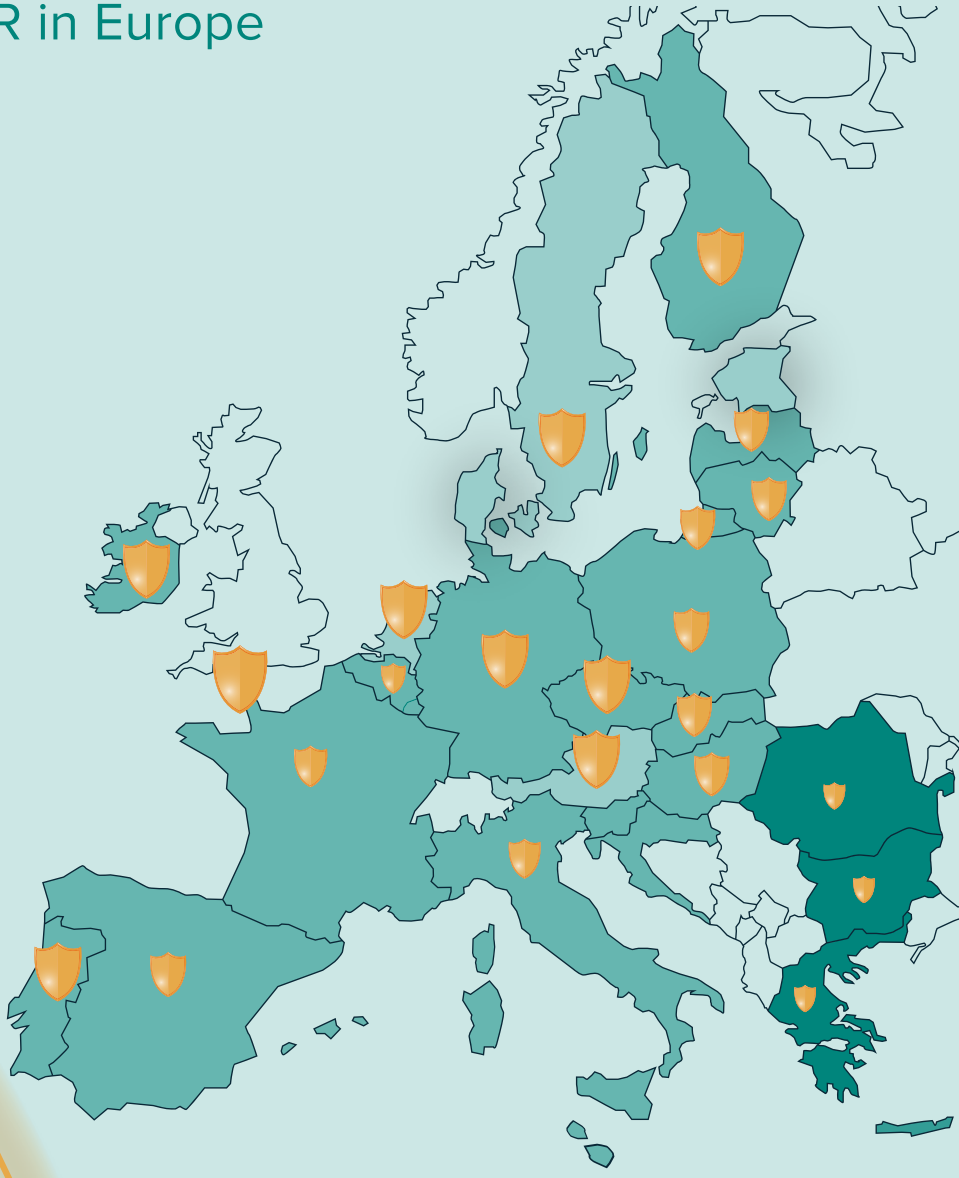
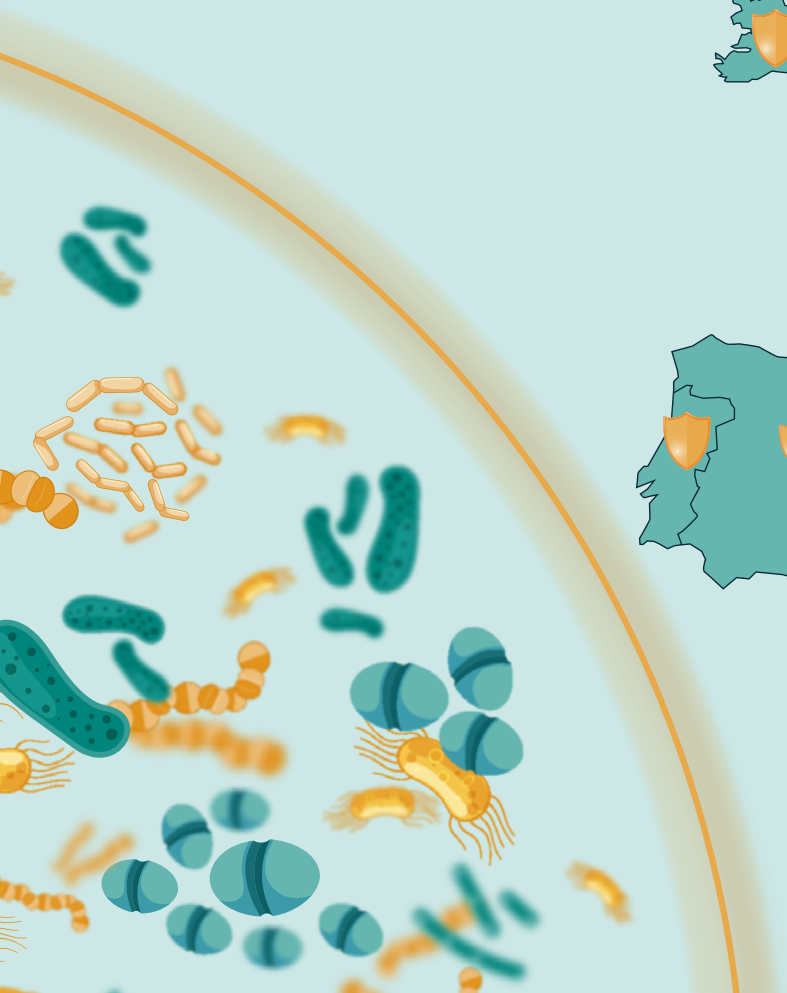
Improving patient access to novel antibiotics

Recommendations for national policies to fight AMR in Europe





VINTURA MSD

Executive Summary

There is an urgent need for the European community to address the overlooked pandemic of antimicrobial resistance

Antimicrobial resistance (AMR) poses a growing threat to Europe's health and economic future and is likely to become the next pandemic. Antibiotic resistance rates vary across European countries and are increasing across the board. Hence, it is imperative to take urgent action. To protect today's patients and future generations against resistant bacteria, we need to implement effective interventions on national and European scales.

Key strategic pillars to fight AMR are known, yet the progress on a sustainable economic model for bringing novel antibiotics to patients is limited

Globally, the key strategic pillars to fight AMR are known, and various European and global initiatives address these priorities. One pillar is to prolong the effectiveness of antimicrobial agents, including antibiotics, through stewardship programs to ensure appropriate use. This preserves antibiotics effectiveness, but leads to an unsustainable return on investments for new antibiotics, as returns are traditionally linked to volumes used. This is one of the reasons why the current economic model fails for novel antibiotics. Consequently, many antibiotics drop out of late-stage clinical development pipelines despite recent improvements in push mechanisms to stimulate early development.

European countries need to advance national policies that enable patient access to novel antibiotics

European-wide pull mechanisms, such as Transferable Exclusivity Extensions (TEE), are being discussed to help create a sustainable return on investments. However, additional opportunities exist at the country level to improve timely and appropriate patient access to novel antibiotics. Countries need to revthink how to assess the value, but also how to price and procure novel antibiotics, as interventions are needed at both European and national levels. This report focuses on national measures to ensure novel antibiotics have clear and feasible progression pathways to patients who need them.

National policy makers should identify and address the key barriers hampering patient access in their country

Distinct market challenges discourage commercialisation. This report describes six barriers national policy makers face in enabling optimal patient access to novel antibiotics: (1) standard value assessment methods not capturing the value of novel antibiotics, (2) financial return linked to volume used, (3) restrictions in reimbursement criteria, hospital protocols or formularies, hampering patient access to treatment they need at the time they need it, (4) cost-driven procurement models, (5) insufficient hospital funding, and (6) suboptimal susceptibility testing.

This report provides policy recommendations and inspiring practices for addressing national barriers hampering access to novel antibiotics

The access barriers countries face differ depending on how the value assessment, pricing, reimbursement, and procurement of novel antibiotics are organised. In this report, we describe the interventions countries have developed per barrier, to inspire decision-makers and stakeholders across Europe. The goal is to facilitate the introduction of policies to ensure patients get access to novel antibiotics when they need them. Now and in the future.

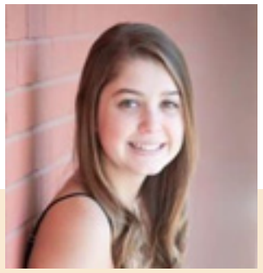
Antimicrobial resistance – an urgent need to anticipate the next pandemic

As antibiotics lose their effectiveness, resistant bacteria may cause death from ‘routine’ interventions such as neonatal care, surgery or chemotherapy.

We could not think of nowaday’s healthcare without surgery, caesarian sections, chemotherapy or organ transplantations. These interventions rely on supporting antibiotics to prevent and treat infectious complications. Yet, as bacteria become resistant, traditional antibiotics lose their effectiveness. As a consequence, investments in treatments will yield less results and treatments that we currently take for granted as routine procedures will become increasingly risky.

Based on the lists of priority pathogens developed by WHO, ECDC and OECD, (2,3,4) this report focuses on six priority bacteria that have been associated with antimicrobial resistance: the Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter species* on the one hand and the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pneumoniae* on the other.[a] All six pathogens are a leading cause of - often hospital-acquired (or in the case of *Streptococcus pneumoniae* mostly community-acquired) - infections (5) and death (3,6).

[a] *See Annex I - Methodology for more details.*



Dying of an antibiotic-resistant infection following cancer treatment (1)

Meredith was diagnosed with Acute Myeloid Leukaemia (AML) at the age of 18. Several rounds of chemotherapy followed which weakened her immune system. This made her vulnerable to infections, but Meredith did well until she contracted Candida, a fungal infection that is not uncommon in AML patients. Only a combination of therapies cleared her infection. Soon after, Meredith was diagnosed with Pseudomonas, a gram-negative bacterial infection. Because the infection was resistant to antibiotics, doctors used colistin which is considered an antibiotic of last resort due to its severe toxic effect on kidneys. However, the infection kept plaguing her and, in the end, reached her bloodstream leading to a fatal septic shock.

Meredith died a year after her AML diagnosis – not of cancer, but of an antibiotic-resistant infection.

Meredith’s story is used with permission of the Infectious Diseases Society of America.

Antibiotic resistance is likely to become the next pandemic: resistance rates and deaths vary across European Countries but are increasing across the board.

The numbers related to antibiotic resistance in Europe already speak for themselves. Antibiotic resistance increased from 2015 to 2020 by 18 percent on average (see Figure 1). Greece is leading the alarming score with an antibiotic resistance rate of 56% in 2020 (7). Although the resistance rates differ and the sense of urgency may vary per country, all countries must act to tackle antibiotic resistance to avoid the rapid proliferation of resistant pathogens across borders.

Figure 1
Antibiotic resistance rates vary across European countries but are increasing across the board.

Source: ECDC Surveillance Atlas, 2022. Based on # of resistant isolates (excl. combined resistance) divided by the number of tested isolates for E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter spp.

Country information was gathered for all EU-27 countries, except the smallest countries Cyprus, Estonia, Latvia, Luxembourg and Malta, and Lithuania due to absence of data.

Lessons learnt from Covid-19

The onset of the Covid-19 pandemic was a wake-up call to the world demonstrating painfully the threats infectious diseases can pose to our populations as well as the effects they can have on our economies (8). We still tend to underestimate the catastrophic impact spreading infectious diseases can have when health systems are not prepared, with vulnerable populations being hit hardest (9). We learned that the development and wide-spread use of rapid diagnostic tests is possible. And that efforts to contain the spread of transmissible diseases are important yet not sufficient; they need to be complemented by available and accessible treatments (10). Therefore, as shown by the World Bank, putting resources into fighting AMR now is one of the highest-yield investments countries can make for future generations: it is estimated that every Euro invested in fighting AMR will generate a saving of in between EUR 1,31 to EUR 1,47 within a year (11).

The human cost of the looming antibiotic resistance crisis

AMR is a problem in the here and now. Globally, an estimated 4.95 million deaths were associated with antimicrobial-resistant bacterial infections and 1.27 million deaths were directly attributable to such infections (3). Should we miss to address AMR effectively, within one generation we will witness a continuous rise in resistance leading to 10 million people dying every year by 2050 (12). The impact on people's quality of life, measured through disability-adjusted life years (DALYs) will be even larger.

"In 2019, more than 1.2 million people worldwide – the population of a city like Brussels – died as a result of antibiotic-resistant bacterial infections."

- Commissioner Kyriakides to the high-level One Health Ministerial Conference on Antimicrobial Resistance (13)

Antibiotic resistance already represents a major public health threat and will increasingly damage population health, similar to what happened when covid-19 spread across the world prior to vaccine availability.

Healthcare budgets under strain

We will not only face rising mortality and morbidity, but our economies will also suffer (14). It is forecasted that if AMR is not addressed, healthcare expenditures in 2050 would increase by 6% in high-income countries, 15% in middle-income countries and 25% in low-income countries (11, 15). Beyond the healthcare budgets, a continued rise in resistance by 2050 would affect our economies by 2% to 3.5% of Gross Domestic Product (GDP) (12). Additional taxes and higher social health contributions might be a way out although difficult to put on the shoulders of an already quickly ageing population and associated reduced workforce (11).

If not appropriately addressed, healthcare expenditures will skyrocket and economies will suffer. The biggest challenge for the global and European community is to bring back momentum and to reprioritise AMR as a key health, security and economic threat.

A decade of international policy initiatives

Since evidence shows that AMR in general and antibiotic resistance in particular represents a major economic and security threat, have European policymakers adequately addressed the issue?

Antibiotic resistance has been acknowledged as a global and European threat for the last decade (see Figure 2) and globally, strategic directions have been set to anticipate the outbreak of a pandemic (18), with various European and global initiatives addressing these priorities (see Figure 3). Among them is the EU AMR One-Health Network which provides members with a platform to share national strategies, action plans and best practices aiming to discuss policy options (16).

Figure 2

A decade of international policy initiatives to address AMR (11, 16, 17)

Sources: Colson et al, 2021, Wellcome, 2020; World Bank, 2017; European Commission, 2022; ICF, 2022; G7 Germany, 2022.

[1]One of only four occasions on which a health issue has been addressed in this forum. [2]HERA will have a role in addressing vulnerabilities and strategic dependencies related to the development, production, procurement, stockpiling and distribution of medical countermeasures relevant to AMR. [3]This EU4Health budget represents a more than 10-fold increase compared to 2021.

