PRICE-CONTROL AND AVAILABILITY OF ANTIBIOTICS: A BALANCING ACT

An analysis of Dutch price-controlling instruments and the availability of antibiotics over the past 10 years

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Abstract

To combat antimicrobial resistance (AMR), the availability of antibiotics (novel and existing ones) is imperative. However, this availability of antibiotics on the Dutch market is declining, and shortages of antibiotics are becoming more frequent. There are concerns that this is negatively impacted by price-controlling instruments present in the Dutch healthcare system. Whether this actually the case, is yet unknown. To assess these potential problems and explore directions for potential future solutions, this research project investigates the effect of the Dutch price-controlling instruments GVS (Medicine Reimbursement System) reimbursement limits, Wgp (Medicines Prices Act) maximum allowable prices and/or preferential policy on the availability of essential outpatient antibiotics on the Dutch market between 2013 and 2022.

Through a quantitative, exploratory and inductive research approach using data from several databases and data sources, results showed a decrease in both the number of essential outpatient antibiotics and the average number of products per essential outpatient PRK (*prescriptiecode*; prescription code) cluster, but no change in the number of suppliers or summed revenue per product. Furthermore, we found that 78% of essential outpatient antibiotics had an AIP (*apotheek inkoopprijs*; pharmacy purchasing price) below its GVS reimbursement limit, and that the GVS reimbursement limit has not put significantly more pressure on essential outpatient products that have been removed from the market than it puts on those still on the market. 31% of all essential outpatient antibiotics has a Wgp maximum allowable price equal to its AIP. In 83% of cases, the Wgp maximum allowable price is also lower than the GVS reimbursement limit and thus the limiting factor in price setting of essential outpatient antibiotics. The average number of products per PRK cluster decreased more steeply for clusters that contained antibiotics included in a preferential policy compared to the clusters that did not, but that the average number of products overall was higher in the clusters which included preferential products. Lastly, results showed that only 1/59 (~2%) preferential outpatient antibiotics was preferential with all 4 health insurance companies.

Taken together, we conclude that 1) the overall market of essential outpatient antibiotics is starting to show signs of impoverishment; 2) the GVS reimbursement limit is not likely to be the (main) reason essential outpatient antibiotics are taken off the market; 3) the Wgp maximum allowable price might be putting undesirable pressure on the price of essential outpatient antibiotics, and is most often the limiting factor in price setting of essential outpatient antibiotics; 4) although the presented data provides indications that the preferential policy might influence essential outpatient antibiotics being removed from the market, many questions remain unanswered as to how and to what extent, and whether this is negatively impacting patients; and 5) the distribution of preferential outpatient antibiotics over the different health insurance policies is unlikely to contribute to availability issues. Future research might focus on the relationship between price-controlling instruments and inpatient antibiotics and could aim to further elucidate the role of the preferential policy on availability issues.

Based on the findings of this report, the recommendations for the Dutch Ministry of VWS are to…:

1. …qualitatively confirm and/or evaluate the findings of this study with pharmaceutical companies, healthcare practitioners and other relevant stakeholders
2. … consider studying the effect of the preferential policy on the availability of medicines in general and antibiotics in particular both qualitatively and quantitatively

3. …determine to what extent the current mitigating policies regarding the Wgp maximum allowable price already sufficiently cover essential antibiotics
4. …consider exempting essential outpatient antibiotics from the Wgp maximum allowable price altogether
5. …not exempt essential outpatient antibiotics from GVS clustering, at least as long as the GVS reimbursement limits are not updated
6. …further investigate the (legal) possibilities of implementing a pilot for a novel reimbursement and/or payment system for essential antibiotics in the Netherlands, while paying special attention to the lessons learned from international initiatives

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List of abbreviations

Abbreviation	Meaning
AIP	*apotheek inkoopprijs*; pharmacy purchasing price
AMR	antimicrobial resistance
ANOVA	analysis of variance
ASMR	*amelioration du service medical rendu*; added therapeutical benefit
ATC	anatomical therapeutic chemical
CBG	See *MEB*
CEPS	*comité economique des produits de santé* ; economic committee for health products
CIBG	*entral informatiepunt beroepen gezondheidszorg*
DRG	diagnosis-related groups
GIB	*geneesmiddeleninformatiebank*; medicines information database
GVS	*geneesmiddelenvergoedingsysteem*; medicine reimbursement system
HTA	health technology assessment
MEB	medicines evaluation board (*College ter Beoordeling van Geneesmiddelen* (*CBG*))
PHI	private health insurance
PRK	*prescriptiecode*; prescription code
R&D	research and development
ROI	return on investment
RQ	research question
SFK	stichting farmaceutische kengetallen; foundation pharmaceutical key figures
SHI	statutory health insurance
SWAB	*stichting werkgroep antibioticalbeleid*; foundation working group antibiotic policy
TFR	*tarif forfaitaire de responsabilité*
VWS	volsgezondheid, welzijn en sport
Wgp	*wet geneesmiddelenprijzen;* medicines prices act
WHO	world health organisation
NHS	national health service
NICE	national institute for health and care excellence
QALY	quality-adjusted life year

1. Introduction

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) as one of the top 10 global public health threats (WHO, 2021). In 2019, 1.27 million deaths worldwide were directly attributable to AMR, which is more than both HIV/AIDS (864,000 deaths) and malaria (643,000 deaths) (Murray et al., 2022). If not acted upon, this number is expected to rise to 10 million deaths per year by 2050 (O'Neill, 2014). While the largest burden of AMR deaths is concentrated in West Africa (Murray et al., 2022), this problem is also present in Europe: in the EU/EEA countries, AMR is responsible for an estimated 35000 deaths each year (Merk et al., 2022).

To be able to combat AMR, availability of effective antimicrobials (both novel and already existing ones) is imperative. This has become more and more of a problem in recent decades, since no new classes of antibiotics have been discovered since the 1980s (Wellcome, 2020). The WHO has declared the current preclinical pipeline of antibiotics 'insufficient' to combat AMR (WHO, 2022), and shortages of generic, older antibiotics are increasing in frequency (Nurse-Findlay et al., 2017; Rizvi & Ahammad, 2022; Shafiq et al., 2021; Shukar et al., 2021). This lack of availability is a major concern because they are considered to be 'cornerstone drugs' of modern medicine. They are necessary for treating infections, but are also crucial for modern medical procedures such as surgeries, organ transplantations and chemotherapy. The continuous availability of antibiotics is therefore essential, now and in the future.

One of the causes for this decrease in availability, is the fact that the antibiotics market is not considered commercially interesting for pharmaceutical companies. Products are prescribed as little as possible, for as short of a duration as possible. Additionally, the most innovative antibiotics are saved as a last resort and therefore get even less use. This, combined with the high R&D costs associated with development of innovative antibiotics, means that the long-term expected return on investment (ROI) is highly uncertain, and has been identified as a major disincentive for pharmaceutical companies to invest in R&D of new antibiotics (Årdal et al., 2018; Clift et al., 2015; Colson et al., 2021; O'Neill, 2016; Todd et al., 2021). For example, the median annual sales of antibiotics in 2011-2015 were US $24-75 million, while those for oncology in 2017 were US $435 million (Daniel et al., 2017; Gotham et al., 2021; Tay-Teo et al., 2019). Companies that do go to market with an antibiotic often fail and go bankrupt, leading to both major pharmaceutical firms and SMEs withdrawing from the market entirely (Colson et al., 2021; Taylor, 2020; The Economist, 2019; Todd et al., 2021). In short, the low expected revenues and ROI result in two problems: companies cease their R&D activities into new and innovative antibiotics, and existing antibiotics are not kept on the market.

To counteract the lack of R&D into innovative antibiotics, governments can use both *push* and *pull incentives*. Push incentives for new antibiotics are used to cover (part of) the R&D costs prior to market approval. For example, the Dutch Ministry of Health, Welfare and Sport (VWS) finances research programs to stimulate the development of new antibiotics (NWO, 2017), and numerous international organizations (e.g. AMR Action Fund, CARB-X and GARDP) provide research funding at different stages of the drug development process. Even though these push incentives partially cover the R&D costs, they do not compensate for the market failures post market approval. Pull incentives are intended to make the market more attractive and are currently the subject of ongoing debate. These pull incentives could take many different forms. For example, in the current draft of the new European legislation, transferrable exclusivity vouchers are proposed as a reward for a company that develops a novel antimicrobial that meets specific requirements (European Commission, 2023). These vouchers would grant an additional 12 months of data

exclusivity on a product of the companies' choosing or could be sold (transferred) to another company. Other suggestions for pull incentives are – amongst others – market entry rewards and other monetary prizes, higher or alternative forms of reimbursement, minimum revenue guarantees, exclusivity extensions (on the antimicrobials itself), and accelerated approval processes (Årdal et al., 2017; Boluarte & Schulze, 2022).

While the main objective of these pull incentives is to make the market more attractive for bringing new antimicrobials to market, incentivize R&D investments, and ultimately revitalize the antimicrobial clinical pipeline, some of them are also suitable to incentivize keeping already existing antibiotics available and on the market. To this end, governments in Sweden, the UK, Germany, France and the US have started to implement policies that focus on limiting and preventing shortages of antibiotics in their respective countries. The Dutch Ministry of VWS is orienting itself on similar policies. However, before one can decide what – if any – policies are needed to ensure availability of antibiotics on the Dutch market and what lessons can be learned from earlier international initiatives on this topic, a country-specific analysis is needed regarding the causes of the antibiotics shortages in Dutch healthcare context.

Information on the causes of the antibiotic's shortages in the Dutch healthcare context is largely absent. There are concerns that price-controlling instruments – policy instruments intended to keep medicines and healthcare more affordable – could contribute undesirably to shortages of medicines in general (Baltesen, 2023; Brink, 2019; KASSA, 2018; Nieuwsuur, 2018). Voices expressing the opposite opinion, however, are also present (Boogaard, 2023). The Dutch Ministry of VWS has recently acknowledged the undesirable effect these price-controlling instruments may have on medicines with low revenue, and the risks this poses for drug shortages (Minister van Volksgezondheid Welzijn en Sport, 2023b). The extent to which this is the case for antibiotics on the Dutch market, is unknown. Therefore, this report aims to answer the following main research question: what has been the effect of the Dutch price-controlling instruments GVS reimbursement limits, Wgp maximum allowable prices and/or preferential policy on the availability of essential outpatient antibiotics on the Dutch market between 2013 and 2022?

Firstly, in Chapter 2, an overview of the main concepts used in this report will be given. A brief summary of the Dutch healthcare system, as well as the different price-controlling instruments in play will be discussed. Furthermore, the initiatives in Sweden, the UK, Germany, France and the US combatting antibiotics shortages are summarised. In Chapter 3, a quantitative methodological framework to analyse the effect of price-controlling instruments on the availability of essential antibiotics over the past 10 years will be outlined, after which the results of the analysis are presented in Chapter 4. In Chapter 5, the results will be discussed in light of previous literature and the aforementioned international initiatives, after which Chapter 6 concludes the thesis. Lastly, Chapter 7 provides some policy considerations and recommendations for the Dutch Ministry of VWS.

2. Theoretical background

This chapter provides a theoretical background of the topics discussed in this report. First, a brief overview of the Dutch healthcare system will be given, specifically regarding the laws and principles that impact antibiotics. Furthermore, several aspects to keeping the Dutch healthcare system affordable will be discussed, including the three price-controlling instruments under investigation: the GVS (Medicine Reimbursement System) reimbursement limits, the Wgp (Medicines Prices Act) maximum allowable prices and the preferential policy. Next, the term "essential antibiotics" will be defined. Lastly, the international initiatives to combat shortages of antibiotics from France, Germany, Sweden, the UK, and the US will be briefly described after an overview each of the countries' national healthcare systems has been given.

2.1. The Dutch healthcare system

The Dutch healthcare system is based on three core principles: "access to care for all, solidarity through medical insurance (which is compulsory for all and available to all) and high-quality healthcare services" (Ministerie van Volksgezondheid Welzijn en Sport, 2016). Governance of the system is secured through four main healthcare-related acts: the Health Insurance Act (*Zorgverzekeringswet, Zvw*), the Long-Term Care Act (*Wet langdurige zorg, Wlz*), the Social Support Act (*Wet maatschappelijke ondersteuning, Wmo*), and the Youth Act (*Jeugdwet*). Next to the main four acts, there are some additional healthcare-specific acts. Most relevant to the discussion of price-controlling instruments are the Health Insurance Act and the Medicine Prices Act (*Wet geneesmiddelenprijzen*, *Wgp*).

In accordance with the Health Insurance Act, each person that lives or works in the Netherlands, is obliged to take out standard health insurance. Having this health insurance entitles them to all care in the basic health insurance package (*basispakket*) and covers the costs for hospital visits, prescription medication, general practitioner consultations and many other aspects. These health insurances are provided by health insurance companies. In the Netherlands, these are typically not-for-profit organizations. This health insurance system is grounded in solidarity: by having every citizen pay a relatively small premium, the healthcare costs of everyone are covered collectively, irrespective of how much use one makes of it.

For years, the spending on healthcare in the Netherlands has increased: the total cost of healthcare under the Health Insurance Act has steadily risen from 44.4 billion euros in 2018 to 51.4 billion euros in 2022 (Zorgcijfersdatabank, 2023). There is, however, a limit to this healthcare budget. If healthcare spending increases, so does (in principle) the premium charged by the health insurers. This is related to the principle of 'Willingness To Pay' (WTP): how much a Dutch citizen is willing to pay for the treatment of someone else (Kooijman et al., 2018; Zorginstituut Nederland, 2015). A balance between the solidarity principle on one hand, and the WTP and rising healthcare costs on the other hand, is needed to keep the Dutch healthcare system sustainable.

There are several aspects to keeping Dutch healthcare affordable. Firstly, not all healthcare is covered by health insurance. Only the care that measures up to the "state of the art and state of practice" (*stand van wetenschap en praktijk*) is reimbursed from the basic health insurance package (Zorginstituut Nederland, n.d.). In essence, this means that the care must be effective and do what it is meant to do. Whether that is the case for new care, is determined by healthcare professionals, health insurers and patient organizations. Since "state of the art and state of practice" is a rather broad description of what care is admissible into the basic health package, new effective care is admitted into it rather quickly. When it is not clear whether care should be admitted into the basic

health package, the National Health Care Institute (*Zorginstituut Nederland*) will provide independent advice. About 90% of care is admitted into the basic health package via this so-called "open procedure". Admission of outpatient medicines (*extramurale middelen*; those that can be collected at the pharmacy with a prescription, as opposed to inpatient medicines (*intramurale middelen*) administered inside a hospital) and certain expensive inpatient medicines happens through a "closed procedure". In this closed procedure, after approval of the medicine on the Dutch market by the Medicines Evaluation Board (MEB, *College ter Beoordeling van Geneesmiddelen*), the National Health Care Institute tests the medicine against four package criteria: necessity, effectiveness, cost-effectiveness and feasibility (Zorginstituut Nederland, n.d.). All outpatient medicines that are admitted into the basic health package are reimbursed through the Medicine Reimbursement System (*Geneesmiddelenvergoedingssysteem*, *GVS*), explained below in more detail. Antibiotics can fall under both outpatient and inpatient medicines.

A second aspect of keeping the Dutch healthcare affordable is the use of price-controlling instruments. Which price-controlling instruments affect a given medicine, depends on whether that medicine is an outpatient or inpatient medicine. This report will focus on three kinds of price-controlling instruments: the limits for reimbursement as set in the GVS, the maximum allowable prices for medicines as set in the Wgp, and the preferential policy (*preferentiebeleid*).

2.1.1. GVS: REIMBURSEMENT LIMITS

The GVS is a part of the Health Insurance Decree (*Regeling Zorgverzekering*) and contains all outpatient medicines reimbursed in the basic health insurance package as meant by the Zvw (National Health Care Institute, n.d.). All medicines in the GVS are clustered into three lists: List 1A (*Bijlage 1A*), List 1B (*Bijlage 1B*), and List 2 (*Bijlage 2*). The GVS was introduced in 1991 as a means to control healthcare costs and has been recalibrated for the last time in 1999. Although strictly speaking, the GVS aims to control spending on medicines (and might thus be considered a cost-controlling instrument) instead of the true price-controlling nature of the Wgp maximum allowable prices, this report will analyse them in a similar manner.

List 1A contains clusters of outpatient medicines that are interchangeable on a population-level based on the type of indication, the route of administration and the age group (Health Insurance Decree, Article 2.40(1)). Medicines that are included in a cluster in List 1A are subject to a reimbursement limit. The calculation of this reimbursement limit is rather complex and is explained in the Health Insurance Decree (Ellwanger et al., 2014): of each product, the lowest daily price (*dagprijs*) (the cost for the average daily dose of a medicine) is calculated, based on the pharmacy purchase prices (*apotheekinkoopprijs, AIP*) on the 1st of October 1998 (Article 2.42(1)). The lowest daily prices are then averaged into brand prices (*merkprijzen*) (Article 2.43(3)). These brand prices are averaged per group of active compounds (ATC-code). If a cluster contains only one active compound, the average of brand prices per ATC-code is the reimbursement limit of that cluster (Article 2.44(1)). If there are multiple active compounds in a cluster, the prices are averaged once again to form the cluster reimbursement limit (Article 2.44(2)).

