to assume that for general hospitals this may be more challenging [23]. A-teams of non-academic hospitals may have to rely stronger on expert guidelines due to limiting factors like lack of time or resources. These expert guidelines address key elements for antibiotic stewardship but do not address the many issues involved [24]. It is acknowledged that intervening antibiotic prescription requires social and behavioral aspects [25, 26]. Current stewardship programs that focus on recommendations, guidelines and policy as key influences on prescribing behavior also need to consider effective systems that influence prescribers [27]. Likewise, these social, behavioral factors, combined with different local contexts in hospitals suggest introducing ASP as a pure protocol-driven approach is not enough for an effective implementation. Healthcare professionals should be involved in the design of the interventions and the program [27-29]. Also, advising a 'one-size-fits-all'-implementation for ASP may not suffice as experts may have valid reasons to deviate from recommendations in expert guidelines [12]. In the Netherlands, guidelines and workshops are available to assist A-teams in their progress [9]. Even though workshops are helpful to discuss progress with other A-teams, all A-teams still need to (freely) implement ASP themselves in the local context.

A noteworthy aspect for these protocols is that there has to be more nuance in ASP protocols between what A-team tasks are and what tasks are part of higher level infection control or tasks of e.g. the antibiotic committee. Especially in terms of creating and updating protocols, guidelines and the antibiotic formulary there is a lot of overlapping goals and tasks between the A-team and the antibiotic committee. It seems that most A-teams mostly see their primary task as optimizing antimicrobial therapy and supporting the prescribing physicians when needed.

Relating ASP implementation with maturity models

With the concept of maturity models, we want to establish a sequence in the stewardship interventions (*Table 2*). ASP are comprehensive, multi-faceted programs and thus would benefit from a manageable, step-by-step introduction of its interventions [30, 31]. In the interviews it also became apparent that hospitals preferred to take care of the 'low hanging fruits' first. The idea of maturity models is that if one maturity level is operating satisfactory, one can proceed with the next. Positive experiences from starting with the 'easier' interventions may help to advocate for scaling up antibiotic stewardship in the hospital.

Table 2: Suggested maturity model for implementing ASP interventions based on interviews

Maturity level	Relevant interventions
Maturity level 0 (preparatory activities)	(no ASP interventions in this stage)
Maturity level 1 (initiating a basic ASP)	A-team, updated protocols and formulary
Maturity level 2 (“low hanging fruits”)	Reserve list, clinical rules for IV-PO switch
Maturity level 3 (auditing prescriptions)	Audit, surveillance (internal)/point-prevalence
Maturity level 4 (structural improvements)	Education, Decision support, surveillance (external)/benchmarking

Before starting with ASP, the microbiological infrastructure needs to be available and ready. Antibiotic stewardship is only one pillar of infection control and depends on available diagnostics and hygiene or infection prevention [32]. An antibiotic commission needs to exist and there has to be mandate from higher management, a plan of action and an inventory of current infection control guidelines.

As a first step towards a program, a multidisciplinary A-team must be formed [5]. This team is instrumental in 1) guiding the implementation of ASP and 2) performing tasks as part of the interventions in the program. The composition of the team was already problematic for certain hospitals. Many Dutch general hospitals struggle with the lack of a (full-time) infectious diseases physician or internist, in fact, small hospitals do not even have a full-time clinical microbiologist. So, how will this translate into the tasks? All documents that describe ‘ideal’ ASPs fixate on the trinity of a clinical microbiologist, clinical pharmacist and an infectious diseases physician. The necessary ASP tasks should be central for finding the right team members, not the other way around. The right stakeholders need to be involved in the planning and daily running of ASP so that it is properly embedded in daily processes instead of a mere expert stance on how it should be done. Maybe this is also a reason why introducing more encompassing interventions such as audits or education remains difficult.

The first intervention these A-teams want to implement is to update the available protocols, guidelines and regulations for antibiotic stewardship. Even though all hospitals had an antibiotic formulary, all teams were busy updating it so that it can play an important part in future stewardship interventions. When the guidelines are established, an important next step is the IV-PO switch. Most A-teams agreed that such a switch would be one of the easiest stewardship interventions to implement in the hospital as it can be embedded in current pharmacy processes. Also creating a list of reserve antibiotics seems worthwhile, to add extra actions for prescribing reserved antibiotics. In the Netherlands, full restrictive measures on antimicrobials would cause much commotion.

The next level of maturity in ASP is implementing audits. It is imperative to measure first where audits can be effective. Most A-teams agreed that only a few wards would require an audit. For example, an A-team member said: *'At urology the infections are usually quite standard and easy to cure by following protocols, so they would not really require an audit'*. Another team speculated*: 'Ideally an audit depends on multiple triggers, either 1) lab results, 2) analysis of antibiotic use and 3) upon request by the on-ward specialist/nurse who is part of the A-team'*. To assess where audits are effective, data must be logged to perform a historical cohort analysis to see antibiotic use stratified over wards or specialisms, or, incidences of infections. While collecting this data for internal use, obviously it can also be used for reporting benchmarks externally to e.g. national surveillance initiatives. Another important choice with these audits is whether they are prospective bed-side audits, or, retrospective audits that evaluate guideline adherence and antibiotic use at wards or specialisms. The latter does not intervene directly on a patient level. They are two completely different approaches with both different pros and cons that are beyond the scope of this paper to discuss. Recent expert guidelines seem to prefer the first, so visiting patients, however, A-teams do have this retrospective evaluation as a less resource-consuming alternative.

Judging the progress with educational activities, it seemed education was more seen as a side-process. This is also in line with ASP recommendations where it is seen as a supplementary activity [5]. Even though most A-teams find it a valuable intervention for ASP, it was one of the least thought-through interventions. Here is where the aforementioned social and behaviors aspects may become interesting. Also ASP requires a behavioral change and thus education can play an important role in creating awareness for and adherence to ASP. Decision support is deemed interesting by A-teams but a major obstacle is that it is difficult to do with the existing IT systems. Also the decision support system will be heavily dependent on the protocols and guidelines and the choice of audit. For example, if the intended audience is the actual prescriber, decision support in the form of some patient tailored advice based on dynamic guidelines would be interesting, but, if the team decides to do bed-side audits, it would be more beneficial to focus the decision support on collecting and organizing multiple sources of patient information so that the auditing A-team member has all relevant information easily available.

Antibiotic stewardship implementation tool

We are currently developing an antibiotic stewardship implementation application. This is an online web application part of our Infectionmanager (available at www.infectionmanager.com). The development of this application is based on our research using the CeHRes roadmap that guides the development of healthcare technology [33]. An important part of this roadmap deals with business modeling, which is an activity to establish the necessary implementation conditions for the healthcare technology [34]. In the case of ASP, we used business modeling to make an inventory of implementation conditions for the interventions of antibiotic stewardship. Design is another important aspect of developing healthcare technology and the delivery of content of infection control protocols via online tools has proven to be effective [35, 36]. The design and delivery of content of the online antibiotic stewardship implementation application is therefore based on researched tools of the Infectionmanager, and the Infectionmanager itself. In short, the idea behind this design is that protocols are easier to comprehend and easier to use for healthcare professionals when they are presented, not as a guideline, but as comprehensible pieces of information through e.g. card-sorting [35, 36].

The online application offers a combination of the maturity assessment based on the survey from an earlier article [12] and the ASP maturity model from this study. The maturity assessment contains questions regarding the common ASP implementations. Based on this maturity assessment the tool can output two things: 1) an overview of the maturity of the implementation of ASP. This can be a checklist or a visual presentation. And 2) it acts as a toolkit that gives recommendations for further implementation. We based the structure of these recommendations on the maturity model we made from the experienced implementation progress and issues as expressed in the interviews in this study. The content of these recommendations are combined with expert guidelines and practical advice. In Figure 1 we show an overview of the maturity model for implementing ASP. Each button will have submenus with further implementation information. Also, the maturity assessment allows us to make the advice dynamic. So implementation choices in one stewardship intervention may interact with possible implementation choices in another intervention in the ASP and tailor the advice.

