CELSUS ACADEMIE VOOR BETAALBARE ZORG

Research Report

Cost-Effectiveness of Policies to Limit Antimicrobial Resistance in Dutch Healthcare Organisations

Cost-Effectiveness of Policies to Limit Antimicrobial Resistance in Dutch Healthcare Organisations

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Content

1 Management Summary

Antimicrobial Resistance: A Growing Healthcare Problem

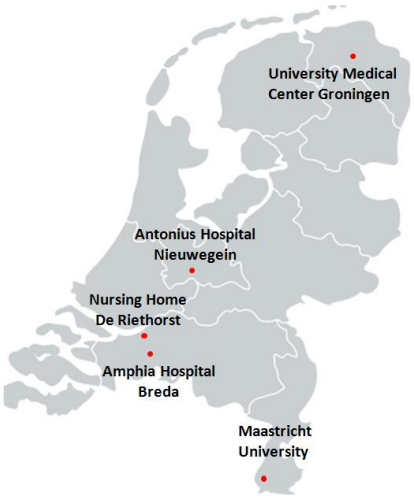
Antimicrobial resistance is a rapidly growing healthcare problem that leads to substantial clinical burden in terms of morbidity, mortality, and lower quality of life. The economic burden is also substantial, in particular due to prolonged hospitalisations and expensive secondary treatment options. Cost-effective antimicrobial policies are thus urgently needed to improve patient outcomes, patient safety, and to keep healthcare sustainable.

The Netherlands holds relatively low rates of antimicrobial resistance. However, also within the Netherlands, considerable differences in antimicrobial policies exist between healthcare organisations. In this report, we describe the content, the effectiveness, and the potential cost-savings of five 'good practices'. The overarching aim is to inspire readers with antimicrobial policies that can be implemented in their healthcare system.

Five Dutch Antimicrobial Policies Considered as Good Practice

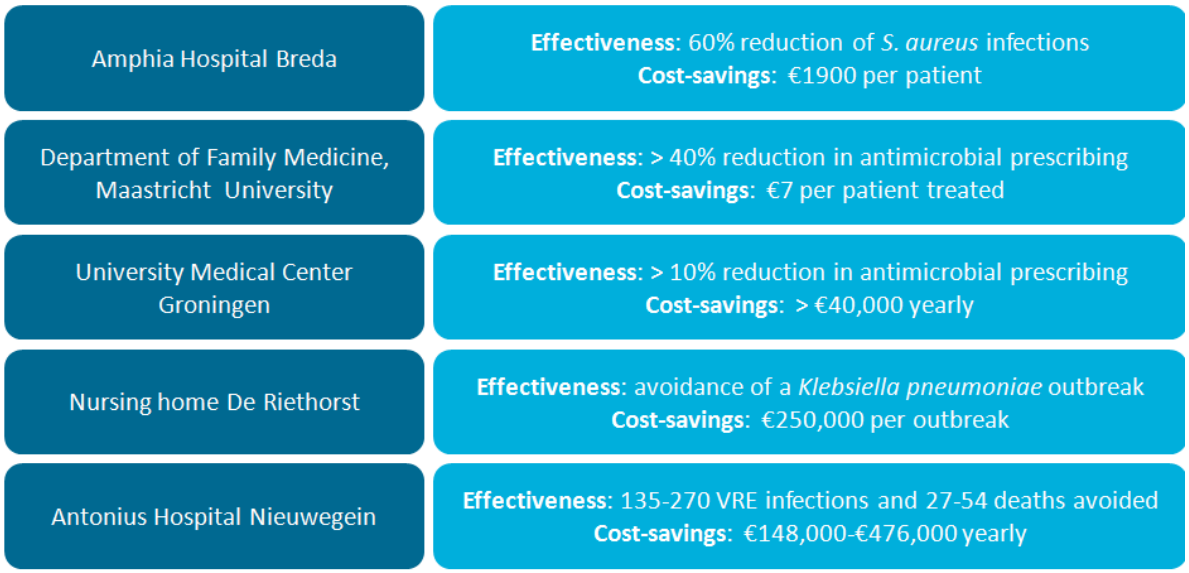
Five Dutch healthcare organisations (three hospitals, one nursing home, and one organisation in general practice) that are considered a good practice regarding their antimicrobial policy were described in a business case. These good practices are:

1. **Amphia Hospital Breda**
   Preventing Surgical Infections in Nasal Carriers of *Staphylococcus aureus*
2. **Department of Family Medicine, Maastricht University**
   CRP Point of Care Test to Regulate Antimicrobial Use in Primary Care
3. **University Medical Center Groningen**
   Antimicrobial Stewardship Teams
4. **Nursing home De Riethorst**
   Control of an Outbreak of Multi-Resistant *Klebsiella Pneumoniae*
5. **Antonius Hospital Nieuwegein**
   Control of a Hospitalwide Vancomycin-Resistant *Enterococcus* Outbreak



All business cases showed cost-effectiveness of the antimicrobial policy. Either by improving adequate use of antimicrobials or by improving adherence to infection control measures. Each of the

antimicrobial policies needed initial investments. In some cases these costs were low (e.g., eradication of nasal carriage of *Staphylococcus aureus* or the CRP Point of Care Test). In others, these costs were much higher (e.g., introduction of antimicrobial stewardship teams or hospital-wide infection control). Nonetheless, all business cases showed high return of investment and short pay back circles (e.g., less use of restricted antimicrobials, shorter length of stay, less healthcare personnel needed). More importantly, patient health and patient safety improved considerably (e.g., fewer antimicrobial prescriptions, fewer infections, and/or lower resistance rates). The key findings are listed in the diagram below.



Three Preconditions for Sustained Cost-Effectiveness

Three important preconditions (that followed from the business cases) will be listed below, which need to be ensured to achieve sustained cost-effectiveness.

1. Surveillance and Feedback in an Open Dialogue Culture

The good practices showed that the combination of closely monitoring professionals' prescribing behaviour (continuously measuring the prescription of antimicrobials and the adherence to infection control guidelines) and tailored (oral or written) feedback on behaviour is key to the effective reduction of unnecessary antimicrobial use and spread of bacteria. The responsibility of these surveillance activities usually consists of a multidisciplinary team of healthcare professionals, including clinical microbiologists, infectious disease physicians, hospital pharmacists, infection control specialists, and quality assurance professionals. The multidisciplinary team should work in an open dialogue culture, based on openness and trust.

2. Sustained Implementation

Sustained implementation is a precondition for long-term cost-savings of antimicrobial policies. Even though cost-effectiveness has been proven for the good practices, the cost-savings might not hold for other EU healthcare systems. It should first be studied whether these good practices fit into the logistics and culture of other healthcare system. Moreover, given the initial costs associated with the good practices, financial barriers may hinder uptake. It thus seems important to study the cost-effectiveness of good practices in other healthcare institutions, whether the antimicrobial policies fit in the culture and logistics of those settings, whether reimbursement is available, and whether elements of good practices need to be adapted, removed, or added.

3. Inter-Institutional Collaboration

Healthcare institutions should cooperate regionally and internationally to fight antimicrobial resistance successfully. Especially in areas with high levels of cross-region and cross-border patient referrals. The high connectivity of healthcare networks will impact the effectiveness of antimicrobial policies. Inter-institutional collaboration should be further encouraged and implemented in the near future.

Antimicrobial Policies Considered as Good Practice Lead to More Sustainable Healthcare

This report shows that several cost-effective antimicrobial policies are available to limit the spread of antimicrobial resistance successfully in Dutch healthcare organisations. EU-wide implementation of (the most effective components of) the good practices described in this report can lead to a reduction of infections with microorganisms, more adequate use of antimicrobials, and a reduction of antimicrobial resistance rates. These outcomes will lead to improved patient safety and patient health, contributing to more sustainable healthcare. Now, and in the future.

2 Introduction

Background of Antimicrobial Resistance

Antimicrobial resistance is a worldwide and growing public healthcare problem [1-3]. The recently published report '*Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations (December 2014)*' shows that increasing antimicrobial resistance leads to substantial clinical burden in terms of morbidity, mortality, and lower quality of life [4]. Resistant bacteria cause at least 50,000 deaths per year in Europe and the US. If we do not improve adequate use of antimicrobials, it has been estimated that approximately 10 million people will die as a consequence of antimicrobial resistance in the year 2050. The economic burden will also be substantial, in particular due to hospitalisations, expensive secondary treatment options, and productivity losses for patients at work. Thus, intervening is necessary to keep healthcare sustainable for every citizen [5]. Cost-effective antimicrobial policies can help to achieve this. To achieve maximum benefit, these antimicrobial policies should not only be implemented in curative care (primary care and hospital care), but also in elderly care (nursing and residential homes). In addition, in light of the One Health Approach, it is imperative that healthcare organisations cooperate across institutions and sectors.

The World Health Organisation defines appropriate use of antimicrobials as '*the cost-effective use of antimicrobials which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance*' [5]. The objective of antimicrobial resistance policies is to ensure patient safety and to keep future bacterial infections treatable. Healthcare professionals have a particular responsibility to avoid patients acquiring infections. Antimicrobial resistance policies addresses two mechanisms. First, by reducing inadequate prescription and inaccurate use of antimicrobials. Second, by preventing the spread of (resistant) micro-organisms by adhering to infection control guidelines.

