REPORT

Radboudumc

ANTIMICROBIAL RESISTANCE POLICIES
Four good practices from the Netherlands

Niek Stadhouders
Ali Auzin
Stefan Auener
Toine Remers
Patrick Jeurissen
Heiman Wertheim

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Project team:
Niek Stadhouders, PhD
Ali Auzin, MSc
Stefan Auener, MSc
Toine Remers, MSc
Prof. dr. Patrick Jeurissen (advisor)
Prof. dr. Heiman Wertheim, MD PhD

Correspondence:

Radboud University Medical Center, IQ healthcare

P.O. Box 9101 (114 IQ healthcare)

6500 HB Nijmegen, the Netherlands

E: iqhealthcare@radboudumc.nl

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Content

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List of abbreviations

3GC	Third-generation cephalosporins
AMR	Antimicrobial resistance
ASP	Antimicrobial stewardship programme
AST	Antibiotic susceptibility testing
DALY	Disease-adjusted life year
DDD	Defined daily dose
ECDC	European Centre for Disease Prevention and Control
FTE	Full-time equivalent
GP	General practitioner
GRAS	Gonorrhea and antibiotic resistance surveillance
HIP	Hygiene In Practice
IPC	Infection prevention and control
ISIS-AR	Infectious disease surveillance information system for antimicrobial resistance
KNMP	Dutch society for clinical pharmacologists
LTC	Long-term care
MML	Medical microbiological laboratories
NHG	Dutch college of General Practitioners
NIV	Dutch society for infectious diseases
NVMM	Dutch society of medical microbiology
OECD	Organization for economic cooperation and development
OPAT	Outpatient parenteral antimicrobial treatment
PPP	Purchasing power parity
POC	Point-of-care tests
RIVM	National Institute for Public Health and the Environment
RZN	Regional care networks antimicrobial resistance
SFK	Foundation for Pharmaceutical Statistics
SWAB	The Dutch working group on antimicrobial policy
VHIG	Dutch society for Infection prevention in Healthcare
VIZ	Dutch society for infectiology
WHO	World Health Organization
WIP	The Dutch working group for infection prevention

1 Executive Summary

AMR: saving lives and saving money

When president Obama presented the Accountable Care Act, he often paraphrased its goal as 'saving lives and saving money'. There are few places where this is more true than in the global fight against antimicrobial resistance (AMR), which increasingly burdens public health and healthcare budgets. The threat of AMR to human health is estimated to be as high as an annual mortality of 33,000 in the EU in 2015 (2), costing $1.5 billion PPP per year (3). Due to the high costs associated with AMR, investing in policies to combat AMR is likely to save money. For example, hospital based policies are estimated to save up to $1.2 million PPP per 100,000 people, while community-based interventions can save up to $275,000 per 100,000 people (3). Savings are primarily due to shorter hospital stay and less emergency care, since the antibiotics themselves are relatively inexpensive (3).

However, as the current COVID-19 outbreak demonstrates, an outbreak of an infectious disease can have huge costs within or outside the healthcare sector, and might even stall entire economies.

The effects of AMR are less visible, as it concerns a diverse range of pathogens, antibiotics and disease syndromes. With AMR being so diverse and dispersed, the savings of good AMR interventions and governance structures are also challenging to estimate. In this report we present a feasibility analysis of the savings of good AMR practices in the Netherlands, which is known for its low antibiotics prescription and AMR rate. In an earlier report we already analysed five good practices to illustrate the savings potential of prudent AMR interventions. In this report we add four good practices in the area of hospital-based and community-based interventions, as well as in the area of surveillance and governance of AMR.

The first case study, a hospital-based intervention, concerns outpatient parenteral anti-microbial therapy (OPAT). With OPAT patients can be treated at home with intravenous antibiotics for complex infections. OPAT reduces hospital length of stay and improves appropriateness of treatment due to the multidisciplinary nature of the OPAT teams. Cost savings were estimated at € 1,212 per eligible patient. At a large university medical centre this amounted to € 312,780 annually. OPAT is currently introduced across hospitals in the Netherlands through regional and national collaborative platforms. This therapy will have substantial positive effects for the health of people and the bottom line of the financial reports of Dutch hospitals.

The second case study, a community-based intervention, involves an information booklet for GPs. In the Netherlands, the antibiotic prescription rate in the community setting has always been very low, but further reductions are possible especially in out-of-office-hours GP clinics. An information booklet for GPs to educate parents of children with fever reduced antibiotics prescriptions by 3%, which resulted in modest net savings of €5 per 100 patients. Such estimates are conservative, as reductions in AMR burdens could not be incorporated reliably on the benefits side. This business case demonstrates that even in low-incidence countries, interventions in community settings can still achieve net savings to the health system.

The third case study covers the impact of the Dutch surveillance systems. The national surveillance system ISIS-AR is used to showcase the potential benefits and uses of surveillance data. A surveillance network that provides feedback and support is a necessary condition for any integrated AMR strategy. The Dutch surveillance network is a good example of how collaborative national governance can successfully coordinate local initiatives. It is an essential precondition for an integrated AMR strategy.

The fourth case study covers the governance structure for AMR in the Netherlands and how this is perceived by foreign experts. The governance of the Netherlands is described in a thematic fashion using examples of interventions or measures for each theme. Interviews were held with key experts in European countries in order to compare the key differences with other countries and to find out what according to these experts could explain the success of the Netherlands with regard to the low AMR rates.

Maintaining and improving a sustainable healthcare system

These business cases are examples of low-hanging fruit: implementation improves care and lowers health spending. However, uncertainty regarding the costs of AMR and discrepancies between the agents that incur these costs and those that benefit from the intervention may pose barriers to its implementation. A professional and proactive culture allows health professionals to overcome these barriers. All four good practices demonstrate the importance of proactive collaboration. Agreeing on best practices and sharing guidelines also requires effective organisations, such as professional societies and spin-off collaborations.

The global threat of AMR requires that professionals organise and tackle the issues at hand, based on local priorities and needs. Professional-initiated collaboration may improve support for and adherence to good governance and surveillance. This report provides some good practices that hopefully can inspire countries to improve their policies to combat AMR. The report also provides useful insights into the importance of governance structures and surveillance systems, as preconditions to support a coordinated and effective AMR policy.

2 Introduction

Antimicrobials are used to cure microbial infections (e.g. bacteria, viruses, fungi and parasites). However, these microbes can develop resistance against these drugs, and continue to infect their host (4). Current rates of antimicrobial resistance threaten healthcare systems at a global scale, particularly in countries with a high infectious disease burden (5-7). Infections with resistant pathogens increase mortality and morbidity in patients, but also burdens the health system and society as a whole (8). From a patient perspective, costs of AMR include increases in mortality and morbidity, as well as productivity losses and longer hospital stays. From a healthcare perspective, AMR burdens include higher costs of diagnostic testing and second-line antimicrobials, costs of monitoring and outbreak control, and costs of secondary treatments and longer hospital stays (9). In a broader societal perspective, AMR has a negative effect on labour productivity, economic activities such as tourism and trade, new drug development costs and routine medical care, such as surgeries (8, 10, 11). Increases in AMR exhibit network effects: infection rates, and thereby costs, increase exponentially if AMR incidence increases.

It is estimated that across the EU, resistant pathogens cause an additional 33,000 deaths annually (figure 1) (7). Left unchecked, this number could increase to 142,000 deaths per year in 2050 (3). Additional disease burdens, for instance due to more, longer and more severe illnesses, accrue to a loss of 875,000 to 1 million disease adjusted life years (DALYs) in the EU (2, 3). This is also a burden on the health system; the OECD estimates that AMR increases the number of hospital days by 568 million days across the EU (3). Furthermore, increases in AMR affect the safety of many routine interventions (12). Total current AMR costs in the EU amount to $1.5 billion PPP[1] annually, and are expected to increase over time (3). The steadily increasing disease burden of AMR calls to address this threat with coordinated action, including cost-effective antimicrobial policies (13).

[1] PPP: purchasing power parity. Dollar amounts have been corrected for local price levels and purchasing power

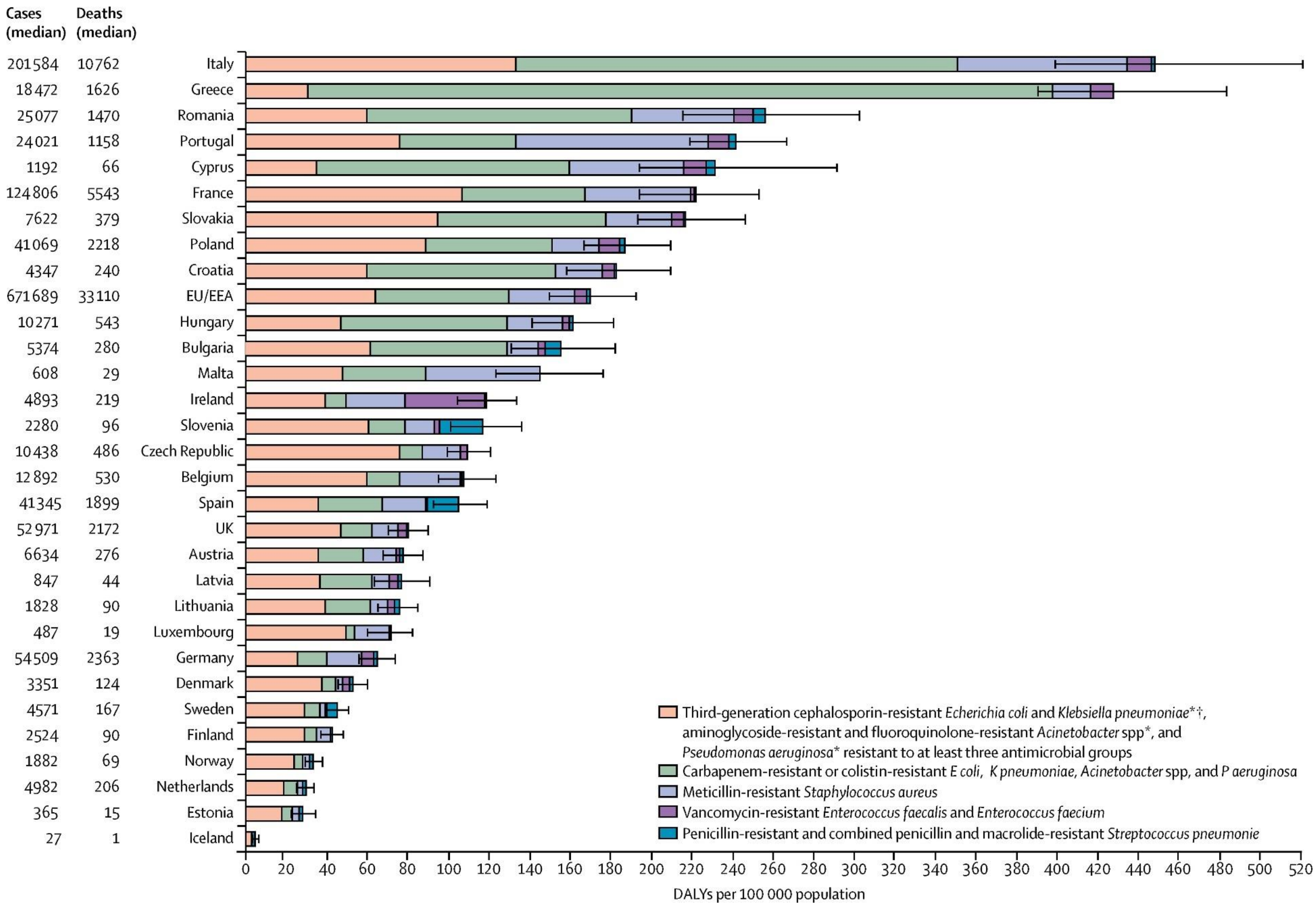

Figure 1: Annual mortality and disease burden due to AMR in OECD countries (Cassini et al, 2019)

To address these staggering health and economic effects, the OECD recommends action in two areas: hospital-based interventions and community-based interventions. Hospital-based interventions, including stewardship programmes and improved infection control render on average a gain of 2,000 DALYs per 100,000 persons per year, making these strategies highly cost-effective, and in most cases cost-saving, with an average net return of $1,200,000 per 100,000 persons. For community-based interventions such as delayed prescribing, mass media campaigns and rapid diagnostic tests, gains will be smaller, but on average still net $270,000 PPP per year per 100,000 persons. Evidently, potential gains will be higher in countries that have a high AMR burden, such as France, Italy and Greece (figure 2). But also in low-incidence countries such as Finland, Sweden and Norway, policies are expected to be cost-saving (3). Implementation of AMR policies usually provides excellent investment opportunities (14-17).

