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Strengthening the sustainability of the off-patent antibiotic supply chain

FINAL REPORT

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Glossary

TERM	DEFINITION
Active pharmaceutical ingredient (API)	Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product that produces the intended health effects. APIs are usually produced by chemical synthesis or by cell culture and extraction. The production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. [1]
Antimicrobial resistance (AMR)	Resistance that 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. AMR can develop as a result of improper antibiotic use, antibiotic shortages and other factors.
Antimicrobial stewardship	A coherent set of actions which promote the responsible use of antimicrobials. This definition can be applied to actions at the individual level as well as the national and global levels, and across human health, animal health and the environment. Effective antimicrobial stewardship programs optimise the use of antimicrobials, improve patient outcomes, reduce AMR and healthcare-associated infections (HAIs), and save healthcare costs amongst others.
High-income country (HIC)	This report uses the World Bank definitions when referring to countries at different stages of economic development. At the time of writing, high-income countries were defined as those with a gross national income per capita of $13,205 or more.
Low- and middle-income countries (LMIC)	This report uses the World Bank definitions when referring to countries at different stages of economic development. At the time of writing, low-, lower-middle- and upper-middle-income countries were

1 Food and Drug Administration. (n.d.). Food compliance program guidance manual and drug administration program. Retrieved January 12, 2023, from https://www.fda.gov/media/75201/download

	defined as those with a gross national income per capita of less than $13,205.
Market sustainability	The ability of a market to provide access to the range of existing off-patent antibiotics over the short, medium and long term. A sustainable market delivers savings while remaining profitable for market participants, maintains a number of suppliers and is responsive to changes in demand and resistant to supply shocks caused by market dynamics.
Off-patent antibiotic supply chain	The processes involved in the production and distribution of off-patent antibiotics. This report examines all stages of the supply chain, including raw material sourcing, API production, finished product development, packaging and distribution for supply sustainability across the life cycle of a product.
Shortage	The lack of a reliable supply of a medicine at any given point across a region or globally, or where demand exceeds supply due to market dynamics, resulting in poorer health outcomes. Shortages analysed in this report are based on a country's database and research in the literature. We consider shortages of licensed off-patent antibiotics only for the purposes of this report.
Stock-out	The absence of a specific formulation and/or dosage of medicine at a given facility.
Supply disruption	An event that causes a disruption in the production or distribution of a medicine. Supply chain disruptions can be caused by events such as natural disasters and pandemics, as well as by market dynamics.
Supply sustainability	The ability of a supply chain to provide a consistent and dependable supply of off-patent antibiotics. Where there are sustainable supply chains, the risk of shortages is reduced and the impact of shortages is limited, with minimal disruptions or weaknesses, from raw material production to medicine distribution.

Executive summary

Antimicrobial resistance (AMR) is one of the major health threats facing the world today. An estimated 4.95 million people who died in 2019 suffered from at least one drug-resistant infection and AMR directly caused 1.27 million of those deaths. [2] Antibiotics are becoming less effective as drug resistance spreads around the world, resulting in more difficult-to-treat infections and more deaths. Improper antimicrobial use has resulted in a sharp increase in drug-resistant infections worldwide, and there is a need to ensure that appropriate antimicrobials, as well as diagnostic tools, are available for physicians to use to ensure patients receive the best treatment possible, thereby slowing resistance. In the context of this public health threat, the AMR Industry Alliance commissioned Charles River Associates ('CRA') to undertake an assessment of the challenges related to ensuring the sustainable supply of off-patent antibiotics, with the aim of identifying a set of policy levers that could strengthen the sustainability of their supply. The intention was to identify whether there were significant differences in the challenges and solutions needed in high-income countries (HICs) versus low- and middle-income countries (LMICs). For this purpose, five case study countries were chosen: Brazil, Germany, India, South Africa and Vietnam.

The approach involved a literature review at a global, regional and national level focused on documenting evidence of the existence of challenges with sustainable supply of off-patent antibiotics, and an interview programme with representatives of global and national organisations focused on identifying the root causes of supply challenges and potential policy solutions to address these.

Supply sustainability is often associated with how often there are shortages and the impact this has on the healthcare system and patients. However, there are challenges in focusing solely on an empirical comparison of shortages, given the lack of a unified definition of shortages across countries and disease areas, as well as the poor levels of data availability and data quality regarding shortages. To overcome this, we did not use a purely empirical approach but focused on examples across several different dimensions:

- The degree to which sustainability has changed over time, based on qualitative evidence
- The degree to which examples of supply issues can be identified
- The degree to which antibiotics contrast with other therapeutic areas

In the context of this report, we define *supply sustainability* as a consistent and dependable supply of off-patent antibiotics. With sustainable supply chains, the risk of shortages is reduced, and the impact of shortages is limited, with minimal disruptions or weaknesses, from raw material production to medicine distribution.

2 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 20 January 2022. doi:10.1016/S0140-6736(21)02724-0.

Concerns regarding the sustainability of off-patent antibiotic supply

The occurrence of antibiotic shortages is increasing worldwide.[3] Consensus in the literature over the last 10 years points towards a worsening of the problem over time.[4,5] Reports, such as the World Health Organization (WHO)'s 2019 meeting report on antibiotic shortages, echo the concern that the frequency of shortages appears to be increasing. These show that this is a global problem that also affects regions responsible for most of the production of antibiotics.[6] While the problem of shortages is not unique to off-patent antibiotics, evidence from the literature and our interviews points towards a greater risk of supply challenges for antibiotics than for many other classes of medicine. In the US, for example, anti-infectives are 42% more likely to be in short supply than all other drugs.[7]

Often shortages are localised and impact some countries but not others, suggesting issues with distribution and access. However, in some cases the impact of shortages is felt worldwide, particularly when there is disruption to the global supply chain. A well-documented example was the global shortage of benzathine penicillin G (BPG), the only recommended treatment for prevention of mother-to-child transmission of syphilis; between 2014 and 2016, 41% of surveyed countries reported a shortage of BPG.[8] The impact of this on patients is clear: in Brazil, for example, only 4.1% of pregnant women with syphilis were adequately treated in 2016 as a result of the ongoing BPG shortage. Pregnant women who received no or insufficient treatment may have passed the infection to their unborn children, potentially resulting in foetal and neonatal death, prematurity, low birth weight, or congenital infection.[9] There are also financial consequences for health systems. Direct costs include additional costs associated with the use of more expensive alternatives when an off-patent option is effective and appropriate but not available. Other, indirect costs can also be incurred, such as increased hospital, pharmacy, personnel and patient costs.[10] Unlike other therapy areas, there can also be a broader societal consequence resulting from antibiotic shortages: the spread of AMR. Physicians may have to substitute a preferred

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3 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6: e006961.

4 Quadri, F. et al. (2015) Antibacterial drug shortages from 2001 to 2013: implications for clinical practice. *Clin Infect Dis*. 60(12): 1737–1742.

5 Pulcini, C. et al. (2016) Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia. *International Journal of Antimicrobial Agents*. 49(1): 98–101.

6 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

7 Raghavendran, V. and Christian, M. (2022) Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map Analysis. Available at: https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines [Accessed August 2022]

8 Nurse-Findlay, S. et al. (2017) Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. *PLoS Med*. 14(12): e1002473.

9 Sarmeiro Araujo, R., Semeão de Souza, A.S. and Ueleres Braga, J. (2020) [In Portuguese] A quem afetou o desabastecimento de penicilina para sífilis no Rio de Janeiro, 2013–2017? *Rev. Saúde Pública* 54.

10 Khumra, S. et al. (2018) Counting the cost of critical antibiotic shortages. *Journal of Antimicrobial Chemotherapy*. 74(1): 273–275.

narrow-spectrum antibiotic for a broad-spectrum alternative, which runs counter to the principles of antimicrobial stewardship and can drive increased resistance.[11]

Root causes of unsustainability and a framework for strengthening sustainability

Through the literature review and interview programme, we identified five interconnected categories of root causes that contribute to unsustainable supply of off-patent antibiotics (**Figure 1**). The areas of weakness are as follows:

(1) The global supply chain is fragile, and there are difficulties in the production of antibiotics.

(2) Demand is often unpredictable and meeting national and local fluctuations in demand is challenging, particularly given the underdevelopment of surveillance systems and limited access to reliable diagnostics in many LMICs.

(3) There are low commercial returns across the supply chain, from raw materials through to finished products. There is an increasing amount of empirical evidence supporting the theory that low commercial returns are contributing to antibiotic supply unsustainability at a global level, highlighting a systemic challenge, but are also resulting from unsustainable pricing and procurement policies in specific countries.

(4) Few off-patent antibiotic manufacturers and even fewer active pharmaceutical ingredient (API) suppliers remain globally as a result of the untenable commercial conditions.[12]

(5) Inefficiencies in supply chain management, distribution and communication also contribute to unsustainability.[13]

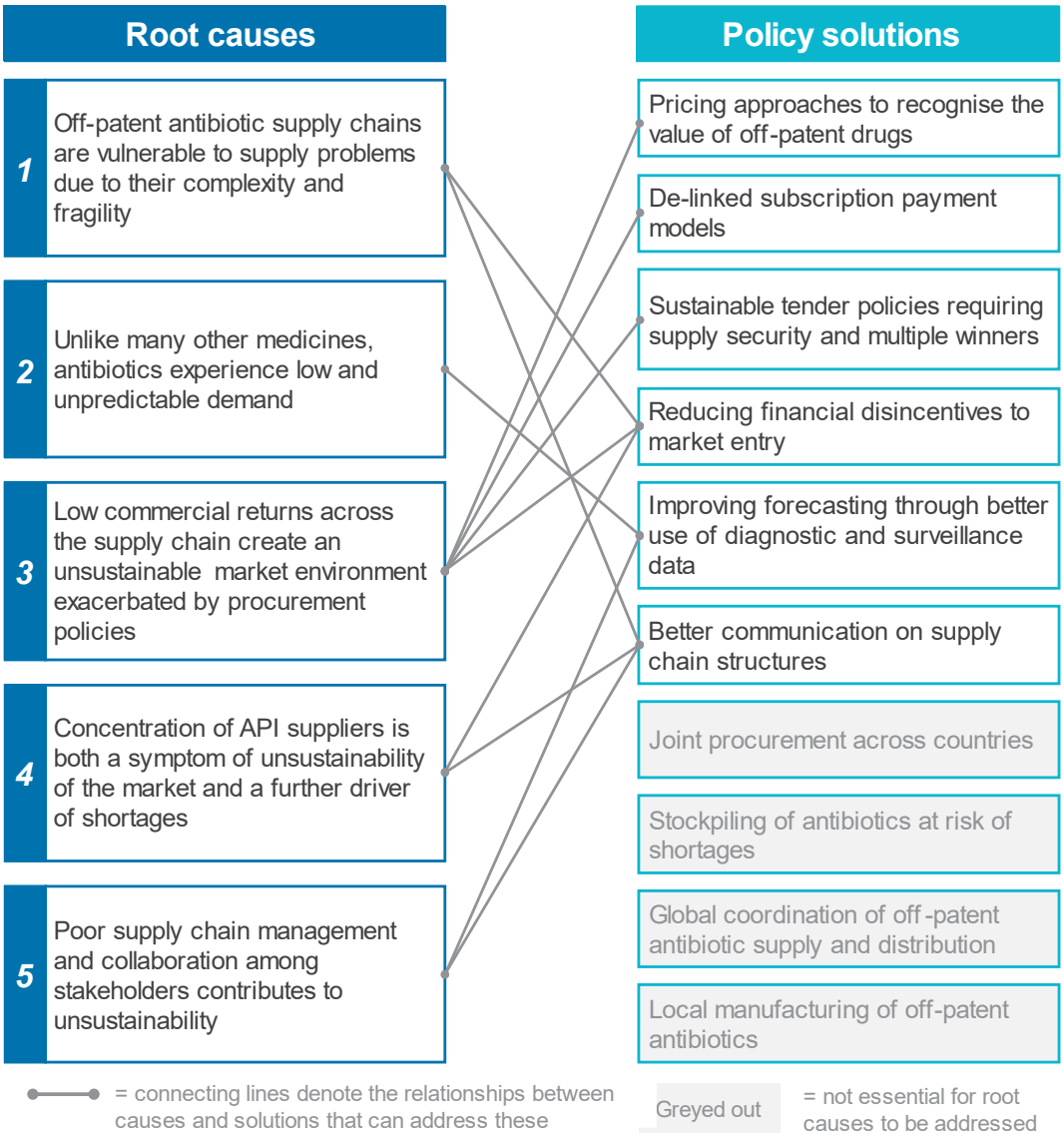
As illustrated in **Figure 1**, a number of different policy solutions have been raised by stakeholders in discussions to address sustainable supply. However, there is likely no single fix that could address these multifaceted challenges, nor is there a simple relationship between challenges and solutions. By enacting a package of solutions, each aiming to tackle a specific subset of these challenges, a more sustainable market could be created. These would range from solutions to address the underlying commercial challenges in the market through more proactive pricing and procurement policies, to solutions aiming to tackle stages of weakness in the supply chain from API production (better communication on supply chain structures between regulators, payers and providers and creation of incentives for new API suppliers to enter) through to management of demand (better use of diagnostic and surveillance data).

11 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

12 WHO (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

13 CRA Expert Interview

Figure 1: Links between the causes of unsustainability and the potential policy solutions proposed to address them



Source: CRA analysis

From our analysis, we suggest that not all of the solutions raised in **Figure 1** are (a) necessary or (b) appropriate actions to take. Firstly, as some solutions have the potential to address multiple root causes, an efficient approach would be to focus on this subset of solutions. There is therefore a need for prioritisation, and we identified six solutions of higher priority (not listed in order of priority):

1. **Pricing approaches to recognise the value of off-patent drugs:** It is necessary to find a balance between addressing the need for health systems to realise cost savings from off-patent antibiotics and addressing the need for off-patent antibiotic

prices to remain financially sustainable in order to ensure supply. Many off-patent antibiotics on the market have been off-patent for years and have already reached low price levels. The low margin can make these commercially unattractive if conditions change. This can be unsustainable for manufacturers; therefore, a more innovative payment mechanism that recognises the value of an antibiotic's continued future availability could reduce the risk of shortages.