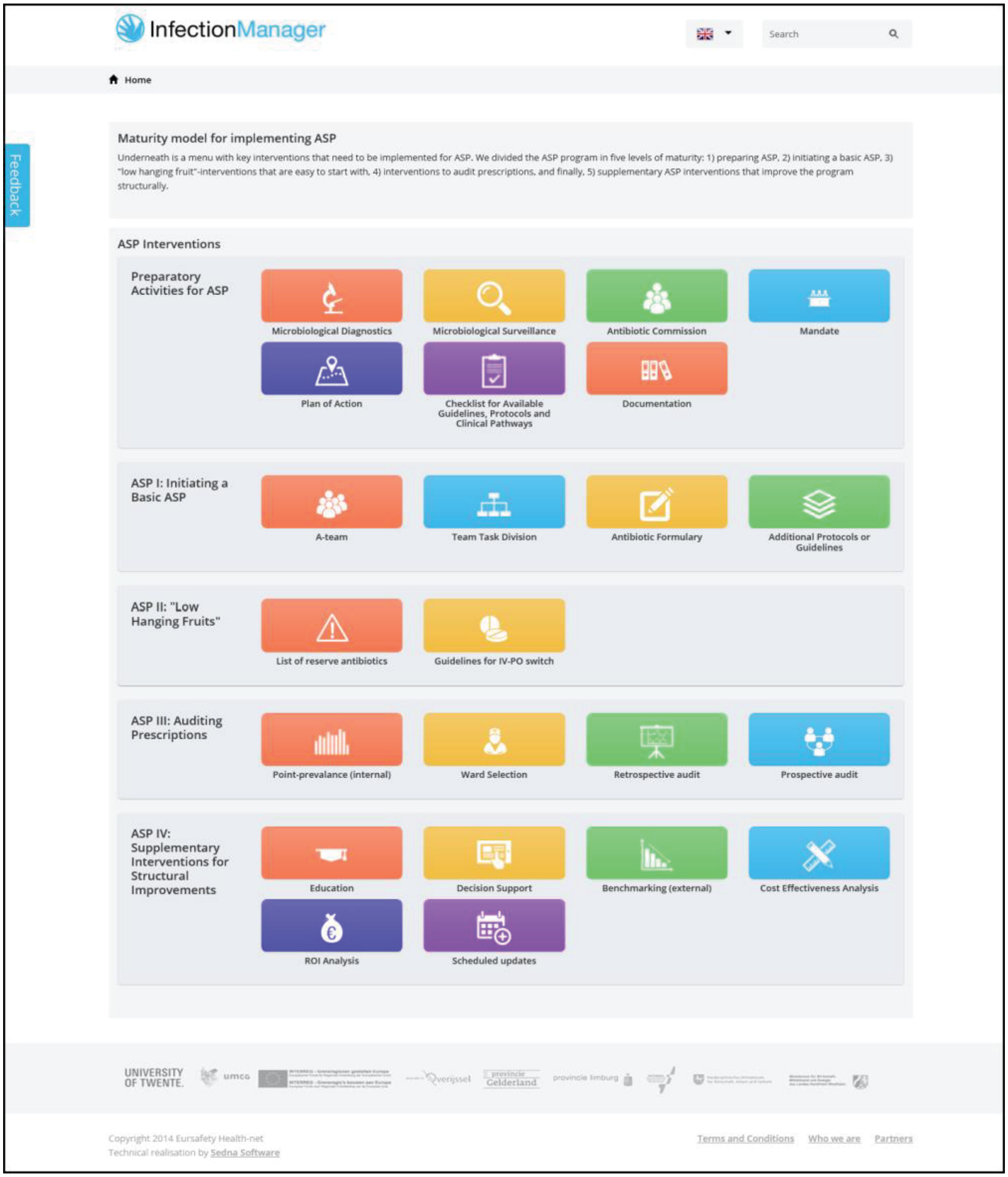

Figure 1: Preview of the antibiotic stewardship implementation support application

For example, in the assessment are a few questions regarding the A-team and their tasks. After answering those questions, the online application can output an overview of the maturity of the 'A-team' intervention, which can be a score (quite similar to e.g. the ASP assessment of the ABS group [37]) or a visual representation. On the aspects where the A-team can be improved, the online application can provide a mix of advice based on expert guidelines with practical tips. This advice is dynamic, so for example, when an A-team is asked for their desired composition of their team and do not have a dedicated infectious diseases

physician in their team, the information in the rest of the application –for this example- how to perform prospective audits can change automatically with a different role for a clinical microbiologist and no further mentions of an infectious diseases physician.
This online antibiotics stewardship implementation application is not a large manifest of protocols, but rather an interactive tool that presents the necessary information in manageable and relevant fragments to A-teams that are in the process of implementing ASP. That also makes it different from the few existing ASP guidelines or toolkits that exist [5-8, 38]. So it is not a static information tool, it is a maturity assessment tool that can evaluate the status quo of an ASP, yet that also recommends next steps to assist A-teams in implementing ASP.

Limitations

At the start of our research, the progress of A-teams became very dependent on the involvement of official agencies such as the SWAB who took a strong responsibility in supporting A-teams with implementing ASP. This however also made A-teams wait on instructions and less focused on their own intervention ideas. A-teams were in a very early stage of ASP during the interviews and thus most interventions were discussed as ideas for a 'would be' situation as they were not actively implemented at that point.

The number of interviewed teams was small as we focused on hospitals that participated in our earlier EurSafety Health-net research, therefore the findings may not reflect the entirety of the Netherlands. However, judging the discussion we had over the results, we think many other A-teams are progressing similarly.

Future research

The online application is currently in an early beta and we plan to release the assessment soon to the public. An important next step is to add information under the structure proposed in Figure 1. Our current focus is to use the insights from participating A-teams in the EurSafety Health-net project and base the information on guidelines and experiences they have obtained. Ideally, we expand this tool on a national or possibly even international scale but that requires help from organizations in infection control such as e.g. SWAB or ECDC for writing the guidelines and information and to provide adequate authority for wider recognition.

Conclusions

We interviewed teams responsible for the implementation of antibiotic stewardship programs in hospitals. Based on their experiences, ideas and expectations, combined with our earlier research and available guidelines, we assessed what is necessary from a practical stance to facilitate the implementation of ASP. First, the A-teams seem to struggle with the comprehensiveness and complexity of the interventions and in order to make the implementation more manageable, we proposed a maturity model for the implementation of ASP interventions. Second, we looked at differences in interventions and the rationale why they are different, to assess what implications these differences have on implementation. These findings and the maturity model are combined into an online antibiotic stewardship implementation tool. This tool is currently in development and will combine an online maturity assessment and tailored advice to facilitate A-teams with implementing ASP.

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Appendix for chapter 7

Interview structure for ASP implementation

Start by explaining the aim of the interview. This interview is a continuation on the questionnaire that was done earlier to assess which ASP interventions were considered interesting for ASP and this interview goes deeper in the implementation aspects of these interesting ASP interventions. The goal is to find out how these interventions are implemented locally, in practice, and better describe the implementation activities necessary to implement these interventions from a hospital perspective.

The program itself

1) How and when did the attention for ASP start?
2) How did this evolve into initiatives?
3) Is there mandate from management? How established? Concrete goals/plans? Formalized?
4) Is there one coordinator (or champion or instigator?)
5) Are FTEs made available? If yes, explain the construction, if no, why not?
6) How many FTEs are your team members using now?
7) Are tasks formalized? Documented? Who did that? What is it based on?
8) Did you use (other) documentation for your ASP plans?
9) Which guidelines?
10) How is the program currently coordinated? Meetings? How often?

ASP: Key intervention #1 – Guidelines, formulary, protocols

In the earlier maturity assessment where we focused on the interventions, it became apparent that establishing new guidelines, protocols or improving old ones were important in the start of ASP. And in a lesser degree also the antibiotic formulary. The antibiotic formulary scored a bit lower because all hospitals (most in .nl) had one and thus was not considered an ASP intervention per se.

1) Which existing guidelines/protocols in your hospitals are important for ASP? (e.g. help with asking for guidelines/protocols necessary for diagnosis, treatment plans of infections, prophylaxis)
2) How are they integrated in ASP? What was necessary to integrate them?
3) Also new guidelines/protocols necessary? Which?
4) Were guidelines/protocols updated? How often? Who?
5) Is adherence measured?
6) What can be improved to the current situation?

ASP: Key intervention #2 – Team

In the earlier maturity assessment, it became clear that teams were being formed. It was at that time also recommended by the SWAB documentation to do so. Because we are talking with each other now, a team has been established in the meantime too, so let us discuss the implementation details.

1) Is the ‘A-team’ (SWAB nomenclature) conform the SWAB guidelines? (to discuss members) If not, what is different?

2) How was the team started? Any obstacles in that process?

3) What are the tasks of the team? (more global) And tasks team members? (specific tasks)

4) How does this A-team have contact with the wards?

5) Is the team also responsible for performing ASP interventions? (e.g. maintaining protocols, doing audits, doing education)

6) What can be improved to the current situation with the team?

ASP: Key intervention #3 – Education

Education was seen as an important intervention to start with too. Although in the earlier maturity assessment hospitals were not really doing much educational activities yet. But respondents stated that education is needed for awareness why ASP is necessary and to explain the ASP interventions.

1) What should the message of education be?

2) Subsequently what should the goal of the education be? Create awareness? Change attitude or behavior? Improve knowledge?

3) Who should be educated? (specialists who deal with infections? Anyone who prescribes? Even wider focus (e.g. nurses etc too)?)

4) How (workshops, etc)? Frequency?

5) Are there resources available for education?

6) Is there perhaps a role for eHealth in education?

7) As educational activities hardly started, what were the barriers? What makes this process go less smooth? What is necessary to have, let say, an educational program off the ground in a few weeks?

ASP: Key intervention #4 – Audit

Audits were the most preferred form of influencing antibiotic prescription, as opposed to e.g. restriction or approval strategies. This is conform the global tendency of ASP implementations that audits get a central role in ASPs. However, these audits are all very different in the literature! Most hospitals were not actively doing an audit at the time of our earlier assessment.

1) First of all, are you actively doing an audit? Planning to? When?

2) Where?

3) How were these audits started?

4) Wat was necessary to start?

5) How is the process of this audit? Which activities? By who? Frequency?