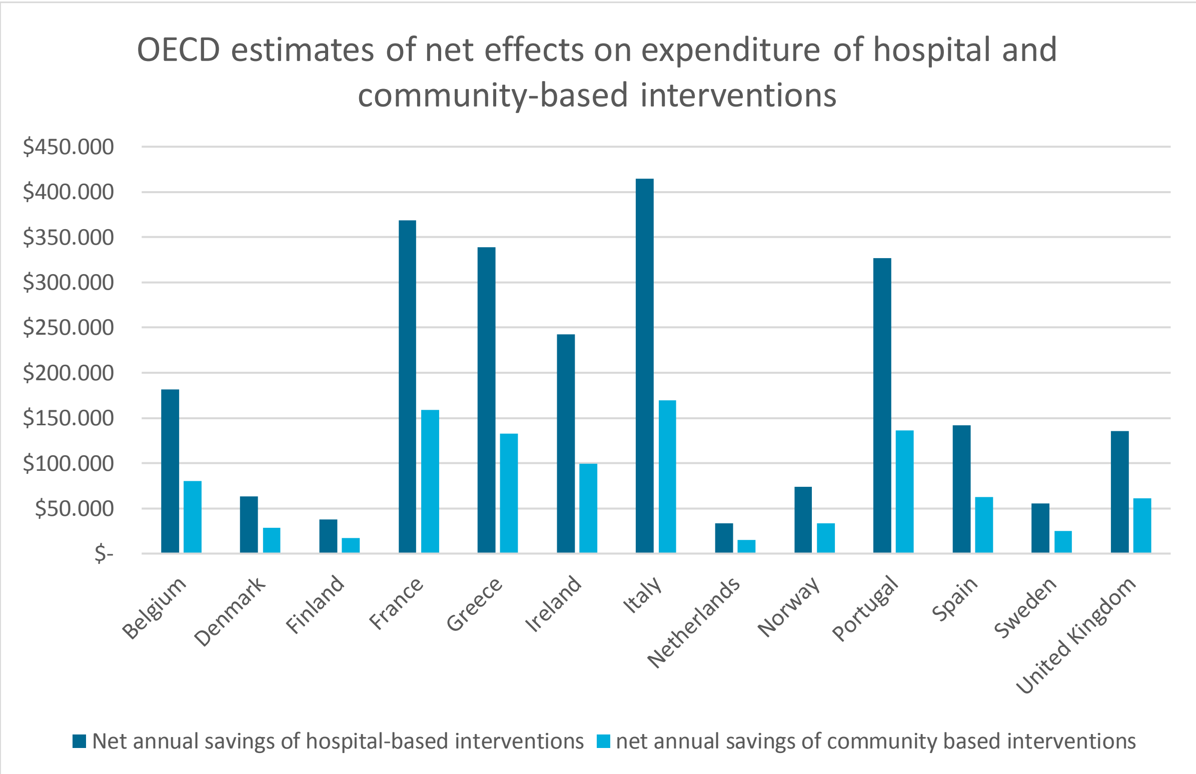

Figure 2: Net savings of hospital-based and community-based interventions (OECD, 2018)

The Netherlands, being a densely populated country with a high use of antibiotics in the agrarian sector (18), recognised the threat early on and acted accordingly based on precautionary principles (19-21). As a result, antimicrobial resistance and antimicrobial use in the Netherlands are among the lowest in the world, despite a high population -and livestock- density (6, 22). One key to this success is the extensive coordinated action to address AMR (23). Examples of 'good practices' and cost-effective interventions are required in both hospital settings and community settings, including evidence on how these policies have been integrated into a coordinated system to address AMR. For example, the Food and Agriculture Organisation of the United Nations (FAO) includes four key pillars in its action plan: awareness, surveillance and monitoring, governance and promotion of good practices (24). A previous report identified five cost-effective good practices for the Netherlands (box 1). Based on the findings of this report, the Dutch Ministry of Health, Welfare and Sport asked us to describe four additional good practices and, where possible, construct a business case based on costs and benefits of these good practices. This report identifies additional good practices, and elaborates on existing surveillance and governance structures in the Netherlands. The following research questions will be addressed:

- Which (additional) interventions can be considered good AMR practices in AMR?
- Can business cases be constructed from these good practices to demonstrate savings for the health system?

Box 1: Cost-effective AMR policies in the Netherlands

In 2015, five good practices on AMR were collected for the Netherlands; three in a hospital setting, one in a long-term care (LTC) setting and one in a primary care setting. All good practices showed cost savings, ranging from a modest €7 per patient treated, towards €1,900 per patient treated (table 1), demonstrating that even in a low-incidence country significant cost savings can be obtained by tackling AMR. The preconditions that the researchers included were attention to sustained implementation, inter-provider collaboration and surveillance and feedback in an open dialogue culture (1).

Amphia Hospital Breda	**Effectiveness**: 60% reduction of *S. aureus* infections **Cost-savings**: €1900 per patient
Department of Family Medicine, Maastricht University	**Effectiveness**: > 40% reduction in antimicrobial prescribing **Cost-savings**: €7 per patient treated
University Medical Center Groningen	**Effectiveness**: > 10% reduction in antimicrobial prescribing **Cost-savings**: > €40,000 yearly
Nursing home De Riethorst	**Effectiveness**: avoidance of a *Klebsiella pneumoniae* outbreak **Cost-savings**: €250,000 per outbreak
Antonius Hospital Nieuwegein	**Effectiveness**: 135-270 VRE infections and 27-54 deaths avoided **Cost-savings**: €148,000-€476,000 yearly

Table 1: Overview of good practices to reduce AMR (2015)

Selection and reporting of good practices

This report aims to describe good practices in the Netherlands that contribute to a low AMR occurrence. In order to identify good practices we searched the literature for articles describing AMR interventions and policies. These were then grouped to identify areas of intervention and policy. We identified five major areas of intervention, based on 489 interventions listed in 75 articles: 1) infection prevention and control, 2) appropriate use of antimicrobials, 3) therapy optimization, 4) development of new antimicrobials and 5) resistance outbreak control measures. Furthermore, three supportive policy areas were identified: 1) antimicrobial stewardship programmes (ASP) and multidisciplinary teams, 2) monitoring and surveillance, 3) education and awareness. A short description of each area is found in appendix 1. Within each area we searched the grey literature and consulted with experts , which resulted in a list of 38 good practices (appendix 2). This list was discussed within the project team, and the potential good practices were graded based on available evidence, importance, relevance and diversity. After presenting promising good practices to the national AMR expert group, the Ministry of Health, Welfare and Sports selected six potential good practices for further assessment (Appendix 3). After contacting experts and collecting additional information, one potential good practice was excluded due to lack of information (integrated infection prevention policy). Two other promising practices, the SWAB antibiotics booklet and the national surveillance report (NethMap), were reframed into a single good practice: the overarching surveillance structure ISIS-AR. The Ministry of Health, Welfare and Sports agreed to delve into and report on the following four good practices:

1. Multidisciplinary teams to facilitate outpatient parenteral antimicrobial treatment (OPAT)
2. A booklet for childhood fever to reduce antibiotic prescriptions in out-of-hours primary care
3. The national AMR surveillance network: critical information for national and local AMR efforts
4. Collaborative AMR governance in the Netherlands: an international comparison

For each of these practices, we assessed the potential to construct a business case. To collect information, one or more experts were consulted and additional literature was collected. For the first two good practices we were able to develop a formal business case. Business cases were based on direct costs and benefits in the health system. This includes labour and production costs, while on the benefits side this includes prescriptions, treatment costs and labour. Indirect costs, such as startup subsidies, productivity losses, morbidity or societal costs were not taken into account due to the unavailability of reliable estimates (11, 25). This implies that we severely underestimated the cost-effectiveness thresholds. We translated cost and benefits into monetary terms where possible, to calculate annual savings or savings per patient treated.

Business cases are based on available evidence provided by experts, which falls short of formal cost-effectiveness analysis. Business cases should therefore be viewed as indicative, but low-level evidence on cost-effectiveness. However, given the high indirect costs of AMR, a broader or more encompassing perspective would likely increase the total benefits, and thereby cost-effectiveness (3). For the surveillance and governance practices, we did not have sufficient information available on costs and benefits to construct a formal business case. These good practices are therefore descriptive in nature.

3 Multidisciplinary teams to facilitate outpatient parenteral anti-microbial treatment (OPAT)

This business case was designed in collaboration with dr. Jaap ten Oever (Radboudumc)

Introduction

Patients with serious or persistent bacterial infections who cannot be treated with oral antibiotics require intravenous (IV) antibiotics. In most cases, if the patient is clinically stable it is safe to administer IV antibiotics at home. This is called Outpatient Parenteral Antimicrobial Therapy (OPAT). OPAT reduces length of hospital stay and thereby reduces the direct risk of transmission of resistant pathogens from or to this patient. It decreases the exposure of the patient to secondary hospital infections. OPAT is found to be preferred by patients and to be cost effective (26). Despite these advantages, many hospitals struggle with the implementation of OPAT due to lack of experience and coordination among healthcare professionals.

Both internationally and nationally, there is high variation in the way OPAT is organised and delivered (27). In some hospitals a single infectious diseases (ID) specialist may be consulted before discharging the patient with OPAT, while other hospitals have more formal structures to promote efficient and safe use of OPAT. In 2008, Gilchrist et al. developed a roadmap of how OPAT should be organised to minimise risks and failures (figure 3). The use of a (formal) OPAT team, which includes an ID specialist, a pharmacist, and a specialised nurse, plays a crucial role in this process (28, 29). Antimicrobial stewardship teams should be closely involved in the organisation of OPAT (30).

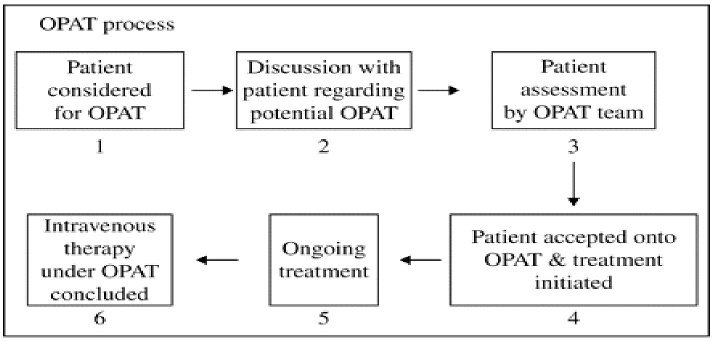

Figure 3: Steps in OPAT process by Gilchrist et al. 2008

Effects of a multidisciplinary OPAT team

Consultation of a multidisciplinary OPAT team increases appropriateness of OPAT, reduces antibiotic consumption and increases substitution to lower-risk treatments. In the USA, for example, mandatory consultation of an OPAT team resulted in denial of OPAT in 10% of patients. Of these patients, approximately 90% could be substituted to oral antibiotics, while for the remainder no further antibiotic therapy was recommended (31). A second study found that 14% of OPAT treatments could be prevented and hospital stay could be reduced by an average of 6.5 days in 6% of the patients (32). Consultation of an ID specialist prior to OPAT discharge has been shown to decrease inappropriate use and improve patient outcomes (33, 34).

While guidelines recommend consultation of an ID specialist prior to OPAT discharge, there are indications that current adherence is suboptimal. For example, a study at a Dutch hospital showed that in only 39% of the cases a formal ID specialist consultation took place before discharge (35). This study also found that consultation of an expert team would have improved the treatment schedule in 28% of patients referred for OPAT (35). Recognising the benefits of a multidisciplinary OPAT team, the Radboud University Medical Center initiated such an intervention in 2017 (see box 2).

Box 2: A multidisciplinary OPAT team at the Radboud University Medical Center

Before 2017, OPAT at the Radboud University Medical Center was initiated and monitored by the treating physician, sometimes with the help of a nurse practitioner with experience in OPAT. A formal multidisciplinary approach and structural follow-up of patients was lacking. In 2017, the Radboud UMC introduced a multidisciplinary team to support other departments with OPAT. This team consists of an ID specialist (medical microbiologist), a transfer nurse, a nurse practitioner infectious diseases and a hospital pharmacist, as visualized in figure 4 (Radboud UMC Nijmegen). In the new system, patients are referred to the multidisciplinary OPAT team by their physician. The team assesses eligibility for home IV and develops a treatment plan. After the patient has been discharged, medication is administered by home care/district nurses. In case of complications, the patient and/or district nurse can contact the OPAT team.

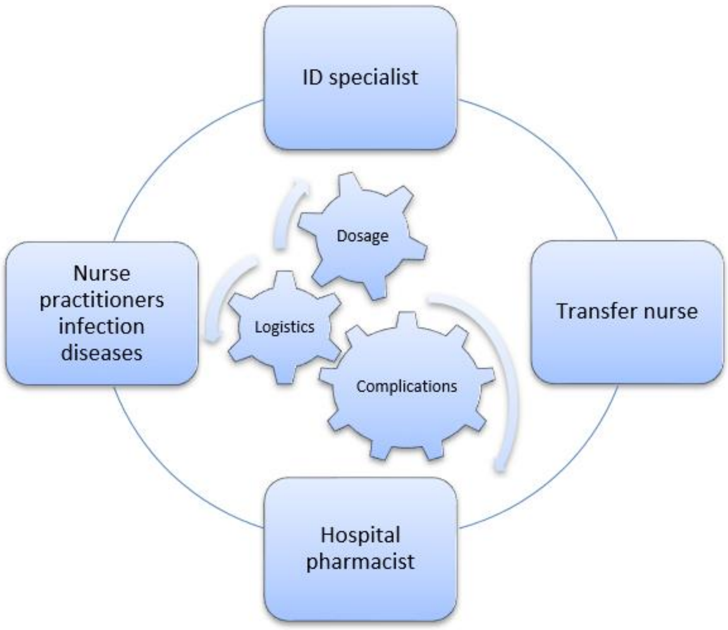

Figure 4: Multidisciplinary OPAT team at the Radboudumc

Of 129 referred patients, 111 were actually discharged with OPAT, while 18 patients were treated with oral antibiotics. Compared to the six months before this intervention, 26 additional patients received OPAT instead of inpatient care. Cost savings were estimated at €103,350 (€206,700 per year), primarily due to a reduction in hospital stay of these patients (an average of 30 days per patient). Furthermore, time from request to OPAT discharge has been reduced by one day for 86 out of the 111 patients, rendering an additional €22,790 (€45,580 per year). The remaining 25 patients were delayed from discharge due to clinical events. Potential future discharge optimization of these patients was not included in the business case, but may offer additional cost savings. Oral switches were not registered prior to the introduction of the new OPAT team. However, in the first six months after the introduction of the OPAT team, 6 out of 18 (33%) registered oral switches were due to the input of expert information provided by the OPAT team. As a result, 196 days of OPAT were substituted with a less costly option. This translates to savings of €25,480 (€50,960 per year). Lastly, the OPAT team allowed substitution of 9 additional patients from inpatient settings to a less expensive clinical outpatient setting, which translated to a reduction of 2 inpatient days for 18 patients per year. These savings were estimated at €4,770 (€9,540 per year).