The reimbursement limits have, in principle, not been changed since the last recalibration in 1999. The first product to enter a cluster determines the reimbursement limit (Article 2.42(2)), and the limit does not change when new products enter that same cluster. Only if a new cluster forms (to treat a new indication, via a new administration route or for a new age group), a new reimbursement limit will be set at that point in time. For products with multiple dosages on the market, the reimbursement limit is linearly correlated with the amount of active compound (Article

2.46). The reimbursement limit for combination preparations (medicines consistent of multiple active compounds in one product) is equal to the sum of the separate cluster limits (Article 2.47).

If a medicine is priced above the reimbursement limit, the patient is expected to pay the difference. Based on how the reimbursement limit is calculated, there should always be an interchangeable product that requires no additional payment. Patients will often choose to then switch to that product. While this policy's main intent was to lower the spending on prescription outpatient healthcare, an unexpected but welcome side effect was that companies started lowering their prices to get closer to or on the reimbursement limit, resulting in more lower-cost alternatives.

List 1B contains medicines that are not interchangeable on a population level. Therefore, these products cannot be clustered like the medicines on List 1A. The medicines on List 1B do not have a reimbursement limit (National Health Care Institute, n.d.). Medicines on List 1A or List 1B can additionally be placed on List 2 if reimbursement is subject to additional requirements or conditions. In this case, reimbursement can – for example – be reserved for only a select patient population. The limits set in List 1A – or the lack thereof in List 1B – still apply.

In the context of antibiotics, it is currently unknown what the relationship is between the AIP and the reimbursement limit as set by the GVS for the antibiotics that are still on the market, or how this relationship was for the antibiotics that were taken off the market. Since most reimbursement limits have been set based on AIPs of 1998, chances are that the current AIPs have changed. If for most products the AIP is higher than the GVS reimbursement limit, patients will often have to pay extra. On one hand, this could imply that the GVS is performing its price-controlling (or cost-controlling) purpose successfully. On the other hand, this could also imply that the current reimbursement limits are set too low. If most products have a higher GVS reimbursement limit than its AIP, this might suggest that, on one hand, the reimbursement limits are set too high and not enough pressure is put on prices and spending. On the other hand, in the market of antibiotics, little pressure on prices and costs might be desirable.

2.1.2. WGP MAXIMUM ALLOWABLE PRICES

The Wgp sets maximum allowable prices for medicines in the Netherlands and applies to both inpatient and outpatient medicines (Farmatec, n.d.; *Regeling Maximumprijzen Geneesmiddelen*, 1996; *Wet Geneesmiddelenprijzen*, 1996). The maximum prices are based on the prices of comparable medicines in 4 reference countries: Belgium, Norway, France and the UK. In each of those countries, comparable medicines (based on active compound, dosage and pharmaceutical form) are clustered into product groups. Then, per product group, the lowest price per unit is calculated per brand name using the available packaging sizes. These prices per unit per brand name per product group are then averaged per country. The overall average of the averages per country is the price limit allowed in the Netherlands (Article 2). Selling a medicine for a higher price than the maximum price is not allowed and can be fined €45.000 (Article 4 and 11). No maximum price is set when three or more of the reference countries do not have the medicine on their price list (Article 2). The Wgp was introduced in 1996, and maximum prices are updated every half year if necessary.

It is unknown what the relationship is between the AIP and the maximum allowable price for antibiotics currently on the market. The AIP should never be higher than the maximum allowable price. It would, however, be interesting to investigate what portion of antibiotics has an AIP equal to the maximum allowable price, especially when the product does not have patent-/market-/data-

protection anymore (since this would logically be the moment at which generics could enter the market and prices would go down). If this portion is high, this might indicate that there is a lot of pressure on prices from the Wgp maximum allowable price.

Also interesting would be to investigate whether the GVS reimbursement limit or the WGP maximum allowable price is higher for the antibiotics still on the market. While in theory, these two instruments have a different purpose, they do interact with each other (Figure 1). If the maximum allowable price is lower than the GVS reimbursement limit, manufacturers would still only be able to set their AIP equal to the maximum allowable price. If the GVS reimbursement limit is lower than the maximum allowable price, manufacturers would be able to increase their prices above the reimbursement limit if necessary to keep it on the market, with the "only" consequence being that patients have to pay for the difference. Thus, comparing the effect these two instruments have on each other, might give insight into the pressure overall on the current antibiotic market.

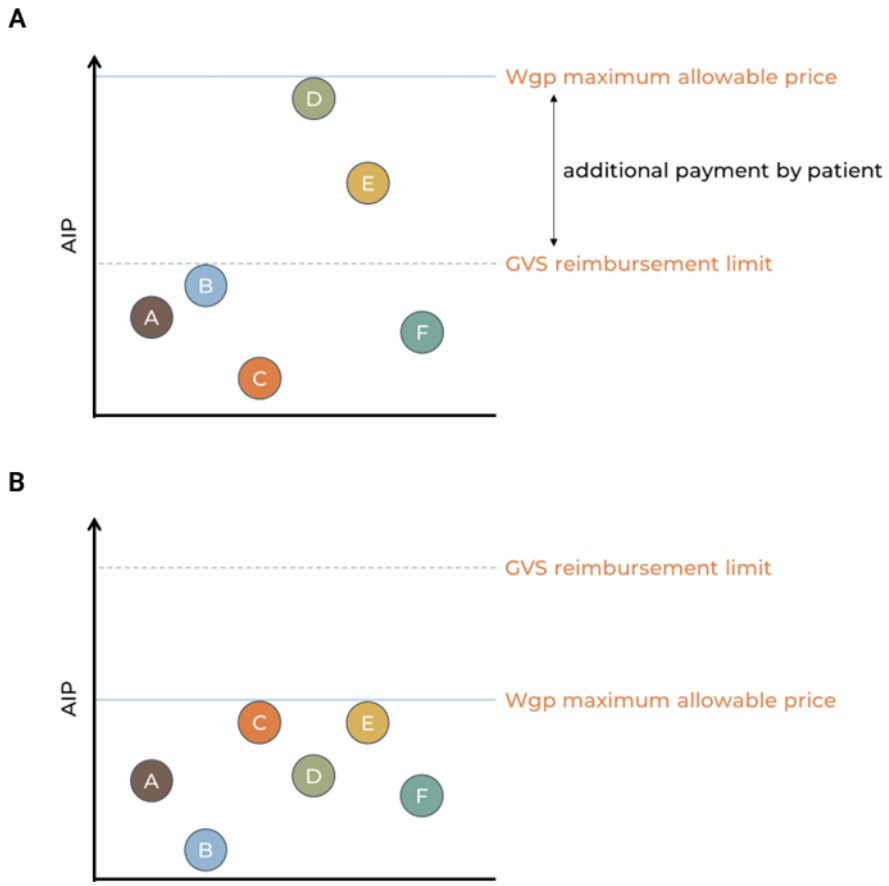


Figure 1 - Simplified and schematic explanation of the price-controlling instruments GVS reimbursement limit and Wgp maximum allowable price. (A) In a situation where a product's Wgp maximum allowable price is higher than its GVS reimbursement limit, the AIP can be higher than the GVS reimbursement limit. However, the difference between the GVS reimbursement limit and AIP has to be paid by the patient. Medicines cannot have an AIP higher than the maximum allowable price. (B) In the situation where the GVS reimbursement limit is higher than the Wgp maximum allowable price, the AIP can only be as high as the Wgp maximum allowable price, not higher. *NB: this picture is meant to illustrate the working mechanisms of the GVS reimbursement limit and Wgp maximum allowable price on an individual product level. The two limits are set on different clusters (GVS clusters and product groups, respectively) and are not necessarily the same (often, in fact, they are not).*

2.1.3. Preferential policy

In some cases, health insurance companies will not reimburse all types and brands of medicines that are present on the Dutch market. They are then said to have a 'preferential policy'. The health insurance companies will select one product per group of medicines with the same active compound (usually the cheapest one) that will be reimbursed. Other products will – except for when there is a medical necessity – not be reimbursed by the health insurance company. This policy has resulted in companies trying to produce the cheapest version of a medicine on the market and has thus led to a price reduction of medicines. The preferential policy is only applicable to outpatient medicines.

Of important note is that this so-called preferential policy is not a policy introduced by the Dutch government, but rather by the health insurance companies themselves. This instrument facilitates them to purchase care efficiently via tenders, based on long-term (usually 2 to 4 years) contracts with suppliers that often include discounts. This, in turn, has contributed to more affordable healthcare in the Netherlands. Henk Eleveld – one of the founders of the policy – estimates that the policy saves around €7.000.000 to €1 billion per year (Boogaard, 2023).

Despite the yielded savings, however, the preferential policy has also been subject to criticism since its start in 2005 from several of its stakeholders (Hollak et al., 2023; Nieber, 2023; Nivel, 2016; Pharmaceutisch Weekblad, 2010). Firstly, there is a concern that the preferential policy leads to lower profit margins for generic companies and a 'race to the bottom'. On one hand, this has led to the generic medicines in the Netherlands being some of the cheapest in Europe. On the other hand, this has led to some companies rather delivering medicines to other countries, since the profit margins are higher there (KNMP, 2023). Secondly, manufacturers that do not win the tender with the health insurance company will have a smaller (or non-existent) sales market for the duration of the tender, which sometimes leads to companies pulling their product from the Dutch market. Thirdly, the reliance of health insurance companies on few major manufacturers means that the supply chain of medicines is vulnerable. If there is a delay or blockage somewhere in the supply chain, shortages of these preferential medicines might occur. Lastly, the policy is also blamed with causing more administrative burden for pharmacists and confusion for patients, since they might receive are different package of medicine each time the preferential medicine changes or when there is a shortage of the preferential medicine. Up-to-date, peer-reviewed academic literature on the topic is scarce. One of the more recent articles written on the topic of using tendering for off-patent outpatient medicines suggests that tendering practices in the Netherlands, Belgium and Denmark all reported to have cost savings, but that the policy could potentially lead to problems with availability (Vogler et al., 2017). The Dutch Ministry of VWS has recently acknowledged these concerns (Minister van Volksgezondheid Welzijn en Sport, 2023b). Although this policy is carried out by health insurance companies, the Ministry can still influence it. This can be done through voluntary (e.g. agreements, advocacy, voicing of concerns) or more binding measures (e.g. legislation).

The same concerns regarding the preferential policy affect the antibiotics market. The expected sales market of antibiotics is already low. The sales market for antibiotics that are not included in the preferential policy of one or more health insurance companies is reduced even further. Furthermore, companies may decide to not (or only later) introduce antibiotics on the Dutch market because of the acting policy. Concerns regarding supply chain vulnerabilities and shortages are also present. However, any definitive answer whether the preferential policy has or has had an effect on the availability of antibiotics remains absent. Therefore, this report investigates the

relationship between the preferential policy in the Netherlands and the presence on and disappearance off the market of antibiotics.

2.2. Essential antibiotics on the Dutch market

Not all antibiotics on the Dutch market are essential. In 2022, the Foundation Working Group Antibiotics Policy (*Stichting Werkgroep Antibioticabeleid* (SWAB)) has categorized combinations of active compounds and routes of administrations of antibiotics in four categories (A, B, C (and (C)), and D) according to what extent these antibiotics are essential for primary and secondary care in the Netherlands (SWAB, 2022). This list was compiled using data from *Farmacotherapeutisch Kompas* (Pharmacotherapeutic Compass), which contains all medicines marketed on the Dutch market. Importantly, this list thus does not contain antibiotics that are not present on the Dutch market but would be essential if they were. Of 97 total active compounds, 73 are classified as essential (category A, B, C or (C)), and 24 as non-essential (category D) (Table 1). Importantly, the three essential categories are not hierarchical, but rather distinct kinds of essentiality.

The list by SWAB is focused on Dutch healthcare. On a global scale, efforts are also being taken to determine which antimicrobials are essential for healthcare. In 2018, the WHO published the 6th edition of their ranking of antimicrobials based on their importance in human medicine worldwide (WHO, 2018). In this ranking, four categories are distinguished: important, highly important, critically important, and critically important with highest priority. Of the 264 antibiotics considered, 10 were considered 'important', 88 'highly important', 79 'critically important', and an additional 87 'critically important with the highest priority' (Supplementary Table 1). Although there is substantial overlap between the list of SWAB and the WHO, in this report, the focus is merely on the Dutch healthcare system and market. Therefore, the SWAB list will be used as basis to determine which antibiotics are essential and which are not.

Table 1 - Categorization of essential antibiotics as used in the 'List essential antibiotics in the Netherlands' (SWAB, 2022).

Category	**Definition of category** (SWAB, 2022)	**Number of active compounds in category**
A	"Essential in the sense of being a first choice (based on effectiveness and safety) for common infections (e.g. respiratory tract infections and urinary tract infections) as reflected in the guidelines for primary and secondary care."	31
B	"Essential in the sense of the absence of an alternative in the event of the absence of this product. Some infections can only be treated adequately with very specific types of antibiotics. Other antibiotics are not sufficiently effective and/or have major drawbacks."	16
C	"Essential in the sense that they are a unique secondary choice. In case of side effects or resistance, the only option is usually to resort to this product. In this context, an antibiotic group or subgroup can also be regarded as essential. In that case, this means that at least 1 product from this group must be available."	21
(C)	"Essential in the sense that the product is theoretically a unique second choice for resistant micro-organisms. In (Dutch) practice, however, there is a lack of experience to substantiate whether these resources will actually be used as such. As a precaution, it is recommended to have these resources available."	5
D	"Non-essential: products do not fall into any of the categories listed above. However, these resources can still be of great value to Dutch practice, for example because of their ease of use or options for home treatment."	24
Total		**97**

2.3. International initiatives combatting antibiotics shortages

The Netherlands is not the only country struggling with availability issues of antibiotics. Therefore, a better understanding of the initiatives other countries are taking to combat this, could be used to inspire national policy in the Netherlands. To this end, the next section will describe the initiatives taken in France, Germany, Sweden, the UK and the US. A basic understanding of the healthcare system context of each country is needed to assess the extent to which policies could be applied in the Dutch context. Therefore, a brief overview of the healthcare system for each country and its price-controlling measures will be provided followed by a description of the policies.

2.3.1. France

The French healthcare system is based on a statutory health insurance (SHI) system that provides basic health insurance to all its residents (Commonwealth Fund, 2020c; European Observatory on Health Systems and Policies, n.d.; *La Protection Universelle Maladie*, 2023). The healthcare system is financed by the government through regional health agencies, and funded by payroll taxes, income tax and tax levies on specific products and industries (Commonwealth Fund, 2020c). For example, pharmaceutical companies fall under a clawback scheme in which they are obliged to give back part of their earnings to the social security budget if their revenue exceeds a threshold (*Accord Cadre Du 31/12/2015 Entre Le Comité Économique Des Produits de Santé et Les Entreprises Du Médicament (Leem)*, 2015; Section 2 : Contribution à La Charge Des Entreprises Assurant l'exploitation, l'importation Parallèle Ou La Distribution Parallèle d'une Ou de Plusieurs Spécialités Pharmaceutiques, n.d.).

Prices of medicines are regulated by the Economic Committee for Medical Products (*Comité Économique des Produits de Santé*, CEPS) in agreement with drug manufacturers. The prices of drugs are based on 1) the added therapeutical benefit, 2) the price of other drugs with the same therapeutic indication, and 3) the estimated volume of sales and the conditions of use (Kamenade, 2018). New innovative medicines are exempted from price negotiations if they have added therapeutical benefit over the already existing drugs. Furthermore, medicines with added therapeutic benefit (*amélion du service médical rendu*; ASMR) levels I (major), II (important) or III (moderate) are guaranteed a list price not lower than the lowest price in four reference countries: Germany, Spain, Italy and the UK (Gotham et al., 2021; Vogler & Rodrigues, 2020). This is a form of external price referencing. In the Dutch healthcare system, external price referencing is applied in the Wgp maximum allowable price. The difference being that the Wgp maximum allowable price is a maximum price, whereas the external price referencing in French context offers a minimal price. To our knowledge, there is no maximum allowable price of medicines on the French market, other than the price agreed upon in price negotiations with the CEPS.

CEPS also advises the French Ministry of Health on the positive list of reimbursable drugs; a list of outpatient drugs that qualify for reimbursement by the SHI. This advice is based on two criteria: 1) it must be an improvement over the current prescribed drugs in the same class, or 2) has to be a decrease in the cost of treatment (Kamenade, 2018). Since 2003, France has been using a system of internal price referencing, TFR (*Tarifs Forfaitaires de Responsabilité*), to stimulate the use and development of generic medicines (Kamenade, 2018). A reference price, as determined by CEPS, is set for a cluster of generic medicines and its originator drug based on the cheapest generic in that cluster. This reference price is the reimbursement limit. If a medicine is more expensive than the reimbursement limit, it will have to pay for the difference out of their own pocket. In its purpose, this mechanism is similar the reimbursement limit set by the GVS in the Dutch

healthcare system. Reimbursement of inpatient drugs happens through a diagnosis-related group (DRG) based system (Gotham et al., 2021; Vogler & Rodrigues, 2020). Inpatient medicines included in the DRG carve-out list (*liste en sus*) – typically those that are particularly expensive – are reimbursed separately (Agence Technique de l'Information sur l'Hospitalisation, n.d.).