2. **De-linked subscription payment models:** In some cases, revising the pricing policies for off-patent antibiotics to guarantee a minimum level of commercial returns would address a fundamental root cause of supply chain unsustainability. By basing payment on the value of the continued availability of an existing antibiotic, rather than by its sales volumes, the commercial environment would become more sustainable for current suppliers. We could expect that consequently fewer suppliers would be incentivised to discontinue production, as they would instead be incentivised to achieve security of supply.
3. **Sustainable tender policies requiring supply security and multiple winners:** In other cases, ensuring that tender contracts are awarded to multiple suppliers – promoting more long-term competition in the off-patent antibiotics market – will be the appropriate solution. It is critical to ensure that each tender winner has a significant market share that generates viable returns in order for the market to be sustainable.
4. **Reducing financial disincentives to market entry:** Reducing the barriers to market entry (and re-entry) could encourage more manufacturers to restart or maintain their supply. On top of the unsustainable commercial conditions experienced by antibiotic manufacturers, currently many health authorities aim to incentivise security of supply by imposing additional penalties (in instances of shortage) and fees (in instances of re-filing in a market from which a supplier has previously withdrawn or registering an off-patent antibiotic in a new market). These make it less attractive to enter the market and mitigating these costs would help make the market more sustainable.
5. **Improving forecasting through better use of diagnostic and surveillance data:** The use of diagnostic tools and AMR surveillance systems can ensure that appropriate antibiotics are available for physicians to use in order to provide their patients with the best treatment possible while also slowing the spread of AMR. In addition, data and diagnostic tools can be used more proactively to predict demand (reducing this risk for manufacturers and payers) and AMR trends.
6. **Better communication on supply chain structures:** The information included in the marketing authorisation dossier demonstrates that MAHs are transparent about their supply chains. Marketing authorisations are filed with the responsible regulatory agency in each market, although these agencies may not always share the data with other agencies within their governments. With improved communication and supply chain knowledge, policymakers can implement mitigation strategies as the risk of shortages rises. However, any policy interventions aimed at increasing supply chain communication and transparency should consider the risks of sharing information and implement safeguards, particularly regarding the sharing of the sharing of sensitive financial, proprietary or anti-competitive information. This puts companies at risk of being driven out of

the market through competitor actions, leading to more consolidation and thus is counter-productive to the goal of retaining existing suppliers and attracting new suppliers. A multi-faceted approach may be required to ensure sustainability is achieved via increased communication, with reforms to procurement occurring in tandem.

Given the unique nature of health systems, we do not anticipate that the same package of solutions would be required or indeed be viable to implement in all countries or for every antibiotic. Using our case-study countries, we evaluated the feasibility and impact of different solutions and concluded that some policy options will be more impactful in HICs compared to LMICs and vice versa. The onus of addressing the underlying market failure in the off-patent antibiotic market lies with HICs, where health systems can afford to pay prices that reflect the value of a sustainable supply of essential antibiotics. In LMICs, increasing healthy competition may be more achievable through removing disincentives and regulations that prevent manufacturers from establishing or maintaining their presence in those markets, and through improving the predictability of demand by reducing rates of self-medication and improving surveillance and forecasting systems.

Common to all countries is a need for greater urgency from policymakers to address the issue of unsustainable off-patent antibiotic supply chains and to implement meaningful policy change.

1. Introduction

Charles River Associates ('CRA') was commissioned by the AMR Industry Alliance to undertake an analysis of the challenges related to ensuring the sustainable supply of off-patent antibiotics.[14] Specifically:

- Review how off-patent antibiotic markets are working today, the extent to which they are unsustainable, the impacts on different stakeholders, and how this varies across regions
- Determine the root causes of unsustainability
- Evaluate a set of proposed policy levers that could strengthen the sustainability of global off-patent antibiotic supply chains, and understand the difference in approach needed to achieve sustainability across different geographic regions

This report was supported by the AMR Industry Alliance. The findings and conclusions contained within are those of the authors and do not necessarily reflect the views of the Alliance or those of the individual Alliance member organizations.

1.1. Background

Optimising patient outcomes and combatting the growing threat of antimicrobial resistance (AMR) requires the availability of and access to a diverse repository of effective antibiotics. AMR can cause more serious illnesses and hospitalisations, resulting in increased healthcare costs and poorer patient outcomes. According to various studies, AMR could cost anywhere from $300 billion to more than $1 trillion per year by 2050 globally.[15] In Europe alone, it is estimated that AMR costs more than €9 billion per year.[16] An estimated 4.95 million people who died in 2019 suffered from at least one drug-resistant infection, and AMR directly caused 1.27 million of those deaths. Data shows that young children are particularly affected. In 2019, one in five deaths attributable to AMR occurred in children under the age of five. [17] Improper antibiotic use has resulted in a sharp increase in drug-resistant infections around the world, and there is a need to ensure that appropriate antibiotics, as well as diagnostic tools, are available for physicians to use to ensure patients receive the best treatment possible, thereby slowing antibiotic resistance.

Much of the global policy focus so far has rightly been on finding ways to incentivise the development of new innovative antibiotics to add to the arsenal of available treatment options. Reform of the innovative antibiotic market is still underway, but promising progress

14 'Antimicrobial resistance' encompasses resistance to all types of antimicrobials (including antibiotics, antivirals, antifungals and antiparasitics). The majority of evidence of market unsustainability comes from antibiotics, and therefore we refer to antibiotics throughout this report. However, many of the findings and conclusions likely apply more broadly to other types of antimicrobials.

15 Dadgostar, P. (2019) Antimicrobial Resistance: Implications and Costs. *Infection and drug resistance*, 12: 3903–3910. https://doi.org/10.2147/IDR.S234610

16 Dadgostar, P. (2019) Antimicrobial Resistance: Implications and Costs. *Infection and drug resistance*, 12:3903–3910. https://doi.org/10.2147/IDR.S234610

17 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 20 January 2022. doi:10.1016/S0140-6736(21)02724-0.

has been seen, with recent proposed solutions focusing on addressing the economic challenges associated with antibiotic development.

However, even if a robust package of incentives were in place to address the market failure affecting the development and commercialisation of novel antibiotics, we must acknowledge that healthcare systems face challenges in ensuring a steady supply of off-patent antibiotics, which remain essential to patient care. Generic products account for around 80%–90% of all drug prescriptions in developed markets[18,19] and even more in emerging markets; for antibiotics the percentage of generic prescriptions is likely to be even higher given the low number of new on-patent products over the last 10 years. Even if new antibiotics are encouraged, off-patent products will remain very important for appropriate patient care in many cases, especially as antimicrobial stewardship means that new antibiotics will be used conservatively to prevent the development of future resistance. Ensuring the availability and access to existing older antibiotics therefore remains essential.

Over the last 10 years, there has been growing concern regarding access to existing generic antibiotics and sustainability of the global supply chain.[20] A number of published articles and reports over the last 10 years, by academics and non-governmental organisations, have explored the magnitude of the problem, the impact on global health security, and potential solutions to improve sustainability.[21,22] These find that the occurrence of antibiotic shortages is rising, with an underlying multifaceted set of supply-and-demand-related causes.

- The World Health Organization (WHO) has focused on antibiotic shortages. A meeting held in Oslo in 2018 convened a range of governmental and non-governmental stakeholders to discuss the issue and concluded that the key contributor to unsecure supply of older antibiotics is the low market returns, driving both financial and societal costs.[23]
- The Access to Medicine Foundation (ATMF) has published a series of reports analysing the antibiotic supply chain and the root cause of its fragility, highlighting the

18 NHS BSA. Medicines optimisation – generic prescribing. Available at: https://www.nhsbsa.nhs.uk/epact2/dashboards-and-specifications/medicines-optimisation-generic-prescribing [Accessed August 2022]

19 AAM (2020) 2020 Report: Generic Drug and Biosimilars Access and Savings in the U.S. Available at: https://accessiblemeds.org/2020-Access-Savings-Report [Accessed August 2022]

20 Global AMR R&D Hub and WHO (2022) Incentivising the development of new antibacterial treatments. Available at: https://globalamrhub.org/wp-content/uploads/2022/05/G7_ProgressReport_FINAL_16.05.2022.pdf [Accessed August 2022]

21 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6: e006961.

22 Quadri, F. et al. Antibacterial drug shortages from 2001 to 2013: implications for clinical practice. *Clin Infect Dis*. 60(12): 1737–1742.

23 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

disproportionate burden in low- and middle-income countries (LMICs) and the need for collaborative efforts to strengthen supply chains.[24]

- PLATINEA is an organisation established in 2016 specifically to find solutions to preserve and enhance the value of existing antibiotics. This group has supported the publication of multiple analyses focused on identifying the root causes of drug shortages and solutions to address them. A common theme underlying many of the 60 root causes identified by PLATINEA in 2020 was the low profitability of generic antibiotics.[25]

Although there is a consensus on the overall challenge, there is a lack of common understanding of what the root causes of supply challenges for off-patent antibiotics are, and whether they are common across countries, and particularly whether high-, middle- and low-income countries experience supply challenges for different reasons.

Most importantly, without a full and common understanding of the root causes, it is difficult to align on the most effective policy response. The European Commission, for example, recognises that medicine shortages are a growing problem in Europe, and aims to have a legislative proposal in place by the end of 2022 with measures to address shortages.[26] In particular, the Commission is considering stronger obligations for supply and transparency, earlier notification of shortages and market withdrawals, enhanced transparency of stocks, and stronger European Union (EU) coordination of supply.[27] The EU Pharmaceutical Strategy specifically recognises that a lack of first-choice antibiotics can result in suboptimal and poorer patient outcomes, an increased risk of adverse events, AMR, and higher healthcare costs.[28] Under the EU One Health action plan, a comprehensive AMR response strategy, there is a focus on increasing the development and availability of new effective antimicrobials both within and outside the EU; however, there is a lack of focus on supply and availability of existing antibiotics.[29]

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24 Access to Medicine Foundation (2018) Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies. Available at: https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies [Accessed August 2022]

25 PLATINEA (2020) [in Swedish] Risk factors for shortages and barriers to the availability of antibiotics in Sweden: PLATINEA's causal map. Available at: https://www.platinea.se/digitalAssets/771/c_771650-l_3-k_platinea-orsakskarta-20200305.pdf [Accessed August 2022]

26 European Commission, Directorate-General for Health and Food Safety, et al. (2021) Future-proofing pharmaceutical legislation: study on medicine shortages. Available at: https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952 [Accessed August 2022]

27 European Commission (n.d.) Revision of the EU general pharmaceuticals legislation. Available at: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en [Accessed October 2022]

28 European Commission (2020) A Pharmaceutical Strategy for Europe. Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en [Accessed August 2022]

29 European Commission Public Health (n.d.) EU action on antimicrobial resistance. Available at: https://health.ec.europa.eu/antimicrobial-resistance/eu-action-antimicrobial-resistance_en [Accessed August 2022]

More limited evidence exists of medicine supply disruption and its root causes in LMICs,[30] and consequently the policy response has been more limited in those markets.

At a global level, the policy debate related to antibiotic-specific supply challenges is at an early stage. In the G7 Health Ministers' 2021 communique on AMR, they acknowledge the "pressures on complex global drug supply chains and the notable threat to healthcare systems posed by antibacterial shortages, exacerbated during the [COVID-19] pandemic", and the need for collaboration to develop a set of recommendations to strengthen antibiotic supply chain sustainability.[31] The G7 commitments do not reference the need to ensure a sustainable market and supply of off-patent antibiotics.[32] This is perhaps because there is a lack of consensus around the key root causes and how to address these for antibiotics. Furthermore, global issues such as the COVID-19 pandemic, rising inflation, and natural disasters can disrupt the supply of off-patent antibiotics. A number of medicines have been reported to be in short supply in countries across all regions, and many countries have reported price increases in medicines due to rising costs and supply chain challenges encountered during the pandemic. While global issues can have an impact on all goods, manufacturers of off-patent antibiotics face these challenges in addition to the specific challenges associated with off-patent antibiotic production.

The objective of this project is to add greater clarity on the root causes underlying market unsustainability and the degree to which this necessitates a coordinated policy response to address the issue. We define sustainability as a market that provides access to existing antibiotics in a variety of country circumstances over the short, medium and long term. A sustainable market delivers savings while remaining profitable, reduces manufacturer exits, and is responsive to changes in demand and resistant to supply shocks caused by market dynamics, aiming to deliver optimal patient outcomes.

1.2. Methodology

To understand the challenges affecting the supply of off-patent antibiotics and to assess policies that are proposed to strengthen supply chain sustainability, as well as evaluate their application to HICs and LMICs, we used a three-step methodology:

- **Step 1:** A literature review of the global off-patent antibiotic market and policy environment
- **Step 2:** A case study analysis of five countries
- **Step 3:** An interview programme with external experts on off-patent antibiotic markets and the challenges of ensuring sustainable supply

30 Sabogal De La Pava, M.L. and Tucker, E.L. (2022) Drug shortages in low- and middle-income countries: Colombia as a case study. *J of Pharm Policy and Pract* 15:42.

31 G7 Health Ministers (2021) G7 Health Ministers' Meeting, communique, Oxford, 4 June, 2021. Available at: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021 [Accessed August 2022]

32 G7 Health Ministers (2022) G7 Health Ministers' Communiqué 20 May 2022, Berlin. Available at: https://www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccfaffd1e37a1/2022-05-20-g7-health-ministers-communique-data.pdf [Accessed August 2022]

A general literature review

We conducted a literature review to determine what factors influence sustainability in off-patent antibiotic medicine markets. The literature review helped inform our hypothesis on the level of challenge with ensuring supply of off-patent antibiotics, the root causes of supply challenges for off-patent antibiotics and the policy solutions to promote sustainability of the off-patent antibiotic market. We used keywords such as 'antibiotic shortages', 'medicine shortages', 'supply sustainability' and 'antibiotic supply chains' to direct our research. The review concentrated on research published in the previous 10 years, and included over 60 academic and governmental policy reports, non-government organisation publications and grey literature sources published on databases such as PubMed, Science Direct, and Google Scholar. Although we captured recent evidence and data where available, limitations in the quality and volume of recent literature resulted in the use of several sources from 10 or more years ago. Quantitative data were extracted from the literature where available, and additional searches were done using national drug databases and secondary sources such as GlobalData.

For the purposes of this study, and to align with the global policy debate, we adopted a focus on the broad concept of 'supply sustainability'. When using this term, we include shortages (as defined by any country case study used to illustrate the issue), but also include any disruption or weakness along the supply chain, from raw materials through to production, storage, procurement and delivery to pharmacies. 'Supply sustainability' also encompasses market withdrawals of antibiotics caused by supply or demand factors and considers redundancies along the supply chain. By adopting a more holistic definition of the problem, we can look across the literature on the complex antibiotic supply chain to identify all relevant areas of fragility.

Country case studies

In the second stage we conducted a more detailed literature review, focusing on five specific countries. The aim of the case studies was to demonstrate how country policy and pharmaceutical market environments can influence the sustainability of off-patent antibiotic supply chains, both positively (tackling shortages) and negatively (creating or exacerbating the challenge). The following criteria were used to select the countries for case study analysis:

- *Level of economic development*: We chose countries that represent a range of levels of economic development, driven by the hypothesis that high-, middle- and low-income countries experience different levels of supply challenge and may require different solutions.
- *Transferability of findings*: We chose countries that can act as models for other similar markets due to health system structure or political similarities.
- *Data availability*: We chose markets where data are available to support an understanding of the supply chain and occurrence of shortages, given the widespread challenges with data availability in this area.
- *Pharmaceutical market structure*: We chose countries that represent a variety of pharmaceutical market structures to understand the impact that differences in the mechanisms used to procure, fund and deliver medicines have on sustainability, and to account for different structures in the policy recommendations.

As a result of this process, we narrowed down our case study countries to Brazil, Germany, India, South Africa and Vietnam based on the specific rationales summarised in **Table 1.**

We did not include a low-income country as a case study because of anticipated challenges with obtaining sufficiently granular information from secondary sources; however, to enhance our analysis, we conducted a supplementary literature review focusing broadly on low-income countries.