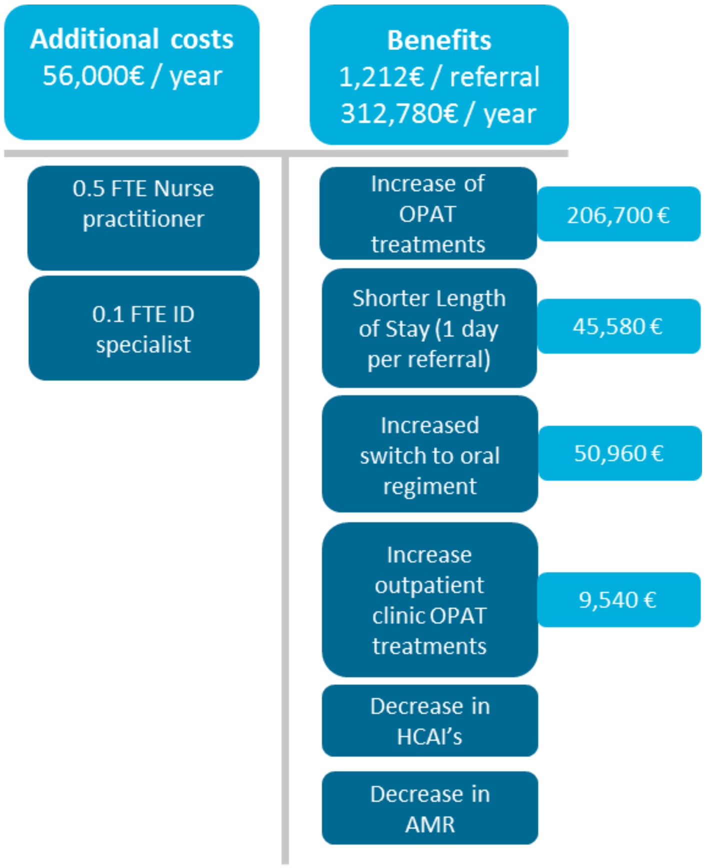

Figure 5: Annualized CBA for OPAT team at the Radboud University Medcial Center

In addition to the monetary gains associated with the introduction of the OPAT team, fewer inpatient days also reduces the risk of exposing other patients to HCAI's and acquiring resistant infections (36, 37). This could potentially lead to a decline in AMR, although this requires further study. Furthermore, improvements in communication and efficiency were experienced by medical doctors and transfer nurses involved in OPAT treatments. This may further increase cost savings, for example due to a reduction in medication and less material spillages. Identification of potential OPAT patients is currently not a core task of the specialised teams. Edwards et al. suggested that ward nurses can play a pivotal role in identifying potential OPAT patients and facilitating referrals to OPAT teams (38). Additional training of nurses could improve implementation and use of specialised OPAT teams.

Potential for broad implementation in the Netherlands

The costs and benefits of a formal OPAT team depend on the number of eligible patients in a hospital. A larger hospital may benefit more from implementing a dedicated OPAT team. However, since time investments are proportional to the number of patients, the intervention is highly scalable. The multidisciplinary team does require additional staffing expenses, while benefits in terms of reduced inpatient days and pharmaceutical expenses may not necessarily flow back to the respective departments. Cost-effective implementation requires making a good business case, including provisions to ameliorate benefits in terms of lower hospital days.

It is currently unknown to which degree OPAT and multidisciplinary OPAT teams are used by hospitals in the Netherlands. However, we know that this is currently not common practice in the Netherlands (35). In the USA, only 26% of the ID specialists had dedicated OPAT teams (39). In the Netherlands, it is estimated that about half of the hospitals have implemented a multidisciplinary OPAT team. Of the seven Dutch University Medical Centers, four have multidisciplinary OPAT teams in place, while two are starting up a multidisciplinary team. OPAT in Maastricht UMC has been incorporated in a broader multidisciplinary process for several home IV therapies. This relatively broad implementation of such a good practice can be partly attributed to extensive information sharing in the national networks of 'the Dutch working group on antimicrobial policy' (SWAB) and the 'regional care networks antimicrobial resistance' (RZN). By providing information and sharing good practices, such networks might contribute to broad implementation and reduced AMR.

Conclusions

Stimulation of OPAT through dedicated multidisciplinary OPAT teams enacts on multiple facets that are part of an integral AMR policy. Reducing hospital stays lowers the risk of acquiring and further spreading (resistant) infections. Furthermore, a multidisciplinary OPAT team increases appropriate use of antibiotics. In the Netherlands, this is shown to be a cost-effective intervention that contributes to a reduced AMR burden. Through regional and national networks, these cost-effective interventions are shared and supported, leading to fast and broad implementation. Achieving full implementation requires increasing hospital awareness through governance, further sharing of good practices through the national and regional networks, and providing sufficient resources to support hospital ASP and formation of multidisciplinary teams.

4 A booklet for childhood fever to reduce antibiotic prescriptions in out-of-hours primary care

This business case was designed in collaboration with dr. Eefje de Bont (CAPHRI, Department of Family Medicine, Maastricht University)

Introduction

Fever is the most common reason for parents to bring their child to their family physician (40). Especially at out-of-hours care, the percentage of children with fever is high (41). Most cases of childhood fever are caused by benign viral infections, and could be addressed with simple instructions from the physician. Nevertheless, about one in three to four out-of-hours family physician consultations result in prescription of antibiotics (42-44); nearly twice as often compared to visits during routine office hours (45). Such unnecessary prescriptions can not only increase antimicrobial resistance, but also avoidable side effects from antibiotics. Adequate measures are therefore needed to reduce antibiotic prescriptions in case of viral fever in children, especially during out-of-office hours.

One predominant factor in the decision of family physicians to prescribe antibiotics is the misguided assumption that parents can only be reassured by prescribing antibiotics (46). A recent study demonstrates that parents do not expect a physician to prescribe antibiotics, but are looking for reassurance and appropriate information on how to cope with their child who is suffering from fever (47). Previous research has furthermore shown that patient information leaflets used during family physician consultations for common infections are promising tools to reduce antibiotic prescriptions (48).

An illness-focused interactive fever booklet for parents

In response to these findings, an interactive booklet to inform parents on childhood fever at out-of-hours care was developed (figure 6) (49). The aim of this booklet is to provide physicians with guidance in informing parents who visit an out-of-hour clinic because of their child having a fever. It contains the following sections (50):

- A self-assessment tool to provide parents with guidance on how to act on their child's fever The tool is based on a traffic light system (ranging from green for the most innocent symptoms to red for the alarm symptoms)
- Information about the advantages and disadvantages of antibiotics
- An overview of the average duration of the most common infectious disease-related symptoms
- A dosage scheme for paracetamol
- Advice regarding febrile seizures and rash.

Figure 6: An illness-focused interactive fever booklet for parents visiting an out-of-hours primary care centre because of their child having fever

Significant decrease in antibiotic prescribing [effectiveness of the intervention]

The initiators of the booklet recently performed a cluster-randomized control trial to study the effect of their booklet on antibiotic prescribing rates at an out-of-hours primary care centre (51). Not all GPs who had access to the booklet actively used it, but those GPs who did showed statistically significant reductions in prescribing antibiotics (prescription rate 22% vs 25%) (51). This means that for every 100 patients who would be provided with a booklet, roughly 3 cases of antibiotics can be prevented.

A net savings of €5 per 100 booklets provided

The booklet has not yet undergone an economic cost-benefits evaluation. However, we can make an estimation of the costs per 100 patients. Printing costs per 100 booklets are roughly €40. In the pilot, existing distribution channels were used to distribute the booklets at zero costs. At a cost of one antibiotic prescription (amoxicillin 5ml 5/7 days + delivery costs) of €15, preventing three cases would save €45 (52). Therefore, providing 100 children with a booklet, and thereby preventing three prescriptions, would result in net savings of €5. Reducing antibiotic prescriptions lowers the prevalence of antimicrobial resistance (AMR).

Although difficult to quantify, a recent study estimated an additional AMR burden of $0.10 to $0.60 per standard unit of antibiotics (8), which would increase benefits by between €1.40 and €11.50 per 100 patients[2]**.** As these estimates are based on the USA, with their higher prescription costs, these figures may be an overestimation of the benefits in the Netherlands**.** We also found additional benefits of the booklet. For example, parents who used the booklet showed a lower intention for additional consultations and the booklet caused a decrease in the total number of prescriptions (51). Adverse reactions, as well as negative onset effects of early exposure to antibiotics could be prevented, saving additional costs (53). However, these benefits are not easily quantifiable. Cost-effectiveness would likely be higher when these additional benefits are taken into account.

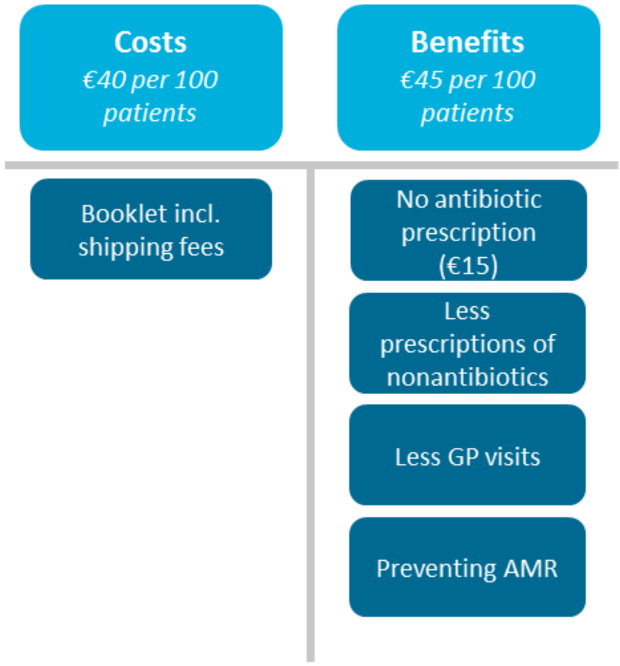

Figure 7: Costs and benefits of an illness-focused interactive fever booklet for parents

From study to nationwide implementation and beyond

The initiators of the booklet extrapolated the results of their study to the Dutch population and calculated that at least 244,000 children with fever visit out-of-hours physicians in the Netherlands (53). The study found that 29% of GPs would actively use the booklet. If 29% of the 244,000 children received a booklet, a total of 2,086 prescriptions would be prevented, resulting in a total savings of €3,477[3]. Because of the positive results, efforts are currently being made for a nationwide implement-tation of the booklet. An online version of the booklet will be developed, which will be freely available on the website thuisarts.nl (54). This will likely reduce total costs and costs per case due to its easy accessibility. The initiators of the booklet, however, stated that physical access to a booklet is important to stimulate use and uptake, meaning that this online version will not replace the booklet entirely.

In terms of implementation in other countries, the initiators of the booklet also deem the booklet suitable for translation and implementation in other Western countries. Translations could improve the impact for non-Dutch speaking parents within the Netherlands as well. As the OECD

[2] Using 3 patients for 5 days at €0.091 (=$0.1) as lower bound and 3 patients for 7 days at €0.546 as upper bound.

[3] If all Dutch GPs actively used the booklet, total cost savings would increase to €12,000.

estimates that costs of AMR as well as benefits of community policies to reduce AMR are higher in most OECD countries, this business case is expected to have a higher savings rate in most other countries (3).

Conclusions

The availability of this interactive booklet in out-of-hours primary care centres has been shown to reduce the number of antibiotic prescriptions at the relatively low costs of €40 per 100 patients. Even in the setting of low prescription rates in the Netherlands, this results in a positive business case of €5 per 100 patients. The booklet can therefore be seen as a relatively inexpensive and easy way to tackle part of the problem of AMR. Lowering GP prescription rates is part of an integrated policy to reduce AMR, and this business case shows the importance of culture and awareness in community solutions to reduce antibiotics use.

5 The National AMR surveillance network: providing critical information for national and local AMR efforts

This business case was designed in collaboration with dr. Annelot Schoffelen, dr. Sabine van Greeff (ISIS-AR) and dr. Mark de Boer (SWAB)

Introduction

Antimicrobial resistance is a multi-layered and complex problem: the European centre for disease control (ECDC) estimated an economical burden of 1.5 billion euro annually in 2007. This estimation was based on approximately 25,000 deaths due to an infection with an antibiotic resistant bacteria in Europe, extra hospital days and subsequent in-hospital costs, combined with an estimated loss of productivity as a result of illness or mortality. It follows that these costs will only rise in the face of increased AMR and associated morbidity and mortality (55). We will describe the national AMR surveillance system in the Netherlands, including its output and contribution to the formation and alteration of guidelines on both a national and a local (hospital) level.

The National AMR surveillance network

In 2008 the infectious disease surveillance information system for antimicrobial resistance (ISIS-AR) was founded as an initiative from the Dutch society of medical microbiology (NVMM) and RIVM/Cib. Both parties are represented in the steering committee. ISIS-AR is a repository of routinely collected antibiotic resistance data from at present 47 medical microbiological laboratories (MML) in the Netherlands that cover 80% of the hospitals. ISIS-AR monitors antibiotic resistance trends for different pathogens over time across the Netherlands. New threats concerning AMR can be discovered in a timely manner through ISIS-AR or other surveillance systems, with the introduction and spread of carbapenem resistance as a recent example (56, 57).