6) What resources are required for the audit? (people, documentations, information, technology?)

7) Is the audit documented? Formalized?

8) Are effects of the audit measured?

9) As not many hospitals have an active audit, why is it so hard to start with audits?

Next interventions are supportive interventions; we will discuss them less thoroughly for time sake

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ASP: Supportive intervention #1 – Decision support

Decision support scored high in our earlier assessment, though there weren't decision support interventions really implemented. Hence we would like to discuss these ideas.

1) How do you see decision support fit for ASP?

2) In which processes (e.g. in the key interventions earlier) can DS be relevant?

3) What kind of DS? (supporting info, tailored advice (e.g. based on patient parameters) automated decisions, or options/recommendations)

4) Role of eHealth / technology?

5) Not many DS yet, what are the barriers?

ASP: Supportive intervention #2 – IV-PO Switch

According to our assessment, the respondents said that IV-PO switch was an important guideline for ASP. [Note: most interviewees already discussed IV-PO switch as an supportive intervention when discussing the guidelines/protocols, so these questions were skipped]

1) Can IV-PO switch be of use in ASP?

2) What is the process? Or how?

ASP: Supportive intervention #3 – Prevalence and Benchmarking

Prevalence and benchmarking should be important to assess where AB use is high or where a high number of infections / complications or what not appear, so where ASP can be real use. Yet, in our earlier assessment it was not deemed a key intervention for ASP itself*.

*) It was seen as part of infection control, not per se ASP

1) Is benchmarking important for ASP?

2) Is (point)-prevalence important for ASP?

3) What is the process? Or how?

Finally, the last interventions we will discuss, are interventions that are not deemed a central part of ASP, or, even not interesting. Instead of discussing them in detail, we ask the team for their thoughts in a few sentences for each intervention:

Reserve antibiotics, Restriction, Academic detailing, Automatic stop-order, Automatic substitution, Antibiotic cycling.

Chapter 8:
General Discussion

General Discussion

This thesis started by introducing business modeling as part of a holistic development approach for eHealth (chapter 2). To develop successful eHealth technology, one has to design a fitting eHealth technology, but, one also has to design a fitting implementation for the technology. Business modeling provides a method to step-by-step involve stakeholders in the implementation (chapter 3). Business modeling is value-driven, which means that it is important to discuss what value these stakeholders expect from the technology. All these values can be combined into a business model to use as blueprint for the implementation of eHealth. The business modeling concept, and its research methods were added to the Center for eHealth research (CeHRes) roadmap. This roadmap was applied in several eHealth research projects in the last years.

Following the introduction of business modeling, the chapters in this thesis elaborate antibiotic stewardship further as the central research case. In a literature study of publications on existing antibiotic stewardship programs (ASP), common characteristics and outcomes of such programs were found (chapter 4). This literature study was used as our first insights in the implementation aspects of ASP and was a basis for our research into implementing ASP. First, the prescribing process of antibiotics -which is the central process that ASP influences- was analyzed. Using business modeling in a focus group at a pilot hospital, we discussed with stakeholders in what ways eHealth could be helpful in the prescription process (chapter 5). The outcome of this analysis resulted in process bottlenecks, possible improvements and also several ideas for eHealth applications that could be offered in different stages of the process to different stakeholders. In the last two chapters, the implementation of antibiotic stewardship was analyzed in a wider perspective. Coincidentally, due to a new guideline, all Dutch hospitals were inclined to start with ASPs. We contacted antibiotic stewardship teams (A-teams) for an implementation maturity assessment to assess the state the ASP implementations were in and what the plans in the direct future were (chapter 6). Our assessment indicated that these plans had differences and consequentially indicated that local conditions influence the implementation of top-down guidelines. Further analysis was planned by interviewing these A-teams in a more bottom-up business modeling approach (chapter 7). During these interviews, the state and plans of ASP implementations were discussed to conclude a maturity model that divides the implementation of ASP in smaller, manageable steps. These interviews were also used to describe some of the differences in the plans, as these differences suggest there has to be a certain customization and dynamic in guidelines to adjust them to local conditions.

Lastly, we are currently working on an eHealth technology that contains implementation advice synthesized from the above research. In short, it will use the maturity model to structure the implementation in steps. It will also use our business modeling findings and practical considerations from the interviews as input to create dynamics in the advice. This eHealth technology, an online antibiotic stewardship implementation application, can support (future) antibiotic stewardship teams to assess and to implement antibiotic stewardship programs.

This general discussion contains answers to the research questions in the general introduction. After that, strengths and limitations are discussed and implications for future research are given. Finally, this chapter ends with an overall conclusion.

The added value of using business modeling in implementation research

Chapters 2 and 3 of this thesis deal with why and how business modeling should be used in eHealth development [1, 2]. As the 'how'-part is delineated step-by-step in a small framework in the discussion of chapter 3, in this general discussion I would like to focus on the 'why'-part, and specifically, focus on emphasizing the added value of using business modeling in implementation research for eHealth. Developing eHealth requires new models that encourage the use of implementation research and business innovation research, to improve the implementation aspects of developing a successful eHealth technology [1, 3, 4]. This broader research view is reflected in the evolution of the definition of eHealth over recent years. Current definitions encompass a much broader, holistic view towards eHealth (and eHealth development) and combine multidisciplinary facets such as social-psychological, business and information technology elements [5-8]. In the introduction of this thesis was said that implementation is a rather abstract term. So what is meant with it? With business modeling, we can approach the development of eHealth holistically, by looking at the necessary social, economic and organizational infrastructures around an eHealth technology that are necessary for it to become successful [1-3]. Stakeholders are asked what they deem important or valuable to the to-be-developed eHealth technology and necessary infrastructure. This value-driven dialogue, as well as co-creation (as stakeholders are involved in the process), is the basis for our holistic development. Too often eHealth researchers focus too much on the technology and immediately plan to imitate successful technology, rather than first looking at implementation possibilities. For example, is that technology really worthwhile to develop? Of course, when one adds business modeling as extra research to the development of an eHealth project, it will cost time, money and other resources. However, it can repay itself. A few important reasons are:

- An acknowledged issue with innovation via eHealth is that marketing is often missing [9]. In other words, researchers spent quite some time and money on designing and developing an eHealth technology, but when this technology goes live, there is no course of action how to bring it to its intended audience. This subsequently leads to a moderate, if not low, uptake of the developed technology. The impact of eHealth technologies is often still considered low and debatable [10]. A benefit of business modeling is that it has this marketing element intrinsic inside the co-creation process [1]. Talking with stakeholders about their expectations will work two ways: 1) you will discover what they want, and, 2) they will also learn what they can expect from the developed eHealth technology [1, 2]. For example, during the focus group as described in chapter 5, microbiologists and physicians realized how process bottlenecks affected the daily practices of each other, leading to more awareness of the problems and eagerness to find a solution [11]. This makes business modeling different to methodologies such as user-centered design to involve users in the (technical) design process [12]. In those methodologies the focus is (mostly) on technology itself. With business modeling the design focus is more targeted towards the chances of success for technology. Business modeling helps to discuss eHealth technology from a perspective what the problems are, how these problems can be solved, how the processes should be, how to fit the solution in daily practices, and what the added value of the technology should be [1, 2]. By discussing this perspective with stakeholders, they can understand what the added value of the technology means for them.

- Another way business modeling can repay itself is that by starting to discuss the implementation at an early stage in the development, the different interests among the stakeholders can be assessed at an early stage as well [1]. These interests shall be determinants to a) decide whether to develop an eHealth technology in the first place, b) determine what the added value should be (and with holistic development this is intertwined with design so it also determines what the technology should be able to do), c) determine what the required social, economic and organizational infrastructures should be to embed the technology in daily practices. For example, in the literature study in chapter 4, we found very few interventions that we could classify as eHealth [13]. This made us wonder whether there is an actual role for eHealth in antibiotic stewardship. With the focus group described in chapter 5, however, we focused on the antibiotic prescribing process and problems related to antibiotic stewardship, and we could ideate with the important stakeholders several eHealth technologies that are worthwhile to further research [11, 14, 15]. By discussing the implementation very early on in the development, it becomes much clearer what the technology should accomplish. In other words, what its added value should be and what the necessary requirements are for the technology and its implementation. This way, a 'Field of Dreams'-scenario, in which an expensive eHealth technology was developed that no one cares about, can be avoided. For example, this is what happened with two large national eHealth projects in England or Canada that both wasted billions due to lack of uptake by patients and professionals [16, 17].

- The plans for sustainability and upscaling of eHealth projects are often not well conceived [9, 10, 18]. Perhaps the necessity or direct need for eHealth is still not strong enough and that is why the eHealth technology is not disruptive but rather seen as a shadow innovation. For example, when an eHealth technology starts to get used, it creates a temporary shadow system with processes aside the normal daily practices. When stakeholders start to notice enough that the new processes are much more pleasant than the normal daily practices, only then the eHealth technology slowly replaces the existing processes. At this stage, possibilities for sustainability arise, or, possibilities to disseminate the eHealth technology elsewhere. In our experience it seems that this process usually goes very slow. On top of that, in many eHealth projects, sustainability or upscaling have not been in proper consideration during the development either. This hinders proving the added value of eHealth. As long as it is not implemented optimally, it will be very difficult to demonstrate how it can be beneficial. Business modeling can help to avoid these issues [1].