Several Dutch healthcare organisations have shown to limit the spread of antimicrobial resistance effectively. Moreover, some of them also claimed cost-effectiveness of their antimicrobial policy. These 'good practices' have therefore the potential to inspire other healthcare organisations. It is however difficult and perhaps impossible to implement these 'good practices' unadjusted to other healthcare organisations. Antimicrobial policies need to be adapted to the context of the adopting healthcare organisation, to the logistics and organisation of the (national and local) healthcare system, and to their culture [6]. Nevertheless, by sharing knowledge about the effective elements of these 'good practices', and by providing insight into their cost-effectiveness, other healthcare organisations will be enabled to implement (components of) 'good practices' in their system. Effective

implementation and sustained use of antimicrobial policies can consequently lead to improved safety and quality of care, which contributes to more sustainable healthcare.

Objective and Problem Statement

The objective of this report is to provide examples of infection prevention and adequate use of antibiotics that have proven to be both clinical effective and of economic value. We describe the content of five Dutch 'good practices' and provide insight into the cost-effectiveness of these antimicrobial policies. The objective will be translated into the follow research questions:

1. What are inspiring examples of infection prevention and adequate use of antimicrobials to limit antimicrobial resistance? To answer this question, we will use examples from hospitals, nursing homes, regional partnerships, and from primary care.
2. What is the cost-effectiveness of these antimicrobial policies?
    - What are the investments made?
    - What are the potential health benefits and cost-savings?
3. What is the type of evidence used to determine cost-effectiveness?

3 Methods

Recruitment of the Good Practices

We searched in our own network for well-known good practices of antimicrobial use policy or infection control policy. Eventually, we selected ten Dutch healthcare organisations (five hospitals, three nursing homes, one regional partnership, and one organisation in primary care). The research team received their contact details and contacted each organisation to ask them for participation in the current study. If the organisations were willing to participate (all organisations were), the research team made a first inventory of the following topics:

1. The content of the infection control policy / antimicrobial use policy;
2. The costs of the infection control policy / antimicrobial use policy;
3. The effectiveness of the infection control policy / antimicrobial use policy;
4. The quality of the cost data and the effectiveness data.

The purpose of this inventory was to investigate if the necessary information to design a cost-effective and valid business case could be obtained. Business cases are examinations of all necessary costs related to the antimicrobial policy relative to the health and financial benefits of the antimicrobial policy, including recommendations for implementation.

Selection of the Good Practices

Five of the ten good practices were selected for designing a business case. The ten good practices received quality scores from one member of the research team (author EO) on the following criteria:

1. The level of inspiration (innovativeness, feasibility, potential for implementation);
2. The level of cost-effectiveness (potential for health and financial gain);
3. The level of methodological quality of cost and effectiveness data.

The quality scores were discussed in a team meeting. The five good practices with the highest overall quality score were selected for designing a business case. Three hospitals were selected, one nursing home, and one organisation in general practice. The other good practices are only shortly described in the current report. The five good practices are presented in Table 1.

Table 1: The five good practices selected for designing a business case.

	Healthcare Institution	Antimicrobial Policy
#1	Amphia Hospital Breda	Preventing Surgical Infections in Nasal Carriers of *Staphylococcus aureus*
#2	Department of Family Medicine, Maastricht University	CRP Point of Care Test and Communication Skills Training to Limit Antimicrobial Use in Primary Care
#3	University Medical Centre Groningen	Antimicrobial Stewardship Teams
#4	Nursing Home De Riethorst	Control of an Outbreak of Multiresistant *Klebsiella Pneumoniae*
#5	Antonius Hospital Nieuwegein	Control of a Hospital-wide Vancomycin-Resistant *Enterococcus* Outbreak

Design of the Business Cases

Each business case was designed similarly. The structure used for the business cases was the following:

1. A short background of the healthcare problem;
2. A content description of the infection control policy / the antimicrobial use policy;
3. The effectiveness of the infection control policy / the antimicrobial use policy (e.g., in terms of patient safety, patient health, or antimicrobial use);
4. The costs associated with the infection control policy / the antimicrobial use policy;
5. A calculation of the potential financial savings;
6. The potential for implementation;
7. Conclusion and recommendations.

4 Good Practices

The five business cases will be presented in the following sections.

Good Practice 1: Preventing Surgical Infections in Nasal Carriers of *Staphylococcus aureus*

Pre-Operative Screen-And-Treat Strategy of *Staphylococcus aureus* Leads to a 60% Reduction in Surgical Infections

Nasal carriage of *Staphylococcus aureus* (*S. aureus*) is a major risk factor for surgical infections. Researchers from the Amphia Hospital Breda investigated the impact of the so-called screen-and-treat strategy aimed at identification and removal of *S. aureus* shortly before surgery. The researchers proved cost-effectiveness of the non-invasive, screen-and-treat strategy: a little effort and small financial investments can make a big difference in infection rates.

Background MRSA: EU-Wide Burden and Control

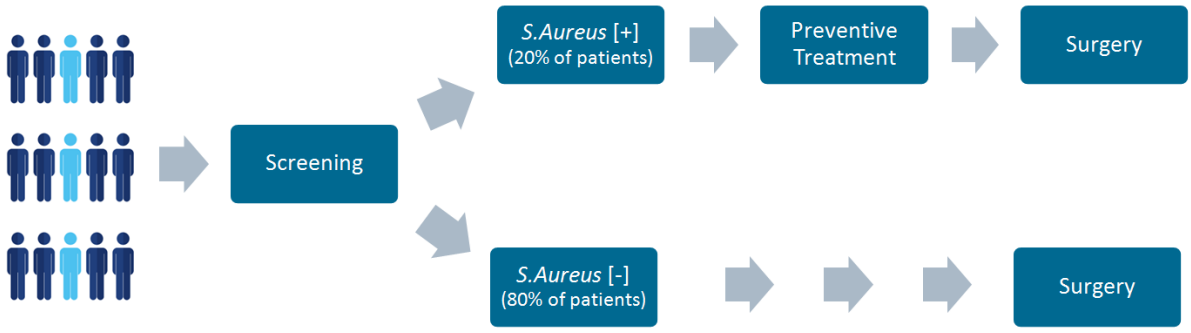
S. aureus is worldwide the most common hospital-acquired infection [7]. Infection rates are increasing due to the widespread dissemination of meticillin-resistant *S. aureus* (MRSA). In 2008 there were an estimated 380,000 infections in EU hospitals. Infection with MRSA is associated with substantial morbidity and mortality [8]. MRSA accounts for 5400 attributable deaths and for more than 1 million in-hospital days. The attributable hospital costs caused by MRSA are also considerable, reaching approximately €380 million annually.

The control of *S. aureus* has traditionally focused on preventing cross-infection between patients. However, it has been repeatedly shown that most *S. aureus* infections originate from patients' own flora (i.e., presence in the nose) [9]. Approximately 20% of the healthy population carries *S. aureus* and is considered a well-defined risk factor for subsequent infection in various patient groups. *S. aureus* should therefore be removed from the nose before surgery to prevent infections.

Screen-And-Treat Strategy

The Amphia Hospital Breda uses a non-invasive screen-and-treat strategy to prevent surgical infections with *S. aureus*. The strategy entails rapid identification of *S. aureus* carriers by means of screening (a real-time polymerase-chain-reaction assay), followed by treatment with mupirocon nasal ointment and chlorhexidine soap. The screen-and-treat strategy is illustrated in Figure 1.

Figure 1: The screen-and-treat strategy to prevent surgical *S. aureus* infections



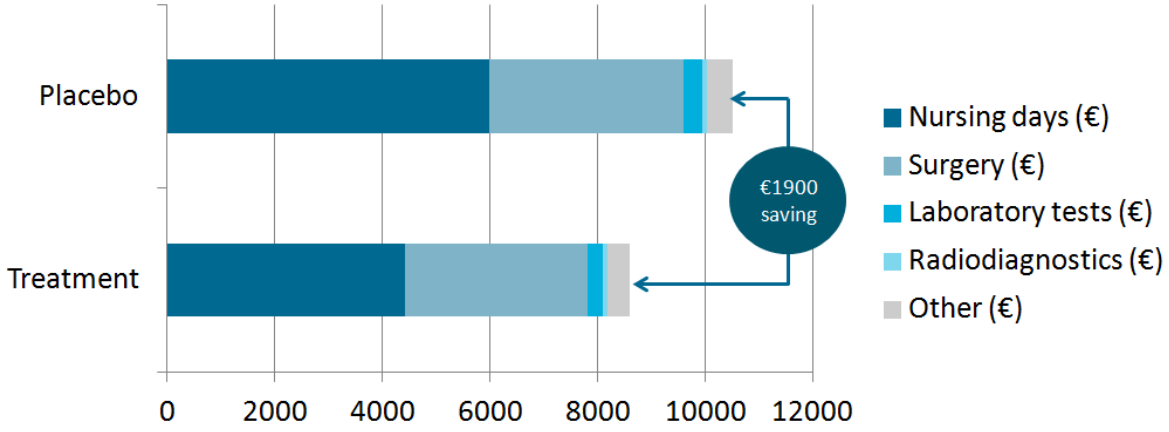
60% Reduction of S. aureus Infections

Jan Kluytmans and colleagues studied the effectiveness of the screen-and-treat strategy in five Dutch hospitals [10]. It was the first study that used a double-blind, randomised, controlled trial design to examine this strategy. The study showed that the screen-and-treat strategy results in a statistically and clinically significant reduction in *S. aureus* infections during surgery. The rate of *S. aureus* infection was 3.4% (17 of 504 patients) in the screen-and-treat strategy group, compared to 7.7% (32 of 413 patients) in the placebo group. The results of this trial provide solid evidence for preventive effectiveness: the risk of hospital associated *S. aureus* infections was reduced by nearly 60%. Moreover, a Cochrane review conducted by researchers from the same study group confirmed effectiveness [11].