Collection of data

ISIS-AR data is based on routine antibiotic susceptibility testing done by the participating MMLs. The data is generally received monthly in a fixed format and contains a multitude of information concerning demographic data on the patient and epidemiological data concerning the isolated micro-organism(s). A number of MMLs participate in the 'Eenheid van Taal in antibioticaresistentie' (literal translation: Unity of Language in antibiotic resistance) programme made by the NVMM, Nictiz and RIVM. This programme aims to implement standardised communication of microbiological, clinical and epidemiological data between stakeholders, for example by developing standardised lab code sets to be used in laboratory information systems. These MMLs are able to send data to ISIS-AR on a daily basis. A dedicated multidisciplinary team at RIVM handles all incoming data. All data is translated to standardised codes to facilitate analysis.

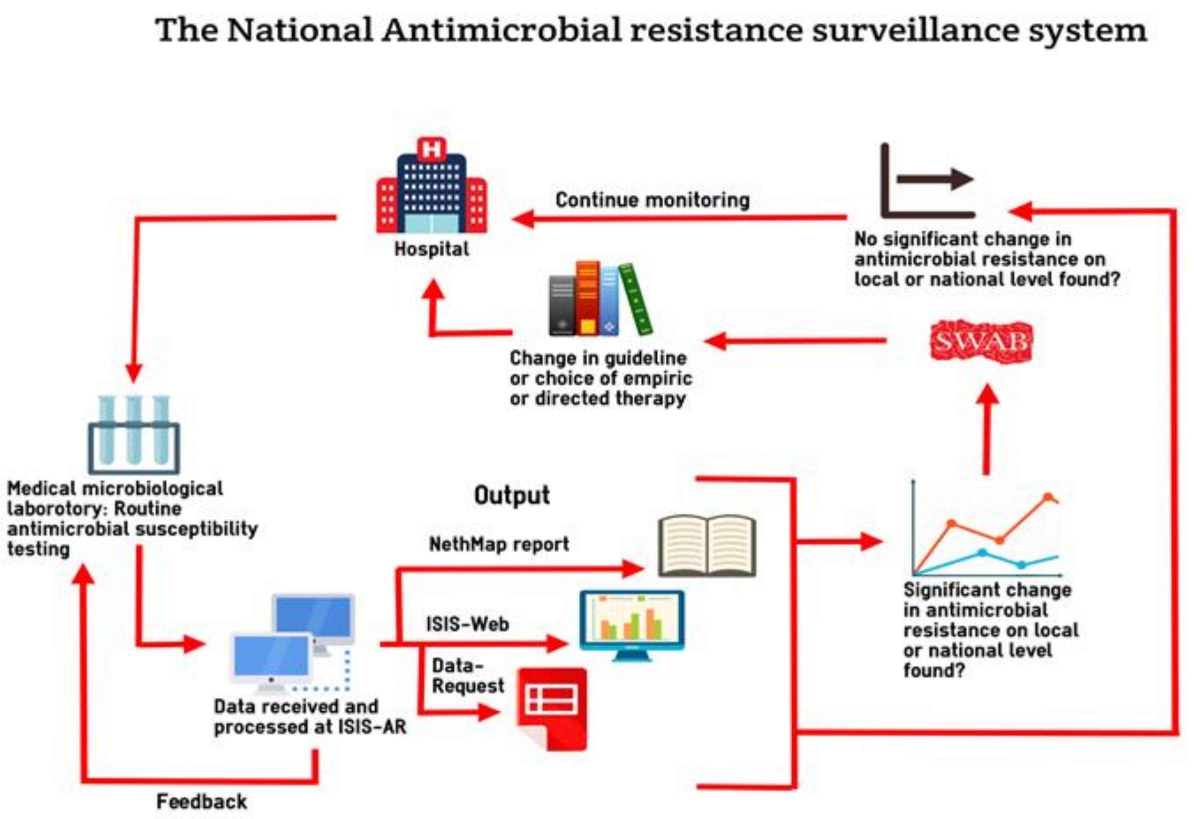

Figure 8: Data flow from hospitals to ISIS-AR and back. Aside from the output that is generated by ISIS-AR, there is also a direct feedback to the MML providing the data

The data that ISIS-AR collects come from voluntarily participating MMLs throughout the Netherlands . In 2008 eight MMLs participated in the surveillance programme and in 2019 this number had increased to 47 (of the total of 55 MMLs in the Netherlands). Another 6 MMLs are in the process of joining the surveillance programme. The MMLs cater to either general practitioner (GP) practices, long-term care facilities, public health facilities and both general and university hospitals. That way it is possible that a single MML caters to multiple hospitals or has multiple sites. For that reason the number of hospitals that are being surveyed is larger than the number of MMLs. ISIS-AR is able to cover 80% of the hospitals in the Netherlands with the data it currently receives.

Reporting of ISIS-AR data

Reporting is done in various ways. An annual report (NethMap[4]), access to reports through a publicly accessible portal and with additional information for participating laboratories (ISISweb), or tailor-made for specific requests that in some cases need to be approved by a committee. Furthermore, data

[4] https://www.rivm.nl/documenten/nethmap-2019, Accessed on January 30, 2020

on blood stream infections of specific bacterial pathogens is reported by ISIS-AR on a European level to the ECDC[5].

Reporting of ISIS-AR data: NethMap

NethMap is an annual report on the prevalence of AMR, the consumption of antimicrobials, and the implementation of antimicrobial stewardship in the Netherlands. The report is constructed by the Dutch working party on antibiotic policies (SWAB) together with RIVM. The production of the report started in 2003. The data currently used in NethMap is obtained from multiple surveillance systems; the Netherlands reference laboratory for bacterial meningitis in Amsterdam, the gonorrhoea and antibiotic resistance surveillance (GRAS), the anaerobic pathogen surveillance, the *C. difficile* surveillance, the azole resistance surveillance and the NIVEL all contribute to the report. However, ISIS-AR is a major contributor for the surveillance data in NethMap. The antibiotic consumption data used in the report come from the Foundation for Pharmaceutical Statistics SFK as well as the individual hospitals and their clinical pharmacists. NethMap is the leading report regarding nationwide trends in resistance and antibiotic consumption. These data can for instance be used by national guideline committees for the infectious diseases concerned to choose appropriate antibiotics.

Reporting of ISIS-AR data: ISISweb

ISISweb is a web interface presenting ISIS-AR data. The interactive website facilitates professionals by giving them access to different types of data, be it national (publicly available) or their own data (password protected), which they can then use for benchmarking and overseeing trends. These reports can for instance be used by hospital Antibiotic Committees to adjust their antibiotic policies. Institutions that do not participate in ISIS-AR can only use national data and apply these to their local policies.

In 2018, a survey was done by ISIS-AR regarding the use of ISISweb and user satisfaction (unpublished data). The survey was done in 18 MMLs in the Netherlands, where a total of 18 medical microbiologists, three data managers/epidemiologists/data scientists and one infection prevention professional responded. The survey showed that 13 out of the 18 (72%) MMLs made use of ISISweb, with medical microbiologists being the most common user. The respondents reported that ISISweb was mostly used to gain insight into the local prevalence of antimicrobial resistance, to compare the local prevalence of antimicrobial resistance to the national figures and for defining empirical antibiotic treatment.

[5] https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data, Accessed on January 30, 2020

Reporting of ISIS-AR data: Data requests

Professionals can request tailor-made data sets from ISIS-AR, for research purposes with regard to specific AMR subjects. The request is reviewed by a board, after which the data set is sent to the researcher, who can then proceed to analyse the data as seen fit. Approximately 3-6 requests are made on a yearly basis and used for research purposes. Professionals can ask specific questions regarding the prevalence of resistance at ISIS-AR, in addition to the data sets that can be requested. The epidemiologists working at ISIS-AR will then do the analyses on the database and give answers (mostly aggregated and anonymized data) to the questions asked. These specific questions amount to 20-25 on a yearly basis and vary in complexity as well as extensiveness.

The Dutch working party on antibiotic policies (SWAB)

The SWAB is a national working party created in 1996 by the collective effort of the Dutch society for infectious diseases, the NVMM and the Dutch society for clinical pharmacologists. The main objective of the SWAB is to optimize the use of antibiotics, in order to contain the further increase of antibiotic resistance and minimize the costs for the use of antibiotics. SWAB creates guidelines for antibiotic use for a multitude of infectious disease syndromes. These guidelines are meant for use on adults in the hospital setting. Currently, 12 up-to-date guidelines have been published, apart from the archived guidelines that are mostly outdated versions of the currently available ones. These guidelines are written by specialists in the field, using currently available literature to give recommendations relating to the proper treatment for infectious disease syndromes or regarding antibiotic prophylaxis regimes in order to prevent infections. In nine of these guidelines, the authors make use of the surveillance data provided by ISIS-AR in some way to motivate the decisions and recommendations made regarding the choice of treatment. Of the remaining three guidelines, two reference other surveillance systems such as the Dutch reference laboratory for meningitis and the annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). These guidelines are used by professionals throughout the Netherlands, making them very effective tools to optimize antibiotic use on a national level.

SWAB antimicrobial guide

SWAB hosts an online antimicrobial treatment guideline known as SWABID[6]. At its conception, SWABID was originally an amalgamation of nine different local antimicrobial guides from nine hospitals (of which eight were academic hospitals). SWABID is a comprehensive collection of treatment

[6] https://adult.swabid.nl/, Accessed on January 30, 2020

protocols for most infectious disease syndromes commonly found in the hospital setting and includes both empiric and directed treatment. The online version was created in 2006 and includes a national version and a hospital tailor-made version. The national version is readily available for everyone and usually contains multiple recommendations regarding antibiotic treatment for many of the infectious disease syndromes. The hospital specific version of SWABID is a local modification by the hospital antibiotic committee based on for instance local resistance data or a reluctance to use a certain antibiotic for toxicity reasons (e.g. aminoglycosides and nephrotoxicity). Most hospital specific SWABIDs generally follow the national version of the antimicrobial booklet.

Antibiotic Committees from individual hospitals make a choice, from the recommendations in the national guideline, regarding the antimicrobial treatment that they prefer for the treatment of specific infectious disease syndromes. This SWAB encourages local hospitals to make this choice based on their local surveillance data. This helps to further guide the physicians that eventually make use of the local SWABID guide. A relatively small proportion of hospitals make use of their own antimicrobial guide as opposed to using the SWABID guide. A study in 2015 comparing 50 antimicrobial guides (both non-SWABID based and SWAB based) found that local non-SWABID based guides were significantly less comprehensive, less guideline-compliant and less accurately kept up-to-date when compared to the SWABID local guides (58). The authors concluded that the quality of the local antimicrobial policies would likely improve when a local customizable version of the national SWABID guide was used (58).

Using surveillance to alter empiric therapy protocols and guidelines

Surveillance data as provided by ISIS-AR facilitates tailor-made guidelines and protocols on a national and local level. Antibiotic resistance is a broad term covering a multitude of different types of bacteria that we most often split into a Gram-positive and a Gram-negative group. The resistance to antibiotics in the Gram-positive bacteria from clinical specimens in the past years has not increased significantly and therefore does not have any significant impact on guideline changes at the moment. For example, the rate for MRSA in blood cultures in the Netherlands is currently 1.2% and has been stable between 2014 and 2018. Similarly, the rate of clindamycin resistance is currently at 11% in *Staphylococcus aureus*, although there has not been a significant or clinically relevant trend between 2014 and 2018 (59). The prevalence of resistant Gram-positive bacteria such as MRSA or penicillin resistant pneumococci (0% in GP patients and 1% in hospital patients) is low in the Netherlands compared to other European countries, in part due to the pro-active stance of the Dutch medical professionals with regard to rational antibiotic treatment, relatively low antibiotic consumption in comparison with other European countries (60) and the measures that are in place to contain the problem, such as the MRSA search and destroy policy (61). Even though the resistance rates are low at the moment, the threat of resistance in this group should not be underestimated (61).

The antibiotic resistance problem in the Gram-negative bacteria group is more alarming. Resistance to third-generation cephalosporins (3GC), as a result of extended spectrum beta-lactamases and AmpC cephalosporinases, is on the increase (59). The third and fourth generation of cephalosporins have been classified as critically important antibiotics for humans by the World Health Organization (62). Subsequently the use of carbapenems (a reserve broad-spectrum antibiotic) has increased from 0.6 DDD/100 patient days in 2006 to 2.0 DDD/100 patient days in 2017 (59).

Most changes in antibiotic treatment recommendations are in guidelines that include Gram-negative bacteria with their significant increases in resistance. It is prudent to change the (empiric) antibiotic treatment protocol when the prevalence of certain resistant micro-organisms increases to an unacceptable level defined by experts. The full process, from the moment a change is seen through surveillance of AMR up to the point where a decision is made to change the guideline or treatment protocol, can be seen in Figure 9.