Table 1: Case study countries selected for the analysis

Region	Country	Main rationale for selection
Latin America	**Brazil**	Regionally significant upper-middle-income market with documented antibiotic shortage problem
Europe	**Germany**	Politically relevant high-income market, particularly given G7 presidency at the time of our research
Asia-Pacfic	**India**	Globally significant market with mixed procurement structure and substantial private market. One of the world's largest antibiotic producers and exporters
Asia-Pacfic	**Vietnam**	Lower-middle-income market with hospital-driven procurement and management of antibiotics
Africa and Middle East	**South Africa**	Regionally representative upper-middle-income market; documented antibiotic shortage problem

For each case study country, we gathered data on the off-patent antibiotic market situation (including the AMR burden, market availability of antibiotics, occurrence of shortages and impact of these, and degree of reliance on external sources of active pharmaceutical ingredients (APIs). We also examined the policy environment. To do this, we examined academic studies and reports, governmental and non-governmental publications, and grey literature including local media reports.

External stakeholder interviews

Finally, we interviewed key experts on the sustainability of off-patent antibiotic medicines, in order to pressure-test and supplement findings from the literature review and particularly to gain a deeper understanding of country case studies. The discussion focused on the challenges of ensuring supply of off-patent antibiotic medicines, the root causes of supply challenges, and potential policy solutions to promote the sustainability of the off-patent antibiotic market. Seven discussions were conducted between May and August 2022. Some stakeholders have requested to be anonymous in the final report. Table 2: List of external interviewees

Region		Name	Organisation / Affiliation
	Global	Dr Jonathan Rodrigues	World Health Organization

		Blinded	Global nonprofit healthcare foundation
		Professor Enrico Baraldi	PLATINEA
		Dr Jeremy Knox	Wellcome Trust
		Mr Yann Ferrisse and Dr Jennifer Cohn	GARDP
	Brazil	Dr Luciana Giusti	University of São Paulo
	Germany	*Blinded*	Payer at German health insurance fund
	India	*Blinded*	Infectious disease physician and academic
	South Africa	Carol Ruffell	Head of the regional DNDi/GARDP office
		Dr Sarah Stacey and Dr Tahir Ismail	Division of Infectious Diseases, Department of Internal Medicine at Charlotte Maxeke Johannesburg Academic Hospital
	Vietnam	Dr Justin Beardsley	Oxford University Clinical Research Unit in Ho Chi Minh City; University of Sydney

1.3. Structure of the report

The structure of the report is as follows:

- Chapter 2 examines the fragility of off-patent antibiotic supply chains.
- Chapter 3 summarises the key root causes of supply chain instability.
- Chapter 4 provides a framework for improving supply chain sustainability.

2. Concerns regarding the sustainability of off-patent antibiotic supply chains

In this chapter, we consider the evidence on the sustainability of off-patent antibiotic supply chains today and how this varies across our case studies. We first look at evidence on how sustainability is changing and then consider the implications of this for different stakeholders.

2.1. Sustainability: the challenge of definitions and data availability

Supply sustainability is often equated with how often there are shortages and the impact this has on the healthcare system and patients. There are a number of issues with focusing on a single metric.

Despite the long-standing and widespread challenge of drug shortages, there is not a unified definition of the term. Focusing just on the term 'shortage', an EU study found 26 unique definitions of drug shortage amongst Member States, and the WHO has found 56 definitions in use worldwide.[33] Because of the variation in use of the term shortage, it is difficult to compare data across countries. Work is ongoing in some regions to harmonise the definitions used, but the issue has not yet been resolved.[34]

Antibiotics shortages are also likely to differ from shortages in other therapeutic areas. For example, there are definitions already in wide use that characterise shortages as periods of time in which demand for a drug exceeds supply. [35] Antibiotic shortages may arise due to a spike in demand after a prolonged period of low demand. This means we need to be careful when comparing shortages in antibiotics to those in other disease areas.

Finally, even if we were to have a standardised definition, making comparisons across countries would be challenging due to poor levels of data availability, transparency and quality in many countries with respect to shortages,[36] particularly when separating out a particular class of medicine, such as antibiotics. To overcome this, we did not use a purely empirical approach but focused on examples across a number of different dimensions:

- The degree to which supply sustainability has changed over time
- The degree to which examples of supply issues can be identified
- The degree to which antibiotics contrast with other therapeutic areas

33 Shukar, S. et al. (2021) Drug Shortage: Causes, Impact, and Mitigation Strategies. *Front. Pharmacol*. https://doi.org/10.3389/fphar.2021.693426

34 European Medicines Agency (2019) Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA). Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf [Accessed August 2022]

35 Shukar, S. et al. (2021) Drug Shortage: Causes, Impact, and Mitigation Strategies. *Front. Pharmacol*. https://doi.org/10.3389/fphar.2021.693426

36 Alsheikh, M. et al. (2016) A Comparison of Drug Shortages in the Hospital Setting in the United States and Saudi Arabia: An Exploratory Analysis. *Hosp Pharm*. 51(5): 370–375

For the purposes of this report, we consider unsustainability to be a lack of a sustainable supply of a medicine at any given point across a region or globally, or where demand exceeds supply due to market dynamics, resulting in poorer health outcomes. A sustainable supply is a consistent and dependable supply of off-patent antibiotics, with a reduced risk of shortages.

2.2. Evidence on global antibiotic supply chain sustainability

Antimicrobials are critical medicines that play an important role in the treatment of infectious diseases; their advancement has not only helped to lower infectious disease mortality but also enabled technological advances in cancer therapy, transplantation and surgery.[37] However, there is evidence that over the last few decades, the global supply of antibiotics has become less sustainable.

1 – Occurrence of shortages and unavailability of antibiotics is increasing

Evidence indicates that despite growing awareness of the problem, the occurrence of antibiotic shortages is increasing worldwide.[38] Although few countries have data that are comparable over time, we can look at data from the US. In the US, where there are strong centralised shortage reporting systems (and therefore data are considered to be more accurate than in other regions), the occurrence of new shortages rose by 380% between 2006 and 2011, with a steady decline since 2011.[39] Between 2007 and 2013, the number of antibiotics on shortage increased at a rate of 0.35 additional drugs per month (or 4 per year).[40] In 2020, antibiotics were 42% more likely than all other drugs to be in short supply.[41] The WHO's 2019 report on antibiotic shortages also echoed the concern that the frequency of shortages appears to be increasing, even in regions that house most of the production of antibiotics.[42]

2 – Examples of a lack of sustainability across international markets

Despite the lack of comparable data across countries, evidence of the global problem of off-patent antibiotic supply can be identified through high-profile examples occurring over the last 10 years. In 2010, 15 countries reported national stock-outs of injectable streptomycin, an antibiotic used to treat tuberculosis and other serious infections. The WHO

37 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*, 6(11): e006961

38 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6(11): e006961

39 Drug Shortages Summit (2014) Available at: https://www.pewtrusts.org/-/media/assets/2015/02/2014-drug-shortages-summit.pdf [Accessed August 2022]

40 Quadri, F. et al. (2015) Antibacterial drug shortages from 2001 to 2013: implications for clinical practice. *Clin Infect Dis*. 60(12): 1737–1742.

41 USP (2022, May) U.S. Pharmacopeia Medicine Supply map analysis shows increased shortage risk for antibiotics. Available at: https://www.usp.org/news/usp-medicine-supply-map-analysis-shows-increased-shortage-risk-for-antibiotics [Accessed August 2022]

42 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

estimated that 110,000 people across 41 countries would lack access, with the global shortage escalating.[43] Between 2014 and 2016, 41% of surveyed countries reported a shortage of benzathine penicillin G (BPG); BPG is the only recommended treatment to prevent mother-to-child transmission of syphilis.[44]

Across our five case study countries, despite the differences in their level of economic development and health system structure, there is consistent evidence of antibiotic shortages, indicating that no region is unaffected by the problem:

- *Europe*: Germany, despite having one of the best-funded health systems in the world,[45] experiences the impact of global supply chain disruptions. Following the breakdown of the piperacillin supply chain in late 2016, the Federal Ministry of Health reported a state of emergency in January 2017.[46] Generic antibiotics have been particularly highlighted as a medicine group that is more frequently subject to shortages.[47] Further, cost pressures on generic medicines in Germany have increased substantially, which has been linked to a reduced security of supply, according to industry sources.[48]
- *Asia-Pacific*: In Vietnam there is poor documentation of drug shortages, but the problem appears widespread. Of the 34 Departments of Health hospitals surveyed by the Ministry of Health in 2022, 28 reported drug shortages, including reserve antibiotics used to treat critically ill patients.[49] India, despite being a global hub for antibiotic production, is not unaffected. The availability of essential antibiotics such as ampicillin and penicillin has been documented to be as low as 0.0%–2.5% across health facilities.[50] Recently a high-profile widespread shortage of the antifungal drug amphotericin B occurred in the midst of the COVID-19 pandemic (when it was used to treat fungal infections in COVID patients), with parallel increases in the prevalence of other drug-resistant fungal infections.[51]

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43 Editorial (2010) Shortage of streptomycin: time for a change of approach? *The Lancet.* 376(9754): 1712.

44 Nurse-Findlay, S. et al. (2017) Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. *PLoS Med*. 14(12): e1002473.

45 https://data.oecd.org/healthres/health-spending.htm [Accessed August 2022]

46 Tröbitscher, N. (2017) [In German] Piperacillin: BMG ruft Notstand aus. Available at: https://www.apotheke-adhoc.de/nachrichten/detail/pharmazie/bmg-bestaetigt-versorgungsmangel-fuer-piperacillin/ [Accessed August 2022]

47 Melck, B. (2018) Drug supply shortages in Germany. Available at: https://www.pharmaceutical-technology.com/pricing-and-market-access/drug-supply-shortages-in-germany-html/ [Accessed August 2022]

48 https://www.progenerika.de/topics/security-of-supply/supply-shortages/?lang=en

49 Ministry of Health (2022) [In Vietnamese] Dự kiến đến 15/7, thêm 3.000 thuốc, nguyên liệu làm thuốc, sinh phẩm y tế được gia hạn số đăng ký. Available at: https://moh.gov.vn/tin-lien-quan/-/asset_publisher/vjYyM7O9aWnX/content/du-kien-en-15-7-them-3-000-thuoc-nguyen-lieu-lam-thuoc-sinh-pham-y-te-uoc-gia-han-so-ang-ky [Accessed August 2022]

50 Kotwani, A. and Holloway, K. (2013) Access to antibiotics in New Delhi, India: implications for antibiotic policy. *Journal of Pharmaceutical Policy and Practice*, 6:6.

51 Arun, A.B. et al. (2021) Antifungal drug shortage in India amid an increase in invasive fungal functions during the coronavirus disease 2019 (COVID-19) pandemic. *Infection Control & Hospital Epidemiology*, 1–2.

- *Latin America*: In Brazil, a difference can be observed between public and private hospitals, with private hospitals less affected by drug shortages (75% of facilities reporting a problem) than public hospitals (90% of facilities reporting a problem).[52] The global BPG shortage affected Brazil acutely, particularly in poorer areas,[53] and with shortages still being reported in 2019.[54]
- *Africa and Middle East*: In South Africa, chronic shortages of essential medicines are a major national problem.[55] Antibiotic shortages are common, with 83% of hospitals experiencing an antibiotic shortage in a six-month period.[56] There are large interprovincial differences: one national study found that stock-outs of HIV and tuberculosis medicines in the three months prior ranged from 12% of health facilities in one province to 74% in the most affected province.[57]

3 – Comparisons show antibiotic supply chains have a greater risk of failure than other medicines

In the US, the FDA has reported that antibiotics are among the top five classes of drugs in shortage, which collectively account for over half of total drug shortages.[58] On their own, antibiotics are 42% more likely to be in short supply than all other drugs in the US.[59] Antimicrobials are frequently reported to be in short supply, according to research conducted across Europe. In France, for example, a study that examined 1,833 different active substances between 2012 and 2018 discovered that the majority of drugs in short supply (63.4%) were old products. Anti-infectives for systemic use ranked first (18%), followed by drugs for the nervous and cardiovascular systems, antineoplastics, and immunomodulators (17.4%, 12.5% and 10.4%, respectively).[60] The European Association

52 Regional Pharmacy Council of the State of São Paulo (2021) [In Portuguese] Abastecimento de Medicamentos e Produtos Para a Saúde. Available at: http://www.crfsp.org.br/images/arquivos/Relatorio_abastecimento_word.pdf [Accessed August 2022]

53 Sarmeiro Araujo, R., Semeão de Souza, A.S. and Ueleres Braga, J. (2020) [In Portuguese] A quem afetou o desabastecimento de penicilina para sífilis no Rio de Janeiro, 2013–2017? *Rev. Saúde Pública* 54.

54 Cordão, M. (2019) [In Portuguese] Brasil atravessa crise no fornecimento de penicilina para tratar sífilis. Available at: https://www.brasildefato.com.br/2019/06/11/brasil-tem-crise-no-fornecimento-de-penicilina-que-trata-sifilis/ [Accessed August 2022]

55 https://stockouts.org/Home/About [Accessed August 2022]

56 Chigome, A.K. et al. (2019) Availability and Use of Therapeutic Interchange Policies in Managing Antimicrobial Shortages among South African Public Sector Hospitals; Findings and Implications. *Antibiotics*. 9(1): 4.

57 Hwang, B. et al. (2019) Stock-outs of antiretroviral and tuberculosis medicines in South Africa: A national cross-sectional survey. *PLoS ONE*. 14(3):e0212405.

58 Drug Shortages Summit (2014) Available at: https://www.pewtrusts.org/-/media/assets/2015/02/2014-drug-shortages-summit.pdf [Accessed August 2022]

59 Raghavendran, V. and Christian, M. (2022) Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map Analysis. Available at: https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines [Accessed August 2022]

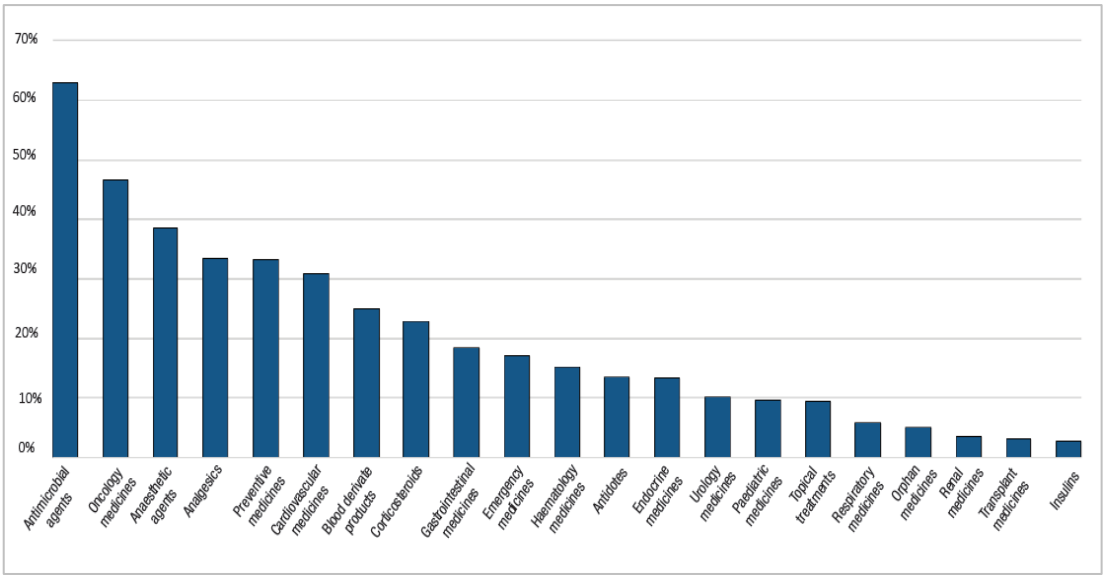
60 Benhabib, A., Ioughlissen, S., Ratignier-Carbonneil, C. and Maison, P. (2020) The French reporting system for drug shortages: description and trends from 2012 to 2018: an observational retrospective study. *BMJ open*. 10(3) e034033. https://doi.org/10.1136/bmjopen-2019-034033

of Hospital Pharmacists' annual survey of drug shortages finds that antibiotics are consistently one of the drug types reported to be most frequently in shortage. From 2014 to 2019, between 63% and 77% of European hospitals experienced shortages of antibiotics.[61] More than half of these hospitals reported that antimicrobial drugs are the most common drug shortage in their hospital (**Figure 2**).