A Cost Saving of €1900 per Patient

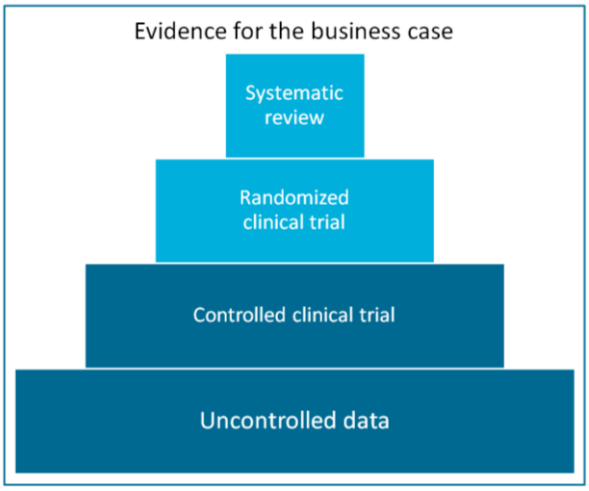
The screen-and-treat strategy also underwent an economic evaluation [12]. The study showed that the screen-and-treat strategy is highly cost-effective from a healthcare perspective. Data from the 'Planning and Control' department were used to calculate the patients' hospital costs. All costs made during the 12 months after (cardiothoracic or orthopaedic) surgery were taken into account. The mean total hospital costs for a screened-and-treated patient undergoing surgery were considerably lower than costs for a placebo-treated patient (€8600 vs. €10,500). This difference was primarily caused by a reduction in hospital stay of almost two days due to fewer infections. Much less nursing time at the IC was therefore required. Given that screening is relatively cheap (around €20), and treating even cheaper (€5 for the mupirocon nasal ointment and €5 for the chlorhexidine soap), the financial investments are almost negligible. The distribution of hospital costs for both groups is illustrated in Figure 2.

Figure 2: Mean hospital costs per patient for placebo and treatment group.



The results of this study show clear benefit of the screen-and-treat strategy in cardiothoracic and orthopaedic surgery. A total of €400,000 per thousand surgeries could be saved, based on the nasal *S. aureus* carriage rate of 20%. Worldwide millions of surgical procedures are performed each year. Huge numbers of patients would therefore benefit from this screen-and-treat strategy, accompanied by large savings. Based on these remarkable findings, both in terms of effectiveness and cost-effectiveness, the US Centers for Disease Control have decided to include this strategy in their top recommendations for safer healthcare.

High Potential for EU-Wide Implementation



Despite the proven (cost-)effectiveness and the fact that mupirocin nasal ointment and chlorhexidine soap are considered relatively safe, several practical barriers may hinder widespread adoption and implementation. First, preoperative screening in the outpatient department and in-patient treatment demands some time and effort from healthcare personnel even though this is only a few minutes. Second, patients sometimes enter the hospital shortly before surgery. In those cases the healthcare personnel do not have the opportunity to treat patients preoperatively. The physician must therefore remember to send a prescription to the pharmacy to facilitate the patient starting treatment at home. Nevertheless, the additional time and effort for screening, treatment, and

prescribing are minimal and do not outweigh the large benefits in terms of patient safety and quality of care. An effort can and should be made to achieve more widespread and sustained use.

Conclusion

Screening for *S. aureus* nasal carriers and treatment with mupirocon nasal ointment and chlorhexidine soap results in a substantial reduction of surgical infection rates and hospital costs. Given the negligible costs of this treatment, and the relatively low burden for healthcare workers, this screen-and-treat strategy can enhance safety and quality of care and provide a considerable return on investment.

This business case was designed in collaboration with Jan Kluytmans (Medical Microbiologist, Amphia Hospital Breda).

Good Practice 2: CRP Point of Care Test to Regulate Antimicrobial Use in Primary Care

A Rapid Diagnostic Tool to Limit Antimicrobial Use for Acute Bronchitis

Lower respiratory tract infection (LTRI) is one of the most common reasons to consult primary care, accounting for 17 million consultations in the EU annually [13]. Acute bronchitis accounts for 80% of these LTRIs [14]. Even though evidence suggests that acute bronchitis benefits little or not at all from antimicrobials, GPs prescribe them to 80% of the patients [15]. Moreover, unnecessary prescribing may lead to serious side effects, such as antimicrobial resistance. Limiting antimicrobial use in the treatment of LTRI is therefore a priority in the prevention of antimicrobial resistance.

Diagnostic uncertainty and patient expectations are major drivers of unnecessary antimicrobial prescribing [16]. Both predictors should be addressed to decrease unnecessary prescribing and to optimise patient outcomes. An intervention that has shown to address both predictors effectively is the C-reactive protein (CRP) Point of Care Test, enhanced with communication skills training.

Diagnostic Uncertainty and CRP Point of Care Test

The CRP Point of Care Test is a highly accurate diagnostic tool to differentiate between acute bronchitis and pneumonia. A low CRP test result reassures the GP that other diagnostics and antimicrobial treatment are unnecessary. The CRP test can be done swiftly in everyday general practice by using a finger prick blood sample. The CRP test results are available after a few minutes. Figure 1 illustrates how the CRP test can support decisions about antimicrobial treatment.

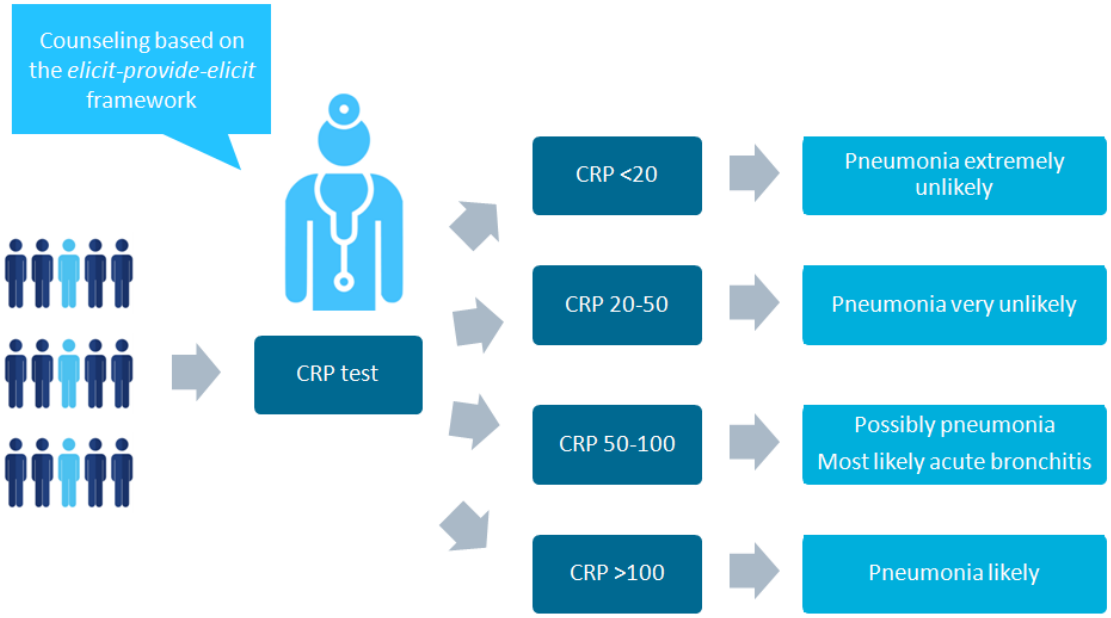
A Communication Skills Training to deal with Patient Expectations

A range of non-medical factors influence the decision about antimicrobial treatment. Important examples are perceived patient pressure, patient satisfaction, and patient expectations. GPs often find it difficult to strike a balance between satisfying patient expectations and evidence-based prescribing. Yet, inappropriate prescribing reinforces misconceptions and may affect future help seeking and expectations. A communication skills training can therefore improve non-antimicrobial disease management.

A communication skills training was developed by researchers from Maastricht and Cardiff universities and incorporated fundamental elements from patient-centred communication strategies, adapted to shared decision making about infection treatment. The main objective of the communication strategy is to *elicit* patients' expectations, *provide* evidence-based information on the natural course of common infections and the balance of effects and side effects of antimicrobials, and

elicit the patients' understanding to facilitate non-prescribing decisions and increase patients' self-care in the future, while relying less on antimicrobials.