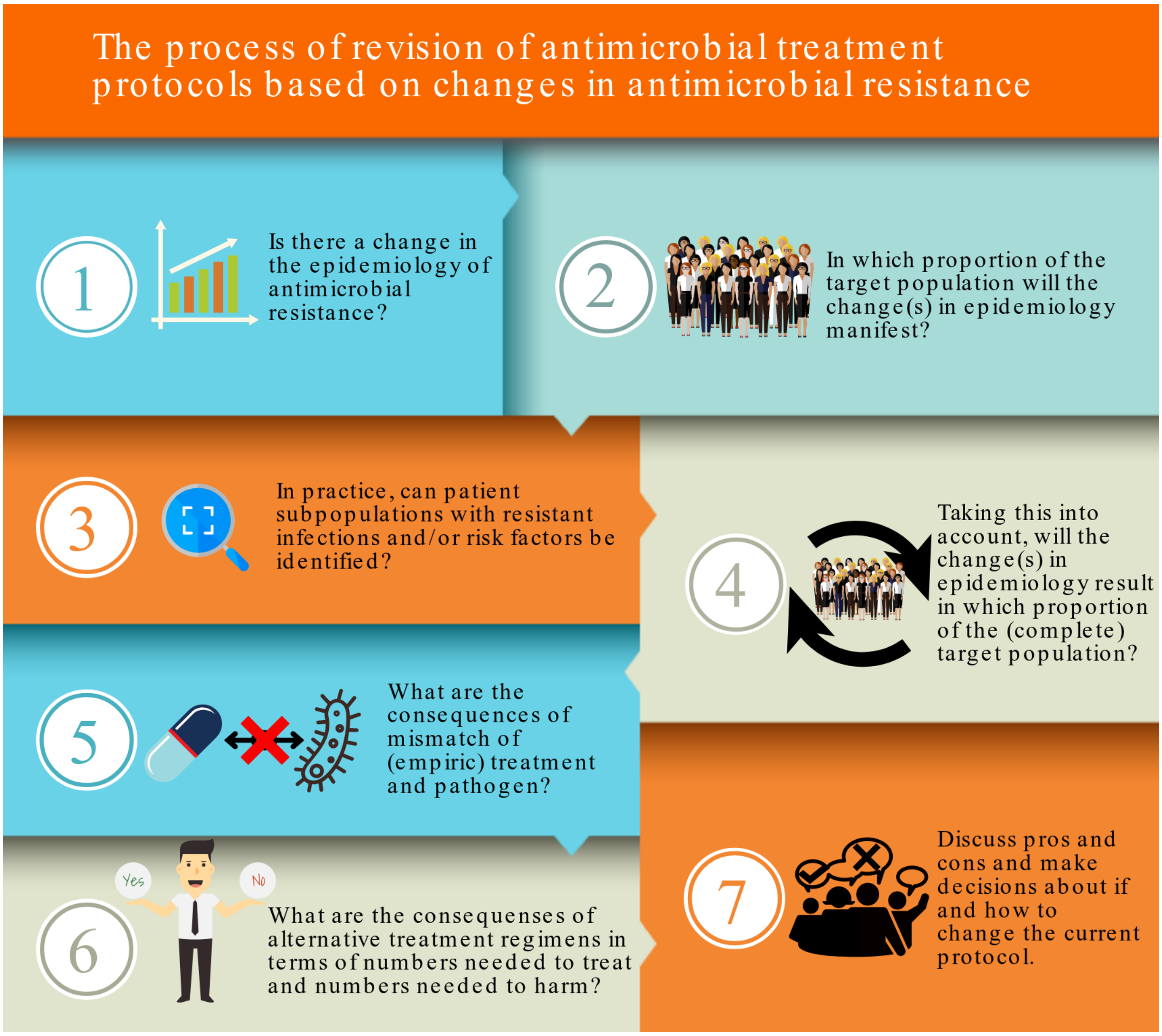

Figure 9: The process of revising antimicrobial treatment protocols

The consequences of not changing the protocols in a timely manner will be an increase in morbidity and mortality rates. The process of revision of antimicrobial treatment protocols is triggered by changes in epidemiology of antimicrobial resistance. However, the exact threshold for changing empiric treatment is currently not fully understood and is generally based on expert opinions. The quality of choosing the right antibiotic for a guideline is therefore largely dependent on high quality surveillance of AMR.

Cost-effectiveness of surveillance

Surveillance is one of the cornerstones in the battle against AMR, facilitating informed decision making regarding interventions (box 3) and guidelines on antimicrobial use and infection control, as well as the monitoring of AMR. The estimation of the costs and benefits of surveillance are complex, due to the fact that it is part of the basis of a wide variety of measures and interventions. A national surveillance programme such as ISIS-AR is relatively cheap. The data on which it has been based are routinely generated by MMLs, the only difference is that it is now sent to the national surveillance programme. Using a national surveillance system that makes use of routinely generated data from MMLs is the economic equivalent of low-hanging fruit. The benefits of surveillance arise from an adequate response to the information provided. However, certain benefits such as the impact on public health outcomes will not be immediately evident (63).

Threats to the quality of surveillance

It is prudent to note that the effectiveness of surveillance fully depends on the stability and consistency of reporting by the MMLs. Factors such as break-point changes for antibiotic susceptibility testing (AST), changes in the way AST testing is done (e.g. new machines) or different specimen testing behaviour by clinicians can impact the quality of the surveillance data (64). Continuous investments and maintenance is important to sustain the effect of surveillance systems, as budget cuts or cost containment policies could lower data reliability, for example due to selective sampling (e.g. patients could refuse diagnostic cultures when they have to pay a deductible).

Box 3: Use of surveillance data by professionals, a case study

Taking the 3GC resistance problem as an example we can review two measures for the containment of AMR recently implemented in the Radboud University Medical Center, one of the university hospitals in the Netherlands. One measure that can be taken is restricting the use of the target drug for the resistance mechanism. In 2019 the Radboud UMC decided to de-escalate the antibiotic treatment protocols at a local level for certain infectious disease syndromes that are usually caused by Gram-negative bacteria from 3GC to second-generation cephalosporins (2GC), in combination with amikacin (an antibiotic from the aminoglycoside group). This restriction in use of 3GC will expectedly lead to less 3GC resistance and in the long term potentially decrease the use of carbapenems. Such antibiotic policy changes rely heavily on surveillance data. Surveillance is the cornerstone in all possible measures that can be taken to contain a resistance problem, both in identifying the problem and monitoring of policy changes.

Conclusions

In 2019 the WHO interagency coordination group on antimicrobial resistance published a report for the Secretary-General of the United Nations in which they emphasize the urgent need to strengthen national surveillance and regulatory frameworks in all countries. This would contribute to an effective national response to antimicrobial resistance in many ways (62). Surveillance of AMR gives insight into the epidemiology of resistant micro-organisms, which is paramount for decision-making purposes on a national and a local level and to monitor the effectiveness of the implemented measures. Surveillance programmes such as ISIS-AR in tandem with guidelines and antimicrobial guides produced by the SWAB will in many ways contribute to the containment of AMR and the subsequent economic burdens associated with it. Furthermore, the adherence to evidence based guidelines, based on surveillance data, has been proven to improve the clinical outcome of patients and reduce the development of antimicrobial resistance (65, 66). This directly affects the mortality and morbidity associated with infections due to multi-resistant bacteria.

The surveillance infrastructure supports the health system to curb the rise of AMR, which makes for a prudent investment opportunity, even if direct benefits may not be immediately visible (63). The clear need for good surveillance is illustrated by the fact that most current active guidelines use recent surveillance data for their decision making.

6 AMR governance in the Netherlands: an international comparison

Introduction

Good governance is essential in coordinating AMR efforts, ranging from prevention, diagnostics as well as treatment. In their efforts to reduce the threat of AMR, countries could learn from each other's experiences, especially from countries with good AMR governance structures. In this good practice we strived to explicate the governance structures in the Netherlands in a thematic manner, delve into the cultural aspects of AMR and collect the opinion of experts from other countries regarding the success of the Netherlands.

The Netherlands has one of the lowest human antibiotic consumption rates in Europe, both on a hospital and on a GP level (figures 10a and 10b). The Netherlands has been restrictive in their antibiotics, having used strict infection control measures for resistant bacteria for several decades, as key professionals thought being precautionary is better than solving resistance later. These figures have been based on ECDC data and have been generated on the ECDC platform for antibiotic consumption (64). Besides low antibiotic use, the Netherlands also has low prevalence of antibiotic resistance. Table 2 shows the prevalence of third generation cephalosporin resistance in the common bacteria *Escherichia coli* and *Klebsiella pneumoniae* and the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) in European countries. These figures show how the prevalence of these resistant bacteria can vary wildly between countries. The Netherlands has one of the lowest resistance numbers in Europe for these bacteria, which translates to a lower estimated disease burden and thus costs of AMR (3). In the next sections, we will look at several of the factors contributing to the Dutch success with regard to low AMR.

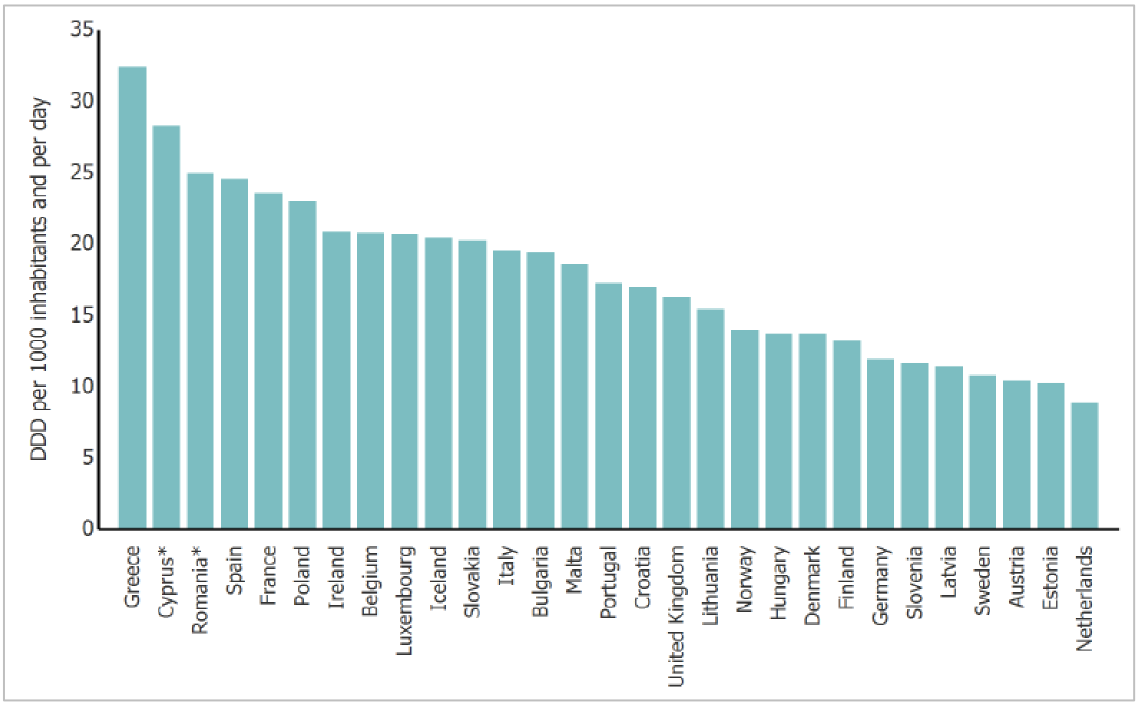

Figure 10a: Total antibiotic consumption in the primary care sector for systemic use in European countries in 2018*

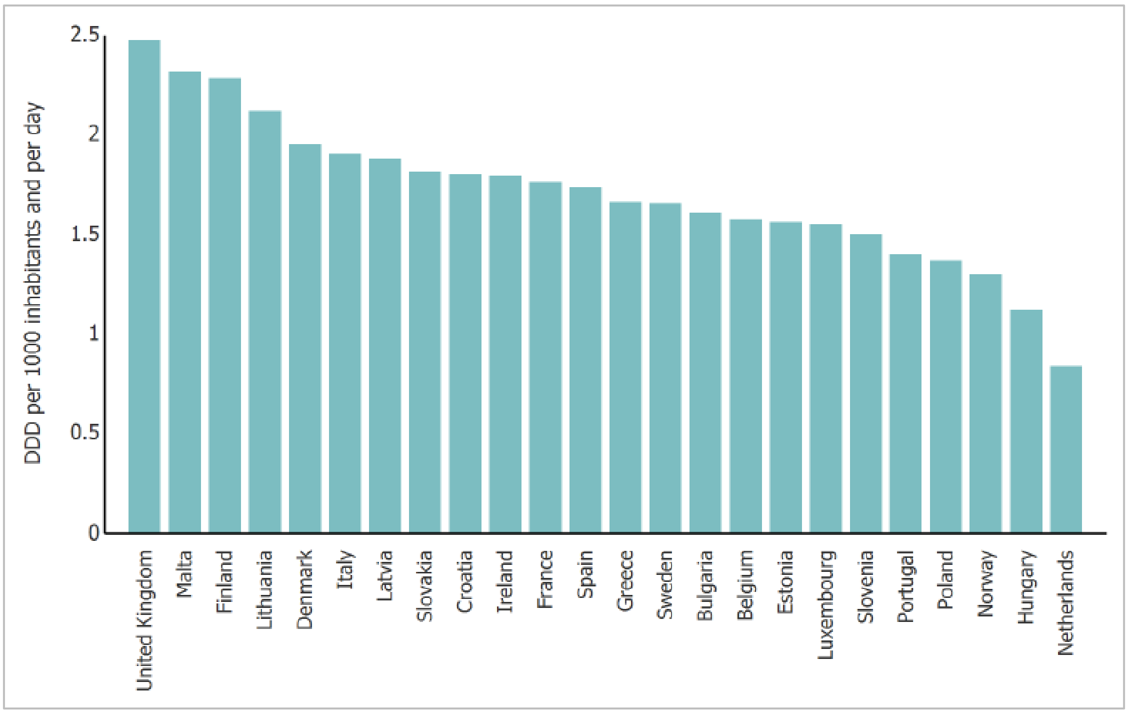

Figure 10b: Total antibiotic consumption in the hospital sector for systemic use in European countries in 2018*

Table 2: Prevalence of antibiotic resistance and estimated health expenditure on AMR for selected European countries*				
Country	MRSA rates	Prevalence of third-generation cephalosporin resistance in E. coli strains	Third generation cephalosporin resistance in K. pneumoniae	Average annual health care expenditure associated with AMR, 2015-2050[1]
Belgium	9.1	9	21.4	$ 240,397
Denmark	1.7	7.7	6.5	$ 79,969
Finland	2	7.6	4.5	$ 46,513
France	12.1	9.6	30.8	$ 525,667
Greece	36.4	19.3	70.7	$ 559,664
Ireland	12.4	12.9	14.5	$ 375,530
Italy	34	28.7	53.6	$ 662,584
Netherlands	1.2	7.3	11.1	$ 41,164
Norway	0.9	6.8	7.5	$ 93,503
Portugal	38.1	14.7	50	$ 490,964
Spain	24.2	13.8	25.5	$ 190,459
Sweden	1.9	8.3	5.5	$ 69,390
United Kingdom	7.3	11	13	$ 179,183
[1]$PPP per 100,000 persons				

*Data from The European Surveillance System – TESSy, provided by Greece, Cyprus, Romania, Spain, France, Poland, Ireland, Belgium, Luxembourg, Iceland, Slovakia, Italy, Bulgaria, Malta, Portugal, Croatia, United Kingdom, Lithuania, Norway, Hungary, Denmark, Finland, Germany, Slovenia, Latvia, Sweden, Austria, Estonia, Netherlands and released by ECDC. The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

Governance, antibiotic use and resistance

In 2018, the World Health Organization (WHO) published their report "Future Global Governance for Antimicrobial Resistance". This document focused on a global collaborative offensive against AMR. Furthermore, the report conveyed a set of minimum requirements for an effective AMR governance mechanism, proposing a model structure for future global governance of AMR (67). In addition, multiple themes were identified. We will look at the Dutch situation according to these themes.