Abbreviations: AMR: Antimicrobial resistance; EC: European Commission; EU: European Union; FAO: Food and Agriculture Organization; MS: Member State; OIE: World Organization for Animal Health; R&D: Research & Development; UN: United Nations; WHO: World Health Organization.

Figure 3
Global strategic pillars and selected initiatives to fight AMR (15,20)

FOCUS OF THIS REPORT

Improve awareness and understanding of AMR

Awareness of AMR and promotion of behavioral change is needed, through public communication programs that target different audiences in human health, animal health, agricultural practice and consumers.

WORLD ANTIMICROBIAL AWARENESS WEEK

EUROPEAN ANTIBIOTIC AWARENESS DAY

AMR PATIENT GROUP

Strengthen knowledge through surveillance and research

AMR surveillance of resistance rates and antimicrobial use (human/ animal/ agriculture), as well as international information sharing are key AMR containment measures.

EARS-Net

GLASS Global Antimicrobial Resistance and Use Surveillance System

Reduce the incidence of infections

Many of the most serious and difficult-to-treat resistant infections occur in health care facilities. Better hygiene and infection prevention measures are essential to limit the development and spread of multi-drug resistant bacteria.

ICARS INTERNATIONAL CENTRE FOR ANTIMICROBIAL RESISTANCE SOLUTIONS

Prolong the efficacy of existing antimicrobials

Over-prescription and easy access (e.g., sales over-the-counter/via the Internet) speed-up AMR. Antimicrobial stewardship, i.e. the prevention of excessive and inappropriate use of antimicrobials in animal and human healthcare is key.

ESAC-Net

Promote the development of novel antibiotics

Antimicrobial stewardship can have the unintended effect of reducing investment in new antibiotics. New pricing and reimbursement systems are needed to develop the economic case for sustainable R&D investment.

AMR ACTION FUND

CARB-X Combating Antibiotic-Resistant Bacteria

GARDP Global Antibiotic Research & Development Partnership

ND4BB

REVIVE Advancing Antimicrobial R&D

repair

GLOBAL AMR R&D HUB

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

jpiamr Joint Programming Initiative on Antimicrobial Resistance

MEPs fight AMR
MEP Interest Group on Antimicrobial Resistance

EU-JAMRAI Joint Action Antimicrobial Resistance and Healthcare-Associated Infections

One HEALTH EJP

Sources: WHO, 2015

The first three pillars identified to contain AMR are to improve public awareness and understanding of AMR, secondly to strengthen knowledge and data through surveillance and research, and thirdly to reduce the incidence of infections. The fourth strategic pillar is to preserve antibiotic agents and prevent overuse through stewardship programs to ensure appropriate use. This leads to a low demand with the unintended effect that investments in novel antibiotics are hampered (see next chapter).

Therefore, the European Commission, the G7, WHO and other stakeholders have recognised the need to promote the development of novel antibiotics (the fifth pillar), through continued push- and new pull mechanisms to create a sustainable economic model for the development of novel antibiotics.

"Make the economic case for investment, through new market models for investment and access."

- WHO Global Action Plan on Antimicrobial Resistance, adopted by the World Health Assembly, 2015 (18)

"Development of novel antimicrobials or alternatives is a prime example of unmet medical need, given the lack of therapeutic options to address AMR... Current incentive models do not provide a sustainable solution; new business approaches are required, including new incentives to develop antimicrobials as well as new pricing systems."

- European Commission Pharmaceutical Strategy for Europe, 2020 (19)

"We will continue to ... incentivise the development of new antimicrobial treatments with a particular emphasis on pull incentives"

G7 Leaders' Communiqué, 2022 (20)

A number of initiatives address the fifth pillar in promoting the development of novel antibiotics:

- The *AMR Action Fund* will bridge innovative drug candidates in the pipeline through the most challenging later stages of development, ultimately providing governments time to make the necessary policy reforms to enable a sustainable antibiotic pipeline (21).
- *CARB-X* supports the early development pipeline of new antibiotics, vaccines and other products to combat the most dangerous drug-resistant bacteria (22).
- *GARDP* - the Global Antibiotic Research and Development Partnership created by WHO and the Drugs for Neglected Diseases initiative – aims to accelerate the development of new antibiotics to improve the treatment for drug-resistant infections (23).
- The *REVIVE* platform of *GARDP* connects and supports the antimicrobial discovery, research, and development community (24).
- The *REPAIR* (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund will invest in companies involved in discovering and early-stage development of therapies targeting resistant microorganisms (25).
- The IMI programme, *New Drugs 4 Bad Bugs* comprises of eight projects in partnership between industry, academia and biotech organisations to find solutions to the scientific, regulatory and business challenges that are hampering the development of new antibiotics (26).
- The *Global AMR R&D Hub* is a global knowledge centre for AMR research and development (27).

These initiatives mainly support R&D of novel antibiotics, but with commercial challenges being a top reason for antibacterial agents to drop out of the pipeline in late-stage clinical development, we continue to see manufacturers of new approved antibotics struggle to remain commercially viable, with some filing for bankrupcy (28–32). Without an effective and sustainable market enabled by pull mechanisms, the antibiotics pipeline will remain inadequate to bring novel antibiotics to patients who need them. This is explained in more detail in the next chapters.

Various initiatives are seeking to increase R&D by push incentives. But without an effective national market - enabled by pull incentives - there will not be enough new antibiotics.

Key barriers in bringing novel antibiotics to patients

Push mechanisms help support the clinical development of novel antibiotics, especially during the early development period referred to as the “valley of the death”, whereas pull mechanisms aim to reach a sustainable economic model that ensures patient acces to novel antibiotics, now and in the future.

For pharmaceutical companies, the pathway from the discovery and development of new antibiotics until they reach the patients, that is from bench to bed, is lengthy, complex, risky and expensive (42). It can take anywhere from 10 to 20.5 years during which just 1 in 15 antibiotics will ultimately be approved and reach patients (33). During this journey, companies must pass four important stages (see Figure 4).

During the first stage of research and development, push mechanisms can help support the clinical development process of novel antibiotics, especially during the early development period referred to as the “valley of death”.

Pull mechanisms can be provided at European level at the moment of marketing authorisation: to stimulate the development of new orphan medicines for treatment of rare disease for example, the European Commisison ensures market exclusivity for a period of 10 years. Such a European pull mechanism does not exist for novel antibiotics, although various proposals are currently being discussed. These include a Transferable Exclusivity Extension (TEE) and multinational purchasing based on (partially) delinking volume and financial return (34–36).

Both push and pull mechanisms are crucial to overcoming early- and late-stage development challenges and bringing novel antibiotics to patients.

However, in order to ensure sustainable patient access after marketing authorisation, additional mechanisms are needed. It is now up to the policymakers in the individual European countries to introduce national policies to improve access and ensure that existing and pipeline products have clear and feasible progression pathways to European patients who need them (37).

“... countries are uncertain which incentive is appropriate for their country, how to implement an incentive, and how much it will cost.”

- EU-JAMRI and Global AMR R&D Hub, Incentivizing antibiotic access and innovation, 2020 (38)

This requires optimal approaches to value assessment, pricing, reimbursement, and procurement can improve patient access to novel drugs and ensure a sustainable revenue to invest in new antibiotics (8).

For all that, national pricing, reimbursement, and procurement systems vary. So, which mechanism can work to provide patients with timely access to novel antibiotics?

Let’s look in more detail at the main barriers countries encounter following the marketing authorisation of novel antibiotics in Europe and the solutions several countries have implemented through national pricing and reimbursement policies.

Figure 4
Four important stages to bring novel antibiotics to patients

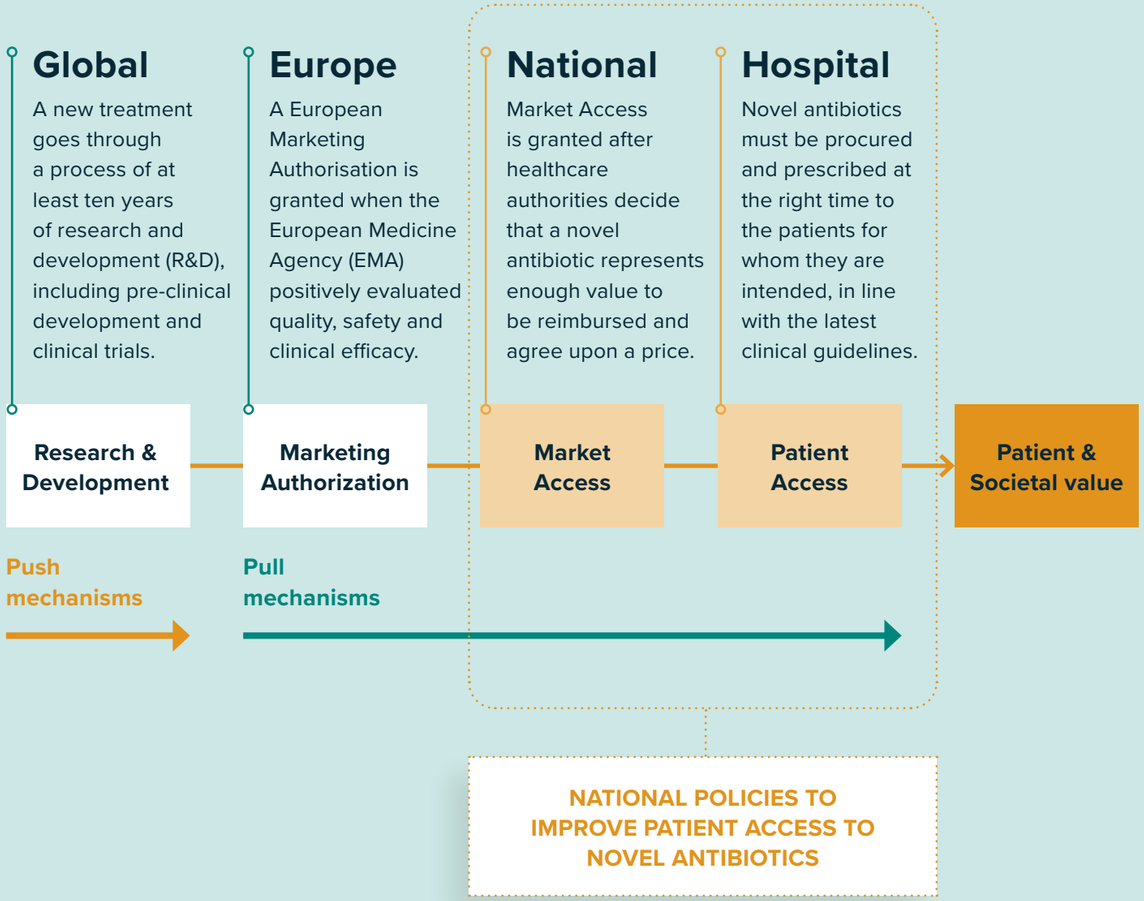
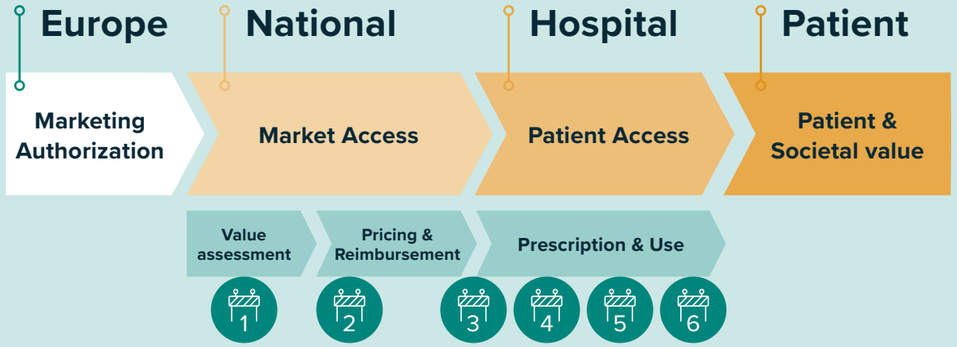


Figure 5
Six national barriers for hampering sustainable patient access to novel antibiotics



1. Standard value assessment methods not capturing the value of novel antibiotics
2. Financial return linked to volume used
3. Restrictions in reimbursement criteria, hospital protocols or formularies
4. Cost-driven procurement models
5. Insufficient hospital funding
6. Suboptimal susceptibility testing

First barrier

Standard value assessment methods not capturing the value of novel antibiotics

Standard value assessment frameworks do not capture the full value of novel antibiotics targeting multi-resistant pathogens (38). This is caused by two key factors.

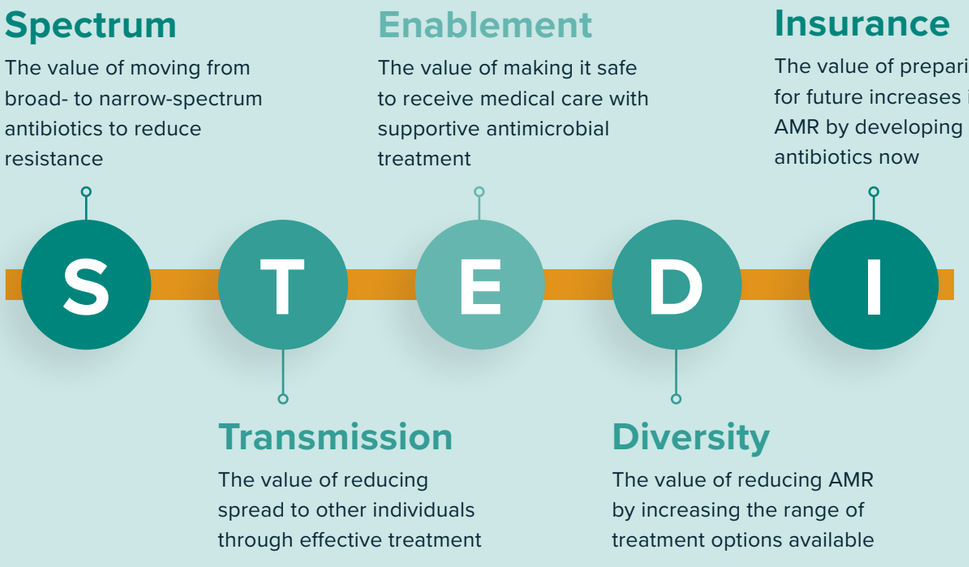
First, antibiotics are typically approved based on non-inferiority trials. This study design is mainly applied because of ethical concerns related to making a comparison against an antibiotic which is known to be ineffective, to demonstrate superiority (39). Consequently, the monetary value is anchored at the level of existing, often generic, therapies.