Figure 1: The CRP Point of Care Test enhanced with communication skills in primary care



45% Reduction in Antimicrobial Prescribing

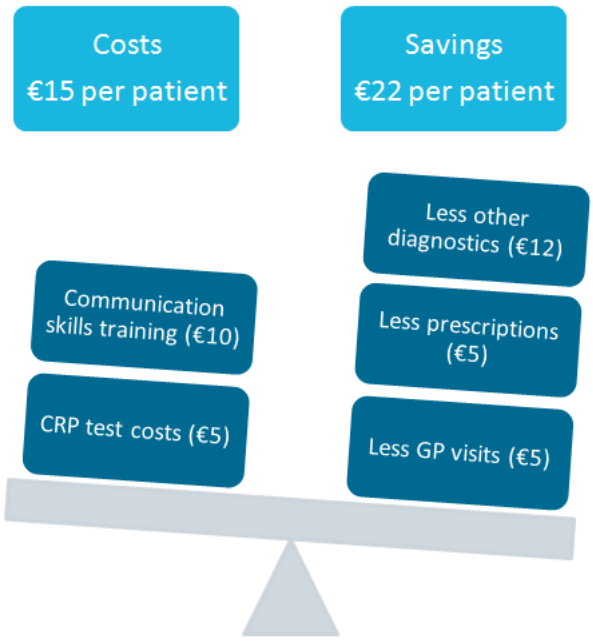
Jochen Cals and his colleagues (Maastricht University, the Netherlands) recently investigated the effectiveness of the CRP Point of Care Test with enhanced communication training [17]. The effectiveness was studied in a large-scale, pragmatic, randomised trial with a one-month follow-up period. The combined intervention resulted in a statistically and clinically significant reduction in the number of antimicrobial prescriptions. The antimicrobial prescribing rate was 68% in the control group (usual care), compared to 23% for patients in the combined intervention group. The researchers claimed that between 150,000 and 240,000 antimicrobial prescriptions could be saved annually, assuming nationwide implementation in the Netherlands. Importantly, despite the substantial reduction in antimicrobial prescribing, patients' recovery and satisfaction were similar in both study groups.

A Saving of €7 per Treated Patient

The CRP Point of Care Test enhanced with communication skills training also underwent an economic evaluation [18]. The economic analyses showed that the cost-savings are larger than the initial investments, even after just one month of running the programme. Patients in the intervention group required less additional diagnostics (e.g., chest X-ray and spirometry), used less antimicrobials, and

visited the GP less often than control group patients (accounting for a cost-saving of €22). Given the low intervention costs (€15 per patient) and the fact that the CRP test can be performed in just three minutes, the feasibility and financial investments cannot be hurdles for further implementation.

Figure 2: Costs and effects of the CRP Point of Care Test



The one-month follow-up period was too short to capture all potential health and economic benefits. The benefits are distant and primarily related to avoidance of antimicrobial resistance. A reduction of antimicrobial prescriptions might lead to long-run benefits. A model-based economic evaluation is therefore needed to build a bridge between antimicrobial prescribing, antimicrobial resistance, and life-years saved. Nevertheless, the short-term effects found on antimicrobial prescribing are considerable and may merit further EU-wide implementation, while taking into account variations within countries and healthcare systems.

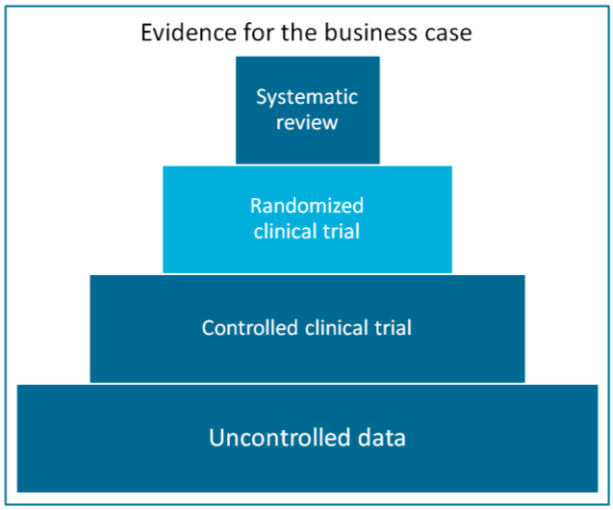
Proven Transferability

Given the high potential of CRP Point of Care Test, a multinational study was conducted to examine its transferability across languages, cultures, and health systems [19]. The effectiveness of CRP Point of Care Test was studied in the Netherlands and four additional EU countries (United Kingdom, Poland, Spain, and Belgium). GPs across nations were trained online to interpret CRP tests adequately and to communicate these effectively. Although online training can be assumed to be less effective than face-to-face training, it has a wider reach, lower costs, and it does not require trained staff on-site. Even though several practices had little interest in reducing antibiotic prescribing and most of them had limited experience with research, the study proved transferability between very different primary care settings. Hence, the CRP Point of Care Test did not only show efficacy in countries with low

prescribing rates, such as the Netherlands and the UK, but also in countries where resistance rates are higher and thus where interventions are needed most.

Conclusion

GPs use of CRP Point of Care Test and training in enhanced communication skills had a major effect on antimicrobial prescribing for LRTI, without affecting clinical recovery or patients' satisfaction. Taking into account the low intervention cost, the minor time investments, and the proven transferability of CRP Point of Care, EU-wide implementation can ensure patient safety while assisting physicians to support non-antimicrobial prescribing decisions and having a positive effect on antimicrobial resistance.



This business case was designed in collaboration with Jochen Cals (Department of Family Medicine, Maastricht University).

Good Practice 3: Antimicrobial Stewardship Teams

Antimicrobial Stewardship can Limit Antimicrobial Resistance Successfully

Inappropriate use of antimicrobials contributes to increasing antimicrobial resistance rates [20]. To control the spread of antimicrobial resistance, the Dutch government has made an antimicrobial stewardship team (also called A-team) mandatory for every hospital. The main objective of stewardship teams is to stimulate appropriate antimicrobial use. Costs are associated with the development of stewardship teams. However, stewardship teams will also reduce antimicrobial resistance rates, the use of expensive restricted antimicrobials, and the length of hospital stay. Stewardship teams will therefore enhance quality of care, while also yielding large cost-savings. Not only in the long run, but also shortly after implementation.

Content of a Successful Stewardship Team

Antimicrobial stewardship has been defined as '*the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for treatment or infection prevention, with minimal toxicity and minimal impact on subsequent resistance*' [21]. The objective of antimicrobial stewardship is threefold. First, to help each patient to receive the most appropriate antimicrobial with the correct dose and duration. Second, to prevent antimicrobial overuse, misuse, and abuse. Third, to minimise the development of resistance. Much evidence is available that stewardship teams enhance the quality of antimicrobial use.

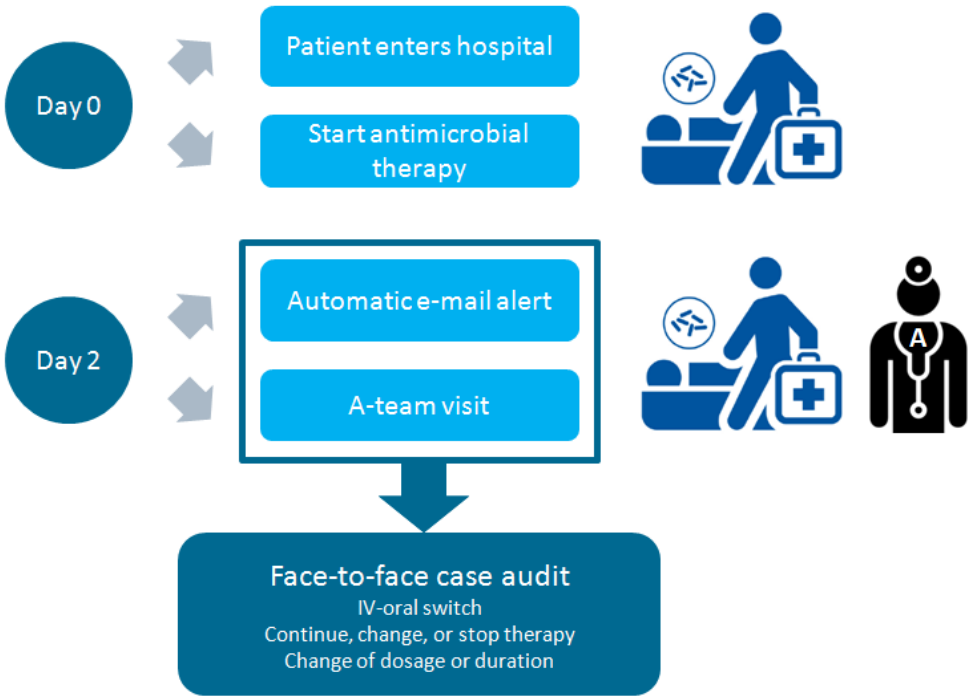
Four elements are key to designing a successful antimicrobial stewardship programme:

1. The stewardship team performs active surveillance by monitoring hospital-wide antimicrobial use and resistance;
2. The stewardship team provides tailored feedback on antimicrobial therapy. The recommendations are based on clinical guidelines and patient diagnostics. The feedback is provided both face-to-face and by a pharmacy e-mail alert system. The e-mail alert provides treatment recommendations about IV-oral switch, selection and dosing of antimicrobials, and the use of restricted antimicrobials;
3. The stewardship team provides continuous education and training to healthcare professionals about appropriate antimicrobial use;
4. The stewardship team includes a multidisciplinary team of professionals, preferably clinical microbiologists, infectious disease physicians, hospital pharmacists, and a quality assurance professional.

The UMCG Antimicrobial Stewardship

The University Medical Centre Groningen (UMCG, the Netherlands) implemented an antimicrobial stewardship that is generally similar to other hospitals' stewardships but has an important unique element: the *face-to-face day 2 case audit*. The aim of the day 2 case audit is to streamline therapy *as early as possible*. The hospital pharmacist sends an automatic e-mail alert to all stewardship members 48 hours after start of antimicrobial therapy. It triggers a case audit, which consists of a stewardship member visiting the ward to discuss the patient's therapy with the bedside physician. They decide together on further treatment (e.g., IV-oral switch and dosage), based on available diagnostics and local guidelines. The therapy will be discussed again after 30 days of treatment. These face-to-face consultations are used to create an effective learning moment. The use of persuasive e-mail alerts has been developed with behavioural scientists from the University of Twente. The stewardship team collaborates with other teams in the regional network to foster exchange of knowledge, experience, and good practice.