The optimization of antibiotic use

On a national level, the Dutch working party on antibiotic policies (SWAB) has been responsible for producing and updating guidelines on diagnosis and treatment of infectious disease syndromes since 1996. The professional societies that initiated the SWAB were the Dutch society for infectious diseases (NIV), the Dutch society for medical microbiology (NVMM) and the Dutch society for clinical pharmacy. Furthermore, in 1996 SWAB introduced a national antimicrobial guide called SWABID, eventually creating an online version in 2003. Most hospitals in the Netherlands use SWABID and either adhere to their guidelines or adapt their guidelines from the national ones. In addition, the SWAB facilitates education of professionals on subjects of AMR and appropriate use of antibiotics and antimicrobial stewardship. A practice guide on antimicrobial stewardship has been made available. On a hospital level antibiotic-teams (A-teams) safeguard the quality of antimicrobial prescriptions. The SWAB is essential in the education and training of these A-teams. As a minimum requirement, the A-team should consist of a medical microbiologist, an infectious disease specialist and a clinical pharmacist. Moreover, the SWAB monitors antimicrobial stewardship in hospitals.

Surveillance and monitoring AMR

The national AMR surveillance system "Infectious disease Surveillance Information System for Antimicrobial Resistance" (ISIS-AR) was founded as an initiative from the NVMM and RIVM/Cib, with both parties as representatives in the steering committee. More information about ISIS-AR can be found in the previous chapter, where this surveillance information system has been described in more detail. Other AMR surveillance programmes in the Netherlands focus on smaller themes within AMR. In addition, there are surveillance programmes for specific diseases.

At a regional level, both the hospital and the public sector collaborate in local healthcare networks for AMR. These networks help to facilitate medical microbiological laboratories (MMLs) to participate in the national surveillance network. In fact, they also facilitate the transfer of nationwide information regarding trends on antibiotic resistance, antibiotic use and outbreaks of resistant micro-organisms to the proper actors in a region[7]. Moreover, many hospitals in the Netherlands conduct surveillance with their own data on AMR and antibiotic consumption.

Supporting research and development on AMR

There are several programmes and initiatives to support research and development on AMR. The Dutch government incentivises research on AMR, for instance through ZonMW funding[8]. The ZonMW programme antibiotic resistance was started in 2016 and will continue until 2023, focusing on an integrated One Health approach. The Netherlands participates in the Joint Programming Initiative on AMR (JPI-AMR), an international cooperation between 27 countries worldwide to combat AMR. The Dutch government also currently invests in the development of new antibiotics both on a national and an international level. The Netherlands Antibiotics Development Platform was initiated in 2017 and serves to facilitate the development of new antibiotics and treatment methods. Additional funds were made available by the Dutch government for research and development of new antibiotics through the Global Antibiotic Research and Development Partnership, which is governed by the WHO.

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[7] https://www.nvmm.nl/zorg/zorgnetwerken-en-amr/ , accessed on January 30, 2020

[8] https://www.zonmw.nl/nl/onderzoek-resultaten/geneesmiddelen/programmas/programma-detail/antibiotica-resistentie-abr/", accessed on January 30, 2020

Improving awareness of AMR across different sectors

To improve awareness of AMR across different sectors, the government started an information campaign in 2016 regarding influenza and antibiotics, with the slogan: "Antibiotics are not anti-flu medication" and "antibiotics are not anti-cold medication." On 18 November 2019, the European day for antibiotics, the RIVM opened an AMR-themed escape room for three days in Utrecht (68). The recently established regional healthcare networks (Zorgnetwerken) for AMR also contribute to spread awareness of AMR and improve collaboration between the public health sector and the hospitals.

A multi-sector global cooperation balanced on national action

Antibiotic resistance is a global health problem, and consequently a globally coordinated strategy is needed. The Netherlands has historically prioritised antibiotic resistance on an international level. Examples are the ongoing support of the WHO in the implementation of the Global action plan on antibiotic resistance and the technical support provided by the RIVM to WHO member states for the implementation and consolidation of AMR surveillance. During its EU presidency in 2016 the Netherlands promoted the One Health approach to the governance of AMR.

Financing and incentives, as well as supporting resource constrained countries

The WHO, FAO and OIE have recently set up a multi-partner Trust fund to support low and middle income countries in their battle against AMR. The Netherlands has recently made 4.5 million euro available to help the startup of this fund (69). Antibiotic resistance in the agricultural sector can impact human health in the long run. The Netherlands showed a discrepancy between the use of antibiotics in the human health sector and in the agricultural sector. Consequently, action was taken in response to this discrepancy, decreasing the use of antibiotics in the agricultural sector with 64% in 2018.

Professional societies

The Netherlands is a country with a long tradition of guideline development when it comes to antibiotics, infectious diseases and infection prevention and control (IPC). The professional societies in the Netherlands are generally pro-active in nature and are leading in drafting these guidelines; collaborating in working parties and projects to further the cause against antibiotic resistance, regularly together with governmental institutions. In Table 3 we see some examples of these collaborations. One of the most successful collaborations on a national level was the implementation of the MRSA Search and Destroy policy. The success of this policy is in part related to the early implementation, when MRSA rates were still low. The rates have been kept low as result.

Table 3: Examples of collaborative initiatives in the Netherlands		
Purpose	Project or working group	Societies involved
Optimizing the use of antibiotics, in order to contain the further increase of antibiotic resistance and minimize the costs for the use of antibiotics	National: The Dutch working party on antibiotic policies (SWAB) Local: Local A-teams in hospitals	SWAB: Dutch society for clinical pharmacists (NVZA), Dutch society of medical microbiology (NVMM) and the Dutch society for infectiology (VIZ) A-teams: Generally consisting of ID specialists, medical microbiologists and clinical pharmacists
Surveillance of AMR	National: ISIS-AR Local: Individual hospitals (making use of their own surveillance data from the laboratory information system)	ISIS-AR: SWAB (specifically the NVMM) and the RIVM/Cib Regional Healthcare networks: Consisting of a multidisciplinary team of epidemiologists, medical microbiologists, ID specialists, clinical pharmacists and data-analysts Individual hospitals: Surveillance is mostly done by the medical microbiology department
Publishing guidelines concerning infection prevention for the healthcare sector and answering any questions regarding infection prevention	The Dutch working group for infection prevention (WIP)*	NVMM, VIZ and the Dutch society for Infection prevention in Healthcare (VHIG)
Annual report concerning AMR, consumption of antibiotics and quality of antimicrobial prescription in Netherlands	Nethmap	ISIS-AR, SWAB, the Foundation for Pharmaceutical Statistics (SFK) (originally a joint venture of SWAB and RIVM. Later based on ISIS-AR data since 2008)

**The Dutch working party for infection prevention (WIP) was created in 1988 by the NVMM, VIZ and the Dutch society for Infection prevention in Healthcare (VHIG). Its main goal was to create and publish national guidelines for infection prevention in the healthcare sector. In addition, the WIP provided a helpdesk to answer questions relating to infection prevention. The WIP was disbanded in 2017, currently there is work in progress to found a new working party, picking up where the WIP left off. The national guidelines published by the WIP are still in use, although they are not up to date anymore. The helpdesk is currently staffed by the RIVM.*

Moreover, the Netherlands historically has a strong GP-oriented culture, with professional GP associations that promote prudent antibiotics prescribing. Approximately 80% of the antibiotics are prescribed by GPs in the Netherlands. The Dutch college of General Practitioners (NHG) has been publishing guidelines for GPs since 1980. They often collaborate with the proper authorities on a particular subject, such as the professional societies of the pharmacists (Dutch society for clinical pharmacologists, KNMP), medical microbiologists (Dutch society of medical microbiology, NVMM) and infectiologists (the Dutch society for infectiology, VIZ) when the guideline concerns infectious disease syndromes. The guidelines pertaining to infectious disease syndromes aim to promote the rational prescribing of antibiotics. Guidelines are updated regularly, comprehensive in nature and peer-reviewed.

Cultural factors influencing governance and AMR

A high level of antibiotic prescribing and unnecessary prescription of antibiotics are directly associated with an increase of antibiotic resistance (70). As such, restriction in the use of antibiotics could curb the resistance problem. The Netherlands consecutively had one of the lowest antibiotic consumption rates in Europe, both on a hospital level and on a GP level (6), as seen in figures 9 and 10. The antibiotic consumption of a country is in part associated with culture, both of the inhabitants and the professionals working there. The multilayered complexities of cultural dimensions cause many social phenomena that in turn influence the prescribing culture of a country (71).

A study done in 2001 in two cities (Middelburg, Netherlands and Bruges, Belgium) illustrated the difference in lay persons culture. Disparities were found between coping strategies, attitudes towards antibiotics and even disease labeling. These factors, along with different patterns of expectation from a patient visiting a doctor, resulted in higher prescriptions of antibiotics in the Flemish town of Bruges in comparison to the Dutch town of Middelburg (72). The influence of the patient in a doctor's office is an underappreciated factor in the prescription of medication.

Interviews with experts in Europe

In order to view the governance and the role of the Dutch professional societies in the context of Europe, we conducted interviews with key professionals in different European countries. The experts were from the following countries: Belgium, Denmark, France, Spain and Sweden. We invited more experts from other countries to be interviewed, but not all of them responded or had time to participate. The information expressed in the interviews stemmed from their role as experts in their field on their personal behalf and not in their respective roles in their country. We asked questions regarding the presence and pro-activity of professional societies in the different countries. In addition we tried to ascertain who is in the lead (government or professional societies) concerning AMR. The governance of other countries has been described in other documents, but the level of pro-activity and functionality of the different professional societies and their interaction with the government have possibly been underappreciated.

Professional societies in other countries

All experts confirmed that professional societies for infectious diseases were present in their country. Still, it differed per country whether the ID specialists and clinical microbiologists had separate societies or a joint society. Clinical pharmacists almost always had a separate society from the other two specialisms. Other countries have similarly proactive professional societies that collaborate on different topics regarding guidelines and scientific projects. Cooperation with other specialisms concerning infectious disease guidelines and protocols are common practice. One expert stated that the societies in their country worked parallel to each other, making individual plans and eventually coming to an ad hoc collaboration. Another expert mentioned that their professional society was less active in the past due to a lack of cohesion, although this has recently changed for the better. Associations similar to the SWAB are present in most of the countries that we researched.

In general, national guidelines on how to set up antimicrobial stewardship were present in all countries. Most hospitals or regions in the individual countries have the opportunity to create their own personalised guidelines and protocols. One possible downside mentioned was that the quality could vary wildly from one hospital to the next. All but one country had national guidelines concerning infection prevention and control (IPC), similar to the Dutch situation. In some countries these guidelines were legally binding or there were laws concerning IPC. The hospital hygienists of most countries are a separate entity in the hospitals. This is in contrast with the Dutch situation, where the hygienists work in close collaboration with the clinical microbiologists, even sharing the same department. Diagnostic guidelines regarding infectious disease syndromes were almost exclusively developed by the clinical microbiologist community.

The government and the societies

The role of the government and the interaction with the professional societies differed a lot between countries; some had a top-down structure, while most had a system where the governmental agencies responded to threats to public health with guidelines and actions. The professional societies mostly publish guidelines regarding the topics that they find relevant in their fields. These professional societies are in the lead concerning guideline development in almost all of the countries, and as such they decide which subjects are relevant. In general, the government is in the lead concerning the national AMR plans of the respective countries, albeit with input of the professionals.

Expert opinion on the success of AMR governance in the Netherlands

When asked what, in their opinion, explained the success of the Netherlands with regard to the low antibiotic resistance figures in comparison to other countries, the answers were surprisingly uniform on certain subjects.