Several initiatives have been started to stimulate the availability of antibiotics in France through price-controlling mechanisms. Firstly, sales of antibiotics and other medicines combatting AMR are excluded from the turnover liable for the clawback scheme. Secondly, antibiotics with ASMR level IV (minor added therapeutic benefit) are included in the external price referencing and are guaranteed a price not lower than the lowest list price in the four reference countries. At this moment, antibiotics in France are not exempted of internal price referencing and set reimbursement limits.

2.3.2. Germany

The German healthcare system is comprised of a general and mandatory health insurance for all residents, through either a SHI or substitutive Private Health Insurance (PHI) (European Observatory on Health Systems and Policies, 2022). Although the federal government has regulatory power over the healthcare system, decision making is shared with state governments through the Federal Joint Committee, overseen by the Federal Ministry of Health. This body is also responsible for determining the reimbursed care included in the SHI, and the DRG catalogue used in Germany (Commonwealth Fund, 2020d).

In principle, all approved medicines are eligible for reimbursement by health insurance, unless they are included on a negative list (OECD, 2018). This is thus different from the French and Dutch healthcare system discussed earlier, which work with a positive list of reimbursable medicines. From launch, these medicines can be priced freely, but prices must be negotiated within the first year based on the added therapeutic benefit they offer over the existing standard of care (OECD, 2018). If a drug offers added therapeutical benefit, prices are negotiated based on the price of the current standard of care. If there is no added therapeutical benefit, internal price referencing is applied, and the new drug is placed in a cluster with comparable medicines and gets a reimbursement limit (*Festbeträge für Arzneimittel*). There are three levels of comparable medicines (Bundesministerium für Gesundheit, n.d.):

- Level 1: medicines with the same active compounds
- Level 2: medicines with the same active compounds and therapeutic effect
- Level 3: medicines with the same therapeutic effect but not the same active compounds

Both patent-protected and generic drugs can be clustered in these levels. For drugs that only contain on-patent drugs, the reimbursement limit is set as the weighted average of all medicines included in the cluster (Bundesministerium für Gesundheit, n.d.). For the clusters with combinations of on-patent and/or generic drugs, the calculation is more complicated, but – simply put – based on the prices of drugs in the lower third of the cluster (Gemeinsamer Bundesausschuss, n.d.). Similarly to the Dutch GVS, this system aims to result in an overall price reduction for all medicines in a cluster. To our knowledge, there is no system of maximum allowable prices present in the German health care system, other than the prices negotiated between the sickness funds and drug manufacturers.

The German government has taken several specific measures within these described healthcare systems to combat the shortages of antibiotics, and to make their market more

attractive. In 2017, legislation was passed allowing for the consideration of resistance patterns in determining the added therapeutical benefit of antimicrobials (*Verordnung Über Die Nutzenbewertung von Arzneimitteln Nach § 35a Absatz 1 SGB V Für Erstattungsvereinbarungen Nach § 130b SGB V (Arzneimittel-Nutzenbewertungsverordnung-AM-NutzenV) § 5 Zusatznutzen.*, n.d.). This means that even for antimicrobials clinically tested using non-inferiority studies, there is still a possibility to prove additional therapeutic benefit and open the door to price negotiations. Legislation passed in 2020 exempted Reserve antibiotics from the therapeutic benefit analysis and a shorter time to market (*Gesetz Für Einen Fairen Kassenwettbewerb in Der Gesetzlichen Krankenversicherung (Fairer-Kassenwettb-Gesetz-GKV-FKG). Artikel 5*, 2020). Draft legislation currently under review would supplement this with the fact that Reserve antibiotics would be exempted from the price negotiations and can continue to receive the reimbursement price set at market launch (*Arzneimittel-Lieferengpassbekämpfungs- Und Versorgungsverbesserungsgesetz (ALBVVG)*, 2023). Lastly, the German health care system also works with a DRG carve-out list. While the inclusion of antibiotics on this list is possible, no carve-outs have been granted thus far (Gotham et al., 2021).

2.3.3. Sweden

Sweden's healthcare system is based on universal and automatic healthcare coverage for all its residents. Healthcare in Sweden is organized on three levels: national, regional and local (Commonwealth Fund, 2020a; European Observatory on Health Systems and Policies, 2012; TLV, 2023). The national government sets the overall health policy, regulations and supervision. The regions are responsible for financing and delivering the healthcare services, including primary, specialist and psychiatric care. The municipalities are, amongst other things, responsible for elderly care, those with physical or mental disabilities, home care, etc. The system is financed mostly through regional and local taxes and supported by national grants.

Both pricing and reimbursement decisions for outpatient medicines are made by the Pharmaceutical Benefits Board (*Nämden för läkemedelsförmåner*) – part of the Dental and Pharmaceutical Benefits Agency (*Tandvårds- och läkemedelsförmånsverket*, *TLV*) – based on three principles: the human value principle (i.e. equality of all human beings and the integrity of every individual), the need and solidarity principle (i.e. those in greatest need take precedence), and the cost-effectiveness principle (i.e. the cost for a medicine should be in relation to its (medical/humanitarian/socio-economic) benefit). Products eligible for reimbursement are placed on a positive list and are reimbursed in full. Prices are set through value-based pricing, managed entry agreements and auctions for certain products. There is no external or internal price referencing.

One notable system, somewhat similar to the preferential policy employed in the Netherlands, is the system of monthly auctions (TLV, 2023). The purpose of this policy is to keep healthcare costs down. Within this system, pharmacies are obliged to dispense the least expensive product of a group of substitutable off-patent products (generics). This preferred product is determined each month via an auction-like system. To become this so-called 'product-of-the-month', the pharmaceutical company must be able to guarantee availability of the medicine for the entire month. In addition, TLV appoints two back-up products for when unforeseen shortages in the cheapest products occur.

Regions are responsible for the purchasing and/or procurement of inpatient medicines. For inpatient medicines, no national price-agreements are made. Managed entry agreements can be

employed by the regions to lower the price. This can also be done through joint procurement of multiple regions together. Reimbursement also happens on a regional basis, as medicines used for inpatient care are not included on the national benefits scheme.

The Public Health Agency of Sweden (PHAS) has run a pilot from 2018-2022 for a new partially delinked, supply-based procurement and reimbursement model for antimicrobials (Gotham et al., 2021; Public Health Agency of Sweden, n.d., 2017; Schurer et al., 2023). The aim of this pilot was to ensure access to new and innovative antimicrobials for which the Swedish market may otherwise have been too small to be attractive. Within the pilot, manufacturers were guaranteed a minimum annual revenue of SEK 4,000,000 (~EUR 340,000) per product. An additional incentive was given by providing an additional 10% revenue on top of sales if annual revenue exceeded the minimal guaranteed revenue. The regions paid for the use of a product as normal, and the national government paid for the difference once a year if the minimal annual revenue was not met. In exchange for this guarantee, the manufacturers had to keep a supply dedicated to the Swedish market and had to guarantee delivery within 24 hours. The first evaluation of the pilot concluded that the pilot had succeeded in successfully supplying the Swedish market with the selected antimicrobials and that all stakeholders were generally positive (Folkhälsomyndigheten, 2023a, 2023b). Furthermore, several of the antimicrobials were brought to the Swedish market earlier than in other comparable and larger European countries. The major point of improvement identified was a reconsideration of the size and location of the safety stock. Many products were still unsold, which resulted in a lot of waste. Further points of consideration included the fact that these reimbursement models might influence market dynamics, since it was observed that antibiotics not included in the pilot were sold less, and those included in the pilot were sold more. An evaluation of clinical and financial consequences is expected later in 2023.

2.3.4. United Kingdom

All of UK's citizens are entitled to free and automatic universal healthcare through the National Health Service (NHS)[1]. While responsibility for legislation and general policy lies with the national government, the daily management of the NHS falls under NHS England, a government-funded but otherwise independently run organization that is responsible for the healthcare budget (Commonwealth Fund, 2020b).

The National Institute for Health and Care Excellence (NICE) is tasked with setting up guidelines for clinical practice and appraisal of new medicines on their efficacy and cost-effectiveness and advises NHS England on pricing and reimbursement decisions. In primary care, all medicines that are granted access to and registered on the UK market are – in principle – eligible for reimbursement by the NHS. In secondary care, reimbursement decisions lay more with the individual hospitals, and the NICE guidelines and advice on cost-effectiveness play a key role in deciding whether or not to do so.

The height of reimbursement, and indirectly the price of a drug, can be determined via different mechanisms (Castle et al., 2022). Drugs included in the 'Drug Tariff' are reimbursed for the price included therein. The Drug Tariff is a list of medicines (mostly generics) that can be

[1] Strictly speaking, each country within the UK has its own National Health Service (NHS England, NSH Scotland, NSH Wales, and Health and Social Care in Northern Ireland), but all work in a similar manner, have universal health coverage, and fall under the same governmental legislation.

prescribed using NHS prescriptions. The reimbursement amount is determined monthly after a survey of the market. For branded products, the 'NHS list price' is used as reimbursement amount and is set based on certain schemes that limit the price of branded medicines to some degree (the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) and Statutory Scheme). However, none of the measures included in these schemes relate to internal or external price referencing like done in the Netherlands. Lastly, for medicines that do not fall under either the Drug Tariff or the NHS list price, the height of reimbursement is equal to the list price as paid by pharmacies/doctors.

Specifically for antibiotics, NICE, NHS England and NHS Improvement have piloted a novel HTA process and a demand-based, fully delinked payment model in England (Gotham et al., 2021; National Institute for Health and Care Excellence, 2022a, 2022b, 2022c; Rothery et al., 2018; Schurer et al., 2023). The aim of the pilot was "to incentivize pharmaceutical companies to develop new drugs for resistant infections" (Department of Health and Social Care, 2019). They did so through a subscription style model and multi-year contracts, in which pharmaceutical companies were paid a fixed amount each year in exchange for on-demand access to as many doses as necessary. The height of this fixed annual amount is determined by the "value" of a product to the NHS, as determined by the novel HTA process, but to a maximum of £10 million per product. This assessment includes the direct cost to the NHS and resulting QALY gains to treated patient-outcomes, but also includes the wider concept of value beyond the treated patient in the form of STEDI values (Spectrum, Transmission, Enablement, Diversity and Insurance values). Furthermore, it does not consider the incremental cost per QALY per patient, but rather the QALYs at a population level using the eligible population, thereby aiming to quantify the true value of an antibiotic to the entire population. The fully delinked model takes away perverse incentives for manufacturers to increase sales volume and for clinicians to reduce prescriptions because of a high list price. Prescriptions are therefore based purely on clinical need. Preliminary evaluations of the novel HTA process indicated several key challenges in economic modeling in AMR, largely due to the lack of reliable data, the complexity of predictions needed for the future, and the reliance on *in vitro* data to estimate effectiveness (Schurer et al., 2023). This ultimately meant that decisions on the height of the subscription fee were based more on committee deliberation and clinical input rather than quantitative outcomes, and made people wonder whether a simpler model – like the one piloted in Sweden – would be more viable (Schurer et al., 2023).

2.3.5. United States

Residents of the United States do not have universal health insurance coverage. The healthcare system is based on a mix of public and private. Private health insurance is the most dominant form of healthcare insurance coverage, and Medicare and Medicaid (two federal programs) cover elderly people, some of disabled people, and some of the (near-)poor (Commonwealth Fund, 2020e; European Observatory on Health Systems and Policies, 2020). Still, around 10% of the population is uninsured. Whether a medicine is covered by health insurance and, if so, for what amount, depends on an individual's health insurance plan. Equally, the multitude of policies affecting drug prices on both the individual health insurance company and the federal government level make the system highly complex, but include, amongst other things, price negotiations and volume-based rebates (Commonwealth Fund, 2020e).

Specific to antibiotics, the US federal government has implemented several rules, policies and acts to help combat AMR and antibiotics shortages (Gotham et al., 2021): the GAIN Act, IPPS rule, DISARM Act, and (draft) PASTEUR Act. The GAIN Act of 2011 grants certain antimicrobials

five additional years of market exclusivity and provides priority review with the FDA and fast track designation (*H.R.2182 - Generating Antibiotic Incentives Now Act of 2011*, 2011). The 2020 IPPS rule stated that hospitals are reimbursed extra in case of an antimicrobial-resistant case, and changed the rules to exempt antimicrobials from having to prove 'substantial clinical improvement' (which is difficult since many antimicrobials have been studied using non-inferiority studies) to be eligible for add-on reimbursement for new technologies (so-called NATP reimbursement). This last rule has since been replaced by the 2021 DISARM Act, which includes certain novel antimicrobials on the DRG carve-out list (Davidson et al., 2021; *H.R.4127 - DISARM Act of 2021*, 2021). Novel draft legislation up for review in US Congress would open the possibility for novel subscription-based contracts for antimicrobials, like currently being piloted in the UK (*S.1355 - PASTEUR Act of 2023*, 2023). Draft legislation includes the possibility for multi-year contracts valued from US 750 million to US 3 billion, depending on the specific product and its value to society, for a total budget up to US 11 billion over 10 years. Whether and when this legislation will be passed is still unknown.

3. Methodology

This chapter will start by revisiting the research aim and research questions. Thereafter, the research type and strategy, data collection and data analysis methods will be discussed.

3.1. Research aim and question

The main research question of this project was: what has been the effect of the Dutch price-controlling instruments GVS reimbursement limits, Wgp maximum allowable prices and/or preferential policy on the availability of essential outpatient antibiotics on the Dutch market between 2013 and 2022?

Consequently, the following six sub questions were defined:

- **RQ1:** What are the market characteristics of the Dutch antibiotics market regarding number of essential antibiotics and suppliers on the market, available alternatives and revenue between 2013 and 2022?
- **RQ2:** How do the AIP, GVS reimbursement limit and Wgp maximum allowable price of essential antibiotics that are currently on the market relate to each other?
- **RQ3:** Is the relationship between AIP, GVS reimbursement limit and Wgp maximum allowable price different for essential antibiotics that have been removed from the market?
- **RQ4:** Is the GVS reimbursement limit or the Wgp maximum allowable price the limiting factor in the price of essential outpatient antibiotics?
- **RQ5:** Is there a relationship between a PRK cluster having a product included in the preferential policy and the decrease in the number of available products in that cluster?
- **RQ6:** How are preferential outpatient antibiotics distributed between the preferential policies of different health insurance companies?

3.2. Research type and strategy

Since the purpose of this research project was to elucidate the effects of the price-controlling instruments on the availability of antibiotics on the Dutch market, it used an exploratory approach with an inductive, fixed research design. In this type of research, one takes a bottom-up approach, starting with observations, and aiming to ultimately make a generalizing conclusion. Since the data is collected, combined and analysed from existing data sources, and randomly assigning groups over dependent variables is not possible for practical and ethical reasons, the research design is also non-experimental.

Given the limited understanding of the problem context in the Netherlands, this research project adopted an empirical approach and used quantitative analyses. The types of analyses conducted were a combination of descriptive and explanatory. The descriptive analyses aimed to describe general market characteristics to gain a better understanding of the problem context and phenomena (RQs 1 and 2). Explanatory analyses were used to try and elucidate potential correlations and dependencies that could explain the seen phenomena (RQs 3, 4, 5 and 6).

To be able to explain the effect of the price-controlling instruments have had on the availability of antibiotics over time, a longitudinal approach was taken as opposed to a cross-sectional study.

3.3. Data collection

Data was collected from existing data sources and databases (both openly available and databases with restricted access). The data was collected from the following organizations, and included the following data:

Table 2 - Overview of collected data sources and included and used data types. For each data source is indicated whether this is openly available to the public or only accessible for specific people (e.g. internal databases and systems).

Organization/source	Data included and used	Openly available or restricted access
SWAB 'List of essential antimicrobials in the Netherlands' (*Lijst essentiële antimicrobiële middelen in Nederland*)	Category of essentiality (A/B/C/(C)/D) per active compound and route of administration	Open
Stichting Farmaceutische Kengetallen (*SFK*)	Of all outpatient medicines (that are currently or have previously been on the market) starting with ATC-code J01: - registration number - article number - year of registration - product group - article name - PRK cluster number and description - Revenue per year for the years 2012-2023 - Supplier - number of users (2022)	Restricted
Geneesmiddeleninformatiebank (*GIB*, Medicines information database) from the Medicines Evaluation Board (*College ter Beoordeling van Geneesmiddelen*, *CBG*)	Of products (inpatient and outpatient) that are currently on the market: - registration number - article name - date of registration - active compound - route of administration	Open
CIBG/Farmatec	Of all products starting with ATC-code J01: - article number - registration number - article name - ATC code - GVS cluster code - AIP per package - Number and unit of products per package - GVS reimbursement limit and unit - GVS list (1A/1B) - Removed from the *G-Standaard* (yes/no) - Registration removed from the market (yes/no) - Date of removal from the market - AIP per package at moment of removal from the market - Wgp maximum allowable price (H52) including and excluding revenue, and unit	Restricted
Preferential policies 2023 of health insurers *Zilveren Kruis*, *VGZ*, *Menzis* and *CZ*[2]	Products included in preferential policy per article number	Openly available from health insurance companies' websites

[2] Health insurance companies ASR, Eno and Z&Z take on the same preferential policy as VGZ. Insurance companies ONVZ, DSW and EUCARE do not have a preferential policy.