Withdrawals of antibiotics from the market are also more common than non-antibiotics. A study of medicine approvals between 1980 and 2009 found that 43% of approved antibiotics were subsequently withdrawn (versus 13% of non-antibiotics), most of which were not commercially successful.[62] Additionally, the mean date from approval to withdrawal was 15 years; although patent status was not specifically examined, we assume that most of these antibiotics would be off-patent at 15 years post launch.

The reasons for the particular unsustainability experienced by antibiotics are explored in Chapter 3.

Figure 2: Medicine types most commonly reported in shortage by European hospital pharmacists (2019)



Source: European Association of Hospital Pharmacists (2020) [63]

Off-patent drugs are also particularly affected. Two-thirds of drug shortages reported in the US between 2013 and 2017 were drugs that had a generic version on the market. Older, off-patent drugs experienced shortages to an even greater degree.[64] European data echo

61 Miljković N, Polidori P, Kohl S. (2022) Managing antibiotic shortages: lessons from EAHP and ECDC surveys. *European Journal of Hospital Pharmacy*. 29:90–94.

62 Outterson, K. et al. (2013) Approval and withdrawal of new antibiotics and other antiinfectives in the U.S., 1980–2009. *J Law Med Ethics*. 41(3): 688–696.

63 EAHP (2020) 2019 EAHP Medicines Shortage Report. Available at: https://www.eahp.eu/practice-and-policy/medicines-shortages [Accessed August 2022]

64 US FDA (2019) Drug shortages: root causes and potential solutions. Available at: https://www.fda.gov/media/131130/download [Accessed August 2022]

that medicine shortages occur more frequently for older, off-patent drugs. Of 22,487 shortages recorded in Europe in 2019, 97% were off-patent, with an average time since patent expiry of over 19 years.[65] There is a lack of evidence specific to antibiotics; however, individual hospital-level studies have found that a majority of antibiotic shortages affect off-patent products, consistent with trends observed for other drug shortages.[66]

2.3. The impact of supply disruptions to patients and health systems

Another way to consider how sustainability varies across countries is to look at the impact of disruption.

Relatively few studies have looked at the impact of antibiotic shortages on patient outcomes and overall health and financial costs. However, existing evidence points towards negative impact on patient outcomes and healthcare budgets, underpinned by escalation in the burden of resistance (illustrated in **Figure 3**).

- *Patient outcomes*: Many antibiotic shortages involve 'gold standard' therapies for which there are no effective alternatives. Shortages can force the use of therapeutic alternatives that may have lower efficacy and higher toxicity.[67] The impact this has on patients can be most directly observed by looking at the real-world impact of global antibiotic shortages. For example, in Brazil in 2016, as a result of the widespread BPG shortage, 58.1% of pregnant women with syphilis received insufficient treatment, 26.5% received no treatment, 11.3% of cases were ignored, and only 4.1% were adequately treated.[68] Rates of congenital syphilis increased from 4.0 cases per 1,000 live births in 2012 to 6.5 in 2015.[69] Increased mortality has also been reported as a consequence of antibiotic shortages.[70]
- *Healthcare costs:* Antibiotic shortages can also put a strain on healthcare systems and raise healthcare costs; the WHO has estimated that the increased costs of

65 Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting on behalf of the European Commission (2021) Future-proofing pharmaceutical legislation – study on medicine shortages. Available at: https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952 [Accessed August 2022]

66 Griffith, M.M. et al. (2012) Antimicrobial Drug Shortages: A Crisis Amidst the Epidemic and the Need for Antimicrobial Stewardship Efforts to Lessen the Effects. *Pharmacotherapy*; 32(8): 665–667.

67 Quadri, F. et al. (2015) Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice. *Clinical Infectious Diseases*; 60(12): 1737–1742.

68 Sarmeiro Araujo, R., Semeão de Souza, A.S. and Ueleres Braga, J. (2020) [In Portuguese] A quem afetou o desabastecimento de penicilina para sífilis no Rio de Janeiro, 2013–2017? *Rev. Saúde Pública* 54.

69 Nurse-Findlay, S. et al. (2017) Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. *PLoS Medicine*; 14(12): e1002473.

70 Gundlapalli, A.V. et al. (2013) Perspectives and Concerns Regarding Antimicrobial Agent Shortages Among Infectious Disease Specialists. *Diagn Microbiol Infect Dis*; 75(3): 256–259.

shortages for one antibiotic range between €20m and €30m.[71] At a hospital level, one study suggests a 22% increase in antibiotic costs. The total economic cost can consist of not only the direct costs associated with the use of more off-patent antibiotics but also the indirect costs of treating complications arising from treatment with suboptimal therapeutic options as well as those arising from the creation of market opportunities for substandard and falsified medicines.[72] In response to the global BPG shortages, South African authorities were driven to procure more than 240,000 vials of unregistered BPG from a producer previously found to have falsified regulatory documents.[73] During the BPG shortage, many physicians resorted to prescribing broad-spectrum antibiotics such as azithromycin to patients with rheumatic heart disease, which are less effective and may have unintended consequences for antimicrobial resistance. Another market-related consequence is the decrease in competition leading to an increase in the price of an antibiotic. An increase in the price of doxycycline in the US has been attributed to a national shortage in 2013.[74,75] Many companies have stopped production of doxycycline over the years because of extremely low drug prices as well as high raw material costs, making manufacturing unsustainable. As a result of limited manufacturing capacity and increased demand for doxycycline, a shortage occurred, resulting in a significant price increase.[76] There can also be a cost incurred directly to the patient, particularly in LMICs. In Vietnam, for example, when hospital pharmacies experience shortages, patients (those who can afford to do so) then incur large out-of-pocket costs to buy the medicines privately.[77]

- *Spread of resistance*: While worsened patient outcomes and increased costs are impacts that result – to varying extent – from all drug shortages, antibiotics differ from other medications in that shortages may also result in increased drug resistance. If the appropriate antibiotic treatment is unavailable, physicians may have to substitute a preferred narrow-spectrum antibiotic for a broad-spectrum alternative, which contrasts with the principles of antimicrobial stewardship and can

71 World Health Organization. (2018, December 10). Meeting report: Antibiotic shortages: Magnitude, causes and possible solutions. World Health Organization. Retrieved November 16, 2022, from https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions

72 Khumra, S. et al. (2018) Counting the cost of critical antibiotic shortages. *Journal of Antimicrobial Chemotherapy*. 74(1): 273–275.

73 Guimarães, K. (2017) Available at: https://bhekisisa.org/article/2017-05-25-penicillin-shortages-as-pharma-companies-eye-newer-more-lucrative-drugs/ [Accessed August 2022]

74 Alpern, J.D. et al. (2014) High-Cost Generic Drugs – Implications for Patients and Policymakers. *NEJM*. 371(20): 1859–1862.

75 Alpem, J.D. et al. (2017) Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States. *Clinical Infectious Diseases*. 65(11): 1848–1852.

76 Alpern, J.D. et al. (2014) High-Cost Generic Drugs – Implications for Patients and Policymakers. *NEJM*. 371(20): 1859–1862.

77 https://binhphuoc.gov.vn/vi/news/tin-tuc-su-kien-421/nguyen-nhan-chinh-dan-toi-tinh-trang-thieu-thuoc-vat-tu-y-te-29072.html [Accessed August 2022]

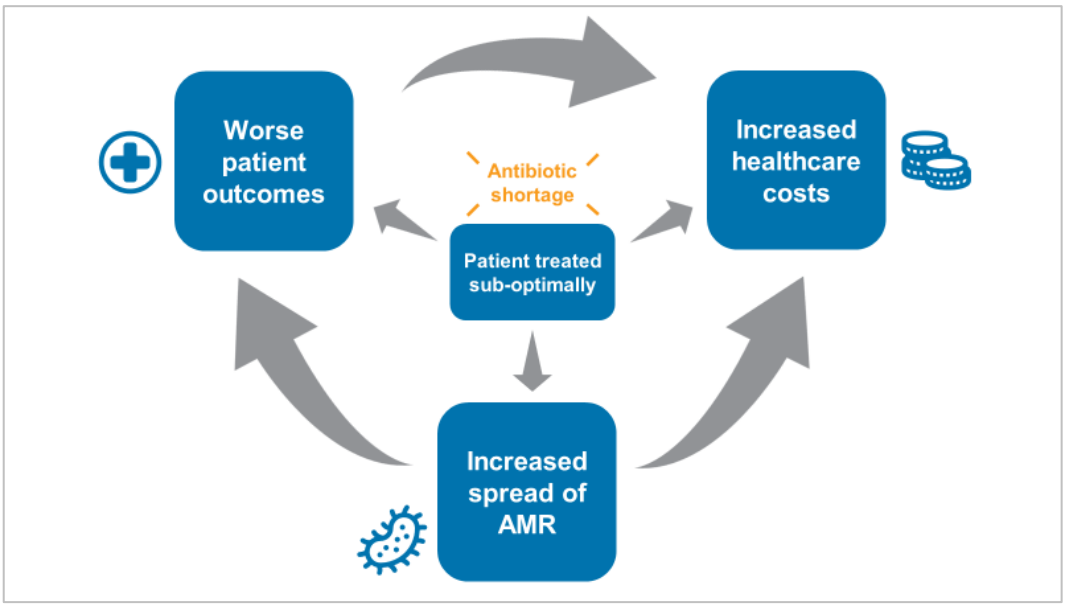
drive increased resistance.[78] This adds to the negative impact of shortages on patient outcomes, as not only do patients not receiving the appropriate antibiotic typically experience worse outcomes, but the spread of resistant bacteria can double the likelihood of patients developing serious health problems and triple the likelihood of death.[79] The economic burden is also increased due to patients requiring longer hospitalisation stays, as well as the need for more intensive care units (ICUs) and isolation beds to prevent the spread of the infection. One example is cefotaxime: the number of companies supplying cefotaxime has decreased in recent years, with only one company supplying it by 2016. Other companies that previously supplied cefotaxime made the business decision to stop production because of the increase in raw material prices. As a result, the sole remaining supplier was unable to meet demand, resulting in a nationwide shortage in the United States. The cefotaxime shortage has disproportionately affected infants, because a comparable cephalosporin, ceftriaxone, which can be used in older children, is generally not used in infants under two months of age due to an increased risk of kernicterus and calcium-ceftriaxone vascular deposits. Because of limited supply, ceftazidime was recommended in place of cefotaxime in infants under two months of age with proven or suspected Gram-negative bacilli infections, particularly meningitis. The use of broad-spectrum therapies in place of cefotaxime may favor drug-resistant bacteria and have a negative impact on patients' microbiomes.[80]

78 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

79 Dadgostar P. (2019) Antimicrobial Resistance: Implications and Costs. Infection and drug resistance, 12, 3903–3910. https://doi.org/10.2147/IDR.S234610

80 Banerjee, R., Thurm, C.W., Fox, E.R., Hersh, A.L. (2018, November 1) Antibiotic shortages in pediatrics. American Academy of Pediatrics. Available at: https://publications.aap.org/pediatrics/article/142/5/e20180858/38547/Antibiotic-Shortages-in-Pediatrics?autologincheck=redirected%3FnfToken [Accessed October 2022]

Figure 3: The interconnected impact of antibiotic shortages



Source: Dadgostar P. (2019)[81]

2.4. Summary

Although there are significant issues with the comparability of data over time and between countries, there is convincing data that sustainability of the off-patent antibiotic market has weakened over time, that it is a widespread issue affecting high-, middle- and low-income markets, and that antibiotics stand out relative to other therapeutic areas. It is also clear that the impact of disruptions in antibiotic markets has significant consequences for patients, the healthcare system and the path of AMR.

Because of these consequences, it is critical to ensure a sustainable supply of antibiotics. The next chapter investigates the root causes of antibiotic shortages and proposes a framework to promote the sustainable supply of off-patent antibiotic medicines.

81 Dadgostar P. (2019) Antimicrobial Resistance: Implications and Costs. Infection and drug resistance, 12, 3903–3910. https://doi.org/10.2147/IDR.S234610

3. Identifying the root causes of supply chain unsustainability

In this chapter we explore factors contributing to the unsustainability of off-patent antibiotic supply. This draws from existing literature analysing root causes of antibiotic supply failures and supplements with insights from interviews undertaken with both global and country-level experts. We use country case studies to illustrate, using real examples, how the identified causes can contribute to supply unsustainability in different types of health systems. Below is a list of the root causes discussed in this chapter:

1. Off-patent antibiotic supply chains are vulnerable to supply problems because of their complexity and fragility

2. Unlike many other medicines, antibiotics may experience low and unpredictable demand

3. Low commercial returns for manufacturers creates an unsustainable market environment exacerbated by procurement policies

4. Concentration into fewer API suppliers is both a symptom of unsustainability of the market and a further driver of shortages

5. Poor supply chain management and lack of collaboration among stakeholders contributes to unsustainability

We see that while some root causes stem from global market challenges, others are more country specific. **Table 3** summarises the causes of some of the most recent shortages globally,[82] As shown in the table, below, the occurrence, magnitude and causes of shortages are varied and complex. We see that, while the most visible disruptions occur at the point of supply (typically at the point of API production), we need to look more deeply to understand the root causes that result in antibiotic shortages.