Secondly, the societal impact of preventing transmission of infections is not being considered in traditional assessments of costs and gains per patient (see Figure 6).[c]

[c]*Furthermore, in some countries the standard HTA process dictates to await pricing and reimbursement (P&R) decisions in a set of other countries, which poses serious barriers in the case of novel antibiotics due to absence, delays and/or negative outcomes of national P&R decisions for novel antibiotics.*

Figure 6

The five value dimensions not captured in traditional value assessment frameworks (40)



Second barrier

Financial return linked to volume used

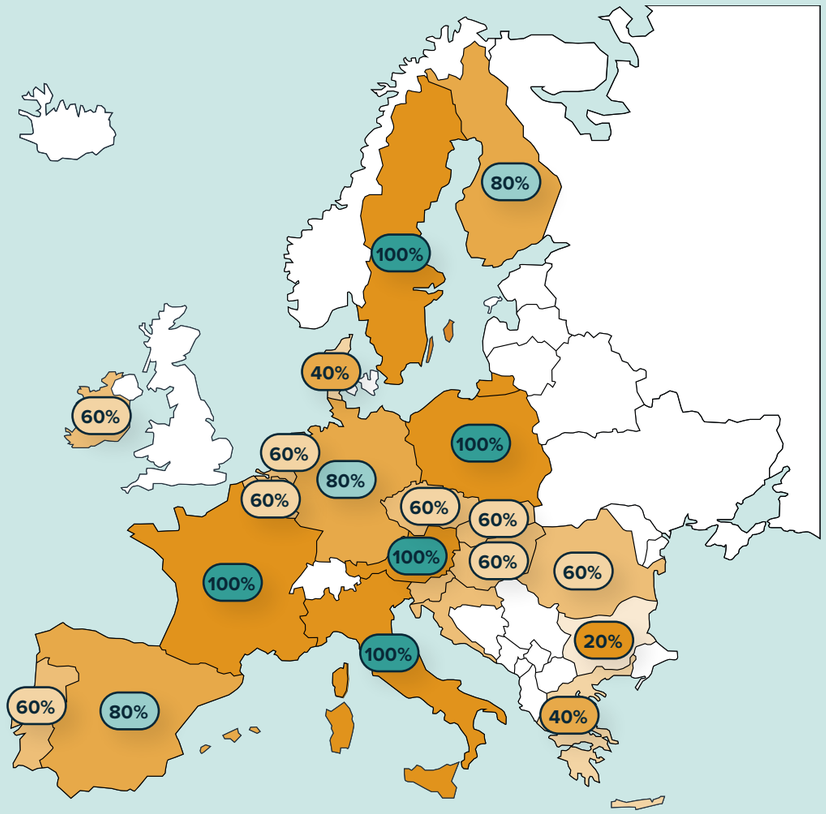
Developing novel antibiotics is a long, complex and risky process (41), particularly for those targeting Gram-negative bacterial infections. But, despite the huge societal costs of AMR, there is limited demand for new antibiotics once they are approved (42).

Like with orphan medicinal products, the low demand volume for novel antibiotics, in combination with a system in which return on investment is driven by volumes used, is a key reason why the current economic model fails for novel antibiotics. In the case of novel antibiotics, the low demand value is due to practitioners rightfully preventing overuse in order to preserve their effectiveness (43). Furthermore, antibiotics are prescribed for a short duration - mostly for just days or weeks - unlike medicines for chronic conditions.

As a consequence of low prices (first barrier) and financial return being linked to volume used (second barrier), small manufacturers of novel antibiotics go bankrupt and large pharmaceutical companies drop out of R&D for novel antibiotics (8,28,32). Or, the investments of making novel antibiotics in a country may not outweigh the costs, leading to unavailability in some countries (see Figure 7).

Not having a viable market for new antibiotics once they are approved, may cause manufacturers not to launch in some countries as investments of making novel antibiotics available may not outweigh the costs.

Figure 7
Availability of novel antibiotics in the European Union



Source: Vintura analysis based on launch status for a group of 5 novel antibiotics (See Annex I, Table 3 for more details).

Third barrier

Access restrictions in reimbursement criteria, hospital protocols or formularies

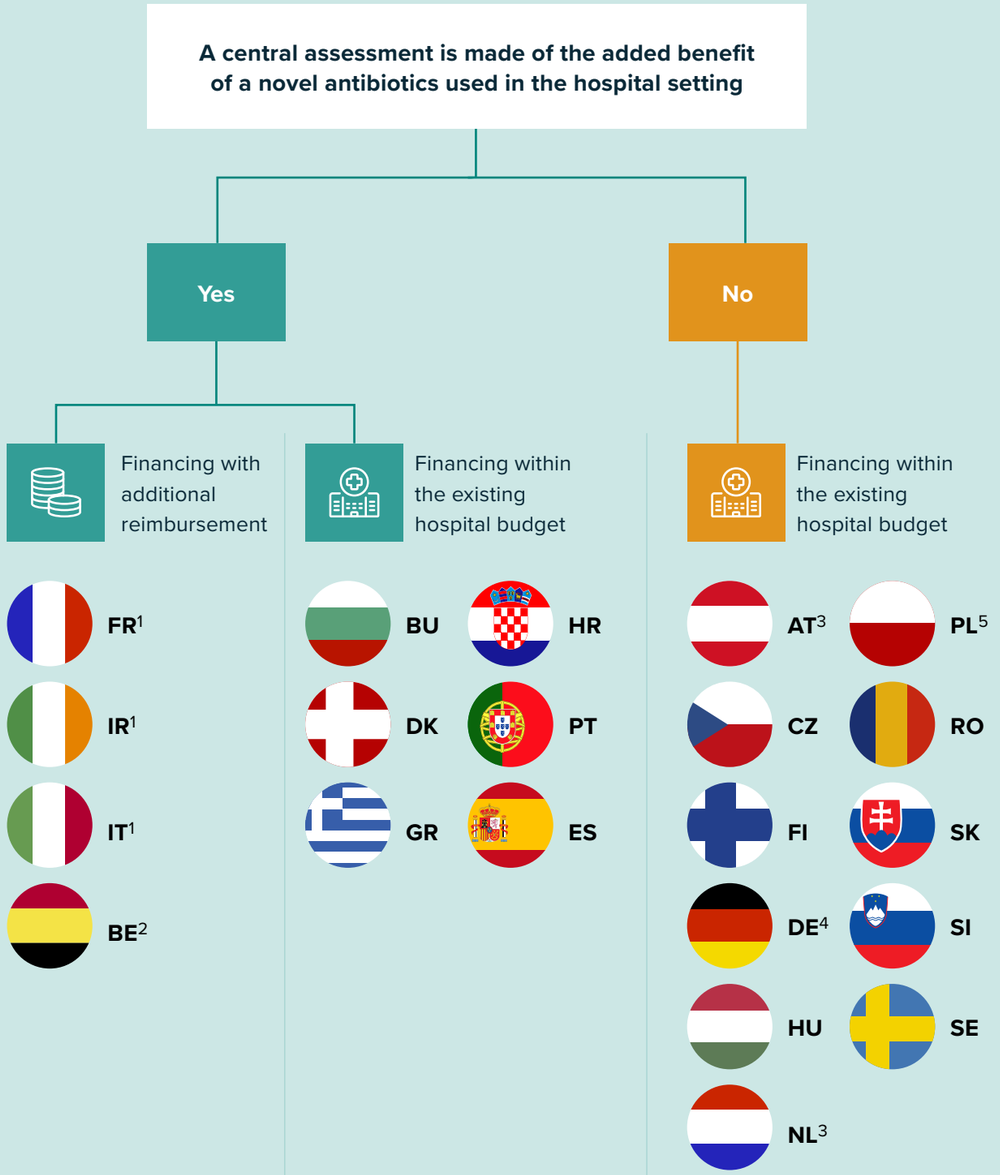
In the context of antimicrobial stewardship, a critical pillar in fighting antibiotic resistance, novel antibiotics are to be used for specific patients only. But in some cases, eligibility criteria for reimbursement, or hospital protocols or formularies may be constrained to too narrowly circumscribed conditions. For example, reimbursement criteria or a hospital formulary may require a non-response to traditional antibiotics or administrative approval first, before a novel antibiotic is reimbursed or can be prescribed. While this represents good antibiotic stewardship in most cases, in special cases of critically ill patients at risk of (Gram-) resistance such a criterium might hamper the application of the latest professional standards and clinical guidelines on empiric treatment. Similarly, diagnostic test may not be reimbursed or included in hospital protocols, or only in specific circumstances after prescribers have substantiated their use (43). As a result, patient access is restricted, not allowing eligible patients to receive the right treatment at the right time.

Fourth barrier

Cost-driven procurement models

In most European countries, procurement of antibiotics is done by the hospital, a group of hospitals, or at the regional level. In these public procurement processes, tenders are a common procurement tool to reward the lowest-priced bid, rather than the bid offering the highest value. This allows for procuring a maximum volume of antibiotics without exceeding the maximum budget. In this model, novel antibiotics are not always procured in sufficient amounts next to broad-spectrum generic antibiotics, as purchasers may be reluctant to pay for higher priced innovative antibiotics, when older, inexpensive, generic and broad-acting antibiotics are available. This hampers availability of the right treatment at the right moment for the right patient (43,45).

Figure 8
Routes of reimbursement of novel antibiotics in European countries



Source: Vintura analysis (see Annexes for details)

[1]Not granted to all novel antibiotics. In Ireland, hospitals can finance within the existing hospital budget in case of a negative reimbursement decision. [2]The additional reimbursement covers only 25% of the costs. [3]The central route is an option, but most often not applied in practice. [4]Novel antibiotics are exempted from a national value assessment. [5]The central route is possible, but not applied in practice. Financing is done within the existing hospital budget, with the possibility of additional reimbursement on a case-by-case basis.

Fifth barrier

Insufficient hospital funding

In most European countries, novel antibiotics are expected to be financed from the existing flat-rate hospital budget (see Figure 8). These budgets, often composed of fixed reimbursement tariffs for a group of services related to a specific diagnosis (a diagnosis-related group, DRG), are not always updated to reflect the cost of latest standard clinical practice. Compared to common, generic – and therefore cheaper – antibiotics, the prescription of novel antibiotics effectively results in higher costs for the hospital, which must settle these costs from the flat-rate (DRG) budget, thereby causing a financial burden to the hospital each time a novel antibiotic is prescribed, which may hamper unconstraint prescription of the right treatment at the right moment for the right patient (46).

Sixth barrier

Suboptimal susceptibility testing

In hospitals, with general practitioners and in outpatient settings, antibiotic susceptibility testing (AST) is used to detect highly resistant strains of bacteria and identify the best targeted therapies in line with good antibiotic stewardship. However, these tests take long to generate results (often 48-72 hours), and may not include the latest antibiotics, contributing to poor adoption and limited use. This adds an additional barrier to timely patient access to novel antibiotics (47).

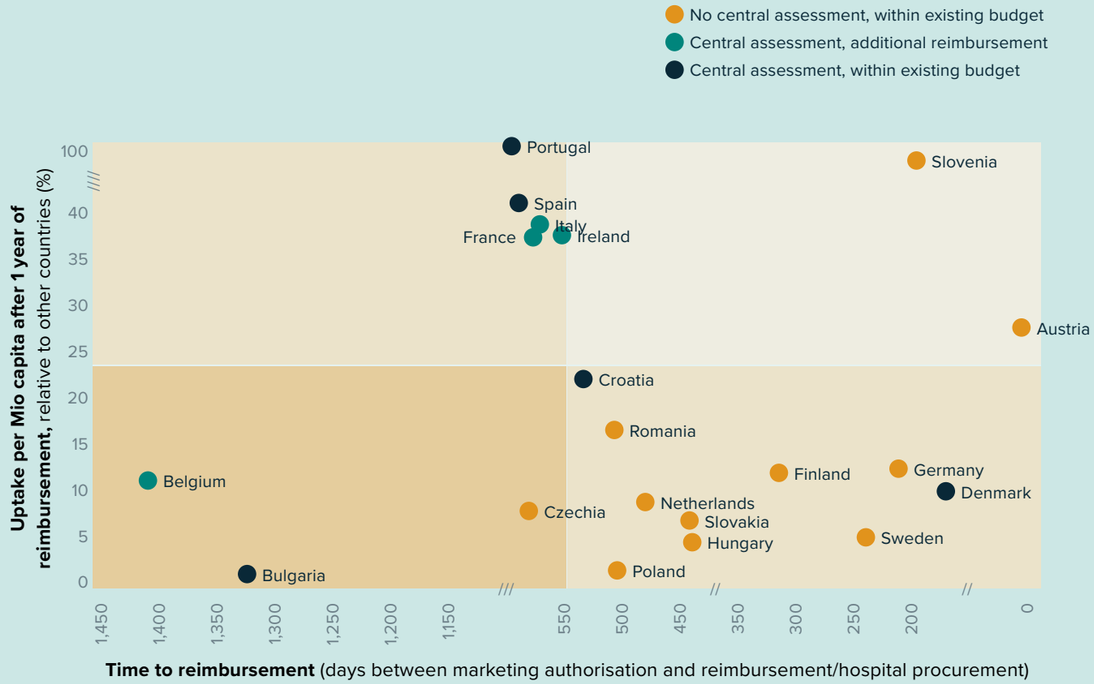
The nature of the barriers may differ per country, depending on how value assessment, pricing, reimbursement, and procurement of novel antibiotics are organised.

The six barriers have a varying impact on patient access to novel antibiotics per country. The days in between marketing authorisation and reimbursement differ, from Denmark where it takes less than 100 days to get a reimbursement decision to Belgium where more than 1,350 days are needed. In terms of uptake of novel antibiotics per 1 million patients after one year of reimbursement, Ireland and France are leading followed by Italy, with Bulgaria and Poland being the last adopters (see Figure 9).

The impact of access barriers may vary, in terms of reimbursement timelines and uptake levels after one year of reimbursement.

Figure 9

Reimbursement timelines and uptake levels after one year of reimbursement of novel antibiotics in European countries (Source: Vintura analysis, see Annex I for more details).



Source: Vintura analysis based on launch status for a group of 5 novel antibiotics (see Annexes for more details).

NOTES: This analysis is based on data for imipenem/cilastatin/relebactam, ceftazidime/avibactam and ceftolozan/tazobactam in countries where these novel antibiotics are reimbursed and purchased. Availability of cefiderocol and meropenem/vaborbactam was too limited to allow for country benchmarking (see Annex I for more details on sources and methodology). As uptake of novel antibiotics per capita is driven by many factors, these results should be used with caution and should serve as a basis for further exploration of causes of uptake delays.

National policies and inspiring practices

A range of national pricing and reimbursement policies to improve access to novel antibiotics have been developed in a number of European countries.

What would be viable solutions to the manifold access barriers? Over the past years, countries like the United Kingdom, Sweden, France, Germany, Czech Republic and Slovenia have implemented a range of policies which are worth to be considered by national policy makers. Together, these initiatives aim to address all the six barriers to sustainable patient access to therapeutic innovation against antibiotic resistance (see Figure 10).

These mechanisms consist of new value assessment methods or value assessment exceptions; new reimbursement models or price anchoring exemptions; a budget carve-out or add-on for the hospitals; and strong clinical guidance. They are described in more detail in Figure 11.

Figure 10
How to tackle the key national barriers hampering patient access to novel antibiotics

Key barriers in bringing novel antibiotics to patients

National policies to consider

	Standard value assessment methods not capturing the value of novel antibiotics	Financial return linked to volume used	Restrictions in reimburse-ment criteria, hospital protocols or formularies	Cost-driven procurement models	Insufficient hospital funding	Suboptimal susceptibility testing
New value assessment method	✓					
New reimbursement model		✓				
Value assessment exception	✓					
Price anchoring exemption	✓					
Hospital budget carve-out or add-on				✓	✓	
Strong clinical guidance			✓	✓		✓

Innovative interventions address the two root causes of all six patient access barriers.