3.4. Database transformation and sample selection

Using the article number, article name and ATC code of each product, the active compound and route of administration were determined from the GIB. These were used to determine the category of essentiality as per SWAB's categorization. Only those products that were deemed essential by SWAB (category A, B, C, and (C)) were included in further analyses.

To be able to compare the AIP (per package) and GVS reimbursement limit (per unit), the AIP per unit was calculated. This was done for both products that were still on the market and those that had been removed from the market using the AIP per package and AIP per package at the moment of removal from the market (CIBG/Farmatec), respectively, and the number of products per package (CIBG/Farmatec).

Products currently on the market were considered to be those not removed from the *G-Standaard* and with their registration not removed from the market. Products no longer on the market were considered to both be removed from the *G-Standaard* and with their registration removed from the market.

3.5. Data analysis

3.5.1. The overall market of antibiotics

The number of essential outpatient antibiotics on the market per year between 2013-2022 was determined by first elucidating the registration year and year of removal (if applicable) per product from the SFK and GIB databases. Then, for each year between 2013 and 2022, the number of products for that year was determined using the SUMPRODUCT() function of Microsoft Excel. Linear regression analysis was performed using R software and the 'carData' package.

To determine the number of PRK clusters containing essential outpatient antibiotics, the PRK number of each product was taken from the SFK database. Then, the number of products in each PRK cluster per year was determined using the same registration years and years of removal as before with the added matrix of PRK number in the SUMPRODUCT() function. Finally, we determined the number of PRK clusters on the market by assessing the number of clusters for which at least one product was on the market using the COUNT.IF() function. Linear regression analysis was again performed using R software and the 'carData' package. To subsequently calculate the average number of products per PRK cluster per year, the earlier calculated number of products in each PRK cluster were averaged for each year. Difference in the number of products per PRK cluster in 2013 and 2022 was calculated using a t-test of independent samples.

The number of suppliers with registered products on the market was determined using the supplier, registration data and date of removal from SFK. For each year, this was determined using the SUMPRODUCT() function of Microsoft Excel. Linear regression analysis was performed using R software and the 'carData' package.

To determine whether all active compound/route of administration combinations deemed essential by SWAB were (or had been) present on the Dutch market, we cross-referenced list from SWAB with the active compounds and routes of administration of all products in the CIBG/Farmatec database. For products that were not present in the database from CIBG/Farmatec, an additional check was performed in the GIB database to verify no products were already on the market but with a different ATC code compared to the J01 used in the CIBG/Farmatec database.

Revenue data was calculated by summing all reported revenue of outpatient essential antibiotics from SFK per year. Trend analysis of overall revenue and median revenue was performed with linear regression using R software and the 'carData' package.

3.5.2. Relationship between AIP and GVS reimbursement limit

AIP/GVS ratios were calculated using AIP per unit and GVS reimbursement limits from the SFK database. Revenues were taken from 2022 as reported in SFK. For products that were removed from the market, revenues from the year prior to removal were determined manually using the date of removal and the revenue reported per year from SFK. Correlation analysis was performed with a chi-squared test. Comparing average revenue between products removed from the market and still on the market was done with a t-test of independent samples.

3.5.3. Relationship between AIP and Wgp maximum allowable price

AIP/Wgp-max ratios were calculated using AIP per unit and Wgp maximum allowable price per unit of H52 (Wgp maximum allowable price of January 2023) including the temporary policy rule (Farmatec, 2023) from the Farmatec/CIBG database. Since it is known that some products have a higher Wgp maximum allowable price than AIP – although theoretically not possible – ratios that were >100% were set at 100% for better comparisons. Statistical analyses were performed using a chi-squared test and Pearson's correlation.

3.5.4. Relationship between GVS reimbursement limit and Wgp maximum allowable price

GVS/Wgp-max ratios were calculated using the GVS reimbursement limit and Wgp maximum allowable price per unit from the Farmatec/CIBG database. Comparing of the means happened through a dependent samples t-test.

3.5.5. Preferential policy

Lists of preferential products were accessed through the health insurance companies' websites (CZ, 2023; Menzis, 2023; VGZ, 2023; Zilveren Kruis, 2023). Determination whether a product was or was not included in a preferential policy was done based on article number. Category of essentiality was determined using the SWAB List of essential antimicrobials. PRK clusters that included a preferential product were determined using the PRK cluster numbers of the preferential products. All other PRK cluster were considered not to have a preferential product included for the purpose of this analysis. ANOVA and interaction analysis was performed in R software using the 'lsmeans' package. Linear regression analysis was performed in R software using the 'carData' software. Comparing the difference in slope coefficients happened through an independent samples t-test using pairwise comparisons of the interaction coefficient with the non-interaction coefficients.

Using the preferential status, we determined the number of preferential policies a product was included in. We then used the number of users per product from SFK to determine the users per article.

4. Results

4.1. The overall market of essential outpatient antibiotics

The first step in gaining more insights into the market of antibiotics, was to analyse the overall market characteristics. To do so, we determined the number of essential outpatient antibiotics on the market per year based on the registration and removal date of each antibiotic (Figure 2A). Results showed a significant (p < 0,0001) downward trend in the number of essential outpatient antibiotics on the Dutch market, with a decrease of 33% from 2013 (720) to 2022 (480).

The removal of antibiotics from the market is not inherently bad. If comparable alternatives remain on the market and are reliably available, this would not have to be an issue in itself. One way to investigate this is to look at PRK clusters: clusters of medicines with the same active compound, dosage, pharmaceutical form, route of administration and – if applicable – the same excipients. If at least one medicine of a PRK cluster remains available, this would not have to impact patient care. Analysing the trends within PRK clusters of essential outpatient antibiotics between 2013 and 2022 (Figure 2B) showed a slight but significant (p = 0,0008) decrease of 10% in the number of PRK clusters containing at least one essential antibiotic between 2013 (155) and 2022 (139). The average number of products per essential outpatient PRK cluster significantly (p = 0,0003) decreased from 4,21 (±4,12) to 2,81 (±2,79) (Figure 2C). Of the total 166 essential outpatient PRK-clusters that were present on the market at some point in the last 10 years, 10 were introduced for the first time, and 25 ceased to be present.

Next, we analysed the number of suppliers with products registered on the market over the years (Figure 2D). Linear regression showed that the number of suppliers did not change significantly (p = 0.92) between 2013 and 2022, suggesting that the removal of products happens on a product-basis instead of on a company-basis and does not explain the decrease in registered essential outpatient antibiotics.

The essential antibiotics list of SWAB differs from the classification of PRK clusters, since it only looks at active compound and route of administration (not at dosage, pharmaceutical form and excipients). It is therefore less specific but could point to overall trends in the market. Of the 73 combinations of active compounds and administration routes indicated to be essential by SWAB (both inpatient and outpatient), 69 are currently represented on the Dutch market and 4 are not (ampicillin/sulbactam, benzathine benzylpenicillin, paromomycin and sulfafiazin). For three of the four combinations, this has not changed in the past 10 years. The last antibiotic with benzathine benzylpenicillin as active compound was removed from the market in 2016.

Lastly, we wondered whether this decrease in available essential antibiotics and PRK clusters was also reflected in the reported revenue, since the lack of revenue in the antibiotics market is mentioned as one of the reasons for companies pulling their products off market (Plackett, 2020). Strikingly, the summed reported revenue of all outpatient essential antibiotics had not significantly (p = 0,21) changed between 2013 and 2022 (Figure 3A and Supplementary Table 3). This was corroborated by analysing the mean and median revenue per year per product (Figure 3B), which revealed a significant upwards trend between 2013 and 2022 for both the median (p = 0,006) and mean (p = 0,0004) revenue per article.

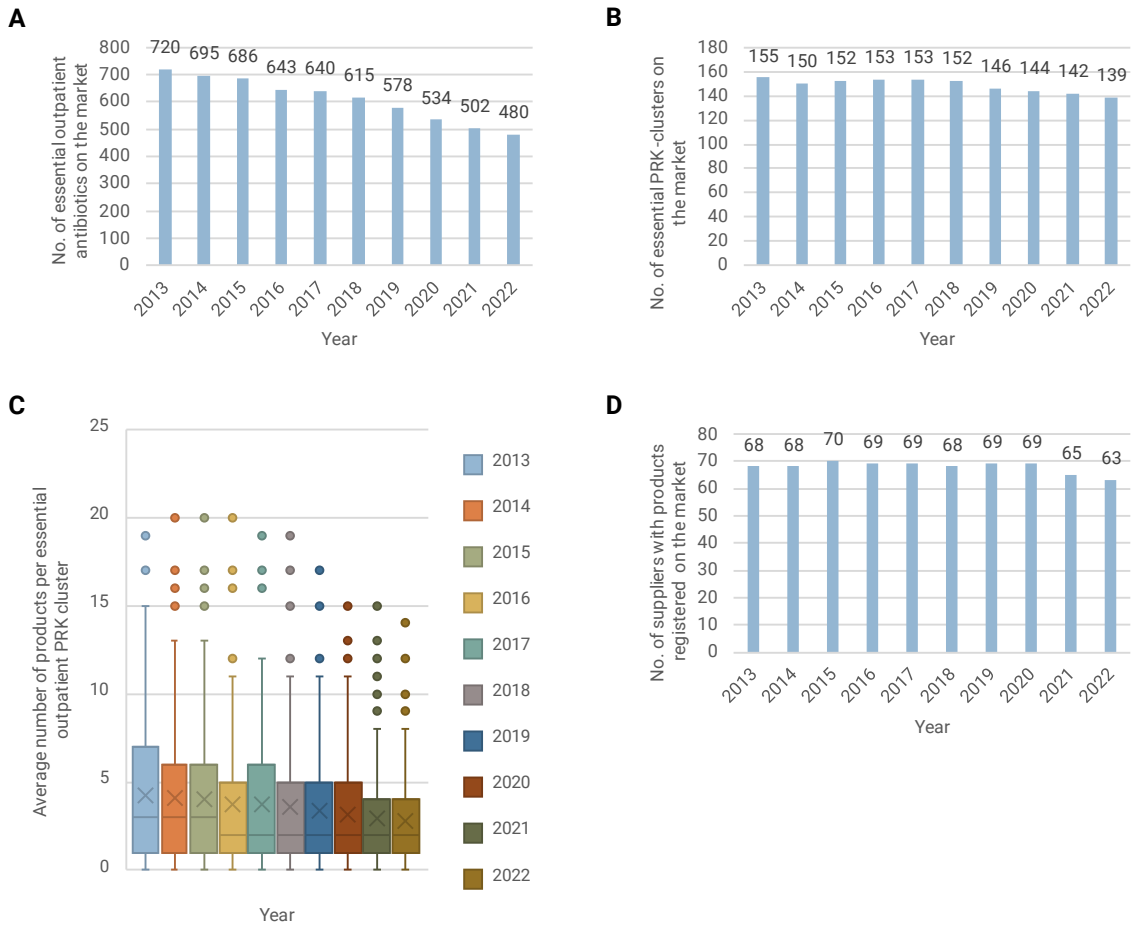


Figure 2 – General analysis of the overall market of essential outpatient antibiotics. (A) Number of essential outpatient antibiotics registered on the Dutch market for each year between 2013 and 2022. Number of available products per year was calculated using the registration date and date of removal from the market. (B) Number of PRK clusters present on the market containing essential outpatient antibiotics for each year between 2013 and 2022. (C) Average number of products per essential outpatient PRK cluster as represented in box-and-whisker plots. Dots are outliers, cross (X) represents mean. (D) Number of suppliers with essential outpatient antibiotics on the market for each year between 2013 and 2022. Numbers in graphs A, B and D are data labels.

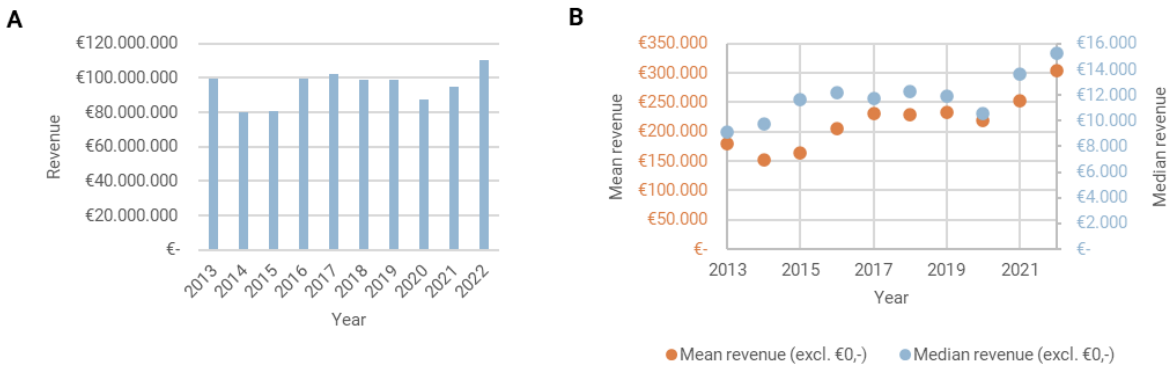


Figure 3 - Revenue of the essential outpatient antibiotics market. (A) Summed revenue of all essential outpatient products as reported by SFK between 2013 and 2022. (B) Mean (orange) and median (blue) revenue per article of essential outpatient antibiotics as reported by SFK between 2013 and 2022. Mean and median revenue values do not include €0,- revenues.

4.2. Relationship between AIP and GVS reimbursement limit

To determine how the AIP and GVS reimbursement limit of outpatient essential antibiotics relate to one another, we looked at the ratio between these two characteristics. This was done separately for essential outpatient antibiotics that are currently registered on the market, and those that are not, to elucidate whether these two groups differ in the extent to which they experience (or have experienced) pressure from the GVS reimbursement limit.

4.2.1. Products that are currently on the market

On the 1st of May 2023, 479 essential outpatient antibiotics are registered on the Dutch market, of which 318 are actually marketed (i.e. have not been removed from the *G-Standaard*). Of those 318, 267 are clustered in List 1A of the GVS and thus have a reimbursement limit. 51 are on List 1B, and subsequently do not have a reimbursement limit.

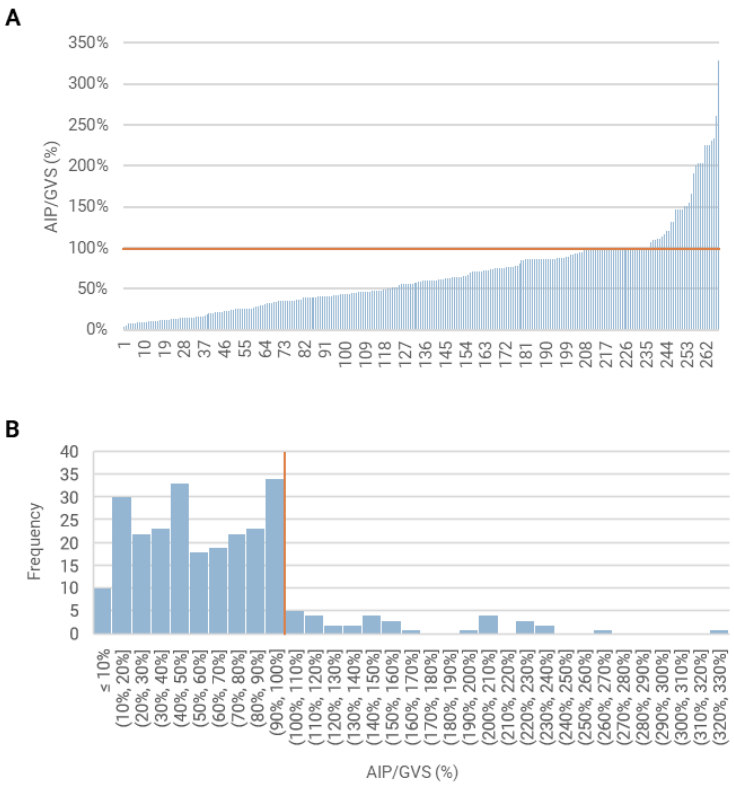


Figure 4 - Relationship between AIP and GVS reimbursement limit for essential outpatient antibiotics that are currently on the market. (A) AIP/GVS ratio per essential outpatient antibiotic on the market. The x-axis is sorted from smallest to highest, numbers along the x-axis indicate the number of products. Each bar represents one product. (B) Histogram of AIP/GVS ratios as depicted in figure A. Orange line depicts an AIP/GVS ratio of 100%.