Figure 1: The face-to-face day 2 case audit

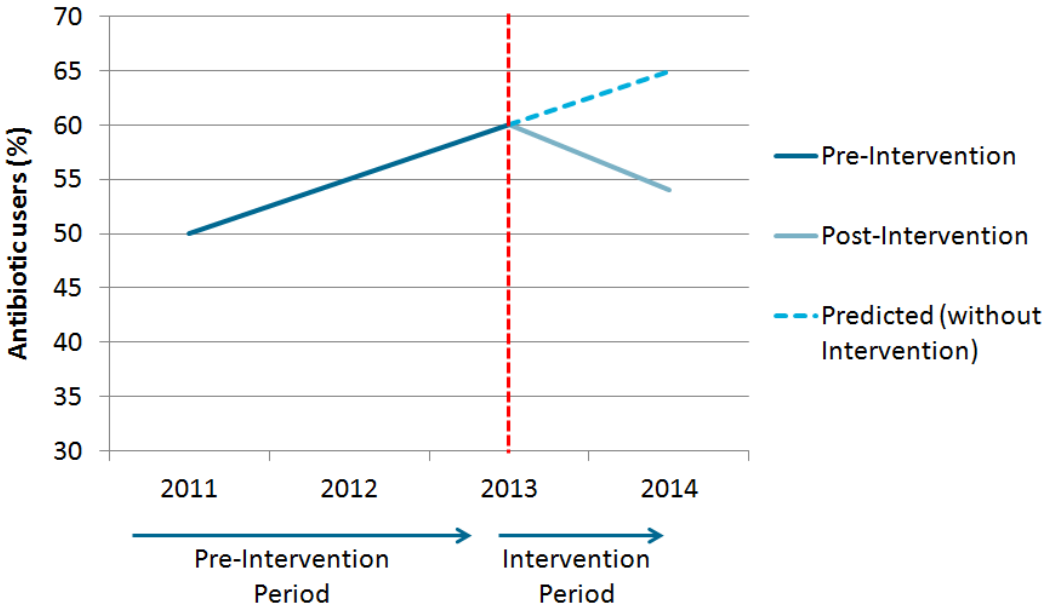


Considerably Fewer Antimicrobial Prescriptions

Alex Friedrich, Bhanu Sinha and colleagues from the UMCG studied the effectiveness of their antimicrobial stewardship programme on a urology ward [22]. The researchers observed a statistically and clinically significant reduction in the number of antimicrobial prescriptions (see Figure 2). The average length of hospital stay was also reduced by more than one day. It should however be emphasised that these results only hold for patients without severe underlying comorbidity.

Nevertheless, given that both antimicrobial use and length of stay predict quality of care, the stewardship seems to have a major impact on sustainability of healthcare.

Figure 2: Antimicrobial use before and after implementation of the antimicrobial stewardship on a urology department

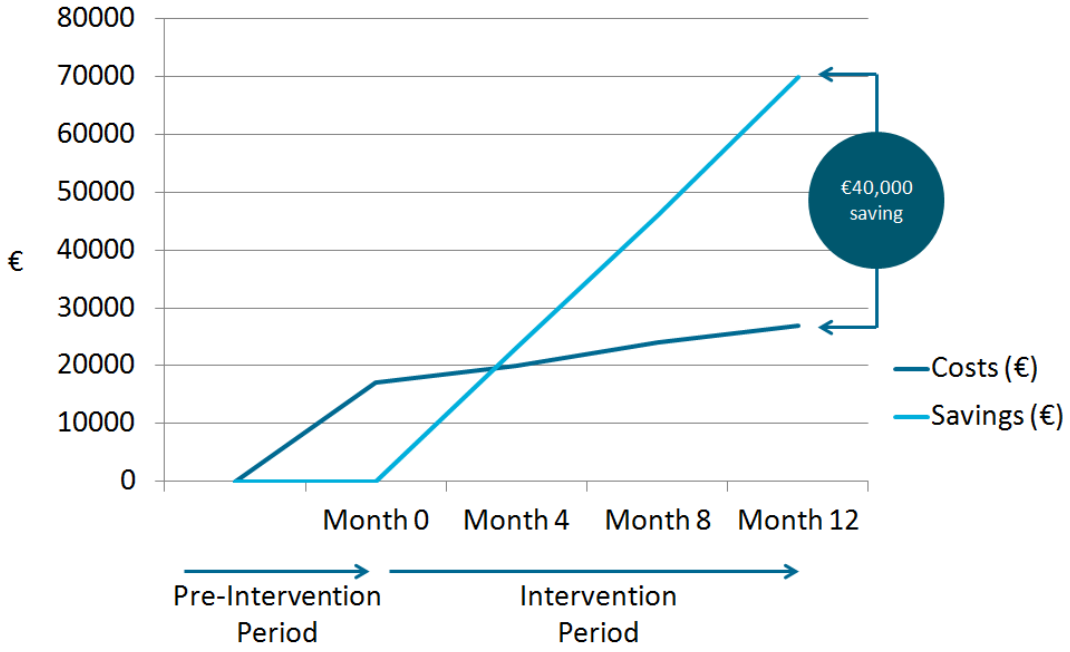


A yearly cost-saving of more than €40,000

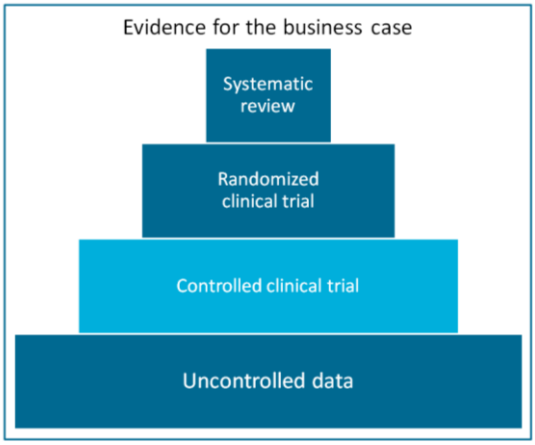
The same research group from the UMCG also studied the cost-effectiveness of the antimicrobial stewardship [23]. The hospital costs from patients in the effectiveness study were compared with a historical cohort from the same urology ward. The hospital costs were divided into pre-intervention costs (stewardship meetings and the development of the pharmacy e-alert programme; €17,000) and intervention costs (case audits, stewardship meetings, and maintenance of the pharmacy e-alert programme; €10,000 per year). Patients treated by the stewardship switched significantly earlier from IV to oral therapy, had a shorter length of hospital stay, and required less nursing time. In total, this accounted for almost €70,000 less hospital costs than the historical cohort during a 12-month period after implementation.

This economic evaluation strongly indicates cost-effectiveness of the antimicrobial stewardship. Moreover, it seems that it takes only a few months to reach a break-even point. This implies that the stewardship can lead to positive return on investments, even shortly after implementation.

Figure 3: Costs and savings of the antimicrobial stewardship



Conclusion



With increasing complexity of infections and the scarcity of new antimicrobials, the future of successful antimicrobial therapy looks challenging. Yet, antimicrobial stewardship can provide practitioners with tools to prevent inappropriate use of antimicrobials and to control the spread of antimicrobial resistance. Although the implementation of antimicrobial stewardships is often underappreciated, many studies have shown that antimicrobial stewardships can effectively prevent antimicrobial resistance. Moreover, the business cases in the present report show that stewardships have an attractive return on investment. By making antimicrobial stewardship part of daily practice, we can improve our safety, quality, and sustainability of healthcare.

More Evidence for Cost-Effectiveness of Antimicrobial Stewardship Teams

Not only the University Medical Centre Groningen proved cost-effectivenss of their antimicrobial stewardship, but also the Canisius-Wilhelmina Hospital (CWZ) Nijmegen.

The key elements of the CWZ stewardship team are antimicrobial vigilance alerts (daily monitoring of antimicrobial use), audit-feedback, and a IV-oral switch programme. The CWZ antimicrobial stewardship team consists of an internist-infectiologist (0.3fte), a microbiologist (0.3 fte), a pharmacist (0.1 fte), and an IT specialist (0.1 fte).

Internist-infectiologist Dr. Tom Sprong and colleagues studied the effectiveness of the antimicrobial stewardship. They showed that more than 50% of all antimicrobial prescriptions were modified due to antibiotic vigilance alerts and audit-feedback. In addition, considerably less restricted antimicrobials were prescribed. They also showed that the antimicrobial stewardship resulted in a 1-day earlier IV-oral switch. An estimation was made of a €40,000 hospital-wide cost-saving over a 12-month period.

This business case was designed in collaboration with Alex Friedrich, Bahnu Sinha, Jan-Willem Dik (Medical Microbiologists at the University Medical Centre Groningen), and Tom Sprong (Medical Microbiologist at Canisius-Wilhelmina Hospital Nijmegen).