In this thesis, business modeling was used to analyze and prepare an implementation for antibiotic stewardship. We looked at existing implementations in literature and in practice (chapter 4), which is necessary for the contextual inquiry in the CeHRes roadmap [3, 11, 13]. In later chapters we involved antibiotic stewardship stakeholders in the research, to co-create a possible implementation for antibiotic stewardship together [19, 20].

Current practices of antibiotic stewardship

While looking at current antibiotic stewardship practices in the literature study in chapter 4, we noticed that there is a publication bias towards academic hospitals [13]. That is no surprise, first, as academic hospitals generally have more academic literature output than general hospitals and second, as academic hospitals have the opportunities -and research funding, often a neglected argument, but not a factor to be underestimated- to try and research antibiotic stewardship. Most hospitals however are not academic hospitals and are required to implement antibiotic stewardship too. The antibiotic stewardship teams (called A-teams in Dutch guidelines [21, 22]) in general hospitals face different practical difficulties to implement antibiotic stewardship, mostly through lack of resources and personnel [23]. For example, in our assessment and later interviews with the A-teams (chapters 6 and 7) it became clear that academic hospitals have infectious disease physicians, yet, most general hospitals do not [19, 20].

There is an interplay between a top-down focus and a bottom-up focus when analyzing the implementations of ASP. In the literature study in chapter 4, it became apparent that most implemented ASPs are based on expert guidelines [13]. Particularly the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines were prominent (also at non-US based hospitals) [24]. At the same time these top-down guidelines are not sufficient for local implementation. These guidelines describe general interventions, yet, detailing the interventions and actually implementing them, requires A-teams to make decisions and actions to implement an ASP as they see fit for their hospital. We therefore used business modeling to also approach the implementation of ASP with a bottom-up perspective. One cannot ignore the top-down guidelines, obviously, as they can contain directives plus they contain eminence or evidence-based advice. Yet, our bottom-up analyses, particularly the interviews in chapter 7, gave insights of the local characteristics, or differences, that occur [20]. This was also the basis for our idea to present an online antibiotic stewardship implementation application to support A-teams.

Based on conclusions from chapters 5, 6 and 7 we can summarize the progress in implementing ASP in the Netherlands [11, 19, 20]. The SWAB (Dutch Working Party on Antibiotic Policy) released a directive document that encouraged Dutch hospitals to start with antibiotic stewardship in 2014 [21]. Using that guideline as directive, by stating a deadline and making it a quality standard evaluated by the Health Inspectorate as per 2014, it encouraged the implementation of A-teams as a mandatory, first step towards an antibiotic stewardship program. However, we noticed in the interviews (chapter 7) that the implementation of further ASP interventions, so after introducing A-teams, in hospitals became slightly stagnant [20]. It is probably a combination of multiple factors: limited time and resources, limited direct urgency for ASP and limited support that causes the stagnating progress.

An extra issue that antibiotic stewardship faces, which was mentioned several times by A-teams in the interviews in chapter 7 [20], is that experts often acknowledge that the Netherlands is doing quite well regarding antibiotic use in our healthcare system. All Dutch hospitals already have their own microbiology lab or have connections with one and all hospitals have an active search-and-destroy policy [25, 26]. Firstly, Dutch patients are rigorously screened for infections such as MRSA to avoid complications and outbreaks. Secondly, clinical microbiologists already frequently communicate about therapy with physicians the laboratory results show it is necessary. A microbiologist said during the interviews in chapter 7, that basically they are already doing antibiotic stewardship for a large part in hospitals, now it just gets the "antibiotic stewardship"-label [20]. It is mostly a step of formalization of ad-hoc processes that are already often done. We cannot influence the urgency for antibiotic stewardship, of course, but we believe that the support towards (general) hospitals is scarce is not helping the progress either.

In sum, antibiotic stewardship programs are currently implemented in Dutch hospitals. However, very few practical literature is available to support the implementation of antibiotic stewardship [22, 23]. A-teams are made problem owner for everything that is antibiotic stewardship, yet A-teams have to find out many things by themselves and it is worth the effort to support them more to advance the implementation of antibiotic stewardship in the Netherlands.

Recommendations for implementing antibiotic stewardship

In chapter 5, 6 and 7 we propose that official expert advices or guidelines can be improved by better reflecting practical considerations [13, 19, 20]. Especially general hospitals can benefit from supporting materials based on e.g. best practices, example documentation, example interventions, etc. A-teams can use this material to choose what fits best within their hospital. In current guidelines, antibiotic stewardship and its interventions are described on a high-level, generic level. The focus in most guidelines is more on assuring that these interventions are evidence-based and proven to be effective in other studies, rather than providing helpful and practical instructions how these interventions can be implemented. As mentioned in the above paragraphs, A-teams still have to figure out all the details how to do that for themselves. ASPs are already active or piloted in Dutch academic hospitals [27-29], and pilots are also evaluated in the Netherlands [30, 31], so much can be learned regarding what works and what does not for Dutch hospitals. However, that information is hardly publically available.

As there is limited information for the practical part of implementing antibiotic stewardship, we got the idea to present the results from our implementation research as an online application to support A-teams with implementing antibiotic stewardship programs. In our maturity assessment we noticed two important issues that the online application can address:

- First, ASPs are comprehensive programs that consist of a collection of interdependent interventions [24, 32-34]. But how can one implement such a program in a manageable way? In chapter 6, we introduced the concept of maturity models to make the implementation of ASP more manageable. The idea behind a maturity model is that an intervention (ASP in our case) is introduced in phases to gradually improve it [35]. Based on the maturity assessment and interviews, we divided the implementation of ASP in five levels of maturity as described in chapter 7 [20]. This allows A-teams to first focus on the necessary preconditions, then setting up a basic ASP and eventually maintaining a complete, comprehensive ASP as described in expert guidelines such as the IDSA/SHEA guidelines [24].

- The second issue that the online application can solve is how one transforms high-level, generic level guidelines into customizable and practical advice. This requires introducing dynamics to the advice. In earlier research at our eHealth research group, presenting hygiene protocols in an eHealth technology was proven to be effective [15, 36]. It makes it easier for healthcare professionals to find information and it presents the information also more comprehensible. A good example of why dynamics are required is the example that is used more often in this thesis, whether or not there is an infectious diseases physician available. If not, this changes a lot in the tasks and responsibilities in the A-team.

We actually already prepared the method to get the dynamics in the online application with the implementation maturity assessment that we used in chapter 6 [19]. We used that assessment to measure the status of implementations of ASPs using an online survey with members of A-teams, but it can also be used to see where A-teams plan to deviate from the 'ideal program' as defined in official guidelines. The online application can use these deviations as 'implementation parameters' to adjust implementation advice from official guidelines and academic literature accordingly [13]. We are also validating the implementation maturity assessment as it is currently also used outside the Netherlands. For example, it is currently used to measure ASPs in Nepalese hospitals by the National Center for Global Health and Medicine in Japan. Because cross-border infection control was an important pillar in the EurSafety Health-net project, we also plan ourselves to use the implementation maturity assessment to measure the maturity of ASP in Germany in the near future.

As a part of our infectionmanager.com that contains online applications to support cross-border infection control we are developing an online application to support A-teams. This application helps A-teams to assess the maturity of their implementation of antibiotic stewardship, using the maturity assessment from chapter 6. The application will show practical advice to A-teams based on current expert guidelines, practical examples and experiences and adjustments that fit the local conditions of the A-teams.

Strengths and limitations

ASP is still a new phenomenon. Especially in the Netherlands, most hospitals only started with ASP at the beginning of 2014. This means they are not an omnipresent or well-established subject to research yet. This leads to our belief that many experts have great ideas how an ASP should be like, but, they are not thoroughly evolved yet. There is international literature and many effect studies of stewardship interventions in e.g. the United States, but for the Dutch situation there remains a level of speculation and possible some pilots of ASPs before pilots can be evaluated, compared and a dominant design for such a program can form. This also meant there was a limited pool of hospitals to research, especially in the beginning of the studies in this thesis as only few hospitals were interested in ASP. Later in the research attention for ASP arose because of the guideline of the SWAB [21] and via the EurSafety Health-net network we could involve more hospitals in the research.

The literature review in chapter 4 was important in the line of the research in this thesis, as it helped our understanding of ASPs for further research, however implementation rationale was scarcely present in the articles we reviewed and that hindered our initial goal to obtain concrete pointers to facilitate the implementation of ASP. The studies based their implementations of ASP on available expert guidelines, yet, rationale how and why individual interventions of ASP were implemented was scarce. In hindsight, an interesting scope for a future systematic review would be analyzing the differences (instead of the commonalities as we did) of implemented ASPs and speculate how and why they are different.

The studies in this thesis are one of the first studies that assess the implementation conditions for ASP from a behavioral and organizational perspective, rather than the more usual clinical view. We combined research instruments from our eHealth research and implementation sciences with the casus of antibiotic stewardship. We believe – as well as experts in infection control and clinical microbiology [37] - that a behavioral view on influencing antibiotic prescribing (and subsequently antibiotic stewardship) is a next step to advance its implementation in hospitals. Combining researchers from the medical field with the social sciences field, and perhaps software engineering too, could result in interdisciplinary research that advances the interventions and implementation of ASP.