Table 3: Examples of recent major off-patent antibiotic shortages

Drug Shortage	Timeline	Regions Affected	Cause
Benzathine penicillin G (BPG)	2015 onwards	39 countries	Only four companies produce the active pharmaceutical ingredient, and due to lack of profitability, production levels were kept low
Piperacillin-tazobactam	2017	Worldwide	Explosion at one of the few factories producing raw material for piperacillin-tazobactam factories supplying the API

Cefazolin	2016 onwards	Japan, India	Decreased production, increased demand, price caps

3.1. Cause 1: Off-patent antibiotic supply chains are vulnerable to supply problems due to their complexity and fragility

Antibiotic supply chains are complex in nature, compared to other therapy areas, and involve partnerships among several stakeholders; the actors must collaborate effectively for the medicines to be manufactured, stored, distributed, and dispensed appropriately.[83] The main stages of the antibiotic supply chain are shown in **Figure 4**. As with other medicines, manufacturing is divided into two parts: primary manufacturers, who oversee production of raw materials and intermediates used to make the API, and secondary manufacturers, who are responsible for combining the API with inactive ingredients, as well as packaging and labelling (Finished Dosage Form (FDF) producers). Once packaged, the product is typically distributed to hospitals and retail pharmacies via a wholesaler.[84]

Antibiotic production is a complex and time-consuming multi-stage process that can be easily disrupted, making it difficult to monitor supply chain metrics and make forecasts. The manufacturing process is lengthy and requires numerous processing changes, as the chemical processes involved in API production can vary between synthetic processes, fermentation processes, and a combination of the two.[85] Furthermore, antibiotics require sterile conditions, and some products, such as fermented antibiotics, require separate facilities to avoid cross-contamination, increasing the number of stakeholders involved in the production process and further complicating the supply chain. Therefore, any minor disruption in the manufacturing process can result in major downstream supply issues. Additionally, a vertically integrated production line for generic medicines is extremely rare, and many stages of the production process are frequently outsourced to contract manufacturing companies.[86,87] There is a lack of communication in the antibiotic production process due to proprietary and confidential information, as well as outsourcing of upstream production processes. As a result, many downstream stakeholders are unable to conduct

83 Access to Medicine Foundation (2018) Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies. Available at: https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies [Accessed August 2022]

84 Granada, A. and Wanner, P. (2019, June) Managing supply chain sustainability risks of antibiotics. Available at: https://www.platinea.se/digitalAssets/843/c_843338-l_3-k_grau---wanner---managing-supply-chain-sustainability-antibiotics-2019.pdf [Accessed August 2022]

85 Granada, A. and Wanner, P. (2019, June) Managing supply chain sustainability risks of antibiotics. Available at:https://www.platinea.se/digitalAssets/843/c_843338-l_3-k_grau---wanner---managing-supply-chain-sustainability-antibiotics-2019.pdf [Accessed August 2022]

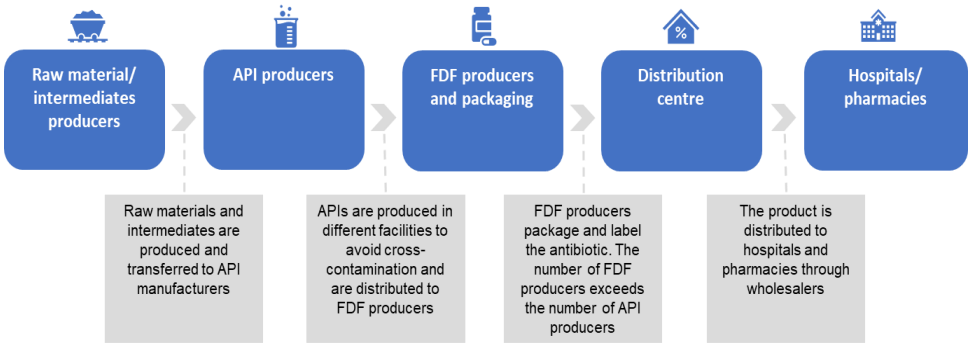
86 Granada, A. and Wanner, P. (2019, June) Managing supply chain sustainability risks of antibiotics. Available at: https://www.platinea.se/digitalAssets/843/c_843338-l_3-k_grau---wanner---managing-supply-chain-sustainability-antibiotics-2019.pdf [Accessed August 2022]

87 Boston Consulting Group and Wellcome Trust (2022) Understanding the antibiotic manufacturing ecosystem. Available at: https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf [Accessed August 2022]

true risk assessments to identify areas of vulnerability and can only react to major disruptions and shortages.[88]

Shortages can also be caused by interruptions in the supply of raw materials. This can be especially problematic when a primary or sole-source supplier of a raw material delays or discontinues production, affecting multiple manufacturers. Even if there are multiple manufacturers of a drug, there may be only one producer of a raw material used in the production of that drug. As a result, any disruption in the supply of that substance will affect all producers of the finished product.[89] Studies have linked increasing redundancy in the supply chain (defined as having some resources in reserve, such as using multiple suppliers and keeping deliberately low-capacity utilisation rates) with a reduced occurrence of shortages.[90] However, regulators have noted that an underlying reason for lack of investments in redundant capacity in off-patent supply chains is the poor market conditions that generic manufacturers encounter. Redundancy represents cost without return on investment in the case of supply disruption. This has led to the development of effective single-source supply chains.[91]

Figure 4: Overview of the off-patent antibiotic supply chain



Source: Adapted from BCG and Wellcome Trust (2022)[92]

Manufacturing challenges, such as quality issues and delays, contribute to the supply chain's complexity and fragility. Because of the complexity of the supply chain for off-patent antibiotics, as well as the interaction of multiple stakeholders, there are multiple

88 World Health Organization (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

89 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

90 Tucker, E. and Daskin, M.S. (2022) Pharmaceutical supply chain reliability and effects on drug shortages. *Computers & Industrial Engineering*. 169:108258.

91 FDA (2020, February) Drug shortages: Root causes and potential solutions. Available at: https://www.fda.gov/media/131130/download [Accessed October 2022]

92 Boston Consulting Group and Wellcome Trust (2022) Understanding the antibiotic manufacturing ecosystem. Available at: https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf [Accessed August 2022]

points in the supply chain where impurities in manufacturing facilities could be discovered, or delays could occur because of poor communication between stakeholders.[93] Research has found that manufacturing-related problems are one of the most common causes of drug shortages. Quality issues are frequently discovered during daily quality checks and post-manufacturing inspections, which need to be resolved before distribution to patients.[94]

Case study:

LMICs: Low- and middle-income countries frequently lack government and health ministry guidance in monitoring and implementing good manufacturing practices. As a result, many manufacturing facilities lack the standardised and sterile conditions required for medication products, which can lead to contamination, recalls and shortages. Antibiotics account for 17% of substandard or falsified medicines reported to the WHO in LMICs, compared to a 10% failure rate for all medicinal products.

Source: Shukar et al (2021)[95]*, Frost et al. (2019)* [96]

In the global BPG shortage, manufacturing quality issues were a factor in prolonging the shortage, as seen in Brazil.

Case study:

Brazil: In 2015, the Brazilian Health Regulatory Agency (ANVISA) withdrew the good manufacturing practice certificate from the API supplier for penicillin manufacturing, which worsened BPG shortages in Brazil.

Source: Araujo, Souza and Braga (2020) [97]

3.2. Cause 2: Unlike many other medicines, antibiotics may experience low and unpredictable demand

Unlike many other therapy areas with a high proportion of off-patent prescriptions, such as oncology and cardiology, it is argued that the demand for antibiotics is subject to

93 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

94 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

95 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

96 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

97 Araujo, R.S., Semeão de Souza, A.S. and Ueleres Braga, J. (2020, November 2) Who was affected by the shortage of penicillin for syphilis in Rio de Janeiro, 2013–2017? *Revista de Saúde Pública*. Available at: https://www.scielo.br/j/rsp/a/kkTwYR7cq7Yb6WHXVMqfcVy/?lang=en [Accessed August 2022]

unpredictable peaks and troughs as a result of infection outbreaks and changing trends of resistance.[98] This can refer to global demand – for example, as observed through the massive increase in demand for antibiotics during the unanticipated COVID-19 pandemic – but it can also refer to patterns of local demand, such as those caused by sporadic infection outbreaks in hospital settings.[99] Furthermore, antibiotics have been overused in medicine, causing them to lose their effectiveness. It is estimated that up to 50% of all prescribed antibiotics are either unnecessary (for example, antibiotics used to treat viral infections) or are not properly "matched" to the bacteria being treated, and thus are not as effective as they could be. This has resulted in an increase in drug-resistant infections around the world, highlighting the importance of diagnostic tests in any strategy to reduce antibiotic resistance.[100] Diagnostic tests can help doctors determine when to start, and more importantly, when to stop, antibiotics, ensuring that patients only get these powerful drugs when they need them. Additionally, diagnostic tests can assist clinicians in determining whether an antibiotic will cure an infection and which specific drug will be most effective. This has the potential to significantly improve patient care while also slowing antibiotic resistance.

Case study:

India outbreak: During the COVID-19 pandemic, the use of steroids in severely ill COVID-19 patients caused an outbreak of mucormycosis (black fungus). As a result, demand for amphotericin B increased rapidly, resulting in a widespread shortage. Prior to the pandemic, the manufacturing volumes of amphotericin B were low due to low occurrence rates and demand. Following the outbreak, many local manufacturers increased supply; however, this was insufficient to address the shortage.

Source: Arun et al (2021)[101]

An unpredicted rise in demand for BPG contributed to the impact of the global BPG shortage in Brazil between 2010 and 2015.

98 Knox, J. (2020, November 1) It's time to fix the antibiotic market. Wellcome. Available at: https://wellcome.org/news/its-time-fix-antibiotic-market [Accessed August 2022]

99 Oliveira Silva, A.R. et al. (2021) Increased Use of Antibiotics in the Intensive Care Unit During Coronavirus Disease (COVID-19) Pandemic in a Brazilian Hospital. *Front. Pharmacol*. 12: 778386.

100 Williams, D.-A. (2021, March 10) Diagnostic tests are vital in the fight against antimicrobial resistance. Global Cause. Available at: https://www.globalcause.co.uk/antibiotic-resistance/diagnostic-tests-are-vital-in-the-fight-against-antimicrobial-resistance/ [Accessed October 2022]

101 Arun, A.B. et al. (2021) Antifungal drug shortage in India amid an increase in invasive fungal functions during the coronavirus disease 2019 (COVID-19) pandemic. *Infection control and hospital epidemiology*, 1–2. Advance online publication. https://doi.org/10.1017/ice.2021.426

Case study:

***Brazil syphilis outbreak**:* Between 2010 and 2014, there was a significant increase in the number of syphilis cases in Brazil, with over 14,000 confirmed cases in pregnant women. Penicillin can be used to treat syphilis; however, if left untreated, it can affect the central nervous system and cause serious complications, and it can be passed on to babies.[1] As a result of the increase in syphilis cases and the global penicillin shortage in 2015, poor patient outcomes and the spread of syphilis were exacerbated. Between 2012 and 2015, the number of babies born in Brazil with congenital syphilis more than doubled, and the demand for penicillin surged.

Source: Guimarães (2016),[102] Andalo (2018)[103]

Antibiotic demand can also fluctuate due to unregulated use, such as in countries with widespread self-medication.[104] Poor infection control practices and disregard for warnings against antibiotic overuse frequently result in AMR and fluctuating demand for antibiotics. The primary reason for self-medication is the high cost of using the healthcare system, such as the consultation fees associated with doctor visits.[105] We can see the impact of self-medication in our case study countries:

Case study:

India self-medication: Self-medication of antibiotics is widespread in India. There is a perception that doxycycline, a common antibiotic, is in short supply due to unchecked stocking and self-medication. Doctors noticed that a number of patients were self-treating at home with doxycycline. Given their concerns about supply, patients were stockpiling the medication, resulting in a market crisis and shortage. Accounting for this unpredictable variation in demand at global and local levels is challenging for suppliers. This is exacerbated by the healthcare system; many healthcare professionals in LMICs frequently prescribe medicines inappropriately, without the results of diagnostic tests. Thus fears of shortages can become self-fulfilling.

102 Guimarães, K. (2016, August) The real infectious disease problem in Brazil isn't actually Zika, it's Syphilis. Quartz. Available at: https://qz.com/763105/brazil-zika-syphilis-infant-mortality/ [Accessed August 2022]

103 Andalo, D. (2018, June) Antibiotic shortages are fueling antimicrobial resistance, say experts. *The Pharmaceutical Journal.* Available at: https://pharmaceutical-journal.com/article/news/antibiotic-shortages-are-fuelling-antimicrobial-resistance-say-experts [Accessed August 2022]

104 Dranitsaris, G. et al. (2017, September 29) Drug tendering: Drug supply and shortage implications for the uptake. ClinicoEconomics and Outcomes Research. Available at: https://www.dovepress.com/drug-tendering-drug-supply-and-shortage-implications-for-the-uptake-of-peer-reviewed-fulltext-article-CEOR [Accessed August 2022]

105 Rather, I.A., Kim, B.C., Bajpai, V.K. and Park, Y.H. (2017) Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. *Saudi journal of biological sciences*. 24(4): 808–812. https://doi.org/10.1016/j.sjbs.2017.01.004

Source: Malik, Frooqui & Bhattacharyya (2022),[106] *Banerjee (2021),*[107] *Frost (2019)* [108]

3.3. Cause 3: Low commercial returns for manufacturers creates an unsustainable market environment exacerbated by procurement policies

Many reports analysing the antibiotic market observe that there are fewer and fewer manufacturers entering or maintaining a presence in the market as a result of low profitability.[109] There is a common perception that manufacturers are struggling and are exiting the off-patent antibiotic market to focus on more profitable areas.[110] Most antibiotics are off-patent today and have faced significant competition from generic manufacturers, which resulted in significant price erosion. Furthermore, because many antibiotics are high-volume products that have been on the market for many years, they have relatively low prices when compared to recent medicines in other classes, in addition to experiencing mandatory price discounts over the years. For example, a recent study showed that the entry of a second generic competitor reduces average prices by half, with further price reductions associated with the third, fourth and fifth generic competitors; this is not limited to off-patent antibiotics, but rather to all off-patent products.[111] As illustrated by the WHO, this can, in theory, lead to prices falling to an unsustainable level, with the result that manufacturers may leave the market, leaving only a few remaining, increasing the risk of shortages (as shown below in **Figure 5**).[112,113] Furthermore, the antibiotic supply chain necessitates the separation of production facilities due to the chemical processes involved

106 Malik, B., Farooqui, H.H. and Bhattacharyya, S. (2022) Disparity in socio-economic status explains the pattern of self-medication of antibiotics in India: understanding from game-theoretic perspective. *R Soc Open Sci*. 9(2): 211872.