- Culture: Both the professional culture of restricted use of antibiotics as well as the general culture in the Netherlands of hesitant use of care was praised as a possible contributing factor to the low consumption of antibiotics and the low resistance numbers. Correcting problems as soon as they develop and sometimes preventing them before they become a problem was mentioned by multiple experts as part of the norm in the Netherlands.
- Guidelines: The longstanding tradition of publishing guidelines and maintaining the quality of these guidelines was mentioned by multiple experts as a possible contributor.
- Collaboration: The strong tradition of collaboration between different professional societies was also discussed, the current structure of cooperation with working groups such as the SWAB and the now disbanded WIP were regarded as beneficial to the Dutch way of operating.
- Long term work on AMR: The Netherlands started to address the problem of AMR far earlier than most other countries in Europe as a precautionary principle.
- Research: Programmes such as ZonMW that incentivise research in general were seen as positive contributors.
- Government: The strong organisation of the healthcare system in the Netherlands, which is well resourced, is considered to be a positive contributor.
- General Practitioners: The contribution of the GPs in the Netherlands was also mentioned as a beneficial factor in the low consumption of antibiotics and the low resistance figures. The Dutch GPs have a relatively strong community and are very active as a society with regard to guideline production and good practices (box 4).

Conclusions

Antibiotic consumption and resistance in the Netherlands are among the lowest in the European Union. The Dutch governance and its healthcare structure have been beneficial to the maintenance of these low figures. In addition, the professional culture and the culture of the lay people in general have contributed to the fight against AMR, already before the problem arose. The interviews with the experts show that the Netherlands is similar in many regards to other countries when it comes to the professional societies and their collaboration with each other and the government. What sets it apart is a longstanding shared and collaborative culture among healthcare professionals, allowing antimicrobial prescription patterns to be kept low.

7 Discussion and conclusions

AMR is a growing threat that needs to be addressed on many levels. In the Netherlands, a country with low AMR incidence, a number of good practices were previously identified in hospital, nursing home and community settings (1):

- Preoperative MRSA screening
- hospital antimicrobial stewardship teams
- outbreak control in a hospital setting
- outbreak control in a nursing home setting
- rapid diagnostic tests for GPs

This reports adds four good practices:

- Multidisciplinary OPAT teams
- AMR information booklet for GPs
- National surveillance system
- Good AMR governance

Together, these good practices show that even in a low-incidence country, interventions are available that reduce AMR and produce cost savings. However, and as a precondition, this requires good governance and surveillance systems as well as professionals having the time and resources to take the lead (figure 11).

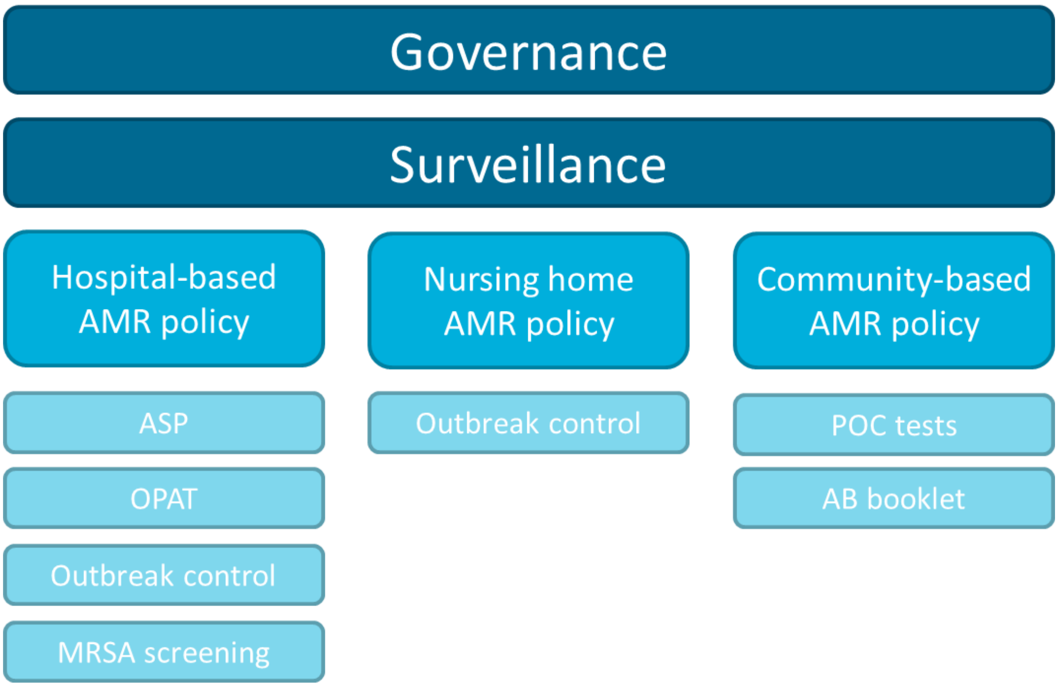

Figure 11: Governance and surveillance overseeing cost saving interventions in hospitals, nursing homes and community settings

Multidisciplinary cooperation: improving OPAT treatment decisions

One intervention available to hospitals to act upon the threat of AMR is to assign multidisciplinary OPAT teams. In-hospital intravenous admission of antibiotics increases chances of (resistant) infection transmissions. Reducing in-hospital length-of-stay through OPAT would lower the chances of development and spreading of resistance. This is especially relevant when incidence of highly resistant pathogens increases locally. A dedicated multidisciplinary OPAT team improves treatment decisions and increases OPAT uptake. This is cost-saving, even when the benefits of lower AMR risks are not taken into account. A multidisciplinary OPAT team is closely linked to the antibiotic stewardship teams (ASP), and such interventions strengthen each other. A strong national surveillance system provides input for appropriate OPAT decisions as well as opportunities to disseminate good OPAT practices throughout the network. As lowering length of stay may reduce hospital income, a supporting culture and AMR awareness will be necessary to counteract adverse financial incentives.

Reducing GP antibiotics prescriptions for feverish children

Antibiotics may be prescribed inappropriately by GPs in order to reassure parents of feverish children. In many cases this fever has viral origins, rendering antibiotics ineffective. While antibiotics prescriptions are low in the Netherlands, they could be reduced even further by interventions that save costs. A booklet with information on child fever is shown to be a cost-saving manner to reduce antibiotics prescriptions, as it reassures parents, reduces time for GPs to explain why antibiotics might not be an effective treatment option, and perhaps also creates awareness for GPs. This intervention is complementary to POC tests, which determine appropriateness of antibiotics. The booklet provides a valuable and cost-saving alternative for prescribing unnecessary antibiotics.

National AMR surveillance systems produce critical information

In 2008 a national surveillance system, ISIS-AR, was founded in cooperation with professional associations and governmental organisations, in line with a cooperative culture of governance in the Netherlands. The close involvement of professional parties increased support for the national surveillance system. A large number of advantages are associated with national monitoring, including dissemination of information, evidence and good practices (73). This information can be used by hospitals and care providers to optimize treatments. Information on local resistance patterns is needed to decide on appropriate treatments. National surveillance systems require close cooperation with local providers and laboratories to obtain a complete image of prescribing and resistance patterns. This may reinforce involvement and shared problem ownership. A surveillance system is a necessary precondition for effective AMR policy, but not sufficient. It requires proactive providers to act upon the information, and effective interventions to address the threat of AMR adequately. National surveillance systems play a critical role in coordinating efforts to address multi-resistant outbreaks, especially if multiple providers are involved.

Governance: an international comparison

The Netherlands has a history of successful collaborative governance in healthcare (74). Collaborative governance has supported good and proactive collaborations in the field of AMR, resulting in low use of antibiotics and a low occurrence of AMR. AMR governance has been embedded in a system that allows for good overall healthcare with infection prevention programmes, high quality diagnostics, and good knowledge on patient management. Several factors are associated with good governance, such as a zero-tolerance culture for not complying with agreed upon guidelines, high professional autonomy and responsibility, a high organisational grade of professionals and adherence to evidence-based guidelines. Cultural aspects may contribute to good governance in the Netherlands, which may be difficult to copy in other countries. However, policy options to stimulate good governance are available. GPs, as major prescribers of antibiotics, act as gatekeepers in the Dutch health system. A historically grounded culture of GP autonomy, professionality and publishing evidence-based guidelines have contributed to low levels of antibiotics prescriptions. Acknowledging the role of GPs as gatekeepers and prudent prescribers can improve the role of GPs in AMR governance. Surveillance systems that originated from professional societies (bottom-up) can improve problem ownership by those in the field and stimulate good practices.

Limitations

The case studies presented in this report have a number of limitations. Cost-effectiveness of the governance and surveillance cases is very difficult to calculate, and thus uncertain. One piece of vital information is missing in all of these business cases: the benefits of reducing AMR threats (25). For example, fewer antibiotics prescriptions lead to lower AMR incidence and fewer in-hospital days lower the risk of hospital-related AMR infections, but the exact relationships, as well as societal costs of AMR incidence remain unknown (11). More information on the benefits of AMR policies may improve the business cases presented in this report. Furthermore, a number of additional variables, such as labour participation, family caregiving, patient satisfaction and health outcomes are not taken into account, although most factors are likely to further increase cost-effectiveness. Similarly, in the case of the child fever booklet, effects of reduced secondary consultations, on-line booklets, GP awareness and spreading through patient networks remain unknown, but are likely to increase cost-effectiveness. This implies that current estimates can be considered conservative. In the multidisciplinary OPAT case, caregivers could put in additional efforts to make the pilot a success, which may reduce the effect in case of broad implementation. Especially in the case of good governance, a country's culture and history partly determine the level of implementation and cost-effectiveness of governance efforts. The cost savings also depend on the incidence of AMR: if the global increase in AMR continues, the good practices will become increasingly cost-effective.

General discussion

This report highlights the fact that AMR policy consists in more than just implementing cost-effective interventions; it requires good governance and surveillance systems, embedded in a high-quality healthcare system. Collaborative AMR governance highly depends on proactive professional associations, supported by an enabling government. On a national level close cooperation between professionals, facilitated by their societies, creates an environment that is beneficial to maintaining low consumption of antibiotics and low rates of AMR, fueled by a sense of urgency to combat AMR. Furthermore, cooperation ensures that good practices are being shared and that good quality guidelines are developed. Good governance ensures high-quality national surveillance systems and multidisciplinary cooperation. Surveillance systems facilitate professionals to address AMR threats and to provide locally tailored solutions. In a hospital setting, multidisciplinary teams and stewardship programmes can safeguard appropriate use of antibiotics through measures such as OPAT, step-down therapy, and MRSA screening. Surveillance may provide an early warning system for multi-resistant infection outbreaks, allowing swift and adequate responses. On a specific note, the large LTC sector in the Netherlands necessitates close involvement in surveillance systems, and close cooperation with the hospital sector in case of outbreaks. Increasing awareness of AMR in patients and GPs, for example through information booklets, can reduce unnecessary antibiotic prescriptions.

One potential barrier to the implementation of these cost-saving interventions is that savings may accrue to different agents than those making the costs. For example, reductions in GP prescriptions benefit payers, but GPs may have to invest in purchasing the booklets. Also within a hospital, benefits and costs may accrue to different departments. Reductions in bed days may benefit certain clinical departments, while supportive departments (medical microbiology, pharmacy) may incur additional costs. This requires compensation mechanisms within a hospital. Similarly, national monitoring agencies may not be compensated for their initial investments by the hospitals and providers that benefit from these services. This requires good financial stewardship of public agencies, insurance companies as well as the provider administration. Current trends of cost containment and increases in professional workloads pose a risk to the accomplishments in the field of AMR. Low levels of AMR are difficult to sustain, and without proper investments, resistance levels could increase rapidly.

Conclusions

The increasing threat of AMR to public health and healthcare budgets calls for interventions on all levels. These interventions will likely reduce the costs associated with AMR in the short and longer term. This report describes four good practices: good AMR governance to coordinate AMR policies, surveillance systems to support development of good quality guidelines, multidisciplinary teams to improve treatment of patients with complex infections at home (OPAT), simple information booklets to improve antibiotic use in out-of-hour GP patients. An important lesson is that integrated AMR policies require multidisciplinary efforts to set up cost-effective governance and surveillance systems. Culture is an important but hard to steer on factor in proactive AMR governance. The good practices in the Netherlands show that even in a setting where governance and monitoring already result in low prescription rates and resistance occurrence, cost-effective interventions are available to further reduce the threat of AMR. Policy changes regarding reimbursements, infection prevention, diagnostics or treatment need to consider long term consequences for surveillance and AMR in general. The good practices in this report can provide examples for countries aiming to reduce AMR, allowing stakeholders to design business cases that compensate for their initial investments. Global action is required to tackle this problem, and learning from each other's experiences will be an important step on that road.

8 Appendix 1 : Categories of interventions to address AMR

This section provides a brief overview of AMR interventions commonly featured in the literature. Aim was to identify important areas in designing integral strategies to combat AMR. Based on 287 interventions listed in 80 articles, five major areas of intervention were identified: 1) infection prevention, 2) appropriate use of antimicrobials, 3) therapy optimization, 4) development of new antimicrobials and 5) resistance outbreak control measures. Furthermore, three supportive policy areas were identified: 1) stewardship programmes, 2) monitoring and surveillance, 3) education and awareness.

Antibiotic resistance starts with occurrence of infections. A high infection burden, combined with suboptimal treatment increases the chance of resistance development. Unchecked, resistant pathogens can spread across regions and countries. Effective infection prevention and control lowers occurrence of infections, thereby reducing the chance of resistance development. When infections do occur, restrictive and accurate prescribing of antimicrobials is required to prevent (multi)resistance development. This requires adequate diagnosis and therapy. As resistance could always emerge, development of new drugs increases possibilities to effectively treat resistant pathogens. To prevent further spreading of multi-resistant infections, effective isolation and control protocols need to be in place. All these areas require coordinated action: stewardship programmes and multidisciplinary teams coordinate and streamline AMR policy on a local level. On a regional and national level, surveillance systems are required to monitor antimicrobial use as well as the occurrence and spreading of resistant pathogens. Lastly, national policies and education are necessary to create awareness and to build the necessary skills. These areas are discussed in more detail below.