Corrective interventions compensate for the consequences of standard value assessment methods not capturing the value of novel antibiotics and the lack of a sustainable economic model.

Figure 11
National policies to foster access to therapeutic innovation against antibiotic resistance

New value assesment method

New HTA methods are needed to capture the value of (1) moving from broad- to narrow-spectrum antibiotics to reduce resistance; (2) reducing spread to other individuals through effective treatment; (3) making it safe to receive medical care; (4) reducing resistance by increasing the range of treatment options available; and (5) preparing for future increases in the prevalence of resistant infections by developing new antimicrobial agents now.

New reimbursement model

New, central financing and procurement models in which volumes used are delinked from commercial returns for pharmaceutical companies ('financial delinkage' or 'subscription' models) offer the double benefit of ensuring a minimum guaranteed annual revenue enabling manufacturers to launch and not withdraw, whilst not incentivizing use (being consistent with good stewardship). When applied by a critical mass of countries, it also incentivizes longer term R&D of novel antibiotics.

Value assessment exception

An alternative to developing a new HTA method is to introduce an automatic exemption of the central value assessment. A solution which is already used for orphan medicinal products in some European countries. Novel antibiotics meeting certain criteria automatically qualify as having therapeutic added value. Because of this status, prices are not automatically anchored to prices of other antibiotics (often generics) and/or prices in other countries.

Price anchoring exemption

An alternative to introducing an HTA exemption, is to introduce an exemption from automatic price anchoring based on internal and/or international reference pricing. This provides a safeguard in situations where the standard HTA frameworks undervalue novel antibiotics, leading to price-setting based on prices of broad-spectrum generic antibiotics.

Hospital budget carve-out or add-on

A separate fund can take the costs of novel reserve antibiotics out of the DRG budget: a "DRG carve-out". Alternatively, extra reimbursement is provided on top of the standard DRG tariff when a novel antibiotic is prescribed: a "DRG add-on". Both mechanisms ensure reimbursement of the higher costs of hospitals for prescribing novel antibiotics within their flat-rate DRG tariff, in case a patient requires a novel antibiotic to treat a resistant infection.

Strong clinical guidance

AMR patients have a wide variety of underlying diseases. Consequently, they are often not well-represented in national patient organizations. Instead, microbiologists and infectious disease specialists have a crucial role in (1) ensuring alignment of national reimbursement criteria or hospital formularies and protocols with the latest clinical guidance, (2) highlighting the importance of optimal testing and access to tests, and (3) inclusion of novel antibiotics in hospital formularies, to ensure the right treatment to the right patient at the right time, taking into account international guidelines and the local AMR situation.

Innovative interventions

Corrective interventions

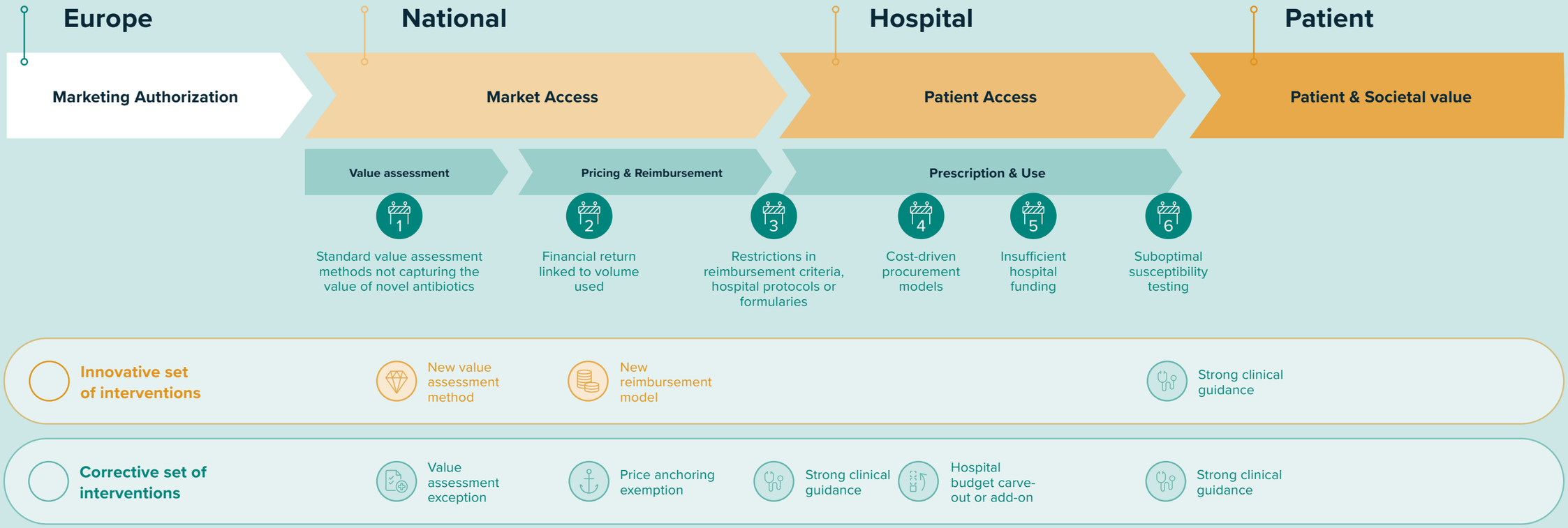
Sources: Colson et al., 2021; Gotham et al., 2021.

Depending on the barriers countries face policy makers will find certain policies more relevant than others. Some of them are innovative such as new value assessment methods and new reimbursement models, while others are corrective in the sense that they provide exceptions and exemptions to standard decision-making related to value assessment, pricing, reimbursement, procurement, and prescription. Regardless of the chosen approach (innovative or corrective), a set of interventions is needed to improve sustainable and appropriate access to novel antibiotics (see Figure 12).

To illustrate the different options policy makers have to improve national access to antibiotics, in the following paragraphs a number of practices are described. Countries may choose to learn from these case examples and adapt them to their national context.

Regardless of the chosen approach (innovative or corrective), a comprehensive set of interventions is needed to ensure an effective national response to facilitate access to novel antibiotics.

Figure 12
Innovative and corrective sets of interventions to improve sustainable and appropriate patient access to novel antibiotics



United Kingdom

A new value assessment framework and subscription payment model

New value assessment methods New reimbursement models

British health technology assessment (HTA) frameworks have long been seeing treatments from a perspective of noncommunicable diseases considering their accrued benefits to an individual patient. This thinking has missed the long-term threat of antibiotic resistance to society and in particular to the sustainability of our health systems. At the same time, pharmaceutical companies are paid for sales volumes of antibiotics which is opposite to good stewardship.

Acknowledging this dilemma, the United Kingdom developed a long-term vision regarding AMR which was complemented by a 5-year national action plan. It described how investing in new antibiotics is commercially unattractive: R&D costs are high, while restrictions put in place to reduce resistance make it difficult for companies to receive a return on their investment (48,49). As a way out, firstly a new HTA framework to capture the full value of novel antibiotics (based on the STEDI principles, see Figure 6) was developed (40,50). Secondly, a new payment model was set up by NHS England and NHS Improvement as a pilot project where companies are reimbursed primarily based on the value of the novel antibiotics to the national health system as opposed to the volumes sold. For the selection of accepted antibiotics, points are awarded based on proven efficacy against the pathogens classified in the WHO Priority Pathogen List (51) as “Priority 1 – 3” with higher points being assigned for efficacy against higher priority pathogens and for indications with a higher unmet need. This “subscription payment model” is accompanied by a cap on the maximum costs per year and criteria related to minimum stock holding.

An innovative and comprehensive set of interventions:

A new value assessment method combined with a new payment model for antibiotics in the United Kingdom

Initial problem

The broad impact of antibiotics is not captured within current HTA systems, which focus on benefits for individual patients. In addition, manufacturers are paid for antibiotics based on the volume sold, which is not consistent with good stewardship. Together, these features lead to a non-sustainable economic model for ensuring patient access to novel antibiotics.

Timelines

- **2015**: Agreement on need for an innovative payment model
- **2017**: EEPRU starts with proposal for value assessment approach (50)
- **2018**: ABPI proposes a subscription model plus HTA reforms
- **2020**: Proposal finalized, tender launched, 2 antibiotics selected
- **2021**: Value assessments based on the new HTA framework conducted for the 2 pilot products
- **2022**: Value assessments outcomes are expected to inform commercial discussions and result in payment model implementation (annual fixed payments) from 2022 onwards (17,52). Discussions are ongoing as to how the model could be applied to potentially more products in the future.

Success factors

A clear sense of urgency was voiced: “We are heading towards a world where antimicrobials no longer work (48).” At the same time, the new HTA evaluation framework and the innovative payment model covered both root causes of the market failure of novel antibiotics.

Impact

The interventions address the two key barriers hampering patient access to novel antibiotics in the UK, thereby significantly improving patient access to novel antibiotics. Should further countries adopt similar HTA valuation frameworks and payment models for novel antibiotics, the incentive for manufacturers of existing and new innovative antibiotics would significantly increase, leading to a more sustainable economic model in Europe.

Applicability elsewhere

All HTA agencies should consider broadening their methodological tool kit and approach to better support solutions addressing the long-term threat of antibiotic resistance . Similarly, all countries should consider novel payment models, since a critical mass of countries is needed for novel payment models to incentivise the R&D of novel antibiotics and a coordinated multi-country procurement approach may not be feasible on the short term (53). Key aspects for further development are related to the cap on maximum costs per year and the data to support the new valuation method.

Sweden

A new purchasing model to partially delink volume and financial return

New reimbursement models

Sweden is piloting a novel procurement and reimbursement model which aims to provide patients with access to novel antibiotics despite limited market opportunities for manfucturers. In this pilot the manufacturer is guaranteed a minimum annual revenue in exchange for timely availability of a certain volume of supply of a novel antibiotic (54).

As long as the regions don't purchase the agreed upon volume, Sweden compensates the manufacturer up to the level of the agreed upon revenue. In this way the pharmaceutical company's economic return is partly decoupled from the actual sales. The pilot study is open to all antibiotics that have proven efficacy against a pathogen in the 'Priority 1: Critical' group of the WHO Priority Pathogen List (51) and have an acceptable safety profile (55).

Partially delinking volume and economic return in Sweden:

Minimum annual revenue for selected originator antibacterials, in exchange for a guaranteed supply volume.

Initial problem

Highly selective use of antibiotics is one of the main pillars in Sweden's fight against AMR. Given the small population and price anchoring of new antibiotics at the level of generics, manufacturers did not launch novel antibiotics in Sweden, as investments for bringing these antibiotics to patients did not outweigh the costs.

Timelines

- **2018**: Government asked the Public Health Agency of Sweden (PHAS) to test a new reimbursement model
- **2020**: Open procurement call where companies are invited to voluntarily submit candidate medicines for the pilot
- Pilot evaluation after 3 years

Success factors

AMR has been high on Sweden's public health agenda for a long time. For more than 5 years industry, government and academia have collaborated on a dedicated platform where they discussed alternative reimbursement models. The follow-up by academics ensured value and credibility (58).

Impact

This initiative represents an innovative approach to stimulate launch and prevent withdrawal in Sweden. More companies are likely to be brought on board when complemented with a value assessment model that better captures the value of novel antibiotics. To maximize the impact of this initiative, it should be complemented by a value assessment that rewards the full value of novel antibiotics.

Applicability elsewhere

Other European countries which struggle with the launch, availability of stock, or withdrawal of new antibiotics because of a limited market size should consider Sweden's approach for their own population.

France

An exception from value assessment, an exemption from price anchoring and a budget carve-out for hospitals

Value assessment exception

Price anchoring exemption

Hospital budget carve-out or add-on

In the French HTA system, medicines are classified according to their added therapeutic value, from level I (major), via level II (important), level III (moderate), level IV (minor) to level V (non-existent). Medicines with added therapeutic value I to III benefit from a guaranteed price which cannot be lower than the lowest price across four reference countries, namely UK, Germany, Italy and Spain. For medicines at a therapeutic level IV or V, prices should be equal or lower than the one of existing therapies. To reimburse hospitals, the French health system uses a DRG based system, where each DRG describes a type of condition or hospital admission. High-cost medicines with added therapeutic value I to IV are eligible for inclusion in a 'DRG carve-out' list (*liste en sus*) and can be reimbursed separately. Medicines including antibiotics may be added to the list under the condition that they are mainly being used for inpatients, that the medicine has an added therapeutic value IV, and that the costs exceed 30 % of the relevant DRG tariff (55).

As an exception, novel antibiotics can receive an added value level IV (minor) despite a non-inferiority trial. Additionally, last resort antibiotics can receive an added value level III (moderate) based on in vitro and microbiologic data. Lastly, the 2020 Innovative Medicine Action Plan allows for re-evaluation of innovative medicines based on real-world evidence (56). This has been applied to a novel antibiotic, leading to an added value level III (57).

Since 2015, for these new antibiotics (and orphan medicines) which are evaluated at added value level IV (minor), another exception has been made in the sense that they benefit from a guaranteed minimum reference price similarly as level I to III medicines (59). The liste en sus includes a number of recently approved antibiotics.

A set of interventions to correct for unintended system effects:

An exception from standard value assessment allowing for a guaranteed minimum reference price and a budget carve-out for hospitals in France

Initial problem

The standard HTA framework used in France applies the criterion of 'substantial clinical improvement'. In these frameworks, the outcomes of a non-inferiority trial lead to anchoring the prices to the ones of existing therapies. In the case of novel antibiotics, this does not reflect the scarcity and value of novel antibiotics targeting multi-resistant pathogens.

In addition, French hospitals are financed via a DRG-system where antibiotics are often expected to be covered within the existing bundled payment for all costs of a given DRG. This suffices for generic antibiotics, yet effectively results in hospital financing when patients face antibiotic resistance and require novel antibiotics, as costs per patient increase without funding increasing accordingly.

Timelines

- **2004**: Activity-based financing reforms led to the creation of the "liste en sus": a list of high-cost drugs reimbursed outside the hospital budget.
- **2015**: The price referencing exemption for antimicorbials with ASMR IV entered into force.
- **2021**: Medicinal products with an ASMR IV are eligible for the "list en sus" as a rule, whereas this used to be an exception.

Success factors

These measures were implemented as part of a broader framework agreement between the French government represented by the Economic Committee of Health Products and the French pharmaceutical industry represented by its trade association (LEEM) (59).

Impact

The guarantee of a minimum reference price provides a safeguard for novel antibiotics where the evaluation process of reimbursement may be undervaluing an antibacterial based on the non-inferiority trials. Because the cost of novel antibiotics are taken out of the capped hospital budget, hospitals are no longer discouraged to use novel antibiotics for patients in need. However, a novel financing model to compensate for the low demand volume (due to good prescription practices) would be needed for a fully sustainable economic model.