107 Banerjee, T. (2021, May) Kolkata: Stocking, self-medication trigger antibiotic shortage . The Times of India. Available at: https://timesofindia.indiatimes.com/city/kolkata/stocking-self-medication-trigger-antibiotic-shortage/articleshow/82585467.cms [Accessed August 2022]

108 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

109 Baraldi, E. (2022, March 4) Causes of antibiotic shortages and the solutions to address them – by Enrico Baraldi. Global Antibiotic Research & Development Partnership. Available at: https://revive.gardp.org/causes-of-antibiotic-shortages-and-the-solutions-to-address-them/ [Accessed August 2022]

110 World Health Organization (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

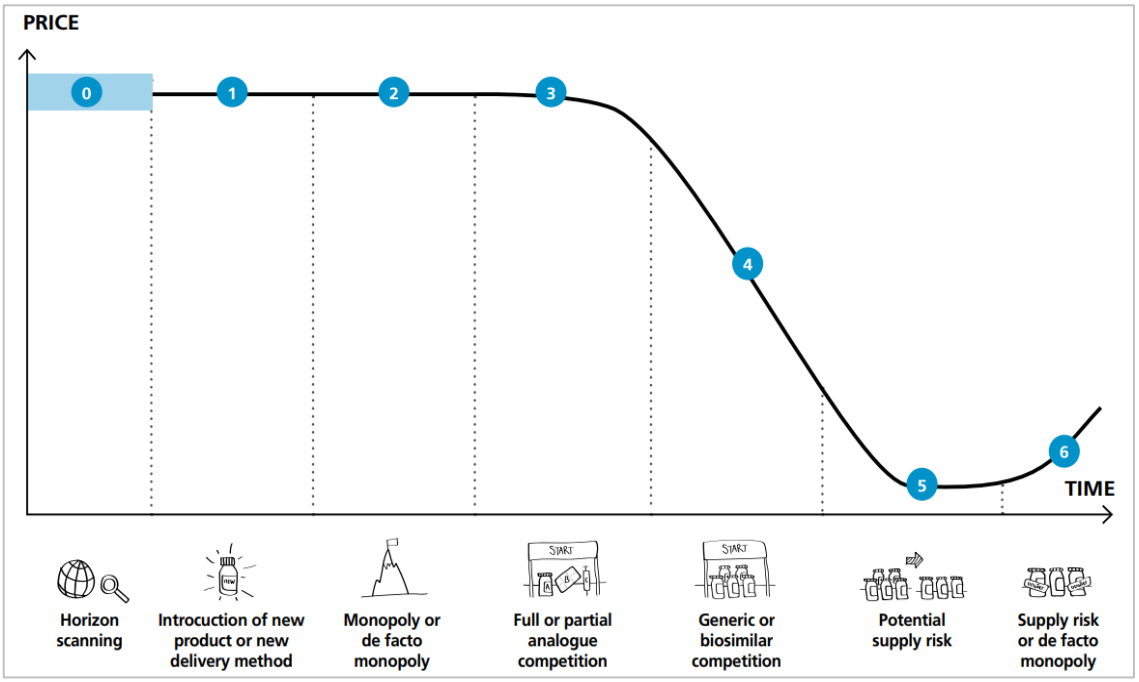
111 Alpern, J.D. et al. (2017) Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 65(11): 1848–1852. https://doi.org/10.1093/cid/cix634

112 Alpern, J. D. et al. (2017) Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 65(11): 1848–1852. https://doi.org/10.1093/cid/cix634

113 World Health Organization (2016, January 1) Challenges and opportunities in improving access to medicines through efficient public procurement in the WHO European Region. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/344000 [Accessed August 2022]

in the manufacturing process. As a result, unlike in other areas of therapy, many manufacturers are unable to achieve efficiencies and cost savings by manufacturing medicines in a single facility. Maintaining the facility becomes extremely difficult and costly if there is insufficient volume for an antibiotic. Another consequence of price erosion is the difficulty that manufacturers may have in optimising supply chain risk management strategies.[114] Due to a lack of commercial returns, manufacturers report that they may be unable to invest in mitigation strategies. Furthermore, because of the low profitability associated with off-patent antibiotic production, the commercial environment affects not only finished product manufacturers, but also many upstream manufacturers (API and raw material producers).[115]

Figure 5: Relationship between price and pharmaceutical life cycle stages



Source: WHO (2016)[116]

Low commercial returns can result in shortages at both global and regional or local levels:

114 Granada, A. and Wanner, P. (2019, June) Managing supply chain sustainability risks of antibiotics. Available at: https://www.platinea.se/digitalAssets/843/c_843338-l_3-k_grau---wanner---managing-supply-chain-sustainability-antibiotics-2019.pdf [Accessed August 2022]

115 Alpern, J.D. et al. (2017) Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 65(11): 1848–1852. https://doi.org/10.1093/cid/cix634

116 World Health Organization (2016, January 1) Challenges and opportunities in improving access to medicines through efficient public procurement in the WHO European Region. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/344000 [Accessed August 2022]

Case study:

***Global impact**:* As described in Chapter 2, in 2014 there was a worldwide shortage of benzathine penicillin G (BPG), the primary treatment for syphilis and for rheumatic heart disease. One of the primary causes of the global shortage of BPG was the product's commercial viability. Given the dynamics of the off-patent antibiotic market, BPG is currently available at a very low price (US$0.11–$0.20 per unit dose). Some countries have also set a price cap on BPG, which keeps the price low. Even if prices were to rise, there is skepticism about whether this would lead to entry of new manufacturers. BPG is an injectable and must be manufactured under sterile conditions, which necessitates a significant financial investment in specialised manufacturing infrastructure. The financial burden and lack of reward associated with manufacturing BPG has discouraged manufacturers from staying in or entering the market, leading to shortages globally.

Source: Cogan, Karrar and Iyer (2018),[117] *WHO (2017),*[118] *Shafiq et al. (2021)*[119]

This dynamic can also be observed at a country level, as seen in India and Germany.

Case study:

India: A study conducted in India discovered a significant decrease in availability of cefazolin, and occurrence of shortage. This has been investigated in a number of studies, which have attributed it to a decline in the annual turnover of cefazolin sales between 2016 and 2017 due to the effect of price controls on essential medicines as part of the government's pharmaceutical price control policy. This has been supported by other studies finding that lower profitability on certain antibiotic formulations, possibly due to price controls, has caused companies to reduce production.

117 Access to Medicine Foundation (2018) Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies. Available at: https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies [Accessed August 2022]

118 World Health Organization (2017, December) Shortages of benzathine penicillin. How big is the problem? And why it matters. Available at: https://www.who.int/news/item/26-12-2017-shortages-of-benzathine-penicillin.-how-big-is-the-problem-and-why-it-matters [Accessed August 2022]

119 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6(11) e006961. https://doi.org/10.1136/bmjgh-2021-006961

Source: Kakkar, Shafiq and Malhotra (2019),[120] *Frost et al. (2019)* [121]

Case study:

Germany: The market for old off-patent antibiotics is unprofitable, which for some of these has resulted in a reduction in supply. The scarcity of older off-patent antibiotics in Germany feeds a cycle of low physician demand, as it drives a perception amongst physicians that the off-patent antibiotic will not be available, which further reduces the perceived market size, making the market for older antibiotics unattractive. The cyclic nature of shortages and reduced physician demand as a result of shortages can further worsen access to antibiotics and disincentivise manufacturers from remaining in the market.

Source: Frost et al. (2019)[122]

There is an increasing amount of empirical evidence supporting the theory that low commercial returns are contributing to antibiotic supply unsustainability at a global level, highlighting a systemic challenge, but are also resulting from unsustainable pricing and procurement policies in specific countries. This has been exacerbated by unsustainable tendering practices and procurement models focused on the lowest cost possible. Over the last 10 years, many countries have implemented procurement models in which the purchaser typically awards the tender to the lowest-bidding company. Therefore, although tendering can support cost savings in the short term, it is linked to long-term negative consequences whereby manufacturers are forced out of the market, leading to competition erosion, and thus higher prices and occurrence of shortages.[123,124]

120 Kakkar, A., Shafiq, N. and Malhotra, S. (2019, January) Ensuring access to 'access' antibiotics: An imminent consideration for sustainable antimicrobial stewardship in the developing world. Taylor & Francis. Available at: https://www.tandfonline.com/doi/full/10.1080/23744235.2019.1574978 [Accessed August 2022]

121 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

122 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

123 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

124 Dranitsaris, G. et al. (2017, September 29) Drug tendering: Drug supply and shortage implications for the uptake. ClinicoEconomics and Outcomes Research. Available at: https://www.dovepress.com/drug-tendering-drug-supply-and-shortage-implications-for-the-uptake-of-peer-reviewed-fulltext-article-CEOR [Accessed August 2022]

Case study:

Germany: In Germany, hospitals use tendering to drive down prices of off-patent products. The incentive to do so is created by the use of a diagnosis-related group (DRG) reimbursement system, whereby hospitals will get higher margins from the use of lower-cost treatments. Discount contracts between statutory health insurance funds ("sick funds") and manufacturers have also been associated with the occurrence of antibiotic shortages, as many of these contracts are with a single supplier.

Source: Frost et al. (2019)[125]

Similar challenges are also observed in LMICs.

Case study:

Vietnam: Vietnam has procurement regulations stating that in order to participate in bids, the price offered must be equal to or lower than the winning bid price of the previous 12 months, thus increasing downward pricing pressure on an annual basis. Many manufacturers struggle to meet the standards and find it unsustainable to compete in the procurement process at such low bid levels. As a result, fewer and fewer manufacturers can enter or remain in the market, which can lead to shortages.

Source: Minh (2022),[126] *Dranitsaris et al. (2017)*[127]

Furthermore, due to the low commercial returns and uncertain demand associated with off-patent antibiotic production, many manufacturers lack the capital to reinvest in upgrading manufacturing facilities and are discouraged from investing in advanced capabilities because the return on such an investment may take years, or may not be achievable.[128] Additionally, companies find it challenging to transfer required documentation from one factory to another. Some countries currently require companies to establish new documentation when moving production sites. The process of obtaining new documentation is costly and time-consuming for many manufacturers, which may

125 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

126 Minh, H. (2022, June 19) What is the 'bottleneck' of the shortage of drugs and medical supplies? Available at: https://baochinhphu.vn/diem-nghencua-tinh-trang-thieu-thuoc-vat-tu-y-te-can-giai-phap-thao-go-nao-102220618235548908.htm

127 Dranitsaris, G. et al. (2017, September 29) Drug tendering: Drug supply and shortage implications for the uptake. ClinicoEconomics and Outcomes Research. Available at: https://www.dovepress.com/drug-tendering-drug-supply-and-shortage-implications-for-the-uptake-of-peer-reviewed-fulltext-article-CEOR

128 Wellcome Trust (2020, February) The growing crisis in antibiotic R&D: opportunities for G20 member action to support sustainable innovation. Available at: https://wellcome.org/sites/default/files/the-growing-crisis-for-antibiotic-r-and-d.pdf [Accessed August 2022]

encourage them to stay in older facilities, increasing the risk of manufacturing problems and supply.[129]

3.4. Cause 4: Concentration of API suppliers is both a symptom of unsustainability of the market and a further driver of shortages

A knock-on impact from the low profit margin and uncertain demand for antibiotics is that there are few off-patent antibiotic manufacturers and even fewer API suppliers remaining – creating further vulnerability to shortages.[130] In the last decade, the majority of antibiotic production has shifted to countries with lower production costs, such as India and China. Data show that India and China are home to nearly 70% of sites manufacturing a representative sample of 40 antibiotic APIs, with India and China representing 35% and 34% respectively. While the number of manufacturing sites is similar between the two countries, the volumes produced per site in China are generally two to three times higher than sites in India.[131] Finished product manufacturers typically contract with API suppliers to reduce production costs and the investment required to maintain manufacturing facilities.[132] An unforeseen issue is that multiple finished product manufacturers may contract with the same API supplier, meaning that a seemingly diverse supply may be overly reliant on a single API source. According to a WHO report, only two API manufacturers produce 10 of the most commonly used antibiotics.[133] As APIs are currently produced in a small number of factories, any disruption at these facilities can have a significant impact on global antibiotic production and supply, and result in months or years of global shortages. For example, an explosion at a Chinese factory caused a long-lasting and global shortage of piperacillin-tazobactam because it was one of the few manufacturers of the required API.[134] The impact of the unsustainable commercial environment on diversity of API supply is evident in our case study markets:

129 CRA Expert Interview

130 World Health Organization (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

131 Boston Consulting Group and Wellcome Trust (2022) Understanding the antibiotic manufacturing ecosystem. Available at: https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf [Accessed August 2022]

132 World Health Organization (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

133 World Health Organization (2018, December) Meeting report – World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf [Accessed August 2022]

134 Beraud G. (2021) Shortages Without Frontiers: Antimicrobial Drug and Vaccine Shortages Impact Far Beyond the Individual! *Frontiers in Medicine*. 8: 593712. https://doi.org/10.3389/fmed.2021.593712

Case study:

***Germany*:** Corden, a German company, stopped producing cephalosporin intermediates in 2017 due to a lack of a financially viable business model in comparison to its foreign competitors. Because Corden has ceased operations, the upstream manufacturing of cephalosporin has shifted to India and China. As a result, the global antibiotic market is heavily reliant on a few countries that produce active intermediates and APIs, making it more vulnerable to supply chain failures and shortages. Furthermore, if there are only a few API manufacturers remaining, antibiotic manufacturers will find it difficult to scale up supply quickly in the event of an outbreak or surge in demand. As previously stated, a manufacturer's ability to scale up production in response to increased demand may be limited due to a lack of investment in upgrading facilities and improving manufacturing processes.

Source: Roland Berger (2018)[135]

Similar challenges are also observed in LMICs.

Case study:

***South Africa*:** South Africa has a limited number of API and finished product manufacturers due to the complexities of manufacturing off-patent antibiotics. Many countries, including South Africa, rely on a few countries for off-patent antibiotic materials and medicines. Because of the manufacturing setup required for antibiotics, there is a lack of local production of antibiotics, particularly injectables, in South Africa. Cephalosporins, for example, require a specific manufacturing setup, raising the barriers to entry. As a result, South Africa is reliant on a few countries for off-patent antibiotics, increasing the systemic risk of the supply of off-patent antibiotics.

Source: CRA expert interview

Finally, concentrated API leads to additional issues when there are global trade restrictions. Global events such as the COVID-19 pandemic highlight the effects of API concentration on antibiotic shortages. API manufacturers in India, China and the United States restricted API production during the pandemic. There were also issues with packing material, disrupted transportation, delayed shipping, delayed customer clearance, and restricted

135 Roland Berger (2018, November) Study on the security of antibiotics supply: Pathways towards a production of antibiotic APIs in Germany and the EU. Available at: https://progenerika.de/app/uploads/2020/09/20181213_ProGenerika_Antibiotics-study-2018_vf-1.pdf [Accessed August 2022]

import–export of APIs and drugs around the world, which hampered access to antibiotics.[136]

3.5. Cause 5: Poor supply chain management and lack of collaboration among stakeholders contributes to unsustainability

Inefficiencies in supply chain management, as well as regional concentration of supply within a country, contribute to the unsustainable nature of antibiotic supply chains.[137] Many interviewees agreed that regional distribution and a lack of infrastructure in some LMICs can impede antibiotic delivery to hospitals and pharmacies.[138] Further, outdated information systems and limited human resources can result in shortages.[139] Even when antibiotic medicines are available, some regions and hospitals within a country are more likely to experience shortages due to poor supply chain management. Government failures to deliver antibiotics to patients in need due to weak health systems and a lack of trained personnel can result in inefficient and ineffective antibiotic distribution.[140]

Case study:

***South Africa*:** In 2014 (Gauteng Province), multiple hospitals experienced medicine shortages as a result of incorrect order quantities based on unreliable consumption data; as a result, the hospital was unable to meet the needs of the patients. The province had implemented RxSolution, an electronic pharmaceutical management system, to manage inventory in public hospitals. Although the system was implemented to improve management and prevent shortages, many hospital employees were unaware of how to use the system properly, and as a result, stock was not received correctly, and the hospitals were unable to meet the needs of the patients. In general, South Africa's national systems for procurement, distribution and supply management of medicines are poorly developed, which has historically contributed to poor availability of essential medicines in specific regions, despite their availability on a national level.

136 Shukar, S. et al. (2021, January 1) Drug shortage: Causes, impact, and Mitigation Strategies. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693426/full [Accessed August 2022]

137 CRA Expert Interview

138 CRA Expert Interview

139 Malan, L. et al. (2018, November) Sustainable access to antimicrobials; a missing component to antimicrobial stewardship–A tale of two countries. Frontiers. Available at: https://www.frontiersin.org/articles/10.3389/fpubh.2018.00324/full [Accessed August 2022]

140 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

Source: Modisakeng et al. (2020),[141] *Malan et al. (2018),*[142] *Coovadia et al. (2009),*[143] *Stop Stockouts (2016)*[144]

Many other LMICs experience a similar challenge.