Good Practice 4: Control of an Outbreak of Multiresistant *Klebsiella Pneumoniae*

How to Control and Prevent a Nursing Home Outbreak of Multiresistant *Klebsiella Pneumoniae*

Given the presence of many vulnerable residents, a multiresistant *Klebsiella pneumoniae* outbreak is a concern of every nursing home [24]. Infections with multiresistant *Klebsiella pneumonia* have been associated with increased costs, treatment failures, and death [25]. In 2013, nursing home De Riethorst in the Netherlands was affected by a multiresistant *Klebsiella pneumoniae* outbreak [26]. The outbreak led to *Klebsiella pneumonia* associated deaths and controlling the outbreak has taken considerable effort and costs (€250,000). This case study illustrates the threat to patient safety of a *Klebsiella pneumoniae* outbreak and the importance of outbreak prevention.

How does Klebsiella pneumoniae spread?

A person can be infected with *Klebsiella pneumoniae* after being exposed to the bacterium. *Klebsiella pneumoniae* can cause different types of healthcare associated infections, including bloodstream, wound, and surgical infections. Infections with *Klebsiella pneumoniae* commonly occur among sick patients and are primarily spread through person-to-person contact. For instance, via hands of healthcare personnel or other persons. *Klebsiella pneumoniae* is not spread through the air. Patients are particularly vulnerable when they are on breathing machines, when having intravenous catheters, or when having wounds caused by injury or surgery.

The Case of Nursing Home De Riethorst

In 2013, a 69-year old patient was transferred from a hospital's isolated intensive care unit to nursing home De Riethorst. A few weeks earlier, the patient was infected with a multiresistant *Klebsiella pneumoniae* bacterium on an intensive care unit in a Greek hospital. Despite the strict contact precautions for this patient undertaken by nursing home De Riethorst, five additional residents were infected with the multiresistant *Klebsiella pneumoniae* bacterium. The multiresistant *Klebsiella pneumoniae* led to severe health risks for infected residents and the infection contributed to the death of one patient.

Nursing home De Riethorst formed a closely collaborating outbreak management team to stop the spread of *Klebsiella pneumoniae*. The team consisted of five internal members: a location manager, a geriatrician, a member from the board of directors, a facility manager, and a communication specialist.

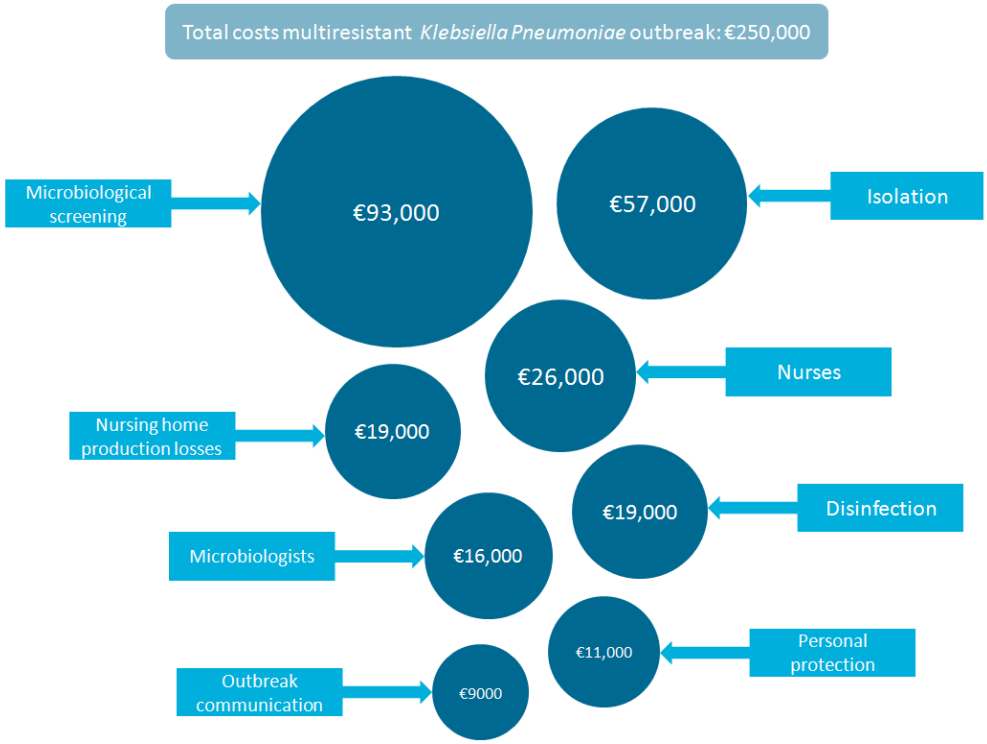
The team also consisted of external members, including a microbiologist and an infection control specialist. The control measures taken to prevent further spread were:

- Transfer of infected residents to a separate location outside the nursing home;
- Isolated treatment for transferred residents;
- Disinfection of the wards where the infected residents were treated earlier;
- Intensive screening on *Klebsiella pneumoniae* for all residents at De Riethorst;
- Development of an improved hygiene and infection control plan;
- Infection control measure audits;
- Communication of the outbreak with residents, family, healthcare personnel, the municipality, other healthcare organisations, and the media (newspapers, internet, television, and radio).

€250,000 Expended to Control the Multiresistant Klebsiella pneumoniae Outbreak

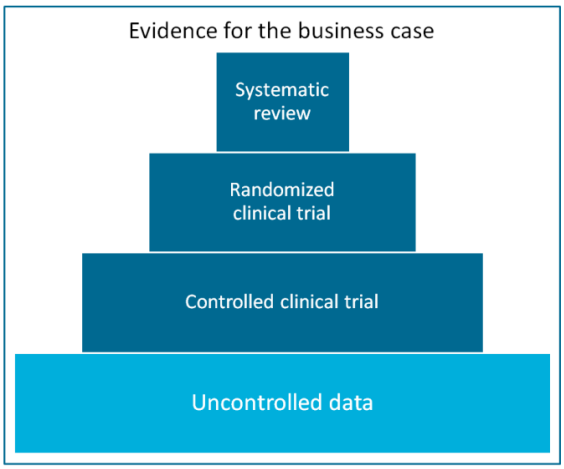
Controlling an outbreak does not only take a considerable effort, but it is also costly. The total expenditure was €250,000 and was paid from the nursing home's budget. The major cost drivers were additional microbiological screening on *Klebsiella pneumoniae* (€93,000), isolated treatment of infected residents (€57,000), and hiring of temporary personnel and staff (€42,000). It took three months to control the outbreak and all residents were intensively screened for more than one year after the outbreak. The substantial costs and severe health risks associated with a multiresistant *Klebsiella pneumoniae* outbreak underline the importance of routine prevention.

Figure 1: Costs associated with controlling the multiresistant *Klebsiella pneumoniae* outbreak



Strict Hygiene Guidelines to Prevent a Multiresistant Klebsiella Pneumoniae Outbreak

To prevent the spread of *Klebsiella pneumoniae* infections between residents, nursing home staff are expected to follow specific infection control guidelines. The guidelines include strict adherence to hand hygiene and wearing gowns and gloves when entering rooms where residents with severe infections are housed. Healthcare facilities must also follow strict cleaning procedures to prevent the spread of *Klebsiella pneumoniae*. Moreover, residents are expected to clean their hands very often. For instance, before preparing food, after using the bathroom, after blowing their nose or sneezing, and before touching their eyes, nose or mouth. Nursing home staff have the responsibility to encourage this. Nursing home De Riethorst currently implements more stringent guidelines for hygiene and infection prevention. An infection prevention specialist is primarily involved to achieve this. The current expenses for infection prevention are €75,000 annually (mainly spent on the infection control specialist, disinfection materials, and diagnostic procedures). This amount equals 0.15% of the total budget.



Conclusion

The outbreak of multiresistant *Klebsiella pneumoniae* at nursing home De Riethorst shows that much effort and high costs are associated with controlling a *Klebsiella pneumoniae* outbreak. Isolated treatment of *Klebsiella pneumonia* positive patients by highly trained personnel and strictly adhering to hygiene and infection control guidelines are key to successful outbreak prevention management. Moreover, hospitals and nursing homes should communicate carefully and effectively when transferring patients at risk to other healthcare institutions.

An Effective Hygiene Improvement Programme at Nursing Home Proteion

Nursing home Proteion has shown that a hygiene improvement programme can enhance adherence to infection control guidelines among nursing home staff.

The key elements of the hygiene improvement programme were continuous education and feedback on adherence to hygiene guidelines (not wearing rings, watches, bracelets, nail decoration, and long sleeves). Nursing home staff were monitored unannounced twice a year and received tailored feedback on their adherence to hygiene guidelines. An infection control specialist (0.4 fte) was

responsible for the programme.

The infection control specialist showed that education and monitoring-feedback on adherence to hygiene guidelines is effective among nursing home staff. During the first unannounced assessment in April 2013, 60% of the nursing home staff were adhering to hygiene guidelines. After two years and four feedback sessions, adherence had improved to 90%.

This business case was designed in collaboration with Adrie de Laat (Manager Care, De Riethorst), Frank Staal (Board of Directors, De Riethorst), Hilco Kivits (Planning and Control, De Riethorst), and Judith Hokkeling (Infection Control Specialist, Proteion).

Good Practice 5: Control of a Hospitalwide Vancomycin-Resistant *Enterococcus* Outbreak

Outbreak Prevention Programmes in Hospitals Contribute to Sustainable Healthcare

Hospital-acquired infections with multiresistant bacteria occur worldwide and are among the major causes of death and increased morbidity among hospitalised patients. An unusual or unexpected increase of these hospital-acquired infections is a so-called *outbreak*. An outbreak should be identified and eliminated as early as possible. Not only to maintain patient safety, but also to avoid huge expenses to control the outbreak. In 2012, The Antonius Hospital Nieuwegein experienced a Vancomycin-Resistant *Enterococcus* (VRE) outbreak. In this case study we use the example of the Antonius Hospital to illustrate that the investments needed to control an outbreak of multiresistant bacteria are about eight times higher than the yearly costs for routine outbreak prevention. In addition, routine outbreak prevention may reduce the risk of multiresistant bacteria to become endemic, preventing additional downstream costs.