Applicability elsewhere

Countries with an HTA system in which outcomes of non-inferiority trials and the criterion of 'substantial clinical improvement' would lead to anchoring the prices of novel antibiotics to the prices of generic antibiotics should consider a completely novel value assessment, or – like France – a corrective measure to guarantee a minimum reference price.

In addition, hospitals in European countries where novel antibiotics are expected to be covered within the existing DRG and have a relatively limited uptake would benefit from the DRG carve-out measure.

Germany

An exemption from standard value assessment and price anchoring

Value assessment exception

Price anchoring exemption

In Germany, since the Pharmaceuticals Market Reorganisation Act (AMNOG) of 2011, a one-year period of 'free pricing' of innovative medicines is in place upon their launch. Simultaneously, the German HTA agency (IQWiG) conducts a central value assessment (the 'early benefit assessment') of the additional benefit offered by a new therapy versus the standard of care. Subsequently, the Federal Joint Committee (G-BA, a central decision body in the German sickness fund system) communicates its findings on the additional benefit and the pricing procedure. Based on the benefit assessment, price negotiations with the central association of statutory health insurances follow.

In 2018 all medicines used in the hospital setting, including novel antibiotics, became subject to the early benefit assessment. However, several challenges became apparent. Given the non-inferiority clinical study designs for novel antibiotics, no added benefit is demonstrated compared to the standard of care. When the early benefit assessment finds 'no added benefit', the reimbursement price is anchored at the price of comparable existing medicines. For antibiotics, in most cases these would be generic medicines.

To address these challenges, in January 2021 the German Bundestag passed a new legislation, the so-called Fair Statutory Health Insurance Law (GKV-FKG), according to which novel ('reserve') antibiotics are exempted from the full scope of a regular benefit assessment and are automatically assumed to have added therapeutic benefit (similar to orphan drugs) in the HTA assessment. Price anchoring is then not applied. To be eligible for inclusion in the 'reserve list', a novel antibiotic must meet certain criteria – amongst others – to be active against multi-resistant bacteria and the number of alternative treatment options should be limited (43,54,60).

A correction of unintended system effects in Germany:

Additional benefit of novel antibiotics is automatically proven. Allowing for an exemption from price anchoring

Initial problem

Given non-inferiority clinical study designs, no evidence is available on the added benefit of novel antibiotics compared to the standard of care. Therefore, prices could not exceed the ones of standard of care (usually generic medicines).

Timelines

- **2018**: All drugs used in the hospital setting become subject to early benefit assessment, including novel antibiotics
- **March 2020**: Legislation providing for exemption of novel antibiotics from regular benefit assessment was published
- **December 2020**: Deadline for Robert Koch Institute (RKI) and Federal Institute for Drugs and Medical Devices (BfArM) to develop criteria for novel antibiotics
- **January 2021**: Legislation implemented; RKI criteria for reserve antibiotics apply

Success factors

German policy makers and the HTA agency have recognised the market failure of novel antibiotics and agreed to give them an orphan-like status.

Impact

Since the legislation was passed in 2021, 5 novel antibiotics have successfully been granted reserve antibiotic status, in October 2021 and January 2022 respectively (61,62). AMNOG assessments, benefit assessments and price negotiations of the these antibiotics are still ongoing. Free pricing will apply for one year after market entry for these antibiotics, after which point the post-AMNOG price will become effective. However, since the negotiated reimbursement amount is not applicable to the hospital sector, manufacturers need to negotiate with hospitals on a hospital-by-hospital basis, and hospitals have to cover the price of novel antibiotics within their existing budget. Improvements in hospital reimbursement are still needed to prevent that an important barrier to sustainable access still exists at the hospital level.

Applicability elsewhere

Countries with an HTA system in which outcomes of non-inferiority trials and the criterion of 'substantial clinical improvement' would lead to anchoring the prices of novel antibiotics to the prices of generic antibiotics should consider a completely novel value assessment, or put – like Germany – a corrective measures in place to guarantee a special status during value assessment.

Czech Republic

A budget add-on for hospitals

Hospital budget carve-out or add-on

In the Czech Republic, medicines used in the hospital setting do not go through a central HTA process. Hospitals decide on formulary inclusion and costs have to be covered from the DRG reimbursement system. In this system, patients are assigned a DRG based on their diagnosis. The hospital receives a fixed amount per DRG, regardless of actual costs ocurred. For specific hospital medicines including novel antibiotics, manufacturers can request a DRG add-on fee to the seven health care insurance companies operating in the Czech Republic. No specific criteria regarding the eligibility of medicines are defined; the decision on a DRG add-on fee for the hopistals is based on a cost comparison with other available antibiotics and the total budget impact for the health care.

Removing financial disincentives for hospitals:

A DRG add-on fee to avoid negative financial repercussions for hospitals in the Czech Republic

Initial problem

In the Czech Republic, hospital medicines are usually financed from a flat-rate budget. This is no problem in the case of cheap, generic antibiotics. However, it poses a financial disincentive for hospitals to prescribe novel antibiotics targeting resistant infections, as the additional costs must be covered within the fixed budget. This effectively leads to the financing of novel antibiotics by the hospital.

Timelines

The possiblity of an add-on fee is not formalized, but has been applied for quite some years.

Success factors

The seven Czech healthcare insurers jointly decide on DRG add-ons and discuss with pharmaceutical companies and their professional societies.

Impact

Once the budget add-on has been decided, novel antbiotics can be used more widely in hospitals, without negative financial repercussions. However, the agreed upon price is not based on a formal value assessment and not reflective of the actual value of the innovative antibiotic. Furthermore, the low demand is limiting the viability of the Czech Republic as a viable market for novel antibiotics.

Applicability elsewhere

Countries who do not have a central HTA system and where hospitals have to cover treatment costs within the scope of a DRG reimbursement system should consider this mechanism.

Slovenia

Strong clinical guidance to inform hospital procurement

Strong clinical guidance

Stakeholders in Slovenia recognised that AMR increasingly threatens the Slovenian healthcare system's ability to treat common infections. In response, a mandatory national AMR surveillance system has been implemented and an action plan to optimise the use of antibiotics has been set up. Mandatory antimicrobial stewardship programs have been implemented in each hospital. In the larger Slovenian hospitals, infectious disease specialists, supported by clinical microbiologists, ICU specialists and pharmacists, form an antimicrobial committee that recommends which antibiotics to put on the hospital's formulary for bacterial infections. Alternatively, smaller hospitals designate at least one dedicated person with additional training in antibiotics stewardship.

Strong clinical guidance in Slovenia:

Hospital formulary decisions are based on clinical advice from the infectious disease specialist.

Initial problem

The emergence and spread of drug-resistant pathogens has been leading to rising antimicrobial resistant infections among patients in Slovenia on one hand, and novel antibiotics were not always included in hospital formularies.

Timelines

- **2005**: establishment of the intersectorial mechanism
- **2011**: by-laws on antimicrobial consumption surveillance and responsible use of antibiotics
- **2013**: audits of antimicrobial stewardship programs

Success factors

The Slovenian Ministry of Health has prioritised AMR and put a mandatory national surveillance system and an AMR action plan in place. Stakeholders share resistance data and regularly follow up. Mandatory antimicrobial stewardship programs have been implemented in each hospital. Consequently, in Slovenian hospitals, clinical advice of infectious disease doctors determines formulary decisions.

Impact

Time to procurement in Slovenia is among the shortest in Europe (see Figure 9) and AMR rates have declined in recent years (see Figure 1); the country shows good susceptibility data and low resistance rates e.g. against Carpapenem for *E. coli*: 0%; *K. pneumoniae*: 0%; *P. aeruginosa*: 13.4 % (7). However, the agreed upon price for novel antibiotics is not based on a formal value assessment. The costs are to be borne by the hospital, leading to a price which is not reflective of the actual value of the innovative antibiotic.

Applicability elsewhere

Countries who do not have a central HTA system and where hospitals have to cover treatment costs within the scope of a DRG reimbursement system should consider this mechanism.

Policy recommendations for European countries

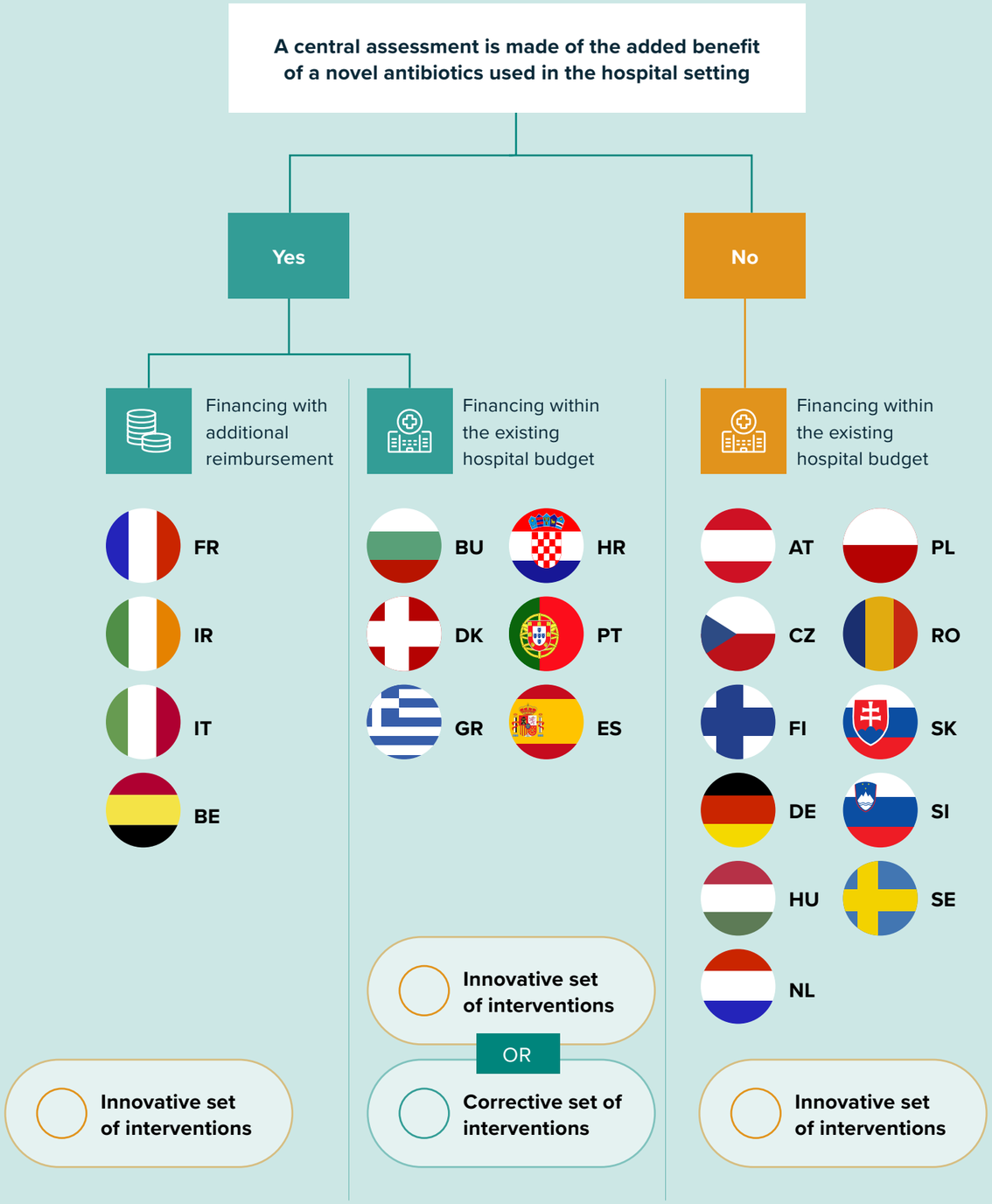
The barriers national healthcare systems face to provide patients with access to novel antibiotics differ. They are based on how the value assessment, pricing, reimbursement, and procurement of novel antibiotics are organised. Depending on whether countries currently have a central value assessment or not, they are recommended to consider an **innovative** and/or a **corrective** set of interventions (see Figure 13).

- Countries that already have a **central value assessment and additional reimbursement in place**, should consider broadening their methodological tool kit to better assess and finance solutions addressing the long-term threat of antibiotic resistance.

- Countries that have a **central value assessment without additional reimbursement** could take the same direction, or could consider going for 'quicker wins' by installing corrective interventions such as exemptions and add-ons.

- Countries that have **no central value assessment and no additional reimbursement** in place, should consider implementing the latest, innovative interventions straight away to avoid putting in place a suboptimal system.

Figure 13
The choice of innovative and/or corrective solutions based on whether a central value assessment is currently performed for novel antibiotics used in the hospital setting.



Source: Vintura analysis, see Annexes for more details

Based on the case examples from other countries, national authorities are recommended to take five steps in the process towards the implementation of national policies to improve patient access to novel antibiotics (see Figure 14). Implementing these mechanisms will require financial resources, but the costs will be modest compared to the problem we will face if AMR is not tackled (43).

First, providing patients with sustainable access to novel antibiotics should be prioritised on national AMR agendas. Only when doctors have novel antibiotics as a standard treatment option at their disposal, we will continue to be able to efficiently treat increasingly common antibiotic resistant infections.

Second, a special status should be designated to novel antibiotics, similarly to orphan drugs. This means recognising that the important societal value of novel antibiotics is not captured with existing value assessment frameworks and that the current market mechanisms fail to ensure sustainable patient access to novel antibiotics.

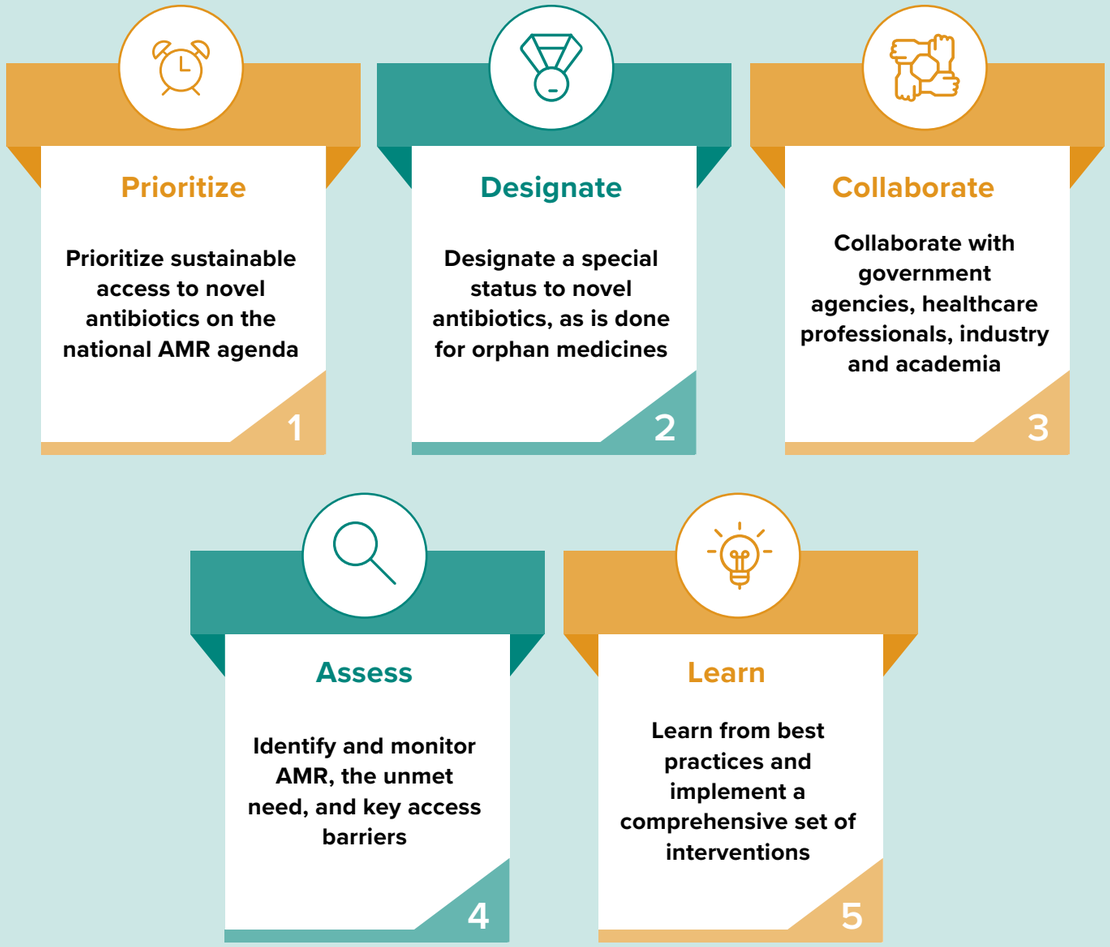
Third, government agencies, professional associations, industry and academia should work together in finding the right solution in their national context.