Case study:

***LMICs*:** Many hospitals in LMICs face bureaucracy barriers impeding purchases from the centralised supply system despite drug availability, resulting in a shortage for the specific locality or region. In some LMICs, supply chains are not optimised to deliver antibiotics over long distances. Some antibiotics may require cold-chain temperature control, which may be difficult in LMICs, affecting the quality and supply of medicines to specific regions within a country. Underdeveloped healthcare systems further complicate antibiotic medicine delivery in LMICs. In India, for example, there is one government doctor for every 10,189 people (the WHO recommends a ratio of 1:1,000), resulting in a shortage of 600,000 doctors. As a result, many patients are unable to receive necessary care.

Source: Pulcini et al. (2017),[145] *Frost et al. (2019)*[146]

In addition to poor supply chain management, antibiotics may face higher supply risks due to barriers to communication throughout the supply chains, in part driven by consolidation of supply chains.[147] According to research, marketing authorisation holders (MAHs) are transparent about their supply chains, as made evident by the information included in the marketing authorisation dossier; however, public authorities do not have access to this information, and countries may lack centralised systems to monitor supply chains for off-

141 Modisakeng, C. et al. (2020) Medicine shortages and challenges with the procurement process among public sector hospitals in South Africa; findings and implications. *BMC Health Serv Res* 20, 234. https://doi.org/10.1186/s12913-020-05080-1

142 Malan, L. et al. (2018, November 1) Sustainable access to antimicrobials; a missing component to antimicrobial stewardship-A tale of two countries. *Frontiers*. Available at: https://www.frontiersin.org/articles/10.3389/fpubh.2018.00324/full [Accessed August 2022]

143 Coovadia, H. et al. (2009) The health and health system of South Africa: historical roots of current public health challenges. *Lancet*. 374:817–34.

144 Stop Stockouts. South Africa: Monitoring Essential Medicines Consortium. (2016) Stop Stockouts. Available at: http://www.stockouts.org [Accessed August 2022]

145 Pulcini, C. et al. (2017) Ensuring universal access to old antibiotics: A critical but neglected priority. *Clinical Microbiology and Infection.* 23(9): 590–592. https://doi.org/10.1016/j.cmi.2017.04.026

146 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

147 Malan, L. et al. (2018, November) Sustainable access to antimicrobials; a missing component to antimicrobial stewardship–A tale of two countries. Frontiers. Available at: https://www.frontiersin.org/articles/10.3389/fpubh.2018.00324/full [Accessed August 2022]

patent antibiotics.[148] Further, many stakeholders in the supply chain struggle to coherently forecast demand to mitigate shortages.[149] Some forecasting systems tend to be inaccurate, which can negatively impact downstream supply and distribution; poor forecasting systems are a key driver of shortages and stock-outs.[150,151]

Lack of communication and transparency throughout the supply chain can result in inefficient distribution and storage of antibiotic medicines. Communication often works between stakeholders that directly work together; for example, communication between hospital pharmacies and distributors is typically relatively efficient. However, communication along the value chain is more complicated – for example, communication between hospitals and producers or even API manufacturers (**Figure 6**). As a result, downstream purchasers and stakeholders are less likely to be aware of specifics surrounding the source of raw materials, intermediates and APIs. Downstream stakeholders may be unaware of the supply chain's heavy reliance on sole API producers and high supply risk due to a lack of communication and transparency in supply chains. Understanding supply chain challenges may help downstream stakeholders make more informed decisions, potentially reducing the likelihood of supply issues. It may also be difficult for downstream stakeholders to communicate with and inform upstream producers about recent infections or emerging trends, potentially leading to shortages. These inefficiencies and lack of communication throughout the supply chain need to be addressed in order to perform better risk assessments and forecasting to better inform supply. Any policy interventions aimed at increasing supply chain communication and transparency should consider the risks and drawbacks of sharing of information to avoid further exacerbating the low attractiveness of the antibiotic market for retaining existing suppliers and attracting new suppliers.

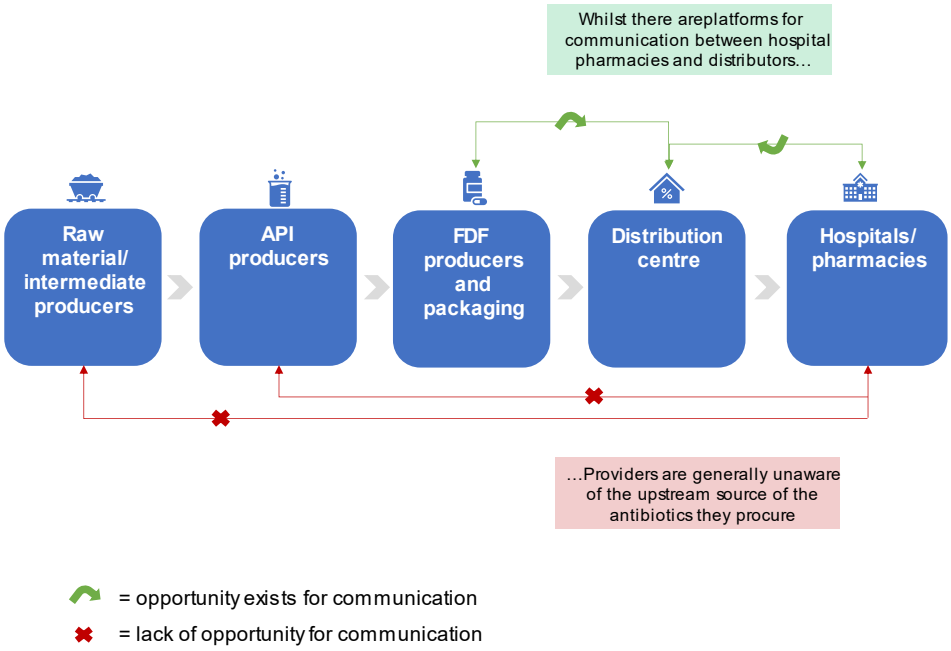
148 Medicines for Europe (n.d.) Medicines for Europe Factsheets on Market and regulatory reforms to ensure availability and resilience of the supply chain. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2021/05/Medicines-for-Europe-Factsheets-on-Market-and-regulatory-reforms-to-ensure-availability-and-resilience-of-the-supply-chain.pdf [Accessed October 2022]

149 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

150 Kakkar, A., Shafiq, N., and Malhotra, S. (2019, January) Ensuring access to 'access' antibiotics: An imminent consideration for sustainable antimicrobial stewardship in the developing world. Taylor & Francis. Available at: https://www.tandfonline.com/doi/full/10.1080/23744235.2019.1574978 [Accessed August 2022]

151 Subramanian, L. (2021, February 28) Effective demand forecasting in health supply chains: Emerging trend, enablers, and blockers. MDPI. Available at: https://doi.org/10.3390/logistics5010012 [Accessed August 2022]

Figure 6: Communication barriers along the off-patent antibiotic supply chain



Source: CRA analysis

3.6. Summary

Overall, we find five categories of root causes leading to unsustainable off-patent antibiotic supply. These represent aggregate themes of the longer list of root causes identified in the literature, for example by PLATINEA.[152] The root causes discussed in this chapter were the most frequently mentioned root causes in our secondary and primary market research. They are relevant for all markets from high income to low income. However, their relative importance varies considerably from market to market.

The table below summarises the root causes of antibiotic shortages and the level of importance across Brazil, Germany, India, Vietnam and South Africa.

Table 4: Summary of root causes of supply chain unsustainability across countries

Cause						
	Fragility of supply chain and manufacturing issues	◕	◔	◕	◕	◑

152 Garlapati, S. and Sewoyo, V. (2019) Improving antibiotic availability by restructuring the supply chain. Available at: https://www.platinea.se/digitalAssets/843/c_843338-l_3-k_garlapati-sevoyo---improving-antibiotic-availability-supply-chain-2019.pdf [Accessed October 2022]

	Low and unpredictable demand	◕	◔	●	●	◑
	Commercial returns	●	●	●	●	●
	Concentration of API suppliers	◑	◕	◑	◕	◕
	Poor supply chain management	◑	◔	◕	◕	◑

Note: Low importance indicates that the root cause has a low impact on the sustainability of the supply chain. High importance indicates that the root cause has a significant impact on the sustainability of the supply chain.

◔ → ● Low High

Source: CRA analysis of primary and secondary research

4. A framework for supply chain sustainability

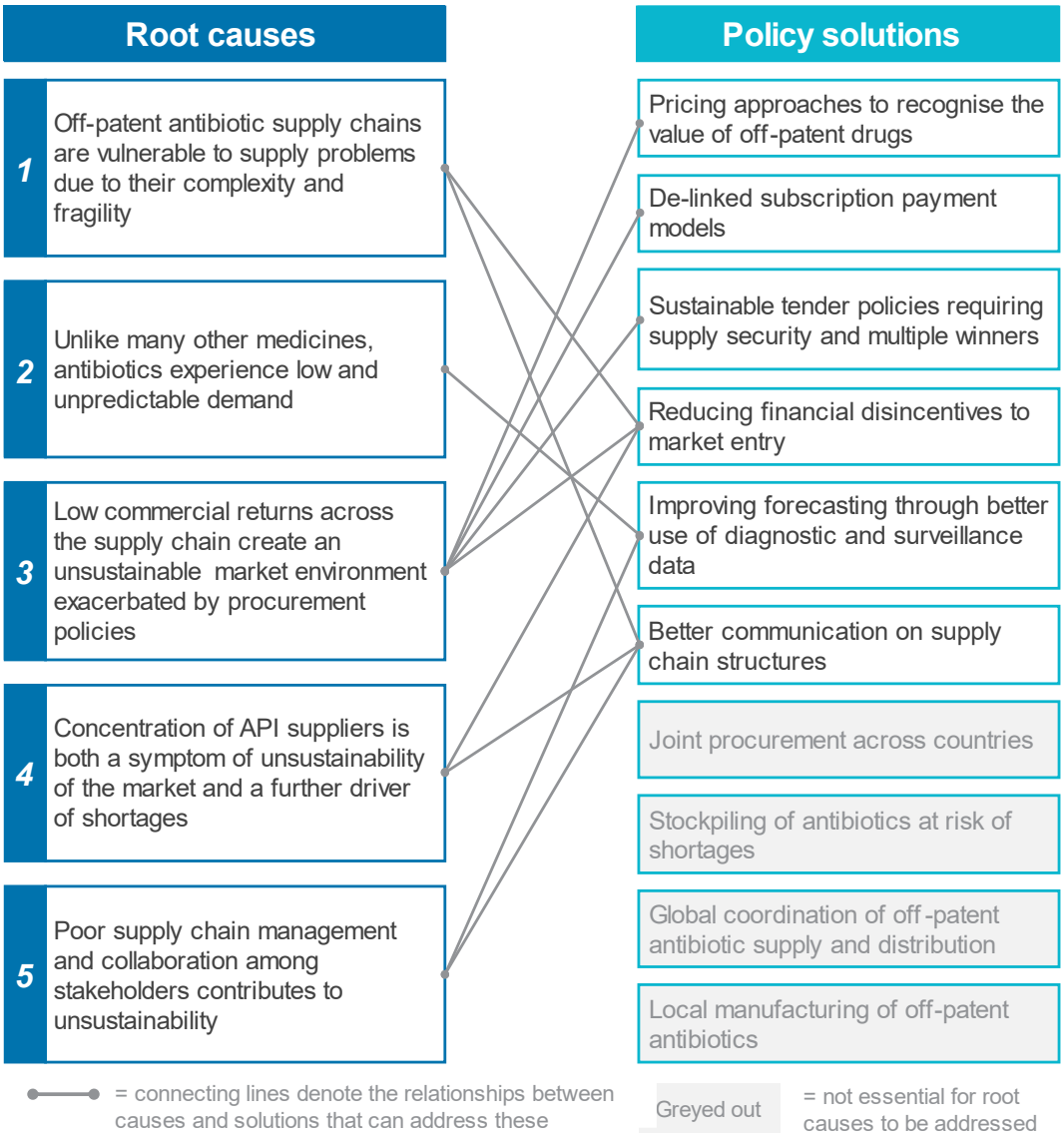
Antibiotic shortages, stock-outs and market withdrawals are symptoms of an unsustainable supply chain and market for off-patent antibiotics. This is not a new problem and has been recognised by many organisations and policy leaders who are active in tackling AMR.[153,154,155] However, less progress has been made on identifying and implementing long-term solutions. In this chapter, we review the potential policy solutions that have been proposed in the literature so far and assess their applicability to addressing the root causes of supply unsustainability we described in Chapter 3. These solutions are presented in order of feasibility and impact, based on our evaluation of each potential solution. The figure below lists each solution and links the root causes discussed in Chapter 3 with corresponding solutions.

153 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

154 G7 Health Ministers (2021) G7 Health Ministers' Meeting, communique, Oxford, 4 June, 2021. Available at: https://www.gov.uk/government/publications/g7-health-ministers-meeting-june-2021-communique/g7-health-ministers-meeting-communique-oxford-4-june-2021 [Accessed August 2022]

155 G7 Health Ministers (2022) G7 Health Ministers' Communiqué 20 May 2022, Berlin. Available at: https://www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccfaffd1e37a1/2022-05-20-g7-health-ministers-communique-data.pdf [Accessed August 2022]

Figure 7: Links between the causes of unsustainability and the policy solutions proposed to address them



4.1. Assessment of potential policy solutions

Policy approach 1: Pricing approaches to recognise the value of off-patent drugs

A balance can be struck between the need for health systems to achieve cost savings from off-patent antibiotics and the need for suppliers to be able to maintain supply at very low price levels. Given that the majority of off-patent antibiotics on the market have been off-patent for years and already reached low price levels, this indicates that there is no longer a strong role for monitoring and managing price erosion. Instead, a more innovative payment mechanism that recognises the value of continued future availability of an antibiotic could be warranted. Multiple approaches have been proposed:

- In France, manufacturers can request a price increase for medicines at increased risk of shortages.[156]
- Similarly, in Sweden, manufacturers of older off-patent antibiotics can apply to the reimbursement authority (the TLV) for a price increase if there is a high risk of shortages resulting from low commercial returns. The Public Health Agency of Sweden (PHAS) has developed a potential mechanism for assessing the value of these older antibiotics in the local epidemiological context and recommends that TLV uses this as the basis for granting price increases in order to be more reflective of the value of the off-patent antibiotic.[157]

Revising the pricing policies for off-patent antibiotics would address a fundamental root cause of supply chain unsustainability, by improving commercial returns. Despite the multifaceted and complex nature of off-patent antibiotic supply failures, many areas of fragility along the supply chain can be traced back to the unviable commercial environment. Low commercial returns over a long time period have resulted in many antibiotic suppliers leaving the market, and those that remain lack incentives to invest in improving the production and availability of older, off-patent products. Therefore, although solving the economic problem in the off-patent antibiotic market is a complex challenge, it has the potential to have positive effects on sustainability at multiple points along the supply chain over the long term, for example by generating revenue that can be reinvested into manufacturing upgrades and incentivising a greater number of suppliers.

There is evidence of potential benefit to health systems, including in LMICs. Awarding higher unit prices for existing antibiotics has been shown in practice to reverse the decision of companies to stop marketing an antibiotic in a given country.[158] Further, antibiotic shortages are associated with corresponding increases in the price of the drug.[159] In either scenario, prices of antibiotics often increase, but through proactive pricing policies, shortages could be avoided. By proactively setting more sustainable price levels, the increased costs to the healthcare system may be balanced out by avoiding the financial cost associated with managing a shortage, as well as the financial cost associated with the corresponding increase in the price of available alternatives when suppliers leave the market. .