The studies presented in chapters 2 and 3 were formative for the business modeling elements in our CeHRes roadmap. The idea of combining human-centered design and business modeling (and later participatory design) came from the start of the research in this thesis. We looked at design processes, business modeling tools, evaluation methods and principles for eHealth and participatory design to present a holistic approach for developing eHealth [3]. The antibiotic stewardship case in this thesis was one of the first cases for which we used the CeHRes roadmap. Other researchers and students applied the roadmap (and subsequently also business modeling) in other research cases to assess stakeholders, value needs from stakeholders and eventually used that as a basis for further design research and implementation. It is difficult to test the direct contribution of business modeling to the development of eHealth technology as you cannot really research the same project twice under different research conditions. Yet, based on our experiences and that of others, we attest that business modeling contributes to a better understanding of the implementation in eHealth research and helps developing eHealth technologies that fit the expectations of stakeholders.

Implications for future research and practice

In chapters 2 and 3 we pose that eHealth can benefit from more attention to implementation [1, 2]. The added value of business modeling was already discussed earlier in this discussion, yet, for the future of eHealth research more interdisciplinary cooperation should be encouraged [38]. There is much more closely related research that could be combined to learn from each other and improve methodologies to implement eHealth technologies. For example, Project Management Professional (PMP) is interesting and holds many similarities with our CeHRes roadmap approach [39, 40]. In the Project Management Body of Knowledge, the Project Management Institute presents a standard for project management, containing methodologies, courses and essential tools. Likewise, research in the field of requirements engineering [41], so a more software orientated focus, can help us improve how we can communicate the needs from healthcare professionals towards the technicians who have to develop it. Even when a technology-savvy eHealth researcher has to communicate with technicians, there may still be things that get 'lost in translation'.

There is no complete, straightforward framework for implementing eHealth thoroughly. Also our roadmap and ideas for business modeling can still be improved and expanded with more (practical, easy-to-use) research instruments to assess stakeholders and their value needs. We should learn from all available methodologies and tools out there that are also used in other research fields and industries.

What makes an implementation of technology in healthcare so complex is that it takes more than just designing a technology. One can discover what else is needed with our business modeling approach, but still, the eHealth technology has to influence many processes, may consist of multiple smaller interventions in one, and will influence many stakeholders. Besides the task of discovering all of these aspects, the implementation itself is also a step that needs to happen. There are development styles available to streamline this more efficiently. For example, agile software development can be used to introduce evolutionary design to develop the eHealth technology in steps [42]. By developing and implementing eHealth in phases, the entire development process becomes easier to evaluate. This allows researchers to evaluate during the development to see whether the technology meets the expectations.

We were facing a similar issue with antibiotic stewardship. It is not just one intervention; it is a program of many interventions that at some level are also interdependent. We solved that issue by introducing a maturity model and divide the implementation of ASP in multiple manageable steps. It can be worthwhile to research into how relatively large-scale, complex healthcare interventions with many stakeholders, can be implemented in smaller steps without losing the bigger picture.

During our research for this thesis, the uptake of ASPs in Dutch hospitals progressed slowly. At first there was hardly an interest in ASP. Earlier in the discussion, I speculated that the urgency for implementing antibiotic stewardship in Dutch hospitals is probably not as dire as in other countries. For example, in the United States or Southern Europe the antibiotic resistance rates are much more problematic than here [43]. Additionally, antibiotic stewardship is only one aspect in improving infection control and perhaps a wider focus towards 'integrated stewardship' is necessary [44]. This would be a more all-encompassing form of stewardship for infection control that embeds antimicrobial stewardship with infection prevention and diagnostics. Considering our EurSafety Health-net project looked at cross-border infection control, we think that abroad, this wider view will also become important. For example, the role of microbiology in German hospitals is different to the Dutch situation. Starting a good antibiotic stewardship there requires a start with a different infrastructure for medical microbiology where microbiologists are actively involved in the processes around antimicrobial therapy. This example demonstrates that ASP is much more than proactively correcting a wrong prescription, it should be part of a much larger infection control program. From an international stance, implementing ASP will face different systems, different social cultures and different practical implementations of interventions. However, for the future of ASP it will be important to learn from each other nationally and internationally and see what works and what does not.

The online application, that we are currently developing, is meant to bridge the gap between top-down guidelines from expert agencies and the bottom-up implementation by A-teams in a hospital. The main goal for this online application is to advance the implementation of ASP, as more practical support can help A-teams to implement antibiotic stewardship. Once the application is finished, we should use it in a cross-border setting and evaluate if and how it advances the uptake of ASP in general hospitals. If it is beneficial, perhaps it is worthwhile to consider this idea to present other programs for infection control in an interactive, comprehensible online application as well.

Conclusion

In conclusion of this thesis, we presented our views on how implementation of antibiotic stewardship programs can be supported using business modeling and eHealth. Antibiotic stewardship programs are starting to appear in Dutch hospitals, yet, hospitals may need extra practical help to help them progress. As the EurSafety Health-net project was a cross-border project, there is also potential to present our implementation research for antibiotic stewardship to German hospitals. We contributed to implementation research in eHealth by introducing our business modeling approach. This subsequently leads to the stakeholder- and value-driven focus in the Center for eHealth research roadmap that supports the holistic eHealth research and development to make eHealth better accessible, manageable, enjoyable and feasible. We contributed to antibiotic stewardship, by investigating the implementation of antibiotic stewardship programs with our business modeling approach. This way, instead of focusing on guidelines, we involved antibiotic stewardship teams, the stakeholders, in value-driven dialogues to explore what they deem valuable and important. This bottom-up approach gave us insights that antibiotic stewardship programs are implemented diversely in hospitals. Finally, we looked at this diversity, and what is causing it, and used that as input for our eHealth technology. Prior research at our research group into presenting protocol-based information via eHealth has proven to be effective. Currently, we are developing an online antibiotic stewardship implementation application that uses this diversity to give customizable, practical recommendations how to implement antibiotic stewardship.

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Samenvatting, Dutch summary

Samenvatting (Dutch summary)

Antibioticaresistentie is wereldwijd een toenemend probleem. Resistente bacteriën zoals methicilline resistente Staphylococcus aureus (MRSA), zijn daardoor moeilijker te behandelen en dit is niet goed voor de patiëntveiligheid. Patiënten die ziek zijn van resistente infecties lopen meer risico's op nare (fysieke) complicaties en kunnen ook komen te overlijden, daarnaast hebben deze patiënten meer behandeltijd nodig en bijbehorende kosten. Er is een aantoonbaar verband tussen de toename van antibioticaresistentie en een overmatig antibioticagebruik. Ook in ziekenhuizen is er winst te behalen met het optimaliseren van het antibioticagebruik. In internationale studies werd aangetoond dat namelijk zo'n 30 tot zelfs 50% van alle voorgeschreven antibiotica in ziekenhuizen verkeerd of onnodig voorgeschreven worden. Als mogelijke oplossing om het antibioticagebruik in ziekenhuizen te beïnvloeden, zijn er richtlijnen voor antibiotic stewardship programma's bedacht door experts van infectiepreventie organisaties. Een antibiotic stewardship programma (ASP) is een programmatische aanpak dat een optimaal gebruik van antibiotica verzekert, met de best mogelijke uitkomsten voor de patiënt, minimale risico's van bijwerkingen, kostenefficiëntie en het stabiliseren of verminderen van resistentie. Er is echter geen consistente aanpak bij dergelijke antibiotic stewardship programma's. Er zijn richtlijnen aanwezig, maar zorgprofessionals in de ziekenhuizen moeten toch zelf uitdokteren hoe de benodigde interventies voor antibiotic stewardship geïmplementeerd moeten worden in hun ziekenhuis. In dit proefschrift wordt daarom vooral gekeken naar de huidige gang van zaken bij en mogelijkheden voor de implementatie van antibiotic stewardship.

Bij onze aanpak om antibiotic stewardship te implementeren speelt eHealth onderzoek een belangrijke rol. eHealth is meer dan technologie. Het implementeren van eHealth (en zorg innovaties in algemene zin) in de zorg beïnvloedt meerdere mensen in hun dagelijkse routines maar ook in sociale en psychologische zin. eHealth vergt daarom een holistisch onderzoek aanpak en daarvoor heeft het Center for eHealth Research and Wellbeing een roadmap ontwikkeld. Deze roadmap ondersteunt eHealth onderzoekers met enerzijds de vormgeving en (technische) ontwikkeling van eHealth technologie, maar anderzijds ook het bepalen van de benodigde implementatie van deze technologie. Rondom de eHealth technologie is een infrastructuur nodig zodat de eHealth technologie ook succesvol kan worden ingezet. Met business modeling kunnen stakeholders betrokken worden in het onderzoek naar deze infrastructuur. Op die manier kan met een 'bottom-up'-manier samen met stakeholders besproken worden wat de meerwaarde van, in dit geval, antibiotic stewardship interventies zou moeten zijn. Deze besproken meerwaardes vanuit de stakeholders kunnen vervolgens geanalyseerd en gecombineerd worden in een business model.