For the essential outpatient antibiotics on List 1A, AIP per unit was divided by the GVS reimbursement limit and expressed as percentage (Figure 4 and Supplementary Table 2 and 4). Results showed that 209/267 products (78%) have an AIP/GVS ratio <99%. 27/267 products (10%) have an AIP equal to its GVS reimbursement limit (AIP/GVS ratio 99%-100%). 31/267 products (12%) have an AIP>GVS. To study whether the AIP/GVS ratio was correlated with revenue, we plot the AIP/GVS ratio against the revenue in 2022 (since products might have been registered at different points in time, mean revenue is a less reliable metric in this case) (Supplementary Figure 1A). Correlation analysis showed a very weak – although significant – positive correlation between the two groups ($r(265) = 0.1251$, $p = 0.41$).

4.2.2. Products that are removed from the market

There are 406 essential outpatient antibiotics that have previously been registered but are now removed from the market (up until 1 May 2023). Of these 406 products, 376 were included on List 1A, and 30 on List 1B. To determine the AIP/GVS ratio of essential outpatient antibiotics that are

no longer registered on the market, we used the AIP per unit at the moment of removal and divided this by the GVS reimbursement limit (Figure 5 and Supplementary Table 2 and 4). Analysis showed that 355/376 products (94%) had an AIP/GVS ratio ≤100% at the time of their removal from the market. 37/376 products (10%) had an AIP equal to its GVS reimbursement limit (AIP/GVS ratio of 99-100%) at that time. The proportion of products with an AIP/GVS ratio ≤100% is significantly higher in the group that is removed from the market compared to the group that is currently registered on the market (X^2 (1, N = 643) = 6,90, p = 0.0086). The proportion of products with an AIP equal to the GVS reimbursement limit did not differ significantly between the two groups (X^2 (1, N = 643) = 0.013, p = 0.91). Taken together, these results indicate that the products that have been removed from the market did not experience more pressure from the GVS reimbursement limit than the products that are still registered on the market.

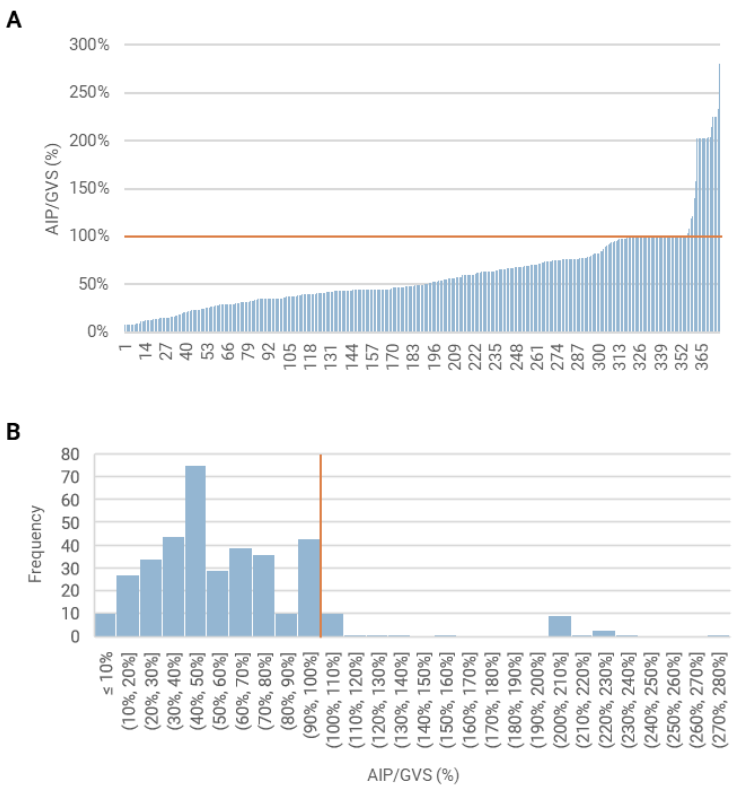


Figure 5 - Relationship between AIP and GVS reimbursement limit for essential outpatient antibiotics that are removed from the market. (A) AIP/GVS ratio per essential outpatient antibiotic on the market. The x-axis is sorted from smallest to highest, numbers along the x-axis indicate the number of products. Each bar represents one product. (B) Histogram of AIP/GVS ratios as depicted in figure A. Orange line depicts an AIP/GVS ratio of 100%.

4.3. Relationship between AIP and Wgp maximum allowable price

To elucidate the relationship between the AIP and the Wgp maximum allowable price and determine to what extent the Wgp maximum allowable price puts pressure on the price of essential outpatient antibiotics, we next investigated the ratio between these two variables.

Of the 318 essential outpatient antibiotics that are currently marketed in the Netherlands, 178 (56%) have a maximum allowable price. The majority of those products (120/178 (67%)) have an AIP/Wgp-max ratio between 90-100%, with 98/178 (55%) having an AIP equal to its maximum allowable price at an Wgp-max ratio ≥99% (Figure 6 and Supplementary Table 2 and 4). This means that, in total, 98/318 (31%) of essential outpatient antibiotics have an AIP equal to its Wgp maximum allowable price. This proportion of essential outpatient antibiotics currently on the market with an AIP equal to its Wgp maximum allowable price (98/318) was found to be significantly higher compared to the proportion of products with an equal AIP and GVS reimbursement limit (27/267) (X^2 (1, N = 445) = 106.8, p = <0.00001). Together, this data suggests that the Wgp maximum allowable price might be putting more pressure on the price of essential outpatient antibiotics currently on the market than the GVS reimbursement limit.

To test whether the AIP/Wgp-max ratio was correlated with revenue, we plot the AIP/Wgp-max ratio against the revenue per product in 2022 (Supplementary Figure 1B). Although correlation analysis resulted in a significant negative correlation between the AIP/Wgp-max ratio and the revenue in 2022, the correlation itself was very weak: $r(176) = -0.1537$, $p = 0.041$.

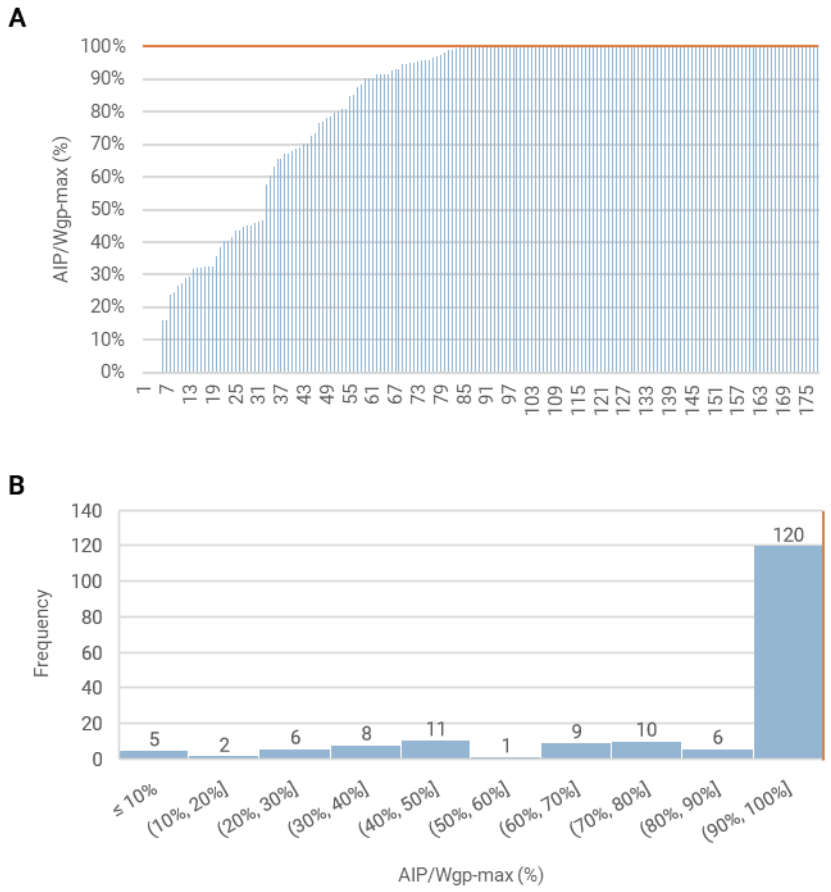


Figure 6 - Relationship between AIP and Wgp maximum allowable price. (A) AIP/Wgp-max ratio per essential outpatient antibiotic on the market. The x-axis is sorted from smallest to highest, numbers along the x-axis indicate the number of products. Each bar represents one product. (B) Histogram of AIP/Wgp-max ratios as depicted in figure A. Numbers above bars are data labels. Orange line depicts an AIP/Wgp-max ratio of 100%.

4.4. Relationship between GVS reimbursement limit and Wgp maximum allowable price

To further test the hypothesis that the Wgp maximum allowable price is putting more pressure on the price of essential outpatient antibiotics currently on the market than the GVS reimbursement limit, we set out to investigate which one of the two was the limiting factor. We did so by calculating the ratio between the GVS reimbursement limit and the Wgp maximum allowable price.

Of the 318 marketed essential outpatient antibiotics, 155 (49%) had both a GVS reimbursement limit and a Wgp maximum allowable price. 129/155 products (83%) had a GVS/Wgp-max ratio of ≥100%, indicating that for 83% of essential outpatient antibiotics currently registered on the market, the GVS reimbursement limit is higher than the set Wgp maximum allowable price (Figure 7AB and Supplementary Table 2 and 4). This was further corroborated by the finding that the GVS reimbursement limit (M = 7.37, SD = 10.94) was significantly higher compared to the Wgp maximum allowable price (M = 4.45, SD = 6.00) using a paired samples t-test

($t(154) = 5.44$, $p < 0.00001$) (Figure 7C). Together, these results showed that the in the majority of cases, the Wgp maximum price is the limiting factor in the price of essential outpatient antibiotics. Additionally, results showed that 148/318 (47%) of essential outpatient antibiotics overall are equal to either their GVS reimbursement limit or the Wgp maximum allowable price.

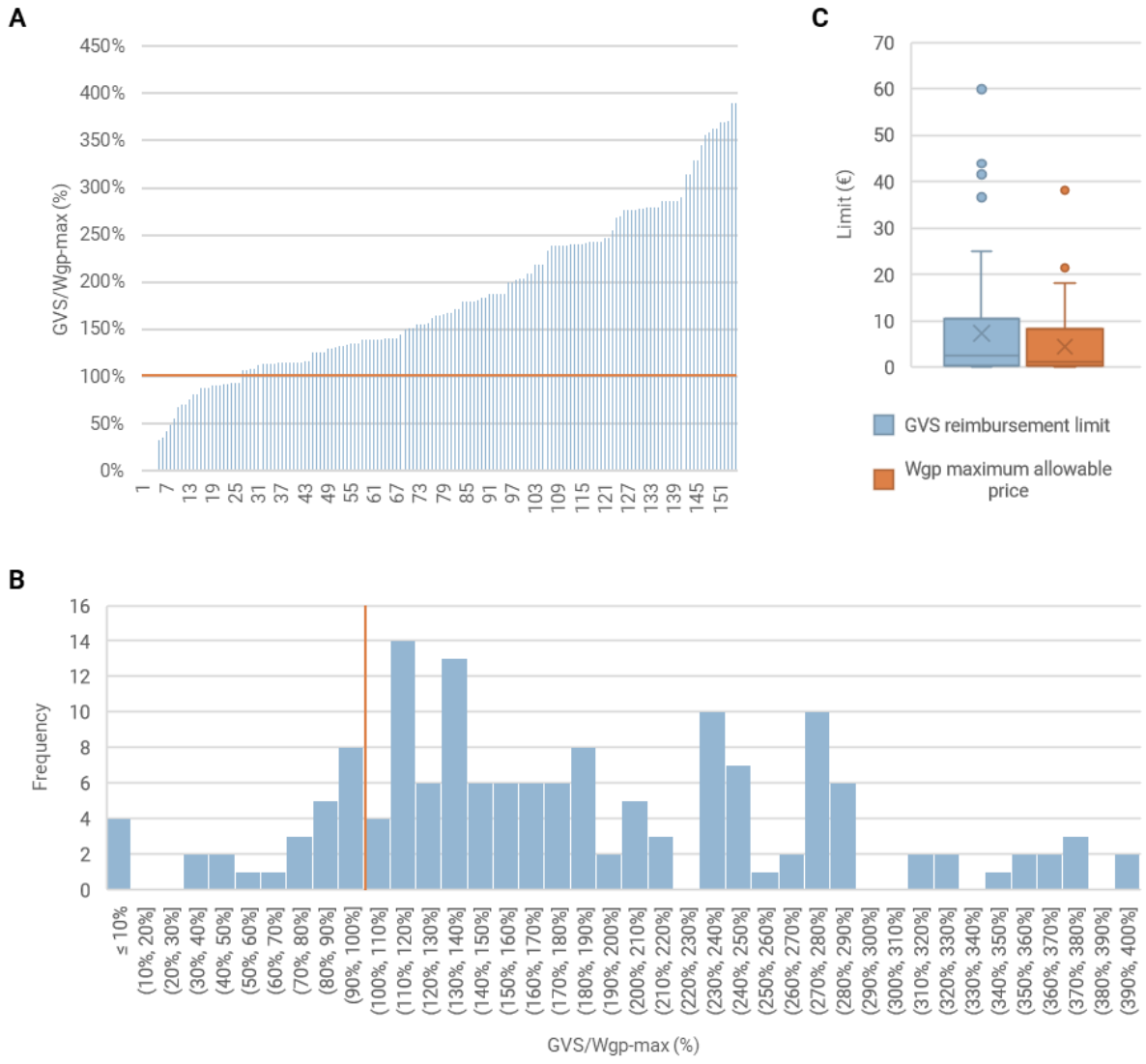


Figure 7 - Relationship between GVS reimbursement limit and Wgp maximum allowable price. (A) GVS/Wgp-max ratio per essential outpatient antibiotic on the market. The x-axis is sorted from smallest to highest, numbers along the x-axis indicate the number of products. Each bar represents one product. (B) Histogram of GVS/Wgp-max ratios as depicted in figure A. Numbers above bars are data labels. Orange line depicts an GVS/Wgp-max ratio of 100%. (C) Box-and-whiskers plot of the GVS reimbursement limits (blue) and Wgp maximum allowable price (orange) of all essential outpatient antibiotics. Cross (X) represents mean, dots represent outliers.

4.5. Preferential policy

Lastly, we wanted to assess what effect the preferential policy had on the availability of essential antibiotics on the Dutch market. To do so, we firstly determined which antibiotics were included in the preferential policy of health insurance companies VGZ, Zilveren Kruis, CZ and Menzis[3]. 59 outpatient antibiotics were included in at least one preferential policy. Almost all (58/59) are considered to be essential outpatient antibiotics according to the categorization by SWAB (Supplementary Table 5).

Next, to investigate the effect of the inclusion of essential outpatient antibiotics in a preferential policy on its availability, we studied the relationship between the preferential status of a product and the subsequent decrease of the alternative products in its PRK cluster (Figure 8A). To do so, a linear regression analysis was conducted to examine the relationship between the variable 'year' and the condition whether the PRK clusters contained preferential products or not on the average number of products per PRK. The main focus was to assess the interaction effect of the conditions and variable 'year', indicating a differential effect of the condition on the average number of products per PRK cluster. ANOVA analysis showed a significant interaction effect between the variable 'year' and the different conditions ($F(1,16) = 77.41$, $p < 0.0001$). This was further corroborated by comparing the regression coefficients of the separate linear regression models: results showed that the slope of the linear regression model of PRK clusters containing preferential essential outpatient products ($\beta = -0.350$, $p = <0.0001$) differed significantly ($t(16) = -8.80$, $p < 0.0001$) from that of the regression model of PRK clusters not containing any preferential essential outpatient antibiotics ($\beta = -0.115$, $p = <0.0001$). Interestingly, however, was that the absolute number of products per PRK cluster was (and remained) higher in the cluster including preferential products compared to those that did not. Together, these results showed that the average number of products per PRK cluster decreased more rapidly in clusters which included a preferential antibiotic compared to those that did not, but still contained more products overall.

If the same article is preferential at many (3 or 4 out of 4) heath insurers, they are said to be at a higher risk of availability issues, since there is a higher reliance on the manufacturer of this article. When looking at the distribution of the preferential outpatient antibiotics over the different health insurance companies, we found that out of the 59 preferential outpatient antibiotics, 37 (63%) are preferential at only one insurer, 18 (31%) are preferential at two health insurance companies, 3 (5%) articles are preferential at three insurers, and only 1 (2%) is preferential at all four health insurance companies (Figure 8B). Lastly, to determine the distribution of users over the categories, we calculated the number of users per article in each category using the number of users per category and the number of articles per category (Figure 8B). Results showed that the highest number of users per product was in the category in which products were preferential with 2 insurers, and the lowest users per product in the category in which products were preferential with all 4 insurers. Together, these results indicate that the distribution of preferential outpatient antibiotics over the different health insurance policies is unlikely to contribute to availability issues.

[3] Health insurance companies ASR, Eno and Z&Z take on the same preferential policy as VGZ. Insurance companies ONVZ, DSW and EUCARE do not have a preferential policy.