Fourth, stakeholders should jointly identify and continuously monitor the level of AMR, the level of access to novel antibitics, and the key barriers hampering access to the right treatment for the right patient at the right time, and address them accordingly.

Fifth, several countries have defined (a set of) policy mechanisms to improve sustainable access. Stakeholders can learn from these practices in order to design comprehensive sets of interventions which are tailored to their national context. The national pricing and reimbursement policies described in this report should serve this process.

This is an urgent call to decision-makers and stakeholders across Europe to introduce national mechanisms to ensure that patients get access to novel antibiotics when they need them, now and in the future.

Figure 14
Five main steps towards the implementation of national access mechanisms



Acknowledgements

We would like to thank Christine Årdal from the Norwegian Institute of Public Health, Maarten van der Heijden and Jonathan Rodrigues from WHO, Bengt Mattson from LIF Sweden, Jan Bungenstock from VFA Germany and Laura Cigolot (Belgium) for their availability for interviews and their valuable input.

Abbreviations

AML	Acute Myeloid Leukemia
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganisation Act), Germany
AMR	Antimicrobial resistance
AST	Antibiotic Susceptibility Testing
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte), Germany
COVID-19	Coronavirus Disease 2019
DALY	Disability-adjusted life years
DRG	Diagnosis-Related-Group
E. coli	Escherichia coli
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EU-JAMRAI	European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections
EUR	Euro
FAO	Food and Agriculture Organization of the United Nations
G7	Group of Seven (CA, FR, DE, IT, JP, UK, US)
G20	Group of Twenty
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee), Germany
GDP	Gross Domestic Product
GKV-FKG	Gesetzliche Krankenversicherung – Fairer-Kassenwettbewerb-Gesetz (Fair Statutory Health Insurance Law), Germany
HERA	European Health Emergency Preparedness and Response Authority

HTA	Health Technology Assessment
ICU	Intensive Care Unit
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen), Germany
LEEM	Les Entreprises du Médicament (Pharmaceutical Industry Association), France
OECD	Organisation for Economic Cooperation and Development
OIE	World Organisation for Animal Health
PHAS	Public Health Agency of Sweden
R&D	Research and Development
RKI	Robert Koch Institute
STEDI	Spectrum, Transmission, Enablement, Diversity, Insurance
TEE	Transferable Exclusivity Extension
WHO	World Health Organization

Country flags and abbreviations

AT	Austria	HU	Hungary
BE	Belgium	IE	Ireland
BU	Bulgaria	IT	Italy
CZ	Czech Republic	NL	Netherlands
DE	Germany	PL	Poland
DK	Denmark	PT	Portugal
ES	Spain	RO	Romania
FI	Finland	SE	Sweden
FR	France	SI	Slovenia
GR	Greece	SK	Slovakia
HR	Croatia		

Glossary

(Time to Patient) Access

Access refers to patients having access to the right therapies at the right time. For the purpose of this report, access is measured by:

- Market Access: the proportion of novel antibiotics that received a European marketing authorisation and are reimbursed in a country.
- Time to Market Access: the number of days elapsing from the date of EU marketing authorisation to the day of completion of administrative processes related to a positive reimbursement decision.
- Patient Access: the actual use in the first twelve months after the first patient is treated under a reimbursement scheme.

Reimbursement refers to a formal reimbursement scheme, thereby excluding early access schemes as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA procedure.

Antimicrobial resistance (AMR)

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat.

Cost-effectiveness

Cost-Effectiveness Analysis quantifies the gains, or regressions, in population health as a result of an innovative therapy against the cost of this therapy. The gains are typically measured in quality-adjusted life years (QALYs). Subsequently, the net costs of the therapy per QALY are quantified. It provides a method for prioritizing the allocation of resources to therapies, by identifying therapies that have the potential to yield the greatest improvement in health for the least resources.

Disability-adjusted life years (DALYs)

One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population.

European marketing authorisation

A European marketing authorisation is granted when the European Medicines Agency (EMA) has positively evaluated i) Quality: Is the quality of the manufacturing process up to standards? ii) Safety: Is the therapy safe? iii) Clinical efficacy: Is the therapy effective? This regional authorisation takes away the requirement to seek marketing authorisation for new medicines from each Member State separately.

External Reference Pricing

The use of medicine price(s) in one or more other countries to serve as a benchmark or reference price for setting or negotiating the price of the product in a given country. List prices are used rather than the net transaction prices. The number of countries considered in the basket varies across countries (ranging from 3 to 30 countries), as does the frequency of price revisions. External Reference Pricing is used in Europe, but European countries are also referenced by non-European countries. Also referred to as International Reference Pricing.

Gross Domestic Product (GDP)

GDP measures the monetary value of final goods and services - that is, those that are bought by the final user - produced in a country in a given period of time (say a quarter or a year). It counts all output generated within the borders of a country.

Health Technology Assessment (HTA)

A multidisciplinary process that assesses and appraises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. It informs the final reimbursement decision.

Medical need (unmet medical need)

Chronically or seriously debilitating diseases or diseases considered to be life threatening and that cannot be treated satisfactorily by an existing (approved and reimbursed) pharmaceutical product are considered and area of high (unmet) medical need.

Non-inferiority trials

Efficacy of a novel treatment is most convincingly established by demonstrating superiority to the current standard of care. However, the problem with novel antibitics targeting resistant infections, is that currently no effective standard of care exists. Therefore, clinical trials often use a non-inferiority design. In this case, researchers begin by testing novel antibiotics in patients infected with serious but susceptible bacteria in order to demonstrate that the novel therapy is essentially as safe and efficacious as more conventional treatments.

Novel antibiotics

Novel antibiotics are newly developed, on-patent antibiotics, which are effective against resistant or multi-resistant priority pathogens.

Pull mechanisms

Pull mechanisms reward the successful approval of a novel AMR medicine that meets unmet AMR needs and can provide a certain return on investment for early-stage AMR programs that is competitive with alternative areas of potential R&D investment. A pull incentive decouples return on investment from volume of sales, supporting appropriate use.

Push mechanisms

Push mechanisms help support the cost of clinical development, especially during the early period referred to as the “valley of death”: the phase between opportunity discovery and product development. During this period, a significant increase in investment is required, at a point in time where the risk of failure outweighs the chance of potential future return.

Reimbursement

European countries need to make evidence-based decisions on public healthcare expenditures. To inform reimbursement decisions for treatment using novel antibiotics, typical questions that need to be answered by national HTA bodies are:

- Medical need: Does this therapy address a health need?
- Relative clinical effectiveness: Is it more effective than current therapies?
- Cost-effectiveness: Is the price a good reflection of the added value?
- Budget impact: Could we afford the overall costs of this therapy?

This is done separately by each country. How countries make these decisions varies, leading to significant disparities in patient access throughout Europe.

Reimbursement criteria

Health Technology Assessment (HTA) should be an unbiased and transparent exercise. Therefore, predefined decision-making criteria are formulated to allow for rational, consistent and transparent reimbursement decisions based on e.g. (unmet) medical need, relative clinical effectiveness, cost-effectiveness, budget impact, societal value and ethical considerations.

Valley of death

Phase during R&D of an innovation between opportunity discovery and product development. During this period, a significant increase in investment is required, at a point in time where the risk of failure outweighs the chance of potential future return.

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Annex 1 Methodology

To illustrate patient access barriers, data analysis was performed on six priority pathogens out of the full lists of priority pathogens developed by WHO, ECDC and OECD (see Table 1 and Figure 1).

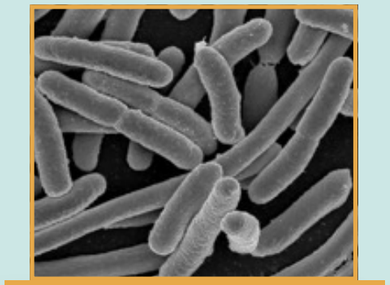
Pathogen	Included in AMR surveillance (WHO/ECDC 2022)	Leading pathogen for deaths attributable to / associated with resistance (Lancet 2022)	Leading cause of infections (EU, OECD, ECDC 2019)	List of priority pathogens (WHO 2020)	In scope of report analysis
Escherichia coli	Yes	Yes	Yes	Yes	Yes
Klebsiella pneumoniae	Yes	Yes	Yes	Yes	Yes
Pseudomonas aeruginosa	Yes	Yes	Yes	Yes	Yes
Acinetobacter species	Yes	Yes (A. baumannii)	Yes	Yes	Yes
Staphylococcus aureus	Yes	Yes	Yes	Yes	Yes
Streptococcus pneumoniae	Yes	Yes	Yes	Yes	Yes
Enterococcus faecalis	Yes	No	Yes	No	No
Enterococcus faecium	Yes	No	Yes	No	No
Mycobacterium tuberculosis	No	Yes	No	No	No
Helicobacter pylori	No	No	No	Yes	No
Campylobacter species	No	No	No	Yes	No
Salmonellae	No	No	No	Yes	No
Neisseria gonorrhoeae	No	No	No	Yes	No
Haemophilus influenzae	No	No	No	Yes	No
Shigella species	No	No	No	Yes	No

Table 1

Selection of six priority pathogens based on the full list of priority pathogens according to WHO, ECDC and OECD.

Figure 1
About the six priority pathogens

Inclusion criteria: included in AMR surveillance (WHO/ECDC 2022), a leading attributable to / associated with resistance (Lancet 2022), a leading cause of infections (EU, OECD, ECDC 2019) and included in the list of priority pathogens (WHO 2020)



Escherichia coli[1]

is one of most common causes of hospital acquired or “nosocomial” infections, including but not limited to complicated urinary tract infections, intra-abdominal infections, and ventilator-acquired infections.

Resistant to:
- Third-generation cephalosporins
- Carbapenems
- Fluoroquinolones
- Aminoglycosides
- Aminopenicillins

Klebsiella pneumoniae[1]

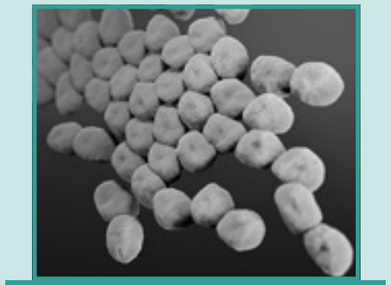
is a common cause of urinary-, respiratory-, complicated intra-abdominal-, and bloodstream infections. It is easily transmitted between patients, leading to nosocomial outbreak.

Resistant to:
- Third-generation cephalosporins
- Carbapenems
- Fluoroquinolones
- Aminoglycosides
- Piperacillin tazobactam

Pseudomonas aeruginosa[1]

is a common cause of infection (including hospital-acquired pneumonia, complicated intra-abdominal infections, bloodstream-, and urinary tract infections) in hospitalized patients, especially those with compromised immune defenses.

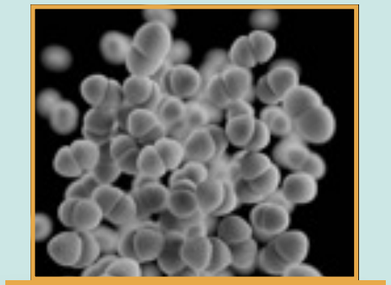
Resistant to:
- Aminoglycosides
- Carbapenems
- Ceftazidime
- Fluoroquinolones
- Piperacillin tazobactam
- Fourth-generation cephalosporin cefepime



Acinetobacter species[1]

mainly cause hospital-acquired infections such as (ventilator-associated) pneumonia, (central line-associated) bloodstream infections and postoperative wound infections.

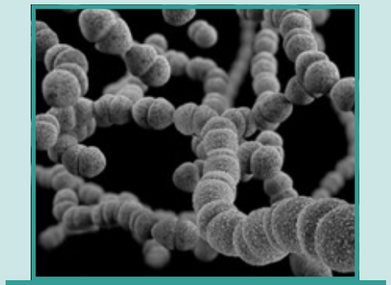
Resistant to:
- Aminoglycosides
- Carbapenems
- Fluoroquinolones



Staphylococcus aureus[2]

resistant to methicillin (MRSA) is one of the most frequent causes of hospital-acquired infections, such as postoperative wound infections and nosocomial pneumoniae. Increasingly, countries are reporting community-associated MRSA as well.

Resistant to:
- Methicillin (MRSA)



Streptococcus pneumoniae[2]

causes a wide range of infections, from mild, self-limiting conditions such as otitis media to more serious infections like community-acquired pneumonia and meningitis, with high mortality in vulnerable patient groups.

Resistant to:
- Macrolides
- Penicillins

Source: ECDC and WHO, 2022.

[1] Gram-negative bacteria, [2] Gram-positive bacteria. NOTE: Bacteria can be characterised as Gram-negative or Gram-positive, based on their structure. Gram-negative bacteria have a thin cell wall plus an outer membrane, whereas Gram-positive bacteria have a very thick cell wall but no outer membrane. (Silhavy et al. 2010). This impacts the type of antibiotics which will be effective, and the likelihood of developing resistance (which is higher for Gram-negative bacteria). (Breijyeh, Z. et al. 2020)

In response to the increasing failure of existing antibiotic treatments against these priority pathogens, a number of new and effective antibiotics have been developed and are currently on-patent. For this analysis we selected five of them which received market authorisation within the last seven years and are used in the acute care setting: cefiderocol, imipenem/cilastatin/relebactam), meropenem/vaborbactam, ceftazidime/avibactam) and ceftolozane/tazobactam (see Tables 2 and 3).