Daarnaast kan eHealth technologie ook gebruikt worden om implementatieadviezen te presenteren. Op basis van het implementatieonderzoek in dit proefschrift, hebben we een maturity model opgesteld voor de implementatie van antibiotic stewardship en dit model verder vormgegeven in een online eHealth applicatie, die teams advies op maat kan geven hoe antibiotic stewardship het beste in hun situatie geïmplementeerd kan worden. De online eHealth applicatie is opgenomen als één van de eHealth applicaties in de Infectionmanager (www.infectionmanager.com). Infectionmanager is een online eHealth platform met informatie en eHealth applicaties voor grensoverschrijdend infectiemanagement voor het EurSafety Health-net onderzoek (www.eursafety.eu) wat bij Universiteit Twente is ontwikkeld.

Kort samengevat, in dit proefschrift wordt business modeling gebruikt als onderzoeksinstrument waarmee de mogelijke implementatie van antibiotic stewardship geanalyseerd wordt en wordt eHealth technologie gebruikt om deze bevindingen verder vorm te geven. De hoofdvraag in dit proefschrift is: Hoe kan business modeling gebruikt worden om antibiotic stewardship te implementeren met eHealth technologie? Deze vraag is opgedeeld in drie deelvragen: 1) Hoe kan business modeling gebruikt worden als implementatie methode (hoofdstukken 2 en 3), 2) Wat is de huidige gang van zaken met antibiotic stewardship programma's? (hoofdstukken 4 en 5), 3) Hoe kan antibiotic stewardship geïmplementeerd worden? (hoofdstukken 6 en 7)

Om de eerste deelvraag te beantwoorden wordt in hoofdstuk 2 business modeling geïntroduceerd als onderdeel van een aanpak voor holistisch onderzoek om eHealth te ontwikkelen en te implementeren. Om een succesvolle eHealth technologie te ontwikkeling, moet niet alleen de technologie zelf aansluiten bij de wensen van de gebruikers, maar moet ook de implementatie ervan aansluiten bij de wensen van de stakeholders. Deze bredere kijk op eHealth, ziet men ook in de definities van eHealth, waar multidisciplinariteit een grotere rol is gaan spelen. Bij het ontwikkelen van eHealth speelt een combinatie van technologische, sociaal/psychologische, medische en bedrijfskundige factoren die allemaal het succes zullen beïnvloeden. Business modeling helpt om de implementatie te laten aansluiten op hoe de stakeholders denken dat de technologie succesvol kan zijn. Daarnaast, door de eHealth technologie te bespreken met stakeholders, wordt voor hun de meerwaarde van de technologie ook duidelijker. Het is daarom verstandig om hier zo vroeg mogelijk in het ontwikkelproces mee te beginnen, zodat vroeg duidelijk wordt wat allemaal noodzakelijk is om de eHealth technologie te ontwikkelen en te implementeren. Dit beïnvloedt elkaar namelijk. Veel te vaak wordt de implementatie van eHealth onderschat, of slecht doordacht, waardoor er vaak veel geld is uitgegeven aan een state-of-the-art eHealth technologie, maar waar verder weinig animo of continuïteit voor is.

Hoofdstuk 3 heeft een meer pragmatischere blik op business modeling en dit hoofdstuk presenteert een stap-voor-stap aanpak voor business modeling als implementatieproces voor eHealth. Naast dat de implementatie van eHealth vaak onderschat of slecht doordacht is, zijn er ook weinig methodieken om dit implementatieproces te ondersteunen. Vooral de concrete stappen die nodig zijn. Onze roadmap aanpak introduceert een stakeholder-gedreven aanpak, dus dat het van groot belang is om te bepalen wie de stakeholders zijn, welke belangrijk zijn en wat zij willen. Daarnaast is business modeling ook een waarde-gedreven aanpak, dat wil zeggen dat in de discussies met stakeholders, hun waarde-verwachtingen centraal staat. Op basis van deze discussies kan vervolgens een business model worden uitgedacht, die als een soort van blauwdruk gebruikt kan worden om de implementatie te beschrijven. Hoofdstuk 3 beschrijft enkele methoden om: 1) stakeholders te identificeren, 2) hun belangrijkheid te bepalen, 3) behoeften en waarde-verwachtingen te definiëren, en 4) om op basis van deze behoeften en waarden een business model op te stellen.

In de hoofdstukken daarna wordt ingezoomd op het onderzoeksthema, antibiotic stewardship. De lijn in deze hoofdstukken zelf zoomt in feite ook in, want we kijken eerst met een breed en internationale focus naar de huidige staat en mogelijkheden van antibiotic stewardship programma's en gaandeweg kijken we steeds specifieker, lokaler en pragmatischer naar antibiotic stewardship programma's. Uiteindelijk worden de bevindingen beschreven voor een implementatiestrategie voor antibiotic stewardship die wij vorm hebben gegeven in een online eHealth applicatie.

De tweede deelvraag richt zich op de huidige gang van zaken, met andere woorden, inventariseren hoe antibiotic stewardship programma's worden geïmplementeerd. Als eerste stap hebben we gekeken naar antibiotic stewardship in internationale literatuur. In deze literatuurstudie keken wij naar de belangrijkheid van interventies, een beschrijving van deze interventies, belangrijke stakeholders en de mogelijkheden om de impact van een antibiotic stewardship programma te meten. Wat opviel is dat de meeste publicaties over antibiotic stewardship over programma's bij academische ziekenhuizen zijn. Dat is op zich logisch gezien daar academici werken die academische output willen hebben en anderzijds dat daar meer ruimte voor onderzoek is. Echter, het merendeel van alle ziekenhuizen zijn niet academisch. Dus hoe doen de gewone ziekenhuizen antibiotic stewardship? Het viel ook op dat, ondanks de aanwezigheid van protocollen en richtlijnen voor antibiotic stewardship, de ziekenhuizen zelf nog de precieze invulling van de programma's moesten uitdenken en dat daardoor er behoorlijke nuanceverschillen zitten in de interventies. Er zijn een aantal basis interventies die vaak voorkomen in de programma's en niet geheel toevallig zijn dit ook de interventies zoals beschreven door de Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA), maar deze richtlijnen beschrijven vooral de meerwaarde en de evidence van deze interventies en niet de praktische implementatie. De praktische vormgeving van de interventies (bijv. welke zorgprofessionals zitten er in een A-team? Hoe doet men een audit?) wordt zeer verschillend opgepakt. De teams die verantwoordelijk zijn voor het implementeren van antibiotic stewardship hebben daarom best nog een flinke kluif aan het uitdenken van alle interventies en kunnen daar praktische hulp bij gebruiken.

Hoofdstuk 5 richt zich op de uitkomsten van de eerste stappen met business modeling in context van antibiotic stewardship. Het is een ‘contextual inquiry’ (zoals de eerste stap in de roadmap heet) voor het vinden van mogelijkheden voor eHealth binnen antibiotic stewardship. Met dit onderzoek werd gekeken naar het proces rondom het voorschrijven van antibiotica in een ziekenhuis. Door deze procesanalyse ontstond een beeld van mogelijke bottlenecks in het proces, de complexiteit van interacties tussen stakeholders en de bijkomstige problemen. Daarnaast hebben we met deze focusgroep ook besproken wat mogelijke verbeterpunten kunnen zijn en hoe eHealth daar een rol bij zou kunnen spelen. Dit heeft geleid tot een lijst van mogelijke eHealth interventies, waarvan we enkelen ook onderzocht hebben voor de Infectionmanager (bijv. een informatieapplicatie voor verpleging, een online antibiotica boekje), en het gaf ons een completer beeld hoe het proces van antibiotica voorschrijven in een Nederlands ziekenhuis verloopt.

De SWAB (Stichting Werkgroep Antibiotica Beleid) een visiedocument uitgebracht waarin ziekenhuizen de opdracht kregen om te beginnen met antibiotic stewardship, en wel, door te beginnen met het samenstellen van een team (A-teams genoemd) die zich bezig moest gaan houden met het implementeren van antibiotic stewardship interventies. Dat bracht ons onderzoek iets meer in een stroomversnelling omdat meer Nederlandse ziekenhuizen in de Nederlands-Duitse grensstreek nu aanleiding hadden om in antibiotic stewardship te verdiepen. Hier ontstond de derde deelvraag ‘hoe kan antibiotic stewardship geïmplementeerd worden?’. Samen met enkele infectiepreventie experts hebben we een ‘implementation maturity assessment’ voor antibiotic stewardship opgesteld (hoofdstuk 6). Dit is een vragenlijst opgesteld op basis van beschikbare literatuur over antibiotic stewardship interventies om het stadium van implementatie van enkele kenmerken van de interventies te meten. Deze assessment hebben we naar enkele A-teams gestuurd die in de meeste gevallen in een zeer prille start van antibiotic stewardship programma’s zaten. Ondanks dat deze A-teams dezelfde literatuur en bronnen raadpleegden, viel op dat de plannen nogal verschillend waren. Dit suggereert dat er lokale belangen of randvoorwaarden zijn die veel invloed op deze interventies hebben.