Infection prevention and control

Interventions aimed at preventing and controlling infections are a vital part of coordinated AMR strategies, as adequate infection control reduces the demand for antimicrobials (3, 72, 75-82). This is particularly relevant for hospitals and long-term care (LTC) institutions, where risk of infections is high (77, 83). A number of measures have been described in the literature to assure a high quality of standard hygienic precautions, including interventions to improve hand hygiene, use of sterile equipment, proper patient cleansing and environment disinfection (3, 6, 55, 59-62, 72, 75, 76, 78, 80, 84, 85). Infection prevention and control may require coordinated action, for example through installment of Hygiene In Practice (HIP) workgroups in hospitals and LTC-institutions (86). Infection prevention and control measures should be integrated with other policies aimed at reducing the chance of catching infections, such as vaccination programmes, health promotion programmes and policies to reduce hospital stays (3, 72, 80, 87, 88).

Appropriate prescribing of antimicrobials

The problem of AMR calls for reductions in the prescription of antimicrobials, specifically antibiotics (89). Key to reducing antimicrobial prescriptions is appropriate use: the right diagnosis, drug, dosage and duration at the right time and setting (84, 90, 91). Interventions to improve appropriate use include the development and implementation of guidelines, auditing and feedback on prescribing patterns, and formulary restrictions (72, 75-77, 80, 84, 87, 91-100).

Availability and improvement of diagnostic tests, such as rapid diagnostic testing, point-of-care tests and antibiograms can aid in selecting appropriate treatment (3, 72, 77, 84, 87, 101-104). Streamlining treatment through de-escalation and dose-optimization is key to reducing antibiotics use and retaining efficacy of antimicrobial treatments (84, 91-94, 96, 98, 100, 103, 105, 106). Furthermore, continuous diagnostic monitoring can improve treatment appropriateness (103, 107).

Multidisciplinary Antibiotic Stewardship Programmes (ASP) can stimulate appropriateness of prescriptions and therapy and adjust protocols based on local needs (96, 103, 108-110), perhaps supported by computer-assisted decision support systems (91, 96, 98, 101, 103, 111, 112). However, this requires national monitoring and cooperative efforts to provide crucial information to ASPs (96, 113). Appropriate use also requires awareness and education, for example through national campaigns and behavioural interventions (99, 103, 114). Physicians need to be educated in adhering to guidelines and appropriate prescribing of antimicrobials (3, 72, 100, 115-117). Furthermore, ensuring universal access to antimicrobials and reductions in the use of unsupervised and illegally imported antimicrobials call for international cooperation (3, 75).

New drug development

Therapeutic alternatives need to be available to treat infections with (multi-)resistant pathogens, which may require the development of new antibiotics and new antimicrobial drugs (77, 84, 87, 89, 118, 119). Rediscovery of old antibiotics could also be an option (120-125), as well as development of novel treatments, such as small-molecule antibiotics, biologicals, effective adjuvants, vaccines, monoclonal antibodies and phages (77, 84, 108). Decolonialisation could be an effective treatment alternative in case of multi-resistance (3, 76, 78, 119). New treatment developments may necessitate global efforts in increasing financial incentives and subsidies for the pharmaceutical sector (75, 124, 126-128).

Resistance outbreak control measures

Precautions need to be in place to prevent spreading of (multi-)resistant pathogens (81, 87). Imperative in identification of multi-resistance is screening and detection (3, 76, 78, 80, 83). Isolation of infected patients and carriers may be necessary once multi-resistance has been detected (3, 76, 77, 80, 129). Preventing spread of resistance may require additional infection prevention and control measures (76). In such a crisis situation, availability of protocols, as well as personnel training, is vital (72).

Antimicrobial stewardship programmes (ASP)

Interventions to prevent AMR may require multidisciplinary coordination within hospitals and LTC institutions. Antimicrobial Stewardship Programmes (ASP) can coordinate AMR efforts (3, 72, 76-78, 82, 84, 91-93, 95, 96, 98, 100, 101, 109, 112-114, 130-133). Multidisciplinary ASPs could include medical microbiologists, infection diseases specialists, pharmacists, clinical specialists, and specialised nurses (100, 103, 134). ASP tasks include developing formularies, guidelines and prior authorisation protocols, as well as therapy streamlining and de-escalation, but also monitoring, providing audits and feedback, and education (81, 93, 94, 100, 103, 106). Evidence, while limited, generally demonstrates (cost-) effectiveness of ASP (92, 96, 113, 135-137). However, differences in implementation of multidisciplinary ASPs are large, both within and between countries (109, 133, 138-140). Therefore, ASPs may require national coordination to provide infrastructure, education, and standardisation (72, 81, 92, 96, 98, 100, 134, 138, 139, 141).

Monitoring and communication

Monitoring AMR on local, national and international levels is critical in providing information for coordinated interventions (23, 72, 77, 83, 84, 94, 101, 103). Within the organisation, ASPs generally coordinate the monitoring of antibiotic prescriptions and AMR occurrence, providing feedback, protocols and accountability to individual physicians (75, 84, 93, 96, 103, 139). Cooperation with clinical microbiology laboratories as key infrastructure helps to provide timely and accessible data (72, 76, 77, 81, 96, 103, 109, 139). These local data need to be bundled on a regional/national level to assess trends in AMR development and provide recommendations tailored to local conditions (72, 77, 80, 81, 84, 93, 94, 96, 103). Furthermore, surveillance data on a national level enables hospital monitoring and benchmarking (72, 130, 142). Fast recognition of AMR outbreaks could provide an early warning system to stop AMR from spreading (84, 129). National efforts to accommodate surveillance requires government coordination and financing (72, 77, 81, 90, 130). In turn, international cooperation is required to monitor AMR beyond national borders (77, 81, 84, 143). To achieve coordinated AMR interventions, awareness, education and training is warranted to involve all stakeholders (77, 81, 84, 89, 91, 93, 96).

Integrated AMR strategy

All groups of interventions, as displayed in figure 1, are interlinked. For example, improving appropriateness through development of protocols requires multidisciplinary ASP teams that are fed by data from microbiology laboratories and national monitoring bodies. Protocols to prevent spreading of resistant pathogens require close collaboration with infection prevention and control experts, and national monitoring to provide an early warning system. Therefore, the battle against AMR requires both an integral strategy and coordinated action. Awareness of the consequences of AMR needs to be raised in patients and professionals, for example through national awareness campaigns (3, 72, 77-79, 100, 134, 144). Cultural aspects are an important driver in coordinated strategy design: professionals need to have a sense of urgency, as well as a zero-tolerance attitude. Furthermore, integrated strategies demand a culture of close cooperation between professionals, for example between medical biologists, pharmacists and infectiology specialists.

9 Appendix 2 : List of potential good practices

Table 1: List of potential good practices, extracted from grey literature and expert consults			
Name	Short description	Category	Grade
Preoperative MRSA screening	Prior to surgery, a screening and prophylaxis protocol is followed upon detection of nasal carriers of (MR)SA, in order to reduce postoperative infection rates	Infection prevention	7
Hand hygiene speed test	Home care organisation Proteion uses a hand hygiene speed test to improve hand hygiene adherence	Infection prevention	7
Hospital infection prevention control	At the LUMC hospital, extensive measures were taken to reduce hospital-acquired infections	Infection prevention	7
Basic hygienic improvement measures	Elderly home provider Rijnland Zorggroep took precautions to improve basic hygienic standards	Infection prevention	7
Hospital - elderly care cooperation	Azora and Slingeland hospital cooperate to improve hygienic standards and prevent infections	Infection prevention	7
Healthcare Inspection initiated improvement	Mandated by the Healthcare Inspection, elderly home care organisation De Betuwe took measures to improve infection prevention and control	Infection prevention	7
Integrated infection prevention policy	Integrated provider Rivas Zorggroep takes measures to reduce infections across the patient pathway	Infection prevention	8
Training volunteers and family caregivers	Viattence trained family caregivers and volunteers in hygienic protocols	Infection prevention	7
Hygiene challenge	5 sites of Humanitas compete with each other to follow infection prevention protocols	Infection prevention	7
Expert infection prevention	An expert infection prevention can support infection prevention teams in designing and following protocols	Infection prevention / ASP	7
Multidisciplinary OPAT teams	To stimulate outpatient intravenous antibiotics treatment (OPAT), a multidisciplinary hospital team assessed eligible patients	Infection prevention/ therapy optimization/ ASP	8
Hygiene in Practice (HIP) groups	Utrecht UMC formed multidisciplinary teams to improve hygienic measures and reduce infections	Infection prevention/ASP	7
Clinical audits	At Diaconessenhuis Utrecht, clinical audits provide feedback on prescribing patterns	Appropriate use	7
Guidelines treatment S aureus sepsis	Guidelines for treatment of S aureus sepsis are not routinely followed	Appropriate use	6

Re-evaluate allergies	Patients may inappropriately indicate being allergic for antibiotics, which could lead to unnecessary use of broad-spectrum antibiotics	Appropriate use	6
Education booklet for GPs in case of child fever	By providing education on antibiotics use to parents visiting their GP with a feverish child, unnecessary prescriptions can be reduced	Appropriate use / education	8
IV/oral switch	Switching from IV to oral antibiotics when appropriate can reduce IV-related infections	Appropriate use / infection prevention / ASP	7
SWAB antibiotics booklet	The antibiotics booklet, published by the Dutch working group on antimicrobial policy, consists of guidelines and protocols to increase appropriateness of prescriptions	Appropriate use	8
Streamlining	The SWAB recommends streamlining to reduce treatment time	Therapy optimization	6
Dose optimization	Dose optimization requires effective protocols and ASP oversight	Therapy optimization	6
CRP point-of-care test	Measuring c-reactive protein, the CRP-test can quickly determine the origin of the infection (viral, bacterial), allowing GPs to determine the appropriate therapy, and reducing unnecessary antibiotics prescriptions	Therapy optimization	7
MRSA Search&destroy	Specialised search and destroy teams detect MRSA and take actions to eradicate the resistant pathogens and contain MRSA outbreaks	Outbreak control	7
Outbreak control of multiresistant Klebsiella Pneumoniae	A nursing home in the Netherlands, De Riethorst, took isolation precautions to prevent outbreak of multiresistant Klebsiella Pneumoniae	Outbreak control	7
Hospital VRE outbreak control	At the Antonius Hospital Nieuwegein, measures were taken to prevent outbreak of Vanomycin-resistant Enterococcus (VRE)	Outbreak control	7
Isolation department in elderly homes	To prevent outbreak, elderly home provider Cedrah opened a separate department for infected elderly	Outbreak control	7
MRSA outbreak control	Elderly home provider Humanitas Deventer, being faced with MRSA outbreak, had to take measures to prevent spread	Outbreak control	7
MRSA outbreak control team	At nursing home ‘t Dijkhuis an MRSA outbreak necessitated formation of a specialised outbreak control team	Outbreak control	7
Isolation measures at a nursing home	An MRSA outbreak at a nursing home required Zorggroep Apeldoorn to take precautionary isolation measures to prevent spreading	Outbreak control	7
Antimicrobial stewardship teams	Formation of multidisciplinary teams, e.g. at the UMCG and CWZ	ASP	6

Nurse specialist in ASP	The Catharina Hospital dedicated a nurse specialist to be part of the ASP “a-team”, which resulted in reductions in treatment time	ASP	7
NethMap	Nethmap is an annual report on antibiotics use and resistance development, that providers can use to design local guidelines and protocols	Monitoring	8
Regional AMR network Netherlands East	In the eastern part of the Netherlands, a regional cooperative AMR network was formed to improve coordination and to monitor antibiotic use and resistance patterns	Monitoring	7
Public-private partnership VALUE-DX	VALUE-DX organises international monitoring and collaboration	monitoring	6
Nursing home Point prevalence measurements	To gain insight into AMR prevalence, nursing home Antonia participated in the national RIVM point prevalence measurement	monitoring	6
Hospital Point prevalence measurements	At the Sint-Maartenskliniek, participating in point prevalence measurements allowed the monitoring of antibiotics use and resistance patterns	monitoring	7
Good governance	Governance structures and culture in the Netherlands allow for extensive and integrated action to combat AMR	Monitoring/ education	8
AMR education programme	Elderly care organisation TMZ organises mandatory education programmes to increase AMR awareness	education	7
AMR e-learning	To increase knowledge and awareness, the VU Amsterdam developed an e-learning course on ASP and infection prevention	education	7

10 Appendix 3: Shortlist of good practices

Table 1: Shortlist of potential good practices, selected form the longlist

Name	Short description	Category	Area of intervention
Integrated infection prevention policy	Integrated provider takes measures to reduce infections across the patient pathway	Infection prevention	Mixed
Multidisciplinary OPAT teams	To stimulate outpatient intravenous antibiotics treatment (OPAT), a multidisciplinary hospital team assessed eligible patients	Infection prevention/ therapy optimization/ ASP	Hospital based
Education booklet for GPs in case of child fever	By providing education on antibiotics use to parents visiting their GP with a feverish child, unnecessary prescriptions can be reduced	Appropriate use/ education and awareness	Community setting
SWAB antibiotics booklet	The antibiotics booklet, published by the Dutch working group on antimicrobial policy, consists of guidelines and protocols to increase appropriateness of prescriptions	Appropriate use	Regional/ national
NethMap	Nethmap is an annual report on antibiotics use and resistance development that providers can use to design local guidelines and protocols	Monitoring and surveillance	Regional/ national
Good governance	Governance structures and culture in the Netherlands allow for extensive and integrated action to combat AMR	Monitoring and surveillance/ education and awareness	National

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