Spread of Vancomycin-Resistant Enterococcus

VRE is a bacterial strain resistant to the antimicrobial Vancomycin [27]. The bacterium can be found in the bowel and on the skin of humans. It is usually spread via contact with hands, surfaces or medical equipment. VRE does not affect healthy and young people, but VRE can be life-threatening for patients with weakened immune systems [28]. An outbreak of VRE is therefore a concern of every hospital [29]. If hospitals do not screen on VRE routinely, there is a serious risk on uncontrolled spread of VRE.

Outbreak Control: More than 2 Million Euros Spent on control of the VRE outbreak

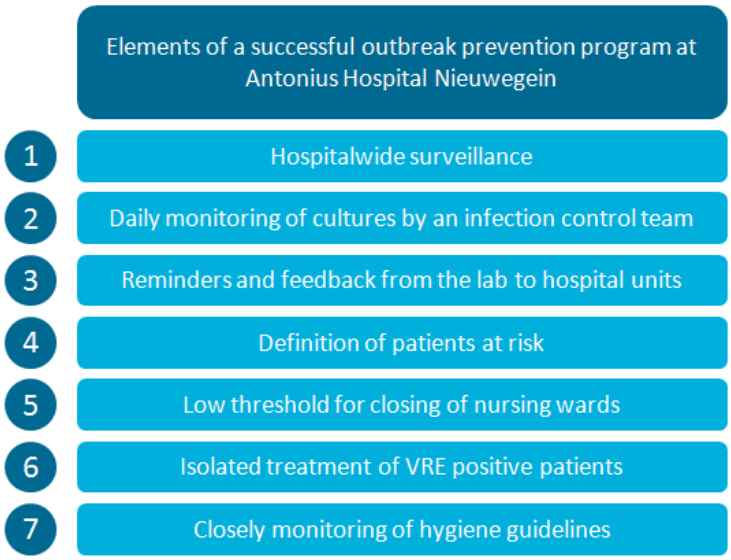
In 2012, a VRE bacterium was detected on a nursing ward of the Antonius Hospital Nieuwegein. The hospital had never previously experienced any problems with VRE. Eventually, three bacterial clones were involved, of which one highly contagious. Carriership of VRE was demonstrated in 250 patients. Twelve of these patients were infected with VRE. The infected patients were mainly treated on nursing wards for internal medicine and oncology. The outbreak was controlled by weekly hospital-wide screening, isolation of patients carrying VRE, closure of wards, and disinfection of rooms. The awareness of healthcare workers for basic hygiene measures was increased by information, training and audits.

The efforts and costs to control the outbreak were considerable. The hospital spent more than 2 million euros. These costs included personnel costs on the wards (cleaning and disinfecting the nursing wards,

additional personnel for treating isolated patients), material costs (gowns, gloves, hydro alcoholic solutions, disinfection procedures), and diagnostic procedures.

Outbreak Prevention: Elements of a Successful Programme

After controlling the outbreak, the Antonius Hospital Nieuwegein implemented a successful outbreak prevention programme, which resulted in full elimination of VRE infections within two years after implementation. Moreover, the prevention programme had some spillover effects to any other possible infection threat. The programme is based on a collaborative working atmosphere in an open dialogue culture, based on openness and trust. The key elements of the prevention programme are displayed in the diagram below.



Outbreak Prevention: Costs estimated at about 1/7th of the Costs of Outbreak Control

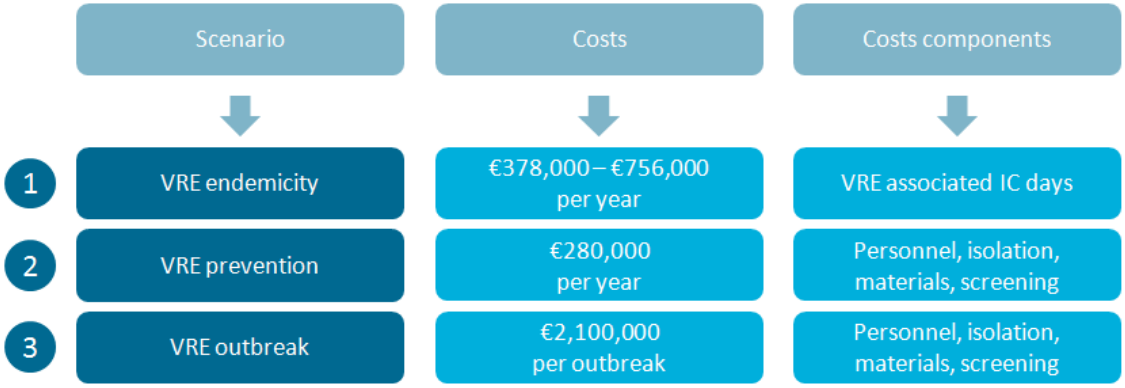
An estimation was made for the costs associated with the VRE outbreak prevention programme. Approximately 200 additional VRE screening cultures are taken each month. Each culture costs €50, including assessment and feedback by the microbiologist. Around €10,000 is therefore spent each month on VRE screening cultures, adding up to €120,000 on a yearly basis. The cultures are taken by nurses, which takes on average 20 hours (€50 per hour) per week (€12,000 on a yearly basis for personnel costs). In the case of early detection, VRE spread is limited, and only a limited number of patients will have to be isolated (additional costs of nursing and materials estimated at €150,000 per year). Incidentally closure of a ward may be necessary. The total costs for this VRE outbreak prevention programme are estimated at €280,000 per year.

Outbreak Prevention: an estimated Yearly Cost-Saving of €150,000

An estimation was also made of the potential health and financial gain of VRE outbreak prevention. Yearly, more than 45,000 patients are being hospitalised at the Antonius Hospital Nieuwegein. If the hospital would not have undertaken any preventive strategies, it was estimated that VRE would become endemic in the hospital and approximately 10% to 20% of the hospitalised patients would carry VRE. This adds up to 4500 to 9000 patients annually. If cultures are not being taken routinely, and if VRE spreads through the hospital, around 135 to 270 blood stream infections would occur per year. Given the VRE associated mortality rate of 20%, 27 to 54 patients with VRE blood stream infections would die each year.

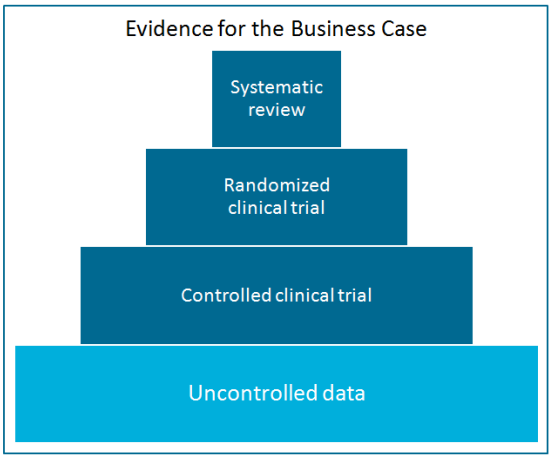
Assuming no routine VRE screening, 27 to 54 intensive care admissions will be associated with VRE. Given the average length of stay of 7 days (€2000 for each day), this accumulates to €378,000 to €756,000 each year. Knowing the €280,000 yearly costs for prevention, a break-even point will be reached within a few months. Moreover, more than €150,000 can be saved annually by implementation of intensive VRE outbreak prevention.

Figure 1: The estimated costs for three different scenarios



Conclusion

The Antonius Hospital Nieuwegein case study underlines the burdensome and costly consequences of an outbreak of a multiresistant bacteria strain, emphasising the urgency of implementing routine prevention programmes. This case, although on uncontrolled data, gives an indication of the effort and costs required for intensive, hospital-wide screening, feedback on therapy in an open dialogue



culture, patient isolation, and adherence to hygiene guidelines. Even though the yearly costs for these preventive strategies can be high (€280,000), the costs are still substantially lower than the costs for controlling an outbreak (>€2,000,000) and the additional costs related to endemicity (€378,000 – €756,000). In addition, the prevention costs probably do not outweigh the additional gain in patient safety and health. Implementation of a hospital-wide outbreak prevention programme can therefore improve patient outcomes and can help to keep healthcare sustainable.

Debate about the Necessity of Routine VRE screening

Although the Antonius Hospital case has shown serious (financial and health-related) consequences of a VRE outbreak, the necessity of hospital-wide screening on VRE is debated [30]. Active screening has been shown to control increasing number of VRE infections. Yet, the cost-effectiveness is still unproven, since VRE is only harmful to a small number of patient groups and infection rates are relatively low. Active screening of patients to identify carriers of VRE therefore remains a hot-button issue that will probably intensify in the near future, especially given the high costs associated with controlling an outbreak and the possible impact on patient safety.

It is also important to emphasise the difficulty of estimating the cost-effectiveness of preventing hospital outbreaks. It depends on several factors, in particular the frequency of outbreaks. However, one of the few studies that examined costs and savings associated with VRE infection control showed similar numbers as the estimations presented in the current case study [31].