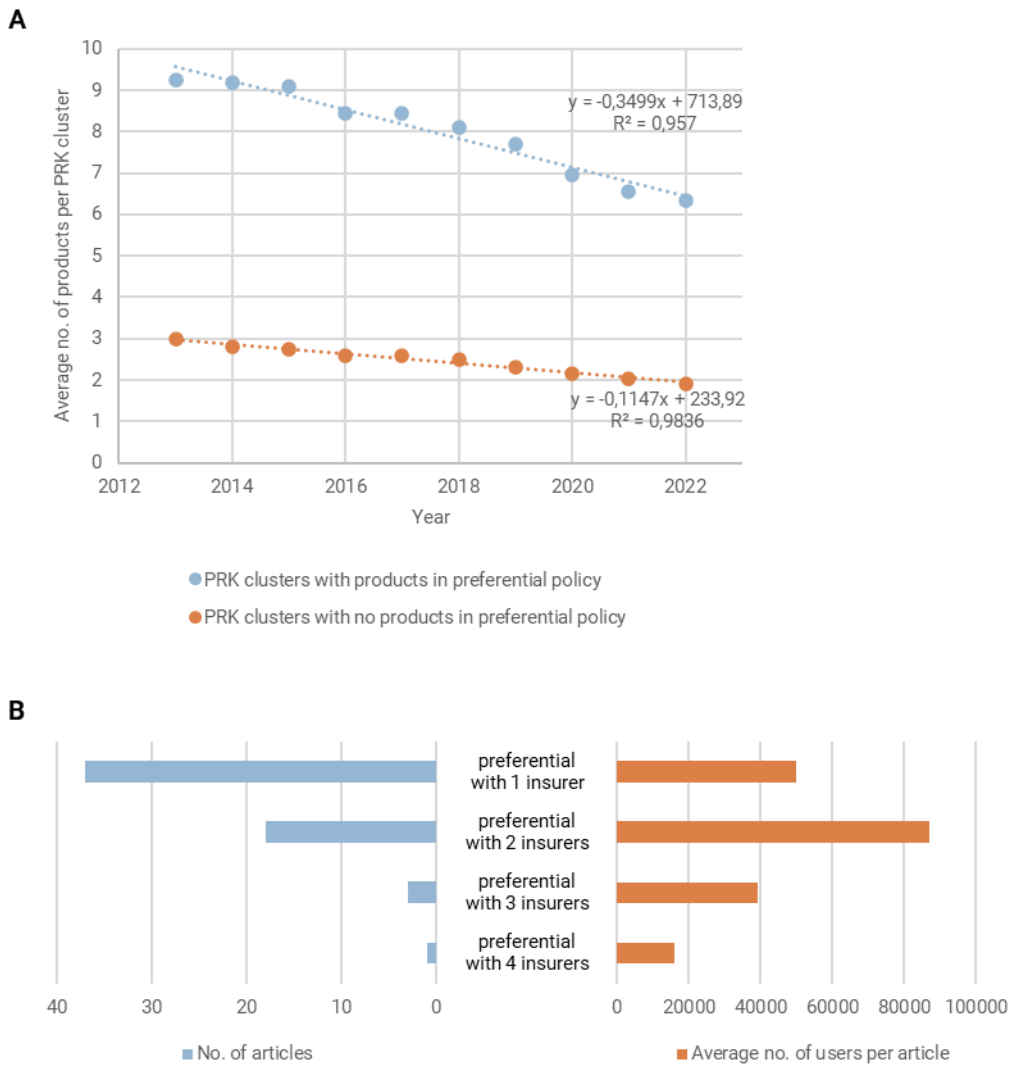


Figure 8 – (A) Average number of products per PRK cluster for clusters that contain preferential outpatient antibiotics (blue) and PRK clusters that do not (orange) for 2013-2022. Formula and R^2 of trend line are depicted in the graph. (B) Distribution of preferential essential outpatient antibiotics over the different health insurance companies. On the left, the number of articles per category is depicted as per the preferential policies of 2023, with on the right the sum of the number of users per category for all products in that category, as reported by SFK over 2022.

5. Discussion

The availability of effective antibiotics is imperative in combatting AMR. In countries all over the world, including the Netherlands, this is being jeopardized by the lack of new and innovative antimicrobials, and the disappearance from the market of existing antimicrobials. This results in shortages and an undesirable outlook for future capacity to treat infectious diseases. Some are worried that price-controlling instruments are contributing to these shortages and create unattractive target markets. Quantitative analyses studying these instruments in relation to the availability of antibiotics on the Dutch market are, however, non-existent. To be able to better assess these potential problems and explore directions for future solutions, this report investigated the effect of the price-controlling instruments GVS reimbursement limit, Wgp maximum allowable price and preferential policy on the availability of essential outpatient antibiotics on the Dutch market between 2013 and 2022.

Analysis of the general market of antibiotics indicated that both the number of essential outpatient antibiotics and the average number of products per essential outpatient PRK cluster decreased significantly between 2013 and 2022. In contrast, the number of suppliers and the total revenue of the essential outpatient antibiotics market showed no significant change, but the mean and median revenue per product significantly increased. Together, these results point to an essential outpatient antibiotics market that might have started to show signs of impoverishment over the past 10 years. Although the absolute number of essential antibiotics has decreased substantially, the number of available essential PRK clusters and essential combinations as defined by SWAB are decreasing less dramatically. Even still, the decreasing number of products per essential PRK cluster is an unwanted trend and might prove problematic in the not too far future if this trend were to continue.

Results showed that the majority (78%) of essential outpatient antibiotics had an AIP below its GVS reimbursement limit. Additionally, we found that the GVS reimbursement limit has not put significantly more pressure on essential outpatient products that have been removed from the market than it puts on those still on the market. 31% of all essential outpatient antibiotics has a Wgp maximum allowable price equal to its AIP. In most cases (83%), the Wgp maximum allowable price is also lower than the GVS reimbursement limit and thus the limiting factor in price setting of essential outpatient antibiotics. Lastly, results showed that the average number of products per PRK cluster decreased more steeply for clusters that contained antibiotics included in a preferential policy compared to the clusters that did not, but that the average number of products overall was higher in the clusters which included preferential products.

The found percentages of essential outpatient antibiotics that have an AIP<GVS and AIP=GVS are similar to those identified in earlier research for all medicines on the Dutch market with low revenue between 2015 and 2020 (Koppers et al., 2021). At the same time, our results indicate that the pressure put on the price of essential outpatient antibiotics by the GVS is not different for products currently on the market compared to those that have been removed from the market. This specific aspect has not been studied before in published literature. Together, these findings point to the interpretation that although essential outpatient antibiotics experience similar pressure from the GVS reimbursement limit as other comparable medicines, it is not likely to be the (only) reason they are removed from the market.

Equally, the percentage of essential outpatient antibiotics with an AIP equal to its Wgp maximum allowable price is similar to other medicines with low revenue on the Dutch market

(Koppers et al., 2021). This leads to the same conclusion, that essential outpatient antibiotics experience similar pressure to the rest of comparable medicines on the Dutch market when it comes to their Wgp maximum allowable price. The arguably even more important question remains, however, whether this pressure from both the GVS reimbursement limit and/or the Wgp maximum allowable price is wanted in the case of antibiotics, or whether their availability should be stimulated regardless of price.

Our results also indicate that for the majority (83%) of essential outpatient antibiotics that had both a Wgp maximum allowable price and a GVS reimbursement limit, the Wgp maximum allowable price was lower than the GVS reimbursement limit. This relationship between GVS reimbursement limit and Wgp maximum price on the Dutch market has, to our knowledge, not been studied in literature before. On the one hand, this result points to the Wgp maximum allowable price being the limiting factor in price setting of essential outpatient antibiotics. On the other hand, it suggests that current GVS reimbursement limits are too high to fulfil their price-controlling purpose for essential outpatient antibiotics. This is a known phenomenon, and one of the reasons why the Ministry of VWS had planned to update the reimbursement limits. However, recently, it was decided that this plan could not continue at this point in time (Minister van Volksgezondheid Welzijn en Sport, 2023a).

The effect of the preferential policy on the availability of medicines has been the subject of little research. Although many concerns are expressed both by stakeholders and in the media for the fact that the preferential policy might contribute to medicine shortages, these claims are not yet substantiated with evidence. One report merely concluded that the number of medicine shortages had increased since the implementation of the preferential policy but could not substantiate any further causation and did not consider e.g. the total number of preferential products (Carp et al., 2018). Therefore, the found results of the current report cannot easily be compared to previous results, making interpretation into a wider context difficult. The finding that PRK clusters with a product included in at least one preferential policy had a steeper decrease of the average number of products per PRK cluster compared to the clusters that did not have a product included in a preferential policy, might be explained by the fact that if one product is preferential, the alternative products in that PRK cluster have an even smaller target market, potentially resulting in removal from the market. Interestingly, we also observed that the average number of products per PRK cluster was higher in the clusters with products in the preferential policies. Potential reasons for this could be, amongst others, that the products included in preferential policies are more essential to have a secure supply of, that they have a bigger target market and are therefore more interesting to multiple suppliers to enter, or other reasons. One might even ask whether the decrease in average products per PRK cluster is necessarily bad, since the overall number of products and alternatives within the PRK cluster is still higher than for the products not included in a preferential policy. Deeper and possibly qualitative research would be needed to provide insight into this question. It would be interesting to investigate whether shortages of essential outpatient antibiotics included in a preferential policy were more or less frequent than the non-preferential products, e.g. using data from Farmanco.

A recent draft report investigating developments in the market of generic medicines investigated the distribution of generic medicines over the different preferential policies (KPMG, 2023). It found that 37 articles (out of how many is not noted, but an estimate of around ~1900 articles can be concluded from the graph, so ~2%) are preferential with all 4 health insurers. It is noted that these 37 products have a relatively high number of users (3.2 million, out of an estimated 21 million users (17%)), but an ‘users per article’ ratio is not calculated. The results of the current

report show a different image: the outpatient antibiotics that are preferential with all health insurers also have a low user base. This suggests that the distribution of preferential outpatient antibiotics over health insurers is not likely to contribute to its availability issues.

5.1. International initiatives

When looking at international initiatives to counteract availability issues of antibiotics, one can generally distinguish two types of initiatives: granting exemptions within existing policies, and new and innovative policies. The German and French initiatives are largely of the first category and focus on price-controlling instruments that are present in their respective countries. French policy guarantees antibiotics with minor added therapeutic value a price not lower than the lowest list price in four reference countries, but no special status is given to antibiotics regarding internal price referencing. In Germany, antibiotics can be included in price negotiations as opposed to being included in internal price referencing groups, even if clinical studies are based on non-inferiority study designs. Additionally, if draft legislation is passed, Reserve antibiotics are even exempted from price negotiations altogether.

These policies in France and Germany related to antibiotics availability and price-controlling instruments are only partly transferable to the current Dutch healthcare context and policy instruments that are in place. In the Netherlands, external price referencing is currently not used for minimum prices like in France, but rather for maximum prices under the Wgp. Furthermore, the Dutch healthcare system does not know price negotiations for most medicines like in the German system (only when medicines are exceptionally expensive will a price negotiation take place). The purpose of these policies overall, however, can be interpreted as 1) exempting antibiotics from internal price referencing (if they have therapeutic added benefit) and 2) letting drug manufacturers determine their own prices without limitations. If transferred to the Dutch healthcare system context, this would be similar to exempting antibiotics from the GVS reimbursement limit and/or exempting them from external price referencing in the Wgp maximum allowable price. Given the findings of this report (that the price-controlling instruments GVS and Wgp maximum allowable price do not limit essential outpatient antibiotics more than other medicines, and that the GVS reimbursement limit was not the (only) reason products were taken off the market), however, one might ask if such measures would truly benefit the availability of antibiotics on the Dutch market. Secondly, evaluations of these policies and/or empirical arguments for why these specific policies have been introduced and whether they have been successful, are currently still missing. Deciding whether the Netherlands should introduce a similar policy rule exempting essential outpatient antibiotics from internal and/or external price referencing is therefore rather difficult.

The more new and innovative policies to ensure availability of antibiotics can be found in Sweden, the UK and draft legislation of the US. The Swedish system is relatively simple. Although the Swedish healthcare system employs different price-controlling instruments, the antimicrobial pilot has little to do with those. Although first evaluations of the Swedish pilot were positive, there were still some points for improvement that should be taken into consideration were this system to be adapted into the Dutch context. Whether national procurement of medicines and/or providing minimal annual revenue guarantees in the Netherlands is legally possible, specifically in the case of antimicrobials, should be the topic of further investigation. The UK's subscription program is currently ongoing, and its approach is being evaluated. First evaluations identified several serious challenges, which should be addressed if a subscription style model is chosen to be implemented

in the Dutch context. The extent to which US subscription models currently proposed under draft legislation will be implemented and whether they will be successful, is still unknown.

Of important note is that, fundamentally, the UK and Swedish pilot have different objectives. The Swedish pilot was explicitly not meant for incentivising R&D efforts (Folkhälsomyndigheten, 2023a, 2023b), where this was the case for the UK pilot (Department of Health and Social Care, 2019). This is directly related to the height of compensation used and available budgets in the two pilots. Therefore, if the Dutch government were to implement a pilot program to stimulate availability of antimicrobials, a clearly defined purpose should be formulated in line with the available budget.

5.2. Limitations and further research

The presented results should be interpreted while acknowledging the following limitations. Firstly, due to the nature of the data (sources), the methodological approach was bounded by a non-experimental research design. Inherently, this means that causation is impossible to prove. For various practical and ethical reasons (*e.g.* the fact that for an experimental research design, one group should have policy interventions and the other group should not, but both groups should still have access to the same medicines), this is also undesirable. Future analyses could adopt a quasi-experimental research design using, for example, data from different countries, to not only assess causality in the problem context, but also to determine whether changes in policy instruments were to be or have been effective (Harris et al., 2006). Quasi-experimental research design has already been used in studying the effect of interventions combatting antibiotic resistance (Alsaggaf et al., 2018).

Secondly, generalizability of results is limited by the chosen scope of essential, outpatient antibiotics starting with ATC code J01 ('Antibacterials for systemic use'). While a substantial portion of antibiotics falls under this ATC code, it is not exhaustive. Future analyses could assess whether the observed results are similar in other clusters that include antibiotics or other antimicrobial compounds. Due to the lack of data on inpatient antibiotics (the requested data had not come in in time for analysis), the scope was limited to outpatient antibiotics. Further investigations could still focus on inpatient antibiotics and could prove valuable in obtaining the full image of the problem and potential solutions, especially since inpatient antibiotics might be more costly and more specialized, making it more problematic if they were to be removed from the market. The degree to which antibiotics are essential was determined using the 'List essential antimicrobials in the Netherlands' from SWAB. This list was specifically drafted with the intent of having a list on which to base policy interventions surrounding availability and access. According to the authors of the list, the list was drafted using the currently available antibiotics on the Dutch market as registered on the website of Pharmacotherapeutic Compass (*Farmacotherapeutisch Kompas*). However, upon closer inspection, not all antibiotics that are registered on the market and are on the website of Pharmacotherapeutic Compass, are indeed included in the SWAB list (for example: dalbavancin and methenamine). Furthermore, it is unknown whether there are certain antibiotics that are currently not on the market anymore but are desired to be available. These would also be missed when using only the SWAB list as guideline. For these reasons, while the list is still an incredibly useful tool and one that is likely to be updated in the future to include more compounds, one should be mindful to follow the list blindly in formulating policy interventions.

Thirdly, a major limitation of this study is the fact that when antibiotics are registered on the market, it not automatically means that these products are also available to patients. For

example, a company may decide to register a product but not sell it. Furthermore, problems in the supply chains or other reasons may result in the product being (temporarily) unavailable. Therefore, future research may focus on combining the observed results of this report with data on shortages from e.g. Farmanco to gain insight into the actual availability of antibiotics to patients.

Fourthly, due to the lack of data on historical Wgp maximum allowable prices at the moment of data analysis, results are limited to comparing the AIP and GVS reimbursement limit with the Wgp maximum allowable price of products that are still on the market. For products that have been removed from the market, further investigation is necessary to compare the Wgp maximum allowable price at the moment of removal from the market with the AIP at that time and analyse whether this differs from the products still on the market. A causal relationship between pressure from the Wgp maximum allowable price and removal from the market will be incredibly difficult – if not impossible – to infer from the available quantitative data. However, more insight could be gathered from qualitative research amongst manufacturers that took antibiotics off the market and might be another area of future studies.

Lastly, one aspect that has not been taken into account in determining the effect of the preferential policy on the availability of essential outpatient antibiotics, is the fact that which product was preferential could (and is likely to) have changed over the past 10 years. However, historical lists of preferential products were unavailable to us at the time of writing. Therefore, we assumed that although the products that were preferential might have changed, the PRK cluster which included preferential products is less likely to have changed dramatically over the past 10 years. Further analyses could be performed to test this assumption more thoroughly.

6. Conclusion

This present research project has investigated the effect of the price-controlling instruments GVS reimbursement limit, Wgp maximum allowable price and preferential policy on the availability of essential outpatient antibiotics on the Dutch market between 2013 and 2022.