Het was dus zaak om te kijken hoe deze lokale belangen en randvoorwaarden dan liggen. Voor het onderzoek in hoofdstuk 7 hebben we contact opgenomen met dezelfde A-teams om langs te komen tijdens één van hun vergaderingen om een kort interview af te nemen. Het doel van dit interview was om meer bottom-up de rationale achter de verschillen boven tafel te krijgen. De verschillen werden inderdaad vooral door lokaal reeds aanwezige processen, personeel, software, etc. beïnvloedt. Met andere woorden, een algemeen implementatieadvies vergt aanpassing aan de lokale praktijk. Op basis van de resultaten van hoofdstukken 6 en 7, hebben we eerst de implementatie van antibiotic stewardship programma's opgedeeld in behapbare stappen. Met een maturity model is het mogelijk om een omvangrijk programma in kleinere stadia te implementeren. In hoofdstuk 7 beschrijven we daarom eerst een basaal programma die verder uitgebouwd kan worden tot een zeer compleet programma zoals vaak beschreven als ideaal plaatje in de beschikbare richtlijnen. Een ander belangrijk aspect is dat er dus een dynamiek nodig is in het advies. Niet ieder ziekenhuis kan antibiotic stewardship hetzelfde implementeren. Daarnaast is het ook zo dat als er bij één interventie iets afgeweken wordt, dat dat zeer waarschijnlijk ook implicaties heeft voor de andere interventies. In feite zijn dus de A-teams verantwoordelijk om de juiste configuratie te vinden voor de meest passende implementatie van antibiotic stewardship.

Het antwoord op de hoofdvraag is een synthese van het maturity model en de benodigde dynamiek. Een eHealth applicatie is in ontwikkeling die een implementatiestructuur en advies-op-maat aanbeveelt. A-teams kunnen de implementatie maturity assessment invullen en op basis daarvan genereert de applicatie een advies welke interventies prioriteit hebben en hoe deze het beste ingevuld kunnen worden gezien de lokale belangen of randvoorwaarden.

Het onderzoek draagt bij aan de doelstellingen van EurSafety Health-net. Door een verantwoorder gebruik van antibiotica kan de patiëntveiligheid verbeteren. Antibiotic stewardship programma's zijn een zeer geschikte manier om zorgprofessionals in ziekenhuizen te beïnvloeden om beter om te gaan met het voorschrijven van antibiotica. Dit proefschrift eindigt met enkele adviezen om de implementatie te structuren en op maat te maken voor ziekenhuizen die daar interesse in hebben. In parallelle onderzoeken werd meer gefocust op de rol van technologie binnen antibiotic stewardship, en zijn met persuasief ontwerpmethodieken enkele eHealth applicaties ontwikkeld om zorgprofessionals te ondersteunen. Het EurSafety Health-net project heeft veel nieuwe inzichten en projecten opgeleverd, niet alleen bij de Universiteit Twente maar ook bij alle andere deelnemende onderzoeksinstanties. Dit heeft geleid tot enkele nieuwe grensoverschrijdende projecten, waaronder Health-i-care, EurHealth-OneHealth en CommonCare. Deze projecten zijn een mooi vervolg op EurSafety Health-net om verdere stappen te maken in grensoverschrijdende samenwerking in zorg en onderzoek, innovatie binnen infectiepreventie, en om de patiëntveiligheid van Europeanen te verbeteren.

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Ik wil Ron Hendrix bedanken voor jouw rol als projectleider van het EurSafety project in de Enschede-Gronau regio, of de ‘Twente club’, wat misschien een betere benaming is. Na jouw verhuizing van Labmicta naar het LVI in Groningen werden de vergaderingen wat minder frequent helaas, maar ik heb veel aan jouw kritische blik gehad. Vooral de blik op haalbaarheid en relevantie voor de medische wereld. Je nam vaak een beetje een advocaat van de duivel stellingname in de soms hevige discussies tijdens onze EurSafety vergaderingen. Werd het te academisch, dan bepleitte jij de praktische relevantie. Werd het te complex, dan moest het simpeler, etc. En zo niet, dan was het wel andersom! Jobke en ik werden weleens tureluurs van Lisette enerzijds en jou anderzijds in deze discussies en dan moesten we de rest van de vrijdag (en later de maandag) eerst een half uur bijkomen van de informatie overload. Maar desalniettemin, jouw inbreng was belangrijk in dit hele project en mijn onderzoekslijn. Oh, en ook onze kleinere side-track technische projectjes voor bijvoorbeeld Herford of publiek-Zipnet waren leuk om te doen ter afwisseling!

De (overige) leden van de promotiecommissie wil ik graag bedanken voor hun inzet om het proefschrift te lezen en te beoordelen, zitting te nemen in de commissie, en -ook al schrijf ik dit nu vooraf- mij te bestoken met enkele pittige vragen tijdens de verdediging van het proefschrift. Het was nog een flinke kluif op het eind, maar het is allemaal gelukt. Bedankt prof. dr. Wim van Harten, dr. Robin Köck, prof. dr. ir. Bart Nieuwenhuis, prof. dr. Jacques Scheres en prof. dr. Leonard Witkamp. Ook is het erg leuk dat Erwin Seydel voorzitter kon zijn bij deze gelegenheid, vooral vanwege jouw hulp om het project startende te krijgen bij de UT. Hiermee is de cirkel soort van rond.

En ook de mensen die bij onze universiteit onderdeel waren van het EurSafety project: Fenne, Lex, Joyce, de bachelor en master studenten en ook enkele technici van buiten de universiteit waarmee ik heb samengewerkt, in het bijzonder Paul Borkent, Rudi Evers, Sjoerd Boerrigter, Peter Hol en Rick Klaassen.

Ik wil de EurSafety Health-net deelnemers bedanken. Het was een leuke internationale groep met vooral veel samenwerking tussen Nederland en Duitsland. Voordat ik aan mijn onderzoek begon had ik een cursus Duits gevolgd, maar de presentaties in het Duits doen was toch wel een uitdaging. Ter info, Duits was op de middelbare school mijn slechtste vak. Mijn docent destijds ging al grinniken nog voordat ik antwoord kon geven op een grammatica vraag en corrigeerde me dan met ‘je zei toch dem? Ja, dat is goed’. Ik was toen dan ook van mening dat het zeer onwaarschijnlijk was dat deze grammaticaal onmogelijke taal in mijn verdere carrière na de middelbare school nog een grote rol zou hebben in mijn leven. Aber ich hätte nicht fälscher liegen können. Vandaar dat mijn 'abgespeckte' kennis van Duits tot een aantal mooie Babylonische spraakverwarringen hebben geleid op bijeenkomsten (tablets vs. tabletten was een mooie!). Gelukkig dat de grens-Duitsers ook zeer bekwaam zijn in het verstaan van Nederlands. Bedankt jullie allemaal. Danke schön euch alle.

Ook mijn directe EurSafety collega's Jobke en Nienke bij de eHealth groep mogen in dit dankwoord niet ontbreken! Job, dank je voor de gezelligheid en de samenwerking in het project. Je was 'partner-in-crime' vanaf 't eerste uur. We begonnen met een cursus Duits in eigen tijd, terwijl we heel lang moesten wachten voordat het project rond was qua financiële organisatie bij de UT. Daarna veel samengewerkt in het begin van het project om het onderzoek voor ons allebei uit te stippelen samen met Lisette en Ron. Later gingen we wat meer ieder een eigen onderzoekstraject in en je hebt me verdorie ook nog ingehaald, hah. Maar het was fijn om met jou samen te werken. Nienke, jij stapte wat later in het project, maar ook met jou was het leuk om samen te werken en jouw rustigere attitude maakte je een zeer goede aanvulling op het EurSafety clubje bij de UT met al die andere schreeuwlelijkerds bij elkaar (ps. niet zeggen dat ik ze zo genoemd heb!).

De Groningers. In het bijzonder Bhanu, Jan Willem, Piet, en Jerome (en Alex had ik al genoemd). Door Alex z'n transfer naar het UMCG ongeveer halverwege ons onderzoek, hebben we elkaar eigenlijk ontmoet en een zeer prettige samenwerking verder gehad. Dat heeft, zo denk ik, de lijn van mijn onderzoek goed gedaan en jullie hebben mij geholpen bij enkele artikelen, waarvoor dank.