This business case was designed in collaboration with Thijs Tersmette (Medical Microbiologist, Antonius Hospital Nieuwegein).

5 Discussion

Main Findings

The objective of the present report was to provide insight into the costs and potential (health and financial) gains associated with infection control and adequate use of antimicrobials aimed at reducing the spread of antimicrobial resistance. The cost-effectiveness of five Dutch good practices was described in business cases. Despite some methodological limitations in some of the business cases, the evidence suggests that several approaches are available to reduce the spread of antimicrobial resistance efficiently. Not only multifaceted and complex approaches were described, but also non-invasive and feasible approaches with a high potential implementation. One good practices has already been implemented in other organisations, even in some other EU countries (CRP Point of Care Test). EU-wide implementation of (the most effective components of) the good practices described in this report can lead to a reduction of infections with microorganisms, more adequate use of antimicrobials, and a reduction of antimicrobial resistance rates. These outcomes will contribute to improved patient safety and patient health, leading to more sustainable healthcare. Now, and in the future.

Lessons Learned

Several lessons can be learned from the present report. The key lessons are listed in the following paragraphs.

Surveillance and Feedback in an Open Dialogue Culture

We strongly emphasise the importance of establishing an organisation-wide safety culture. Key in this respect is the combination of closely monitoring of healthcare professionals' behaviour (prescribing of antimicrobials and adherence to infection control guidelines) and tailored (oral or written) feedback on behaviour. The responsibility should be taken by a multidisciplinary team of healthcare professionals, including clinical microbiologists, infectious disease physicians, hospital pharmacists, infection control specialists, and quality assurance professionals. A precondition for effectiveness is an open dialogue culture, based on openness and trust. Two business cases (Antimicrobial Stewardship Teams and Antonius Hospital Nieuwegein) have shown that effective surveillance and feedback can lead to more adequate antimicrobial prescribing, fewer infections, shorter length of hospital stay, and less antimicrobial resistance.

Inter-Institutional Collaboration

The cost-effectiveness of infection control and adequate use of antimicrobials can be further enhanced through regional cooperation in partnerships. The fight against antimicrobial resistance is usually

targeted at individual healthcare institutions. These are generally seen as the source of antimicrobial resistance. However, the high connectivity of healthcare networks will impact the effectiveness of infection control strategies and adequate use of antimicrobials, as for example is shown in the case 'De Riethorst. Healthcare institutions should therefore cooperate regionally and internationally to fight antimicrobial resistance successfully. Especially in areas with high levels of cross-region and cross-border patient referrals.

Adherence to Infection Control Measures

Infection control measures, though often under-recognised and under-supported, are an essential part of patient safety. These measures aim to control factors related to the spread of infections within the healthcare setting (whether patient-to-patient, from patients to staff and from staff to patients, or among-staff), including prevention via hand hygiene, disinfection, surveillance, monitoring of demonstrated/suspected spread of infection, and management (interruption of outbreaks). The business cases of nursing home De Riethorst and Antonius Hospital Nieuwegein have shown the massive impact of an outbreak to the healthcare institution itself, the surrounding healthcare institutions, and society as a whole. Although outbreaks occur rarely, and that their occurrence is difficult to predict, avoidance of outbreaks should be a priority for healthcare institutions. Moreover, fewer infections require less antimicrobial therapy, ultimately leading to less antimicrobial resistance.

Careful Implementation

A precondition for long-term effects of these policies is sustained implementation of cost-effective approaches. Yet, while the good practices in this report have proven to be cost-effective in their study setting, the transferability to other healthcare institutions (and to other EU countries) has not been examined yet. Although we do not have clear reasons why the cost-effectiveness would be markedly different in other healthcare settings, the elements of infection control and adequate use of antimicrobials may be prioritised less in other healthcare settings, leaving less (financial) room for infection control and promotion of adequate antimicrobial use. It thus seems important to study the cost-effectiveness of good practices in other healthcare institutions, whether the approaches fit in the culture and logistics of those settings, whether reimbursement is available, and whether elements of good practices need to be adapted, removed, or added.

One of the good examples, the CRP Point of Care Test (Department of Family Medicine, Maastricht University) proved to be transferrable. A conclusive study showed that this intervention fits into the healthcare systems of five different countries (UK, Poland, Belgium, Spain, and the Netherlands). The study also showed effectiveness across these borders and cultures. Yet, it is still unclear whether cost-effectiveness also holds for these other countries.

It is more challenging, however, to make valid claims about the potential impact in other countries of more complex and hospital-wide interventions, such as antimicrobial stewardship teams. Even though cost-effectiveness has been proven in the Netherlands, the numbers might not be transferable to other countries. It should first be studied whether antimicrobial stewardships fit into the culture and healthcare system of other countries. Moreover, given the initial costs to develop a antimicrobial stewardship team, financial barriers may also be present. Notwithstanding, even though it can be hard to implement stewardship teams 1-on-1 in other settings, much can be learned from the basic principles that stewardship team entail (e.g., continuous surveillance of antimicrobial use and resistance, and active feedback on therapy).

Perhaps the biggest barrier to implementation of antimicrobial policies are the initial personnel effort and costs. The costs must therefore be justified by demonstrating savings to the institution. The business cases presented here showed that clinical effectiveness can be accompanied by economic value. This can inspire other institutions to investigate and present the investments and savings of their antimicrobial stewardship likewise.

Methodological Limitations

The business cases presented in this report have some limitations. In the following paragraphs we will highlight those that are important for the interpretation of the results.

Variation in the Methodological Quality of Evidence

There is considerable variation between good practices in the quality of evidence used for the business case. Four categories were used to discriminate the methodological quality of business cases, ranging from high to low quality of evidence: (1) evidence from systematic reviews; (2) evidence from randomised controlled trials; (3) evidence from non-randomised controlled trials; and (4) uncontrolled trials. It is important to take the methodological quality into consideration when interpreting the cost-savings for each business case: how lower the quality of evidence, how higher the uncertainty regarding the point estimates presented.

In addition, despite the high accuracy and validity of randomised controlled trials (e.g., business case of Amphia Hospital Breda), it is uncertain whether the results can be generalised to a larger population. The study setting was highly controlled, which implies that delivery of the intervention can be monitored closely and improved if necessary. It cannot be guaranteed, however, that the intervention will be adopted by other healthcare personnel or healthcare institutions, or that the intervention will also be delivered as intended in routine clinical practice. Hence, implementation projects are necessary to enhance sustained uptake.

High generalisability can be achieved by making use of large observational (and usually uncontrolled) data (e.g., business cases of stewardship teams and VRE outbreak prevention). Yet, in these business cases, there is large uncertainty regarding the accuracy and validity of the estimations presented and considerable financial claims have been made. Quasi-experimental trials are therefore recommended to study the accuracy and validity of the presented cost-savings of stewardship teams and outbreak prevention.

Debate about the necessity of VRE screening

Although the Antonius Hospital case has shown serious (financial and health-related) consequences of a VRE outbreak, the debate is still open about the necessity of hospital-wide screening on VRE [31]. Active screening has shown to control increasing number of VRE infections. Yet, the cost-effectiveness is still unproven, since VRE is only harmful to a small patient groups and infection rates are relatively low. Active screening of patients for carriage with VRE thus remains a hot-button issue that will probably intensify in the near future. Especially given the high costs associated with controlling an outbreak and the possible impact on patient safety.

Comparison of Infection Control between Hospitals and Nursing Homes

Without careful consideration, infection control recommendations in hospitals cannot be applied in nursing homes. Adherence to infection control recommendations is generally more difficult in long-term care facilities than in hospitals due to differences in population characteristics, length of stay, staff education level, aim of the organisation (*living* in a nursing home vs. *recovery* in a hospital), and the level of social interaction between patients/residents [26]. In addition, the frequency of diagnostic sampling is generally much lower in long-term care. Detecting and preventing the transmission of highly resistant microorganisms is therefore much more challenging in nursing homes than in hospitals.

One example is the *Klepsiella pneumoniae* outbreak at nursing home De Riethorst. This outbreak started when a 69-year old patient was transferred from a nearby hospitals isolated intensive care unit to nursing home De Riethorst. A few weeks earlier, the patient was infected with a multiresistant *Klebsiella pneumoniae* bacterium on an intensive care unit in a Greek hospital. Despite the strict contact precautions for this patient undertaken by the nursing home, five patients were infected with the multiresistant *Klebsiella pneumoniae* bacterium. Given the relative difficulty of infection control in nursing homes compared to hospitals (outlined in previous section), it could be argued that it may have been wiser to leave the patient at the hospital. On the other hand, it remains debatable whether hospitals should take responsibility for infection control only because hospitals are generally better organised to prevent spread of microorganisms. Nevertheless, the monitoring of patient movements

and direct communication between hospitals and long-term care facilities is of utmost importance to prevent inter-institutional spread. Future efforts should focus on optimising these processes.

Final Conclusion

Given the rapid EU-wide spread of antimicrobial resistance and the limited pipeline of new antimicrobials, cost-effective interventions are urgently needed to improve antimicrobial prescribing and infection prevention. We have presented the cost-effectiveness of five Dutch good practices that have shown to improve antimicrobial prescribing and infection control successfully and efficiently. Other healthcare institutions, inside and outside the Netherlands, can benefit from the presented business cases by implementing (the most effective elements of) antimicrobial policies into their system. Sustained implementation can improve patient outcomes, can lead to substantial cost-savings, and can thereby further ensure sustainability of EU-wide healthcare.

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