Taking all findings together, regarding the overall market characteristics of the essential outpatient antibiotics market, we conclude that the market is starting to show signs of impoverishment. Both the number of essential outpatient antibiotics and the number of available PRK clusters have decreased between 2013-2022. The number of suppliers and the summed revenue of all products has not changed between 2013-2022, the latter due to an increasing mean and median revenue per article.

Regarding the effect of the GVS reimbursement limit on the availability of essential outpatient antibiotics between 2013-2022, we find that the GVS reimbursement limit is putting limited pressure on the prices of essential outpatient antibiotics, that this pressure is the same for products currently on the market as it is for products that have been removed from the market, and that this pressure is similar to the pressure the GVS reimbursement limit puts on other medicines. Therefore, we conclude that the GVS reimbursement limit is not likely to be the (main) reason essential outpatient antibiotics are taken off the market.

Regarding the effect of the Wgp maximum allowable price, we find that the Wgp maximum allowable price is putting significant pressure on the prices of essential outpatient antibiotics, and that this pressure is similar to the pressure the Wgp maximum allowable price puts on other medicines. Furthermore, we identified that the Wgp maximum allowable price is lower than the GVS reimbursement limit in 83% of cases. Therefore, we conclude that the Wgp maximum allowable price is most often the limiting factor in price setting of essential outpatient antibiotics and might be putting undesirable pressure on the price of essential outpatient antibiotics.

Regarding the preferential policy, we conclude that although the presented data provides indications that the preferential policy might influence essential outpatient antibiotics being removed from the market, many questions still remain unanswered as to how and to what extent, and whether this is negatively impacting patients. Furthermore, we conclude that the distribution of preferential outpatient antibiotics over the different health insurance policies is unlikely to contribute to availability issues.

Future research is needed to elucidate the effect of price-controlling instruments on the availability of essential inpatient antibiotics. Equally, more qualitative research into why antibiotics have been removed from the market may provide more valuable insights into the influence of price-controlling instruments and overall market dynamics.

To address the identified problems of price-controlling instruments and availability of antibiotics, inspiration can be taken from international initiatives in France, Germany, the UK, Sweden and the US. French and German initiatives aiming to combat antibiotics availability issues using price-controlling instruments have limited direct transferability to the Dutch healthcare context but could be adapted to fit the used systems and instruments. Nevertheless, given the findings of this study, it is still unclear whether implementing exemptions or novel policies regarding price-controlling instruments and antibiotics would truly solve the (temporary) shortages and essential outpatient antibiotics being removed from the market. However, one should not underestimate the importance of such policies from a political standpoint and the message it

sends to industry, society and other countries. Novel reimbursement and/or payment systems for antibiotics like piloted in Sweden, the UK or currently present in US draft legislation might provide a more sustainable and substantial solution to the identified problems. However, evaluations have already identified opportunities for improvement and future evaluations are needed to assess whether the pilots have achieved their intended purpose.

7. Policy considerations and recommendations

As my internship at the Ministry of VWS comes to a close, the topic of price-controlling instruments, antibiotics and availability will remain very relevant. Overlooking the results of this research project, there is not one easy fix-all solution to the availability issues of antibiotics, as is often the case in policy making. This topic is incredibly nuanced and complex and deserves thorough attention to map the problem context to its fullest extent, converse with the stakeholders involved, and implement policies that adequately and sustainably ensure the availability of essential antibiotics in the Netherlands, now and in the future. To this end, my recommendations to the Ministry of VWS are described below[4].

Firstly, this research project has taken a quantitative approach. This was needed to provide a solid understanding of the Dutch context, but only tells part of the story. A causal relationship with non-experimental design is impossible to prove. More qualitative insights into why products have been taken off the market is necessary next to the quantitative insights gathered in this study. Therefore, I recommend to **qualitatively confirm and/or evaluate the findings of this study with pharmaceutical companies, healthcare practitioners and other relevant stakeholders**.

Secondly, this research project concluded that a lot of uncertainty persists regarding the effect of the preferential policy on the availability of medicines and, more specifically, essential antibiotics. Since there are many concerns regarding this topic in both politics, media and health care, I recommend shedding more light on this topic and **consider studying the effect of the preferential policy on the availability of medicines in general and antibiotics in particular both qualitatively and quantitatively.** This could, for example, be done by quantitatively comparing (for medicines in general) the availability of products per PRK cluster both for clusters including and excluding preferential medicines, and qualitatively investigating the reasons for products being removed from the market when they are not preferential.

Thirdly, assuming that further analyses under the first recommendation corroborate the findings of this report, I recommend to **determine to what extent the current mitigating policies regarding the Wgp maximum allowable price already sufficiently cover essential antibiotics**. If this mitigating measure does not (sufficiently) cover essential antibiotics, I recommend to **consider exempting essential outpatient antibiotics from the Wgp maximum allowable price altogether**.

Fourthly, we concluded that the GVS reimbursement limit is not putting more pressure on essential outpatient antibiotics than it is on other medicines, and it is likely not to be the (only) reason products have been removed from the market. This likely means that exempting essential outpatient antibiotics from internal price referencing in GVS clusters will have little positive effect on their availability. Therefore, I recommend to **not exempt essential outpatient antibiotics from GVS clustering, at least as long as the GVS reimbursement limits are not updated**.

Lastly, this research project has suggested that the availability issues of antibiotics might not (only) lay with price-controlling instruments and that the problem might in fact be the low potential revenue overall that is driving the removal of antibiotics from the market. Therefore, I

[4] The analyses and results of this report have been discussed with colleagues from the Dutch Ministry of VWS and would not have been possible without them. Therefore, the majority of this report is written in first-person plural. These recommendations are my own and are not necessarily reflective of the policy views of the Dutch Ministry of VWS, and are therefore written in first-person singular.

recommend to **further investigate the (legal) possibilities of implementing a pilot for a novel reimbursement and/or payment system for essential antibiotics in the Netherlands, while paying special attention to the lessons learned from international initiatives** such as alignment of the available budget with the intended purpose, the framework with which compensation amounts are calculated, the volume and location of the supply, and the potential for redistribution of products in case underusage is imminent.

References

Accord cadre du 31/12/2015 entre le Comité économique des produits de santé et les entreprises du médicament (Leem), (2015).

Agence Technique de l'Information sur l'Hospitalisation. (n.d.). *Unités communes de dispensation prises en charge en sus*. Agence Technique de l'Information Sur l'Hospitalisation. Retrieved June 21, 2023, from https://www.atih.sante.fr/unites-communes-de-dispensation-prises-en-charge-en-sus

Alsaggaf, R., O'Hara, L. M., Stafford, K. A., Leekha, S., & Harris, A. D. (2018). Quasi-experimental Studies in the Fields of Infection Control and Antibiotic Resistance, Ten Years Later: A Systematic Review. *Infection Control and Hospital Epidemiology*, *39*(2), 170. https://doi.org/10.1017/ICE.2017.296

Årdal, C., Findlay, D., Savic, M., Carmeli, Y., Gyssens, I., Laxminarayan, R., Outterson, K., Rex, J. H., Ciabuschi, F., Hackett, J., Harbarth, S., Hermsen, E., Knirsch, C., Mahoney, N., Murillo, N., Rex, J., Theuretzbacher, U., Baraldi, E., Bettiol, E., … Temkin, L. (2018). *Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access*.

Årdal, C., Røttingen, J.-A., Opalska, A., Van Hengel, A. J., & Larsen, J. (2017). Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clinical Infectious Diseases*, *65*(8), 1378–1382. https://doi.org/10.1093/cid/cix526

Baltesen, F. (2023, March 17). *Artsen maken zich zorgen om tekort medicijnen*. Skipr. https://www.skipr.nl/nieuws/artsen-maken-zich-zorgen-om-tekort-medicijnen/

S.1355 - PASTEUR Act of 2023, (2023) (testimony of Michael F. Bennet). http://www.congress.gov/bill/118th-congress/senate-bill/1355

Boluarte, T., & Schulze, U. (2022). *The Case for a Subscription Model to Tackle Antimicrobial Resistance Another Pandemic on the Horizon*.

Boogaard, J. (2023, March 4). "De échte medicijntekorten in Nederland vallen relatief mee." *NRC*. https://www.nrc.nl/nieuws/2023/03/03/grondlegger-beleid-medicijnprijzen-de-echte-medicijntekorten-in-nederland-vallen-relatief-mee-a4158450

Brink, R. van den. (2019, January 14). *Weer meer medicijnen niet leverbaar*. NOS. https://nos.nl/artikel/2267384-weer-meer-medicijnen-niet-leverbaar

Bundesministerium für Gesundheit. (n.d.). *Festbeträge für Arzneimittel*. Bundesministerium Für Gesundheit. Retrieved June 22, 2023, from https://www.bundesgesundheitsministerium.de/service/begriffe-von-a-z/f/festbetraege-fuer-arzneimittel.html

Verordnung über die Nutzenbewertung von Arzneimitteln nach § 35a Absatz 1 SGB V für Erstattungsvereinbarungen nach § 130b SGB V (Arzneimittel-Nutzenbewertungsverordnung-AM-NutzenV) § 5 Zusatznutzen., (testimony of Bundesministerium für Gesundheit). Retrieved May 2, 2023, from https://www.gesetze-im-internet.de/am-nutzenv/BJNR232400010.html

Arzneimittel-Lieferengpassbekämpfungs- und Versorgungsverbesserungsgesetz (ALBVVG), (2023) (testimony of Bundesministerium für Gesundheit). https://www.bundesgesundheitsministerium.de/service/gesetze-und-verordnungen/detail/albvvg.html

Carp, M., Kraal, A., Bekker, P. de, Denee, L., & Boer, A. de. (2018). *Effecten van het preferentiebeleid op beschikbaarheid van geneesmiddelen*.

Castle, G., Kelly, B., & Gathani, R. (2022). *Pricing & Reimbursement Laws and Regulations | United Kingdom*. Global Legal Group. https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/united-kingdom

Clift, C., Gopinathan, U., Morel, C., Outterson, K., Røttingen, J.-A., & So, A. (2015). *Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales*. www.chathamhouse.org

Colson, A. R., Morton, A., Årdal, C., Chalkidou, K., Davies, S. C., Garrison, L. P., Jit, M., Laxminarayan, R., Megiddo, I., Morel, C., Nonvignon, J., Outterson, K., Rex, J. H., Sarker, A. R., Sculpher, M., Woods, B., & Xiao, Y. (2021). Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem? *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *24*(12), 1828–1834. https://doi.org/10.1016/J.JVAL.2021.06.002

Commonwealth Fund. (2020a, June). *Sweden*. https://www.commonwealthfund.org/international-health-policy-center/countries/sweden

Commonwealth Fund. (2020b, June 5). *England*. https://www.commonwealthfund.org/international-health-policy-center/countries/england

Commonwealth Fund. (2020c, June 5). *International Health Care System Profiles - France*. Commonwealth Fund. https://www.commonwealthfund.org/international-health-policy-center/countries/france#universal-coverage

Commonwealth Fund. (2020d, June 5). *International Health Care System Profiles - Germany*. Commonwealth Fund. https://www.commonwealthfund.org/international-health-policy-center/countries/germany#universal-coverage

Commonwealth Fund. (2020e, June 5). *United States*. https://www.commonwealthfund.org/international-health-policy-center/countries/united-states

CZ. (2023). *Wat is het voorkeursbeleid voor medicijnen?* https://www.cz.nl/service-en-contact/wat-is-het-voorkeursbeleid

Daniel, G. W., McClellan, M. B., Margolis, R. J., Schneider, M., Qian, J., Lavezzari, G., Audi, H., & Fowler, V. (2017). *Value-based Strategies for Encouraging New Development of Antimicrobial Drugs*.

Davidson, B., Payne, H., & Neal, J. C. (2021, May 20). *US Government Continues Investing in Solutions to Combat AMR*. Avalere Health. https://avalere.com/insights/us-government-continues-investing-in-solutions-to-combat-amr

H.R.4127 - DISARM Act of 2021, (2021) (testimony of Danny K Davis). http://www.congress.gov/bill/117th-congress/house-bill/4127/text

Department of Health and Social Care. (2019, July 9). *Development of new antibiotics encouraged with new pharmaceutical payment system*. Gov.Uk. https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system

Ellwanger, N., Everhardt, T., & Thuis, I. (2014). *Proefberekeningen Geneesmiddelenvergoedingssysteem*.

European Commission. (2023, April 26). *Reform of the EU pharmaceutical legislation*. European Commission. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

European Observatory on Health Systems and Policies. (n.d.). *Country overview - France*. European Observatory on Health Systems and Policies. Retrieved June 21, 2023, from https://eurohealthobservatory.who.int/countries/france

European Observatory on Health Systems and Policies. (2012, June). *Sweden*. https://eurohealthobservatory.who.int/countries/sweden

European Observatory on Health Systems and Policies. (2020). United States: health system review 2020. *Health Systems in Transition*, *22*(4). https://eurohealthobservatory.who.int/publications/i/united-states-health-system-review-2020

European Observatory on Health Systems and Policies. (2022, December 22). *Germany: health system summary*. European Observatory on Health Systems and Policies. https://eurohealthobservatory.who.int/publications/i/germany-health-system-summary-2022

Farmatec. (n.d.). *Berekening maximumprijzen*. Retrieved June 6, 2023, from https://www.farmatec.nl/prijsvorming/wet-geneesmiddelenprijzen/berekening-maximumprijzen

Farmatec. (2023). *Tijdelijke beleidsregel maximumprijzen*. https://www.farmatec.nl/prijsvorming/wet-geneesmiddelenprijzen/tijdelijke-beleidsregel-maximumprijzen

Folkhälsomyndigheten. (2023a). *Availability to antibiotics of particular importance*.

Folkhälsomyndigheten. (2023b). *Tillgänglighet till vissa antibiotika*. www.folkhalsomyndigheten.se/publicerat-material/.

Gemeinsamer Bundesausschuss. (n.d.). *Festbetragsgruppenbildung*. Gemeinsamer Bundesausschuss. Retrieved June 22, 2023, from https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/festbetragsgruppenbildung/

Gesetz für einen fairen Kassenwettbewerb in der gesetzlichen Krankenversicherung (Fairer-Kassenwettb-Gesetz-GKV-FKG). Artikel 5, 3 (2020). https://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&start=%2F%2F%2A%5B%40attr_id=%27bgbl120s0604.pdf%27%5D#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl120s0604.pdf%27%5D__1683020679735

H.R.2182 - Generating Antibiotic Incentives Now Act of 2011, (2011) (testimony of Phil Gingrey). http://www.congress.gov/bill/112th-congress/house-bill/2182

Gotham, D., Moja, L., van der Heijden, M., Paulin, S., Smith, I., & Beyer, P. (2021). Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*, *125*(3), 296–306. https://doi.org/10.1016/j.healthpol.2020.11.015

Harris, A. D., McGregor, J. C., Perencevich, E. N., Furuno, J. P., Zhu, J., Peterson, D. E., & Finkelstein, J. (2006). The Use and Interpretation of Quasi-Experimental Studies in Medical Informatics. *Journal of the American Medical Informatics Association : JAMIA*, *13*(1), 16. https://doi.org/10.1197/JAMIA.M1749

Hollak, C., Berg, S. van den, Hermans, J., & Waals, H. (2023, January 9). *Het medicijnentekort is een gevolg van het gevoerde beleid*. NRC. https://www.nrc.nl/nieuws/2023/01/09/het-medicijnentekort-is-een-gevolg-van-het-gevoerde-beleid-a4153686

Kamenade, Y. W. van. (2018). *Healthcare in Europe 2018 - France*. www.french-property.com

KASSA. (2018, March 7). *"Tekort aan medicijnen door preferentiebeleid."* KASSA. https://www.bnnvara.nl/kassa/artikelen/tekort-aan-medicijnen-door-preferentiebeleid

KNMP. (2023, January 14). *Schrikbarend record van aantal geneesmiddelentekorten*. https://www-knmp-nl.proxy.library.uu.nl/actueel/nieuws/schrikbarend-record-van-aantal-geneesmiddelentekorten

Kooijman, M. P., Brabers, A. E. M., & De Jong, J. D. (2018). Solidarity in the Dutch healthcare system: monitoring trends in willingness to pay. *European Journal of Public Health*, *28*(suppl_4). https://doi.org/10.1093/EURPUB/CKY214.116

Koppers, G., Bekker, P. de, Brussaard, A., Carp, M., & Fransen, L. (2021). *Inzicht in de onderkant van de geneesmiddelen markt*.

KPMG. (2023). *Marktonderzoek generieke geneesmiddelen [concept]*.

La protection universelle maladie. (2023, February 8). L'Assurance Maladie. https://www.ameli.fr/assure/droits-demarches/principes/protection-universelle-maladie

Section 2 : Contribution à la charge des entreprises assurant l'exploitation, l'importation parallèle ou la distribution parallèle d'une ou de plusieurs spécialités pharmaceutiques, Légifrance. Retrieved June 21, 2023, from https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006073189/LEGISCTA000006172902/

Menzis. (2023). *Wat is het preferentiebeleid?* https://www.menzis.nl/zorg-en-vergoedingen/medicijnen/preferentiebeleid

Merk, H., Diaz Högberg, L., Plachouras, D., Suetens, C., & Monnet, D. L. (2022). *Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020*. https://doi.org/10.2900/73460

Minister van Volksgezondheid Welzijn en Sport. (2023a). *Afstel GVS-modernisering*.