En natuurlijk ook alle collega's en oud-collega's bij de vakgroep. Wat eerst begon als 'collega's uit de torenkamer', toen een verhuizing naar 'de gang' en vrij snel daarna nog de grote verhuizing naar de Cubicus en later nog een verhuizing in de Cubicus (en eigenlijk het enige voordeel van die verhuizingen was dat ik de papiertorens van mijn bureau kon wegsodemieteren). Anja, Anne Marie, Annemarie, Elly, Erik, Ernst, Femke, Fenne, Floor, Hans, Henk, Hester, Ingrid, Jobke, Jojanneke, Laura, Lex, Liseth, Marieke, Martijn, Martine, Nadine, Nicol, Nienke B., Nienke N., Olga, Oscar, Robin, Roos A., Roos V., Sanne, Saskia A., Saskia K, Stans, Wendy. Sabri en Wim van de financiën. Ik ben vast iemand vergeten in deze lijst. Dank jullie voor de leuke tijd, en voor sommigen ook voor de aanwezigheid op congressen, borrels, wachten op vliegvelden (helaas die ene keer geen 'Mooi Kloten' ansichtkaartje gekocht), kerstdiners, of andere excursies, alwaar we naast professionele activiteiten ook af en toe een alcoholische versnapering konden nuttigen, konden team builden, en wat sightseeing konden doen. De congressen op Sint-Maarten en Guadeloupe waren uiteraard zeker highlights vanwege de exotische oorden, maar Londen, Geneve en Valencia waren zeker niet minder leuk en mooie steden om te bezoeken. Oh, en Lex, we moeten eigenlijk ooit nog een Nieuwjaar duik in Scandinavië gaan doen i.p.v. in Spanje, dat is een nog grotere uitdaging qua temperatuur! Neem wel een grote handdoek mee die keer! ;)

Mijn paranimfen, Robin Kok en Jobke Wentzel. Robin, als oud-collega hadden we snel een band vanwege een gedeelde interesse in trucks, luide gitaren en computers. Dank je dat je veel stukken hebt doorgelezen voor taalcorrecties en inhoudelijke verbeteringen. Maar nog meer bedankt dat je een uitlaatklep was voor enkele (academische) frustraties waar ik jou altijd mee op facebook chat kon storen! En dat we een keer in Amsterdam elkaar stoere truckerverhalen gingen vertellen in een studentencafé waar we wat vreemde blikken kregen, omdat de studenten niet wisten dat we ’t over Euro Truck Simulator 2 hadden. Jobke, naast alle lof die ik je al toebedeeld had als fijne project partner, ook bedankt dat je wilde assisteren als paranimf.

Mijn familie.In de eerste plaats mijn pa. Als kind interesseerde school mij geen ene fluit. Op de basisschool raffelde ik snel de opdrachten af en ging dan uit het raam staren en dromen over baas zijn van een gigantisch softwarebedrijf, iets met rare computerspelletjes maken, een huis met lasers erop voor ongewenst bezoek, enz. Dat was leuker dan school. De Cito-toets ging goed, maar de leraren zagen geen heil in mijn leerinstelling en adviseerden toch mavo/havo. Door jouw koppigheid mocht ik het dan toch maar proberen op het atheneum alwaar ik uiteindelijk begon te snappen dat onderwijs iets is voor zelfontwikkeling en niet een bezigheid om anderen te pleasen. OK, ik heb er een jaartje toen voor moeten blijven zitten maar hoe je het wendt of keert, dit moment is toch zeer belangrijk geweest om mijn verdere opleidingen en dit proefschrift mogelijk te maken. Dus daarom, pa, dankzij jou heb ik dit kunnen verwezenlijken. Nu nog een huis met lasers erop! ;) Ook ma en Simon voor alle support in het dagelijks leven en oom Marinus die op een verjaardag bij oma nog zei dat een promotie juist bij mij zou passen in de periode dat ik daar nog over aan het nadenken was. En de rest van de fam., oma, neefjes, nichtje en bijbehorend potentiële aantrouw! ;) De meesten van jullie weten waarschijnlijk eigenlijk totaal niet waar mijn onderzoek allemaal precies over gaat, maar dat hoeft ook niet.

Ook wil ik een heel belangrijk persoon in mijn leven bedanken. Ik heb jou, Steffi, ongeveer halverwege mijn onderzoek leren kennen. Een gezamenlijke vriend, Dino, had ons op een feestje geïntroduceerd (en soort van toch via de Duitse stoep-veeg-traditie waar jullie het over hadden) en ik wou je een biertje aanbieden, maar had geen geld meer, dus, dat was een goeie binnenvaller en sindsdien hebben we gewoon een hele fijne klik samen. We vullen elkaar aan precies waar nodig. Jij bent mijn rustgevende factor en samen met jouw lieve party-katjes lig ik graag samen op de bank om Frauentausch of een film te kijken. Ik hou van jou.

Also much <3 to my demoscene friends. This crazy hobby that outsiders totally don’t understand helped me spike my creativity and international social skills. You wouldn’t believe how useful Norwegian or Finnish swearwords can be at academic conferences! For faen, vittu perkele! But anyway, best wishes to all the demogroups and sceners I have been closely doing artistic stuff with. Thank you for inspiring me. It was not only a nice way to get my mind off the serious business that comes with PhD stuff, but also was a useful skill set when it comes to fixing bugs in weird third-party PHP code or for something as mundane as doing pretty looking graphics in academic papers. I, in particular, would like to thank Kimmo for being a good friend and your work on the cover design of this thesis. Other sceners who I would like to thank for being a friend and their influence in the last twenty years already are: Peter(x2), Zden, Dennis, Arto, Marcel(x2), Pieter, Susann, Gergely, Andrew, Joonas, Vlado, Sotiris, Niels(x2), Gregory, Tim, Igor, Ivan, Daniele, Luisa, Noud, Tobi, Reza, Thijs, Matt, Jaakko, Niko, Jorge, Ronny, Greg, Ilona, Dries, Pilvari, Marc(x2), Robert, Henning, Matthijs, Kaisa, Nina, Martti, Oystein, Ruth, Barna, Jouni, Charles, Anne Claire, Yves. And I probably forgot to mention some people.

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Goed. That’s a wrap. Op naar nieuwe dingen en ervaringen!

- Maarten
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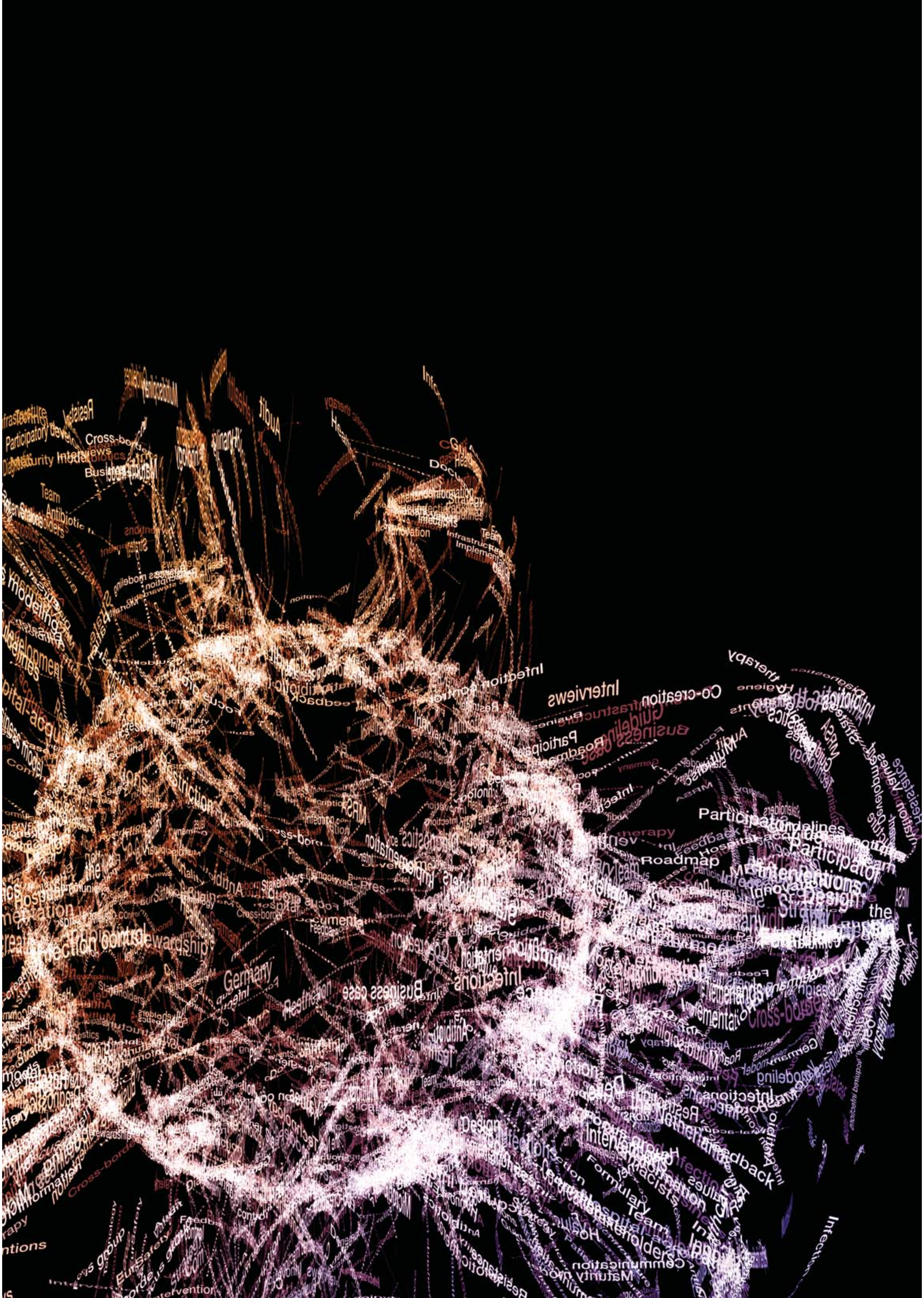
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