Treatment	Marketing authorisation	Indication	Pathogens
amikacin	Oct 2020	NTM lung infections caused by Mycobacterium avium Complex	*Mycobacterium avium Complex*
pretomanid	July 2020	XDR, treatment-intolerant or nonresponsive multidrug-resistant tuberculosis	*Mycobacterium tuberculosis*
cefiderocol	April 2020	**Infections due to aerobic Gram-negative organisms, in adults with limited treatment options**	*Carbapenem-resistant bacteria*, including *E. coli, K. pneumoniae* and other *Klebsiella spp., Enterobacter cloacae, Citrobacter frendii, Serratia marcescens and P. aeruginosa.* Plus *anaerobic bacteria: Bacteroides spp., Fusobacterium spp. and Prevotella spp.; H. influenza, A. calcoaceticus-baumannii complex*
levofloxacin	March 2015	Management of CPI due to *Pseudomonas aeruginosa* in patients with cystic fibrosis	*Pseudomonas aeruginosa*
delafloxacin	Dec 2019	Acute bacterial skin and skin structure infections	Several Gram-positive and Gram-negative bacteria associated with ABSSSIs (*S. aureus* (including MRSA), *E. faecalis* (vancomycin susceptible), and *Streptococcus spp.*)
imipenem/cilastatin/ relebactam	Feb 2020	**HAP and VAP. Bacteraemia that occurs in association with HAP or VAP. Infections due to aerobic Gram-negative organisms in patients with limited treatment options. Includes infections of the blood associated with lung infections**	*Carbapenem-resistant bacteria,* including *E. coli, K. pneumoniae and P. aeruginosa. Plus anaerobic bacteria: Bacteroides spp., Fusobacterium spp.* and *Prevotella spp.*
oritavancin	March 2015	Acute bacterial skin and skin structure infections	*S. aureus* (including MRSA)*, E. faecalis* (vancomycin susceptible), and *Streptococcus spp.*
meropenem/ vaborbactam	Nov 2018	**cUTI, including pyelonephritis; cIAI; HAP and VAP. Includes infections of the blood associated with those infections, infections with limited treatment options**	*Carbapenem-resistant Enterobacterales,* including *E. coli* and *K. pneumoniae* Plus *Enterobacter cloacae species complex*
lefamulin	July 2020	CAP in adults when it is considered inappropriate to use antibacterial agents commonly used for initial CAP Tx / when these have failed	*S. pneumoniae, S. aureus, H. influenzae, L. pneumophila, M. pneumoniae,* and *C. pneumoniae*
eravacycline	Sept 2018	cIAI	Gram-positive bacteria: *E. faecalis, E. faecium, Staph. aureus, Staph. anginosus, E.coli, K. pneumoniae, C. freundii, E. cloacae, K. oxytoca, E. faecalis, E. faecium, Clostridium perfringens, Bacteroides species,* and *Parabacteroides distasonis*
dalbavancin	Feb 2015	Acute bacterial skin and skin structure infections	*S. aureus* (including MRSA), *E. faecalis*, and *Streptococcus spp.*
ceftazidime/ avibactam	June 2016	**cIAI; cUTI; HAP and VAP. Other infections due to aerobic Gram-negative organisms in patients with limited treatment options. Includes infections of the blood associated with infections of the abdomen, urinary tract, or pneumonia.**	Carbapenem-resistant and ceftazidime-resistant *Enterobacteriaceae spp. (*including *E. coli,* and *K. pneumoniae)* and *P. aeruginosa.* Plus *H. influenzae* and *M. catarrhalis*
ceftolozane/ tazobactam	Sept 2015	**cIAI; cUTI; Acute pyelonephritis; HAP and VAP**	Ceftazidime-resistant *Enterobacterales spp, E. coli, K. pneumoniae,* and carbapenem-resistant *P. aeruginosa. Plus H. influenzae, K. oxytoca, P. mirabilis, B. fragilis, S. marcescens* and *Streptococcus spp*.

Used in acute care setting Activity against priority pathogen(s)

Table 2
14 innovative antibiotics were granted a market authorisation since 2015

Source: EMA website (download Public Assessment Reports)
Abbreviations: NTM - Non-tuberculous mycobacterial; XDR - Pulmonary extensively drug resistant; HAP - Hospital-acquired pneumonia; VAP - ventilator associated pneumonia; cUTI - Complicated urinary tract infection; cIAI - Complicated intra-abdominal infections; CAP - Community-acquired pneumonia; CPI - Chronic pulmonary infection.

Novel antibiotic	Marketing authorisation	Indication in the acute care setting	E.coli	K. pneumoniae	P. aeruginosa	Acinetobacter spp.	S. aureus	S. pneumoniae
cefiderocol	23 April 2020	Infections due to aerobic Gram-negative organisms, in adults with limited treatment options	carbapenem-resistant	carbapenem-resistant	carbapenem-resistant	A. baumannii (carbapenem-resistant)		
imipenem/cilastatin/ relebactam	13 Feb 2020	**HAP** and **VAP**. Bacteraemia that occurs in association with HAP or VAP. Infections due to aerobic Gram-negative organisms in patients with limited treatment options. Includes **infections of the blood** associated with lung infections	carbapenem-resistant (CRE/KPC)	carbapenem-resistant (CRE/KPC)	carbapenem-resistant (excl. MBL producers)	A.calcoaceticus-baumannii complex (non-resistant isolates)	(methicillin-susceptible isolates)	
meropenem/ vaborbactam	20 Nov 2018	**cUTI**, including pyelonephritis; **cIAI; HAP and VAP**. Includes **infections of the blood** associated with those infections, infections with limited treatment options	carbapenem-resistant (CRE/KPC)	carbapenem-resistant (CRE/KPC)			(methicillin-susceptible isolates)	
ceftazidime/ avibactam	23 June 2016	**cIAI; cUTI; HAP and VAP.** Other infections due to aerobic Gram-negative organisms in patients with limited treatment options. Includes **infections of the blood** associated with infections of the abdomen, urinary tract, or pneumonia	carbapenem-resistant and ceftazidime-resistant (CRE/KPC/ OXA-48)	carbapenem-resistant and ceftazidime-resistant (CRE/KPC/ OXA-48)	carbapenem-resistant and ceftazidime-resistant (excl. MBL producers)			
ceftolozane/ tazobactam	18 Sep 2015	**cIAI; cUTI;** Acute pyelonephritis; **HAP and VAP**	ceftazidime-resistant (ESBL producers)	ceftazidime-resistant (ESBL producers)	ceftazidime-resistant piperacilline-tazobactam-resistant carbapenem-resistant (excl. MBL producers)			

Activity against resistant pathogen

Activity against non-resistant pathogen

No activity against pathogen

Table 3

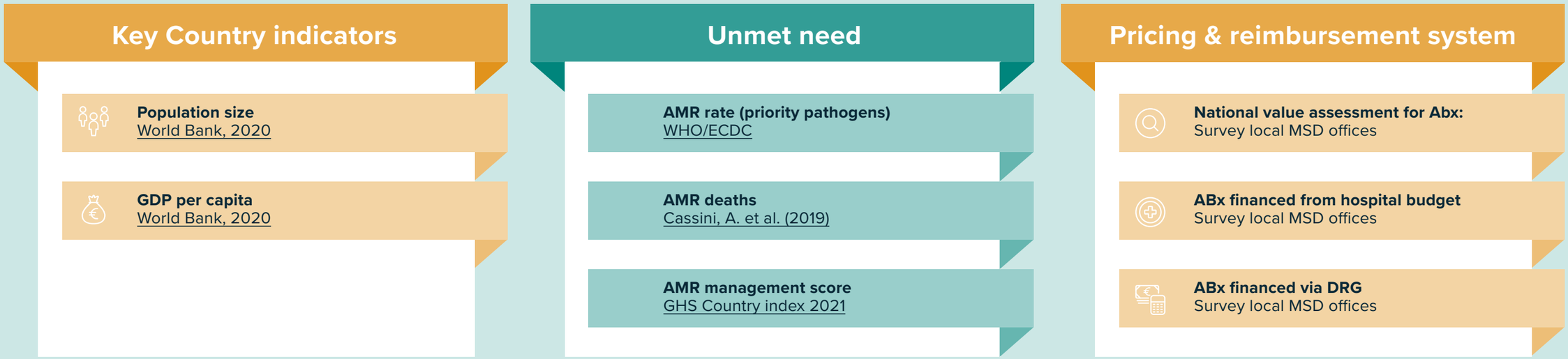
Selected novel antibiotics used in acute care setting

Source: EMA website (product information in European Public Assessment Reports)

Abbreviations: HAP and VAP – Hospital- and Ventilator Acquired (Nosocomial) Pneumonia; cIAI – Complicated intra-abdominal infections; cUTI – Complicated urinary tract infections; BSI – Blood stream infections; CRE – carbapenem-resistant and carbapenemase-producing Enterobacteriaceae; KPC – Klebsiella pneumoniae carbapenemase; OXA-48 – oxacillinase-48 gene; ESBL – extended-spectrum beta-lactamases; MBL – metallo beta-lactamase.

Country information was gathered for all EU-27 countries, except the smallest countries Cyprus, Estonia, Latvia, Luxembourg and Malta, and Lithuania due to the absence of data. For each of the 21 countries in scope, country- and antibiotic-specific information was gathered for a set of indicators using MSD data, desk research and a survey among local MSD offices (see Figure 2).

Figure 2
Information gathered for 21 European countries.



Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	EMA	Survey local MSD offices	IHS (Jan 2022), IQVIA (Apr 2022); validated by local MSD offices			**IQVIA** (cefiderocol; meropenem/ vaborbactam; ceftazidime/Avibactam; ceftolozane/ tazobactam, Jan 2016-Dec 2021; 2022) **MSD data** (imipenem/ cilastatin/relebactam, Jan 2016-Sept 2021	Survey local MSD offices	
imipenem/ cilastatin/ relebactam								
meropenem/ vaborbactam								
ceftazidime/ avibactam								
ceftolozane/ tazobactam								

Regarding the AMR management score per country, two potential sources of information were compared, after which the the GHS Country Index was selected (see Figure 3).

Figure 3
Comparison of two potential sources of information on national AMR management.

Country	AMR Management score - GHS Country index	Rank - GHS Country index	AMR Management score - WHO/ECDC	Rank - WHO/ECDC
Sweden	100	1	3	1
Austria	100	1	2.888888889	2
France	100	1	2.888888889	2
Ireland	100	1	2.555555556	5
Netherlands	91.7	2	3	1
Luxembourg	91.7	2	2.15	8
Belgium	83.3	3	2.888888889	2
Denmark	83.3	3	2.777777778	3
Germany	83.3	3	2.777777778	3
Greece	83.3	3	2.777777778	3
Portugal	83.3	3	2.666666667	4
Spain	83.3	3	2.555555556	5
Italy	83.3	3	2.111111111	9
Latvia	83.3	3	2	10
Malta	75	4	2.777777778	3
Finland	75	4	2.666666667	4
Slovenia	75	4	2.333333333	6
Lithuania	75	4	2	10
Poland	75	4	1.555555556	13
Croatia	66.7	5	2.777777778	3
Slovakia	66.7	5	2.333333333	6
Hungary	66.7	5	1.888888889	11
Bulgaria	66.7	5	1.142857143	14
Romania	58.3	6	1.666666667	12
Czech Republic	50	7	2.222222222	7
Cyprus	50	7	1.888888889	11
Estonia	41.7	8	2	10

GHS Country Index 2021

1.1.1) AMR surveillance, detection and reporting

- 1.1.1a) National plan for AMR priority pathogens
- 1.1.1b) Capacity of national lab/lab system to test for AMR priority pathogens
- 1.1.1c) National environmental surveillance for AMR residues/organisms

1.1.2) Antimicrobial control

- 1.1.2a) National law(s) requiring prescription for antibiotic use (humans)
- 1.1.2b) National law(s) requiring prescription for antibiotic use (animals)

Pro: calculates a single score, academic source, outcome indicators on control

WHO/ECDC, 2022

WHO AMR focal point appointed by the ministry of health

- Multisectoral and One Health collaboration/coordination
- AMR action plan developed
- National surveillance system for AMR in humans
- Submits data to a regional network for AMR surveillance
- Participates in a regional EQA scheme
- Enrolled in GLASS
- IPC in human health care
- Optimizing antimicrobial use in human health

Pro: multilateral source

Con: process indicators, does not calculate score (mean for the various elements is included in the table)

A European benchmark analysis of time to reimbursement and level of uptake for novel antibiotics was performed. This analysis is based on data for imipenem/cilastatin/relebactam, ceftazidime/avibactam and ceftolozan/tazobactam in countries where these novel antibiotics are reimbursed and purchased. Availability of cefiderocol and meropenem/vaborbactam was too limited to allow for country benchmarking (see Figure 4).

Figure 4
Set-up of the European benchmark analysis of time to reimbursement and level of uptake for novel antibiotics.

Research questions

- **What is the time to reimbursement after marketing authorization by the EMA?**
- **After one year of reimbursement, what is the difference in uptake of novel antibiotics?**

Methodology & scope

- In EU-27 countries
- For 5 novel antibiotics (see Table 3)

Country and antibiotics inclusion/ exclusion criteria

Country inclusion and exclusion criteria:
- EU-27
- Excluding smallest countries Cyprus, Estonia, Latvia, Luxembourg and Malta.
- Excluding Lithuania due to the absence of data.

Antibiotics inclusion criteria
- Reimbursed and procured in more than one third of included countries in the analysis

Data collected

- **Marketing authorization date:** Date of official marketing authorization by EMA
- **Reimbursement date:** Date of official reimbursement by national reimbursement agency or, in case of no central reimbursement decision, date of first hospital procurement after marketing authorization[1]
- **Uptake data:** Volume sold per quarter[2]

[1]IHS reimbursement data (extracted Jan 2022) [2]IQVIA (for ceftazidime/avibactam and ceftolozan/tazobactam, extracted Apr 2022) and MSD (for imipenem/cilastatin/relebactam, extracted Jan 2022).

Data analysis

Step 1

Marketing authorisation and reimbursement information
- Collected data for each country, and each antibiotic
  - Marketing authorisation date from EMA
  - Launch status (launched/ not launched)
  - Reimbursement status: reimbursed/ not reimbursed
  - Reimbursement type: within existing hospital budget / additional reimbursement / case-by-case basis
  - Reimbursement date: date of positive reimbursement decision combined with national launch by manufacturer/ date of first uptake in countries where no formal reimbursement decision is needed
- Calculated time between EMA marketing authorisation and reimbursement date

Step 2

Uptake data
- Collected data for each country, and each antibiotic
  - Uptake data from date of first uptake to last uptake data available
- Calculated number of months of uptake data
- Exclude countries with no available uptake data for one of the five antibiotics for the full first 4 quarters

Step 3

Cumulative uptake data
- Using reimbursement and uptake data calculated
  - Cumulative uptake from start of reimbursement per 4 quarters uptake
  - Uptake weighted per capita
  - Relative uptake per country to country with highest uptake per 1mio. capita per 4 quarters uptake

Important notes

The benchmark **highlights country differences, rather than best practices**. Countries with the highest clinical use per therapy were set as the benchmark country (100%) to enable comparison, not to set a standard or best practice. High uptake can indicate high resistance rates and/or suboptimal stewardship in terms of preventing overuse, but at the same time seems to indicate that access hurdles are low compared to other countries.