Minister van Volksgezondheid Welzijn en Sport. (2023b). *Beschikbaarheid medische producten*. https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2023Z04302&did=2023D10105

Ministerie van Volksgezondheid Welzijn en Sport. (2016). *Healthcare in the Netherlands*. https://english.zorginstituutnederland.nl/about-us/publications/publications/2016/01/31/healthcare-in-the-netherlands

Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., … Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0

National Health Care Institute. (n.d.). *Reimbursement of outpatient medicines*. National Health Care Institute. Retrieved May 30, 2023, from https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/assessment-of-outpatient-medicines-for-the-benefit-of-the-medicine-reimbursement-system-gvs/reimbursement-of-outpatient-medicines

National Institute for Health and Care Excellence. (2022a). *Models for the evaluation and purchase of antimicrobials*. NICE; NICE. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials

National Institute for Health and Care Excellence. (2022b, August 17). *Cefiderocol for treating severe drug-resistant gram-negative bacterial infections*. NICE; NICE. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol

National Institute for Health and Care Excellence. (2022c, August 17). *Ceftazidime with avibactam for treating severe drug-resistant gram-negative bacterial infections*. NICE; NICE. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam

Nieber, L. (2023, January 29). Oplossingen zoeken voor medicijntekorten is nu een dagtaak voor apothekers - NRC. *NRC*. https://www.nrc.nl/nieuws/2023/01/29/oplossingen-zoeken-voor-medicijntekorten-is-nu-een-dagtaak-voor-apothekers-a4155625

Nieuwsuur. (2018, August 17). *Het steeds verder oplopende medicijntekort: deze huisarts trekt het niet meer*. Nieuwsuur. https://nos.nl/nieuwsuur/artikel/2246497-het-steeds-verder-oplopende-medicijntekort-deze-huisarts-trekt-het-niet-meer

Nivel. (2016, August 3). *Gevolgen van preferentiebeleid en farmaceutische zorginkoop: ervaringen van gebruikers van hart- en vaatmedicatie.* Nivel. https://www.nivel.nl/nl/publicatie/gevolgen-van-preferentiebeleid-en-farmaceutische-zorginkoop-ervaringen-van-gebruikers

Nurse-Findlay, S., Taylor, M. M., Savage, M., Mello, M. B., Saliyou, S., Lavayen, M., Seghers, F., Campbell, M. L., Birgirimana, F., Ouedraogo, L., Newman Owiredu, M., Kidula, N., & Pyne-Mercier, L. (2017). Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. *PLOS Medicine*, *14*(12), e1002473. https://doi.org/10.1371/JOURNAL.PMED.1002473

NWO. (2017). *Novel Antibacterial Compounds and Therapies Antagonising Resistance (NACTAR)*. https://www.nwo.nl/onderzoeksprogrammas/novel-antibacterial-compounds-and-therapies-antagonising-resistance-nactar

OECD. (2018). *Pharmaceutical Reimbursement and Pricing in Germany*.

O'Neill, J. (2014). *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*.

O'Neill, J. (2016). *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*.

Pharmaceutisch Weekblad. (2010, November 11). *NPCF en KNMP uiten kritiek op preferentiebeleid*. Pharmaceutisch Weekblad. https://www.pw.nl/nieuws/2011/npcf-2018minister-moet-ingrijpen-in-preferentiebeleid2019

Plackett, B. (2020). Why big pharma has abandoned antibiotics. *Nature*, *586*(7830), S50–S52. https://doi.org/10.1038/D41586-020-02884-3

Public Health Agency of Sweden. (n.d.). *Availability of antibiotics*. Public Health Agency of Sweden. Retrieved May 1, 2023, from https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/

Public Health Agency of Sweden. (2017). *Availability of antibiotics: Reporting of Government commission*. https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/a/availability-of-antibiotics/

Regeling maximumprijzen geneesmiddelen. (1996). Overheid.Nl. https://wetten.overheid.nl/BWBR0008023/2015-07-01#Opschrift

Rizvi, S. G., & Ahammad, S. Z. (2022). COVID-19 and antimicrobial resistance: A cross-study. *The Science of the Total Environment*, *807*(Pt 2). https://doi.org/10.1016/J.SCITOTENV.2021.150873

Rothery, C., Woods, B., Schmitt, L., Claxton, K., Palmer, S., & Sculpher, M. (2018). *Framework for value assessment of new antimicrobials: implications of alternative funding arrangements for NICE Appraisal*.

Schurer, M., Patel, R., van Keep, M., Horgan, J., Matthijsse, S., & Madin-Warburton, M. (2023). Recent advances in addressing the market failure of new antimicrobials: Learnings from NICE's subscription-style payment model. *Frontiers in Medical Technology*, *5*. https://doi.org/10.3389/fmedt.2023.1010247

Shafiq, N., Pandey, A. K., Malhotra, S., Holmes, A., Mendelson, M., Malpani, R., Balasegaram, M., & Charani, E. (2021). Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*, *6*(11). https://doi.org/10.1136/BMJGH-2021-006961

Shukar, S., Zahoor, F., Hayat, K., Saeed, A., Gillani, A. H., Omer, S., Hu, S., Babar, Z. U. D., Fang, Y., & Yang, C. (2021). Drug Shortage: Causes, Impact, and Mitigation Strategies. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/FPHAR.2021.693426

SWAB. (2022, December). *Lijst essentiële antimicrobiële middelen in Nederland*. Stichting Werkgroep Antibioticabeleid. https://swab.nl/nl/lijst-essentiele-antimicrobiele-middelen-in-nederland

Taylor, N. P. (2020, January 1). *Melinta files for bankruptcy in another dark day for antibiotics*. Fierce Biotech. https://www.fiercebiotech.com/biotech/melinta-files-for-bankruptcy-another-dark-day-for-antibiotics

Tay-Teo, K., Ilbawi, A., & Hill, S. R. (2019). Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. *JAMA Network Open*, *2*(1), e186875. https://doi.org/10.1001/jamanetworkopen.2018.6875

The Economist. (2019, May 2). *Antibiotics biotech firms are struggling*. https://www-economist-com.proxy.library.uu.nl/business/2019/05/02/antibiotics-biotech-firms-are-struggling

TLV. (2023). *PPRI Pharma Profile Sweden 2023*.

Todd, M. H., Klug, D. M., Idiris, F. I. M., Blaskovich, M. A. T., von Delft, F., Dowson, C. G., Kirchhelle, C., Roberts, A. P., & Singer, A. C. (2021). There is no market for new antibiotics: this allows an open approach to research and development. *Wellcome Open Research*, *6*. https://doi.org/10.12688/WELLCOMEOPENRES.16847.1

VGZ. (2023). *Preferentiebeleid*. https://www.cooperatievgz.nl/zorgaanbieders/farmaceutische-zorg/inkoopbeleid/preferentiebeleid

Vogler, S., Gombocz, M., & Zimmermann, N. (2017). Tendering for off-patent outpatient medicines: lessons learned from experiences in Belgium, Denmark and the Netherlands. *Journal of Pharmaceutical Health Services Research*, *8*(3), 147–158. https://doi.org/10.1111/JPHS.12180

Vogler, S., & Rodrigues, J. (2020). *PPRI Pharma Brief: France 2020*. https://ppri.goeg.at

Wellcome. (2020, January 21). *Why is it so hard to develop new antibiotics?* https://wellcome.org/news/why-is-it-so-hard-develop-new-antibiotics

Wet geneesmiddelenprijzen. (1996). Overheid.Nl. https://wetten.overheid.nl/BWBR0007867/2020-03-19

WHO. (2018). *Critically Important Antimicrobials for Human Medicine*.

WHO. (2021, November 17). *Antimicrobial resistance*. WHO. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

WHO. (2022). *2021 Antibacterial agents in clinical and preclinical development an overview and analysis*.

Zilveren Kruis. (2023). *Preferente geneesmiddelen*. https://www.zilverenkruis.nl/zorgaanbieders/zorgsoort/extramurale-farmacie/preferente-geneesmiddelen

Zorgcijfersdatabank. (2023, March 9). *Totale zorgkosten Zorgverzekeringswet*. Zorginstituut Nederland. https://www.zorgcijfersdatabank.nl/databank?infotype=zvw&label=00-totaal&geg_zvw=jjaarNEW&geg_wlz=jjaarNEW&meta_tabel=kosten&tabel=B_kost&item=

Zorginstituut Nederland. (n.d.). *Advising on and clarifying the contents of the standard health care benefit package*. Zorginstituut Nederland. Retrieved May 17, 2023, from https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/advising-on-and-clarifying-the-contents-of-the-standard-health-care-benefit-package

Zorginstituut Nederland. (2015). Kosteneffectiviteit in de praktijk. In *Zorginstituut Nederland*. https://www.zorginstituutnederland.nl/publicaties/rapport/2015/06/26/kosteneffectiviteit-in-de-praktijk

SUPPLEMENTARY MATERIALS

Supplementary Table 1 - Number of antimicrobials per category based on their importance for human medicine worldwide (WHO, 2018).

Category	Number of antimicrobials in category
Important	10
Highly important	88
Critically important	79
Highest-priority critically important	87
Total	**264**

Supplementary Table 2 - Descriptive statistics of AIP per unit, GVS reimbursement limit and Wgp maximum allowable price for essential outpatient antibiotics. Data on AIP, GVS reimbursement limit and Wgp maximum allowable price comes from SFK. Descriptive statistics have been calculated using Excel. SEM - standard error of the mean; STD.DEV - standard deviation.

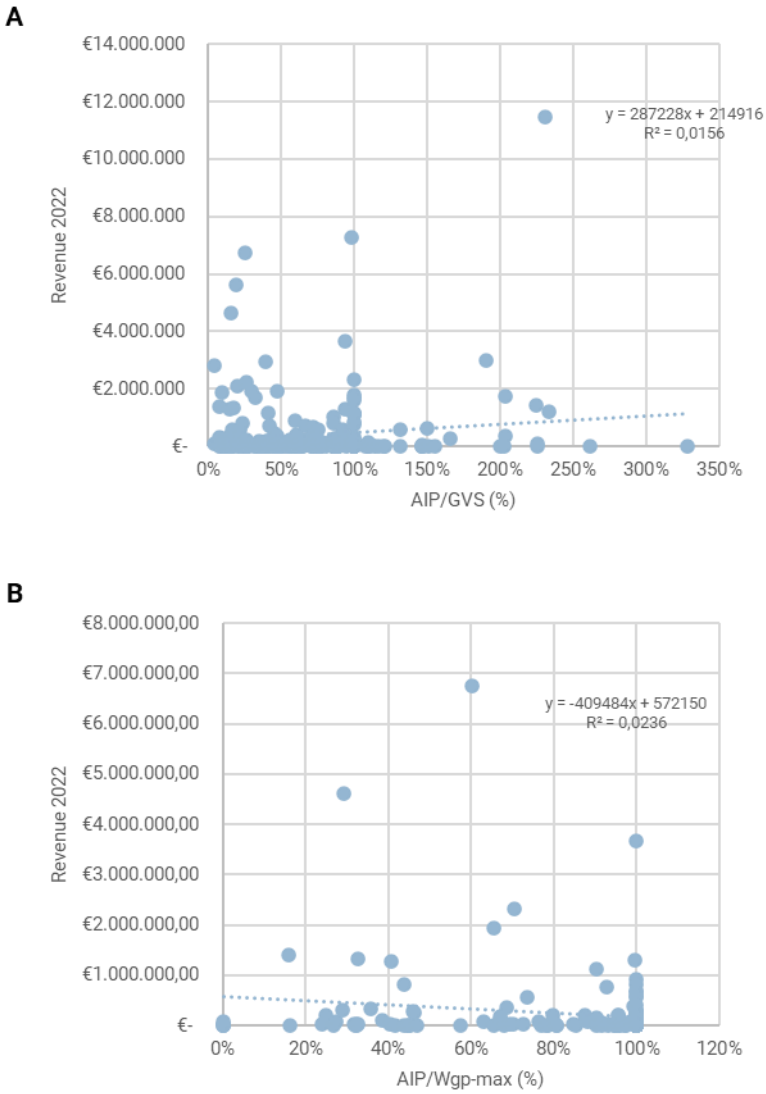
	AIP per unit	GVS reimbursement limit	Wgp maximum allowable price
Mean	€ 4,37	€ 5,07	€ 5,24
Standard error	€ 0,44	€ 0,40	€ 0,86
Median	€ 0,68	€ 0,93	€ 1,46
Mode	€ 9,80	€ 3,57	€ 9,82
Standard deviation	€ 12,73	€ 11,16	€ 12,52
Range	€ 164,90	€ 65,82	€ 119,73
Minimum	€ 0,10	€ 0,13	€ 0,12
Maximum	€ 165,00	€ 65,96	€ 119,85
Sum	€ 3.732,54	€ 3.970,57	€ 1.111,50
Count	855	783	212

Supplementary Table 3 - Descriptive statistics of the revenue for essential outpatient antibiotics. Data has been collected from SFK, and €0,- revenues were excluded from analysis. Descriptive statistics have been calculated using Excel. SEM - standard error of the mean; STD.DEV - standard deviation.

	Revenue 2013 (excl. €0,-)	Revenue 2014 (excl. €0,-)	Revenue 2015 (excl. €0,-)	Revenue 2016 (excl. €0,-)	Revenue 2017 (excl. €0,-)	Revenue 2018 (excl. €0,-)	Revenue 2019 (excl. €0,-)	Revenue 2020 (excl. €0,-)	Revenue 2021 (excl. €0,-)	Revenue 2022 (excl. €0,-)
Mean	€ 179.293,45	€ 152.234,40	€ 163.143,34	€ 205.413,39	€ 231.207,44	€ 229.695,95	€ 233.121,92	€ 220.000,97	€ 253.525,48	€ 304.604,01
SEM	€ 23.182,86	€ 20.428,28	€ 22.446,36	€ 31.086,74	€ 35.149,08	€ 37.191,03	€ 38.386,84	€ 35.475,11	€ 44.733,76	€ 52.308,55
Median	€ 9.130,00	€ 9.713,00	€ 11.653,00	€ 12.199,00	€ 11.703,00	€ 12.317,50	€ 11.932,00	€ 10.607,00	€ 13.611,00	€ 15.230,00
Mode	€ 23,00	€ 20,00	€ 25,00	€ 10,00	€ 259,00	€ 20,00	€ 8,00	€ 15,00	€ 16,00	€ 15,00
STD.DEV	€ 547.135,18	€ 468.070,60	€ 499.904,20	€ 683.908,25	€ 739.802,64	€ 771.209,72	€ 792.295,43	€ 708.614,73	€ 865.109,82	€ 995.238,03
Range	€ 5.410.579,00	€ 5.818.628,00	€ 6.125.982,00	€ 8.078.183,00	€ 7.161.509,00	€ 8.076.984,00	€ 8.777.293,00	€ 6.585.006,00	€ 11.638.258,00	€ 11.471.139,00
Minimum	€ 1,00	€ 1,00	€ 2,00	€ 6,00	€ 8,00	€ 7,00	€ 7,00	€ 8,00	€ 1,00	€ 4,00
Maximum	€ 5.410.580,00	€ 5.818.629,00	€ 6.125.984,00	€ 8.078.189,00	€ 7.161.517,00	€ 8.076.991,00	€ 8.777.300,00	€ 6.585.014,00	€ 11.638.259,00	€ 11.471.143,00
Sum	€ 99.866.449,00	€ 79.923.058,00	€ 80.919.098,00	€ 99.420.079,00	€ 102.424.894,00	€ 98.769.260,00	€ 99.309.937,00	€ 87.780.386,00	€ 94.818.531,00	€ 110.266.653,00
Count	557	525	496	484	443	430	426	399	374	362

Supplementary Table 4 - Descriptive statistics of the ratios used in this report: AIP/GVS of products currently on the market, AIP/GVS of products removed from the market, AIP/Wgp-max, and GVS/Wgp-max. Descriptive statistics have been calculated using Excel. SEM - standard error of the mean; STD.DEV - standard deviation.

	AIP/GVS ratio current	AIP/GVS ratio removed	AIP/Wgp-max ratio	GVS/Wgp-max ratio
Mean	67%	61%	83%	180%
SEM	3%	2%	2%	7%
Median	58%	50%	100%	165%
Mode	87%	36%	100%	115%
STD.DEV	50%	42%	27%	89%
Range	325%	272%	100%	390%
Minimum	4%	8%	0%	0%
Maximum	329%	280%	100%	390%
Sum	17919%	22985%	14715%	27968%
Count	267	376	178	155



Supplementary Figure 1 - Relationship between the AIP/GVS ratio (A) or AIP/Wgp-max ratio (B) and the reported revenue in 2022. Dotted line is linear trend line. Formula and R^2 of trend line are plotted in graph.

Supplementary Table 5 - The division of outpatient antibiotics included in at least one preferential policy per essentiality classification of the SWAB.

Classification by SWAB	Number of antibiotics included in preferential policy
A	37
B	7
C	14
D	1
Total	**59**