Annex 2 Country profiles

Austria

Key Country indicators

Population size
8.9 million

GDP per capita
EUR 44,000

Unmet need

AMR rate (priority pathogens)
11.6%

AMR deaths
3.2 / 100,000 population

AMR management score
100 / 100

Pricing & reimbursement system

National value assessment for Abx:
This is an option, but route often not followed

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Existing hospital budget	*Unknown*	No data	No	Specialist centres only
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	04/2020	Q2 2020	No	Specialist centres only
meropenem/ vaborbactam	20/11/1208	Launched	Reimbursed	Existing hospital budget	10/2019	Q4 2019	No	Yes
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	04/2017	Q2 2017	No	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	10/2015	Q4 2015	No	Yes
Average		**5/5 launched**	**5/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **165 days**		**No national medical guidelines**	**Abx may be included despite lack of reimbursement**

Belgium

Key Country indicators

Population size
11.6 million

GDP per capita
EUR 41,000

Unmet need

AMR rate (priority pathogens)
14.7%

AMR deaths
4.7 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Existing hospital budget	01/02/2022	No data yet	No	Under discussion
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/12/2018	Q2 2017	No	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	01/08/2021	No data yet[1]	Yes (for NP[2] only)	Under discussion
Average		**3/5 launched**	**3/5 reimbursed**	**Special fund plus existing hospital budget**	Average time to reimbursement: **1401 days**		**2/5 included in clinical guidelines**	**1/5 included in hospital protocols**

[1] *Due to a global shortage, the first vials arrived in Q1 2022*

[2] *Nosocomial Pneumonia*

Bulgaria

Key Country indicators

Population size
6.9 million

GDP per capita
EUR 9,000

Unmet need

AMR rate (priority pathogens)
40.9%

AMR deaths
3.9 / 100,000 population

AMR management score
67 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
N/A

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	02/05/2019	Q4 2018	Yes	Protocols are not public
ceftolozane/ tazobactam	18/09/2015	Not launched (planned for 09/2022	Reimbursed	Existing hospital budget	02/02/2020	N/A	Yes	Protocols are not public
Average		**1/5 launched**	**2/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **1321 days**		**Reimbursed Abx included in clinical guidelines**	**Unknown as hospital protocols are not public**

Croatia

Key Country indicators

Population size
4.0 million

GDP per capita
EUR 13,000

Unmet need

AMR rate (priority pathogens)
24.7%

AMR deaths
5.7 / 100,000 population

AMR management score
67 / 100

Pricing & reimbursement system

National value assessment for Abx:
National sick fund assessment

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	15/10/2021	Q4 2020	No	Hospital protocols vary
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	24/05/2018	Q4 2017	No	Hospital protocols vary
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	23/06/2016	Q4 2016	No	Hospital protocols vary
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **530 days**		**No national clinical guidelines**	**No national hospital protocols**

Czech Republic

Key Country indicators

Population size
10.7 million

GDP per capita
EUR 21,000

Unmet need

AMR rate (priority pathogens)
20.5%

AMR deaths
4.6 / 100,000 population

AMR management score
50 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but not for inpatient setting

ABx financed from hospital budget
Yes, in some cases additional reimbursement

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	07/2021	Q4 2021	No	No
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Additional reimbursement	10/2018	Q4 2018	Yes	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Additional reimbursement	10/2016	Q4 2016	To be included	To be included
Average		**3/5 launched**	**3/5 reimbursed**	**In some cases: additional reimbursement**	Average time to reimbursement: **571 days**			

Denmark

Key Country indicators

Population size
5.8 million

GDP per capita
EUR 55,000

Unmet need

AMR rate (priority pathogens)
0.11%

AMR deaths
2.2 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/07/2017	Q3 2017	Yes	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	11/12/2015	Q4 2015	Yes	Yes
Average		**2/5 launched**	**2/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **229 days**			

Finland

Key Country indicators

Population size
5.5 million

GDP per capita
EUR 44,000

Unmet need

AMR rate (priority pathogens)
8.4%

AMR deaths
1.7 / 100,000 population

AMR management score
75 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but not for hospital products

ABx financed from hospital budget
Yes

ABx financed via DRG
Depends on the district

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	Not reimbursed	N/A	N/A	N/A	Yes, b/o sensitivity testing	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	01/08/2020	Q3 2020	Yes, b/o sensitivity testing	Yes (TYKS, HUS; 01/'22)
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Existing hospital budget	01/05/2021	Q2 2021	Yes, b/o sensitivity testing	Yes (TYKS, HUS; 01/'22)
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/05/2017	Q2 2017	Yes, b/o sensitivity testing	Yes (2018-2019)
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	15/12/2015	Q4 2015	Yes, b/o sensitivity testing	Yes (2018-2019)
Average		**4/5 launched**	**4/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **366 days**		**Yes, b/o sensitivity testing**	**Yes**

France

Key Country indicators

Population size
67.4 million

GDP per capita
EUR 35,000

Unmet need

AMR rate (priority pathogens)
0.16%

AMR deaths
8.3 / 100,000 population

AMR management score
100 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Not always (‘liste en sus’)

ABx financed via DRG
Yes (if not on ‘liste en sus’)

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Additional reimbursement	20/01/2021	*No data*	Yes	Yes
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	23/09/2020	Q4 2020	Yes	Yes
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Additional reimbursement	21/02/2020	Q3 2020	Yes	Yes
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Additional reimbursement	15/09/2020	Q2 2017	Yes	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	03/08/2016	Q3 2016	Yes	Yes
Average		**5/5 launched**	**5/5 reimbursed**	**3/5 additional reimbursement**	Average time to reimbursement: **564 days**		**Yes**	**Yes**

Germany

Key Country indicators

Population size
83.2 million

GDP per capita
EUR 42,000

Unmet need

AMR rate (priority pathogens)
0.14%

AMR deaths
2.9 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but exemption for novel Abx

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Existing hospital budget	15/01/2021	Q1 2021	Yes	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	15/06/2021	Q2 2021	Yes	N/A
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	No	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	15/12/2017	Q1 2017	Yes	N/A
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	01/12/2015	Q4 2015	Yes	N/A
Average		**4/5 launched**	**4/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **267 days**			

Greece

Key Country indicators

Population size
10.7 million

GDP per capita
EUR 16,000

Unmet need

AMR rate (priority pathogens)
33.2%

AMR deaths
15.0 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
N/A

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/11/2017	No data	Yes	N/A
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	23/12/2016	No data	Yes	N/A
Average		**2/5 launched**	**2/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **479 days**			

Hungary

Key Country indicators

Population size
9.7 million

GDP per capita
EUR 15,000

Unmet need

AMR rate (priority pathogens)
23.7%

AMR deaths
5.5 / 100,000 population

AMR management score
67 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but not for hospital products

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	06/2021	Q2 2021	No	Hospital protocols vary
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/2018	Q1 2018	No	Hospital protocols vary
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	07/2016	Q2 2016	No	Hospital protocols vary
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **439 days**		**No national medical guidelines**	**No national hospital protocols**

Ireland

Key Country indicators

Population size
5.0 million

GDP per capita
EUR 77,000[1]

Unmet need

AMR rate (priority pathogens)
0.19%

AMR deaths
4.7 / 100,000 population

AMR management score
100 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Only after negative central reimbursement decision

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	Not reimbursed	Existing hospital budget	N/A	N/A	No	No
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Additional reimbursement	02/2021	Q4 2019	Yes	Yes
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Additional reimbursement	11/2017	Q1 2018	Yes	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Additional reimbursement	09/2016	Q4 2016	Yes	Yes
Average		**3/5 launched**	**3/5 reimbursed**	**Additional reimbursement**	Average time to reimbursement: **550 days**			

[1] GDP n Ireland is very high due to corporate tax regulations which skew the data.

Italy

Key Country indicators

Population size
59.6 million

GDP per capita
EUR 29,000

Unmet need

AMR rate (priority pathogens)
0.30%

AMR deaths
17.7 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
No (yes if Cnn-class)

ABx financed via DRG
No (yes if Cnn-class)

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Additional reimbursement	24/06/2021	Q2 2021	No	Yes
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Additional reimbursement	04/06/2022	Q2 2021	No	Yes
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Additional reimbursement	31/03/2021	Q2 2021	No	Yes
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Additional reimbursement	20/01/2018	Q1 2018	No	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Additional reimbursement	03/10/2016	Q2 2016	No	Yes
Average		**5/5 launched**	**5/5 reimbursed**	**Additional reimbursement**	Average time to reimbursement: **562 days**			

Netherlands

Key Country indicators

Population size
17.4 million

GDP per capita
EUR 48,000

Unmet need

AMR rate (priority pathogens)
0.11%

AMR deaths
1.2 / 100,000 population

AMR management score
92 / 100

Pricing & reimbursement system

National value assessment for Abx:
Option to go through national sick fund association for DRG add-on

ABx financed from hospital budget
Yes[1]

ABx financed via DRG
Yes, potentially w/ add-on

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	No	No
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	10/2020	Q4 2020	No	Unkown
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	10/2019	Q1 2018	Yes	Unkown
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	10/2015	Q4 2015	Yes	Unkown
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **480 days**			

[1] In the Netherlands, patient have to pay a capped amount of healthcare costs themselves ('own risk'); novel Abx are part of the costs to which this 'own risk' applies.

Poland

Key Country indicators

Population size
38 million

GDP per capita
EUR 14,000

Unmet need

AMR rate (priority pathogens)
27%

AMR deaths
5.8 / 100,000 population

AMR management score
75 / 100

Pricing & reimbursement system

National value assessment for Abx:
This is an option, but route often not followed

ABx financed from hospital budget
Yes, reimbursement can be request on a case-by-case basis

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Existing hospital budget	07/2020	Q3 2020	No	No
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	02/2020	Q1 2021	No	No
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Existing hospital budget	10/2020	Q4 2020	No	No
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/2019	Q1 2018	No	No
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	01/2018	Q1 2018	No	No
Average		**5/5 launched**	**5/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **499 days**		**Central medical guidelines are present but not up to date**	**Not included in hospital protocols**

Portugal

Key Country indicators

Population size
10.3 million

GDP per capita
EUR 20,000

Unmet need

AMR rate (priority pathogens)
20.4%

AMR deaths
11.2 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	No	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	Early access scheme during ongoing negotiations	N/A	Q1 2021	No	Hospital protocols vary
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	No	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	14/08/2019	Q2 2017	No	Hospital protocols vary
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	17/08/2018	Q4 2016	No	Hospital protocols vary
Average		**2/5 launched**	**2/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **1106 days**		**No national clinical guidelines**	

Romania

Key Country indicators

Population size
19.3 million

GDP per capita
EUR 12,000

Unmet need

AMR rate (priority pathogens)
30.1%

AMR deaths
7.4 / 100,000 population

AMR management score
58 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but not for hospital products

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	03/2021	Q1 2021	No	Yes
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/2018	Q1 2018	No	Yes
ceftolozane/ tazobactam	18/09/2015	Launched, but withdrawn	Reimbursed	Existing hospital budget	04/2017	Q2 2017	No	Yes
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **500 days**		**No national clinical guidelines**	**Reimbursed Abx included in hospital protocols**

Slovakia

Key Country indicators

Population size
5.5 million

GDP per capita
EUR 17,000

Unmet need

AMR rate (priority pathogens)
0.33%

AMR deaths
7.0 / 100,000 population

AMR management score
67 / 100

Pricing & reimbursement system

National value assessment for Abx:
No

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	Not reimbursed	N/A	N/A	N/A	Yes	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	09/2020	Q3 2020	Yes	No
meropenem/ vaborbactam	20/11/2018	Not launched	Not reimbursed	N/A	N/A	N/A	Yes	N/A
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	07/2018	Q3 2018	Yes	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	10/2016	Q4 2016	Yes	Yes
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **439 days**			

Slovenia

Key Country indicators

Population size
2.1 million

GDP per capita
EUR 23,000

Unmet need

AMR rate (priority pathogens)
14.0%

AMR deaths
4.7 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes, but not for hospital products

ABx financed from hospital budget
Yes

ABx financed via DRG
Yes

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	Guidelines not published	No
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	01/09/2020	Q3 2020	Guidelines not published	Yes
meropenem/ vaborbactam	20/11/2018	Not launched	N/A	N/A	N/A	N/A	Guidelines not published	No
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/11/2017	Q2 2017	Guidelines not published	Yes
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	01/11/2015	Q4 2015	Guidelines not published	Yes
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **257 days**		**National abx guidelines not published**	**Reimbursed Abx are included in hospital protocols**

Spain

Key Country indicators

Population size
47.4 million

GDP per capita
EUR 25,000

Unmet need

AMR rate (priority pathogens)
0.21%

AMR deaths
4.1 / 100,000 population

AMR management score
83 / 100

Pricing & reimbursement system

National value assessment for Abx:
Yes

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
imipenem/ cilastatin/ relebactam	13/02/2020	Not launched	N/A	N/A	N/A	N/A	N/A	N/A
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Existing hospital budget	01/11/2021	Q4 2021	Yes	No (<1%)
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	01/11/2017	Q4 2017	Yes	Yes (>90%)
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	01/03/2016	Q1 2016	Yes	Yes (>90%)
Average		**3/5 launched**	**3/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **579 days**			

Sweden

Key Country indicators

Population size
10.4 million

GDP per capita
EUR 47,000

Unmet need

AMR rate (priority pathogens)
0.06%

AMR deaths
1.7 / 100,000 population

AMR management score
100 / 100

Pricing & reimbursement system

National value assessment for Abx:
No

ABx financed from hospital budget
Yes

ABx financed via DRG
No

Antibiotic	Marketing authorisation	Launch status	Reimbursement status	Reimbursement type	Date of reimbursement	Start of uptake data	Inclusion in clinical guidelines	Inclusion in hospital protocols/formularies
cefiderocol	23/04/2020	Launched	Reimbursed	Existing hospital budget	01/2021	Q1 2021	Yes	Likely, but not needed
imipenem/ cilastatin/ relebactam	13/02/2020	Launched	Reimbursed	Existing hospital budget	07/2020	Q3 2020	Yes	Likely, but not needed
meropenem/ vaborbactam	20/11/2018	Launched	Reimbursed	Existing hospital budget	01/2021	Q1 2021	Yes	Likely, but not needed
ceftazidime/ avibactam	23/06/2016	Launched	Reimbursed	Existing hospital budget	04/2017	Q2 2017	Yes	Likely, but not needed
ceftolozane/ tazobactam	18/09/2015	Launched	Reimbursed	Existing hospital budget	10/2015	Q4 2015	Yes	Likely, but not needed
Average		**5/5 launched**	**5/5 reimbursed**	**Existing hospital budget**	Average time to reimbursement: **292 days**			

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Citation: Vintura and MSD, 2022. Improving patient access to novel antibiotics. Recommendations for national policies to fight AMR in Europe.

This report was commissioned and financed by MSD.