Affordability in LMICs may present challenges to implementation of more sustainable pricing policies. However, shortages in LMICs have also driven hospitals to source

156 McDonnell, A. et al. (2022) Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation. Available at: https://www.cgdev.org/sites/default/files/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.pdf [Accessed August 2022]

157 Gotham, D. et al. (2021) Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*. 125(3): 296-306.

158 Årdal, C. et al. (2021) National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics*. 10(6): 749.

159 Mulcahy, A.W. et al. (2021) Assessing Relationships Between Drug Shortages in the United States and Other Countries. Available at: https://www.rand.org/pubs/research_reports/RRA1070-1.html [Accessed August 2022]

alternative supplies outside of a tender contract at a higher price.[160] There may be a price point – in between the current low unit prices paid for antibiotics in LMICs and the high prices paid in shortage emergencies – at which pricing is considered sustainable both for the health systems and for the functioning of a healthy antibiotic market.

Policy approach 2: De-linked subscription payment models

The ReAct network has proposed a de-linked payment model for off-patent antibiotics in return for long-term supply continuity.[161] Progress has been made in the design and piloting of de-linked payment models for on-patent antibiotics, from which there may be some lessons to apply to older, off-patent products.

- PHAS in Sweden has developed a proposed model for decoupling reimbursement from sales volumes in order to ensure guaranteed minimum revenues for manufacturers and in return improve the security of supply of antibiotics. Annual payments to manufacturers would be based on the expected cost of a 'security stock' of the antibiotic, priced at 50% above the average European list price. This model has been designed for on-patent antibiotics but could theoretically be transferable to older, off-patent products, if coupled with a mechanism to determine value that is not based on the average European price (since for older antibiotics, a 50% price increase would still likely be unsustainable).[162]
- The National Institute for Health and Care Excellence (NICE) in England has already begun implementation of a de-linked subscription model pilot, although similarly targeted only towards novel antibiotics. However, NICE has also developed an accompanying methodology for basing the annual payment amount on the full societal value of the antibiotic.[163] This takes into account, for example, that availability of that antibiotic enables chemotherapy, surgery and other medical procedures to go ahead. The value assessment methodology developed by NICE could be applied to off-patent antibiotics to readjust the payment amount.

By basing payment on the value of the continued availability of an existing antibiotic, rather than by its sales volumes, the commercial environment would become more sustainable for current suppliers. We could expect that consequently fewer suppliers would be incentivised to discontinue production, as they would instead be incentivised to achieve security of supply. Guaranteed revenues could de-risk future investments into upgrading

160 Government of Vietnam (2022) [In Vietnamese] What is the 'bottleneck' of the shortage of drugs and medical supplies? Available at: https://baochinhphu.vn/diem-nghencua-tinh-trang-thieu-thuoc-vat-tu-y-te-can-giai-phap-thao-go-nao-102220618235548908.htm [Accessed August 2022]

161 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

162 Gotham, D. et al. (2021) Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*. 125(3): 296–306.

163 https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials [Accessed August 2022]

manufacturing facilities and processes, allowing suppliers to keep up with evolving global demand more effectively.

Thus far, literature on antibiotic procurement reforms has focused almost exclusively on new patented antibiotics. A systemic literature review identifying 141 papers on the topic found that only 4 of these analyses discussed models aimed at ensuring long-term supply sustainability.[164] In high-income countries, existing research, although scarce, suggests positive receptivity to such models for off-patent antibiotics. A survey of 13 European countries in 2019–2020 found that 12 of these countries deemed shortages of existing antibiotics to be a serious problem. Nine countries noted a preference for a novel mechanism to ensure sustainable access to both existing and new antibiotics, with the highest priority for existing antibiotics.[165]

There is also broad agreement in the literature that a new antibiotic purchasing system is needed in LMICs.[166] In India, it has been acknowledged in the literature that while price controls on antibiotics aim to improve access and affordability, they can inadvertently negatively impact their availability.[167] Where there is less clarity in LMICs versus HICs is on the solution needed. A working group composed of policy experts, policymakers and the pharmaceutical industry is currently examining in-depth the current purchasing systems and opportunities for new procurement models in LMICs, including Brazil and India.[168] It will be important for this analysis to consider the role of procurement systems in improving market sustainability and reducing the risk of antibiotic shortages in these markets.

Policy approach 3: Sustainable tender policies requiring supply security and multiple winners

A straightforward mechanism identified in the literature for encouraging more sustainable levels of competition in the off-patent medicine market is to ensure that tender contracts are awarded to multiple suppliers. This ensures that there is not one company solely responsible for supplying a market or a set of markets over a period of time, leaving those markets vulnerable to supply disruptions. It also distributes market share amongst more suppliers, encouraging a higher number of suppliers to stay present in the market. This is not a complex mechanism, and indeed has already been discussed extensively in the

164 McDonnell, A. et al. (2022) Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation. Available at: https://www.cgdev.org/sites/default/files/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.pdf [Accessed August 2022]

165 Årdal, C. et al. (2021) National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics*. 10(6): 749.

166 McDonnell, A. et al. (2022) Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation. Available at: https://www.cgdev.org/sites/default/files/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.pdf [Accessed August 2022]

167 Kumar Kakkar, A., Shafiq, N. and Malhotra, S. (2019) Ensuring access to 'access' antibiotics: an imminent consideration for sustainable antimicrobial stewardship in the developing world. *Infectious Diseases*, 51(5): 395–398.

168 Center for Global Development (2022) Blog post: Building Better Purchasing Systems for Antimicrobials. Available at: https://cgdev.org/blog/building-better-purchasing-systems-antimicrobials [Accessed August 2022]

literature and implemented in many markets.[169] Importantly, implementing such a model to adequately address the commercial failure in the off-patent antibiotic market would require that each tender winner can hold a significant market share that generates viable returns. A multi-winner tender structure in which one winner is allocated a substantial share majority leaving minimal share for other winners (the 'back-up' winners) would not incentivise multiple suppliers to stay active in the market.

A more complex but more sustainable model would be to allocate market share amongst multiple suppliers that source from different API manufacturers.[170] This creates a safety net and protects the market from a cascade of supply issues that result from disruption to one API manufacturer. Implementing this approach will require additional awareness of API sourcing (see policy approach 6 below) to be feasible.

While improving the commercial conditions of the market would provide a long-term solution to the dwindling level of competition in the off-patent antibiotic market, as described in policy approaches 1 and 2, healthier levels of competition could be fostered in the medium term by adopting tendering policies that are more sustainable and supply-oriented. De-linked subscription models (as described in policy approach 2) and tendering reforms (described here) may not both be needed in the same country for the same antibiotic; instead, the optimal procurement approach may depend on the antibiotic.

There are benefits to this approach in both HICs and LMICs. Currently, procurement for off-patent antibiotics is managed with a more short-term outlook in almost all countries. Health systems aim to achieve cost savings by applying tendering processes based solely on price, which erodes profit margins and drives some manufacturers to stop marketing those antibiotics entirely. We know that this can lead to both supply risks and de facto monopolies.[171] In this situation, the purchasing power of procurers decreases, and consequently cost savings may not be achieved. It is therefore a shared goal of both industry and buyers to encourage healthy levels of competition and sustainable cost savings over the long term; this can be achieved through strategic procurement strategies that use selection criteria that consider factors other than price, such as the most economically advantageous tender (MEAT). The MEAT criterion allows the contracting authority to consider criteria that reflect qualitative, technical, and sustainable aspects of the tender submission, as well as price, when making an award decision. For example, one criterion that could be implemented is the inclusion of two API sources in the registration documentation, as this would aid in reducing market concentration.

169 Maniadakis, N. et al. (2018) Shaping Pharmaceutical Tenders for Effectiveness and Sustainability in Countries with Expanding Healthcare Coverage. *Appl Health Econ Health Policy*. 16(5): 591–607.

170 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

171 WHO (2016) Challenges and opportunities in improving access to medicines through efficient public procurement in the WHO European Region. Available at: https://apps.who.int/iris/handle/10665/344000 [Accessed August 2022]

Policy approach 4: Reducing financial disincentives to market entry

Reducing the barriers to market entry (and re-entry) could help encourage more manufacturers to restart or maintain their supply. On top of the unsustainable commercial conditions experienced by antibiotic manufacturers, currently many health authorities aim to incentivise security of supply by imposing additional penalties (in instances of shortage) and fees (in instances of re-filing in a market from which a supplier has previously withdrawn, or registering an off-patent antibiotic in a new market). This adds to the financial risk companies take on when deciding to supply an antibiotic to a given market, which acts as a disincentive to do so. To encourage companies to stay in the market, and to encourage those companies that have previously dropped out to re-enter, it may be appropriate to:

- Revise penalty policies to be proportionate to the circumstances surrounding the shortage
- Remove fees for companies re-filing for marketing authorisation
- Consider fast-tracking the approval of new manufacturers, particularly those who add to the diversity of API supply. In LMICs, this could fall within the remit of the WHO's Prequalification (PQ) Program.[172] In Vietnam, in response to recent widespread shortages, the Ministry of Health has expedited registration of alternative imported products and granted marketing authorisation to hundreds of new drug manufacturers of various medicines.[173]
- Adopt a risk-sharing approach between government and private companies to strengthen supply. For example, the Austrian government made a joint investment of €150m with Novartis Sandoz in 2020 to ensure that production of key antibiotics could continue in the long term.[174] ReAct has also proposed the provision of financial incentives or subsidies that encourage adequate production, particularly for low-margin antibiotics.[175]

By removing disproportionate financial disincentives to marketing an off-patent antibiotic, multiple root causes of unsustainability can be addressed. Manufacturers are likely to see slightly improved commercial returns as the costs associated with entering and remaining in the market are somewhat alleviated. Further, by directly incentivising manufacturers with

172 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

173 Binh Phuoc Provincial Portal (2022) [In Vietnamese] The main reason for the shortage of drugs and medical supplies. Available at: https://binhphuoc.gov.vn/vi/news/tin-tuc-su-kien-421/nguyen-nhan-chinh-dan-toi-tinh-trang-thieu-thuoc-vat-tu-y-te-29072.html [Accessed August 2022]

174 Novartis (2020) News: Sandoz announces plans for joint investment to help strengthen future of antibiotics manufacturing in Europe. Available at: https://www.novartis.com/news/media-releases/sandoz-announces-plans-joint-investment-help-strengthen-future-antibiotics-manufacturing-europe [Accessed August 2022]

175 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

diverse API supplies to enter new markets, the overreliance on concentrated API supply can be lessened. Financial risk-sharing between public and private entities for maintaining existence of production facilities also creates opportunity for improvement of manufacturing quality processes, which is important in preventing shortages arising from the fragile and complex production chain.

Policy approach 5: Improving forecasting through better use of diagnostic and surveillance data

In regulating demand, it is important to consider what is under the control of stakeholders along the value chain and what is not. It is not feasible to change the intrinsically unpredictable nature of infection outbreaks and the spread of drug resistance. However, given the investments made globally to improve detection and surveillance of AMR, it should be possible to use the information being generated from these systems to more proactively predict demand.

Short-term options to improve sustainability of antibiotic supply include improvement of forecasting systems for essential antibiotics so that manufacturers can better prepare to meet demand.[176] Surveillance systems for antibiotic consumption are underdeveloped or lacking in many countries, as are robust systems for understanding current stocks and predicting future requirements.[177] Strengthening forecasting capacity also requires a better understanding of the market demand in terms of epidemiology and AMR prevalence rates, particularly in LMICs where these systems are often not coordinated centrally and therefore are ill-suited to use in predicting future trends.

- In South Africa, where stock-outs of essential medicines are of growing concern, positive progress has been made establishing a National Surveillance Centre, an innovative early warning system with accessible data on stock levels and early warnings in case of probable shortages.[178] The initial focus during a pilot phase is on HIV and TB medicines, but this could be extended to cover essential off-patent antibiotics.
- In Vietnam, the Prime Minister recently emphasised the importance of collecting and using reliable and accurate data on supply levels and anticipated shortages.[179]
- Understanding global demand may also be important for national governments; in South Africa, the Stop Stockouts Project (SSP) advocates for the South African

176 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

177 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6(11): e006961

178 Malan, L. et al. (2018) Sustainable Access to Antimicrobials; A Missing Component to Antimicrobial Stewardship–A Tale of Two Countries. *Front. Public Health*. 6:324.

179 Tiep, P. (2022) [In Vietnamese] Urgently handle the shortage of drugs, medical supplies and medical personnel. Available at: https://www.vietnamplus.vn/khan-truong-xu-ly-tinh-trang-thieu-thuoc-vat-tu-y-te-va-nhan-luc-y-te/800282.vnp [Accessed August 2022]

Department of Health to monitor global demand for essential medicines and conduct horizon scanning to anticipate potential issues.[180]

Although surveillance systems and effective use of surveillance data is not universally strong throughout HICs, the greatest room for improvement in surveillance and data collection is in LMICs. The greatest demand for antibiotics also comes from LMICs, so increasing predictability of demand in these countries could benefit stability of the global supply chain. Shortages attributable to supply chain mismanagement, including poor understanding of demand and inefficient distribution, also appear to be a greater challenge in LMICs. Therefore, while ongoing efforts to strengthen reliability and coverage of AMR data generation in HICs continues to be essential, particular focus may be warranted in improving systems in LMICs. In countries where there is already strong surveillance of AMR and consumption, the policy approach in this case may focus on ensuring that these data are widely communicated and understood, including for example by procurement authorities.

Policy approach 6: Better communication on supply chain structures

Currently, the API source for individual antibiotic products is generally only known by the marketing authorisation holder and the regulatory authority, and not by downstream supply chain stakeholders, such as hospitals or centralised procurement authorities.[181] This has led many academics to support the concept of API supply awareness between regulators, payers and providers to enable a shared understanding of the supply risk in a given country or region.[182,183] The information included in the marketing authorisation dossier demonstrates that MAHs are transparent about their supply chains. Marketing authorisations are filed with the responsible regulatory agency in each market; however, these agencies may not always share the data with other agencies within their governments. Additionally, countries may lack centralised systems to monitor supply chains for off-patent antibiotics, which can create challenges for policymakers in mitigating shortages or supply issues if they are unaware of supply chains.[184]

Over-concentration of API supply is a widely acknowledged root cause of supply unsustainability, as described in Chapter 3. By generating a better understanding of the concentration of API supply through increased communication, this root cause can be

180 Stop Stockouts Project (2018) 4th National Survey Report (2017) Available at: https://stockouts.org/Survey/SurveysAndResearch [Accessed August 2022]

181 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

182 Årdal, C. et al. (2021) Supply chain transparency and the availability of essential medicines. *Bull World Health Organ*. 99(4): 319–320.

183 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

184 Medicines for Europe. (n.d.) Medicines for Europe Factsheets on Market and regulatory reforms to ensure availability and resilience of the supply chain. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2021/05/Medicines-for-Europe-Factsheets-on-Market-and-regulatory-reforms-to-ensure-availability-and-resilience-of-the-supply-chain.pdf [Accessed October 2022]

tackled more directly and proactively by policymakers and payers. One solution that has been suggested is for regulators to implement a notification system that highlights the need for additional API suppliers when there is a risk of consolidation to one supplier. Improving communication and awareness between API suppliers and regulators also has global applicability as over-concentration of API supply is a global problem, affecting both HICs and LMICs.

There are a number of caveats, and potential safeguards would need to be put in place in order not to further incentivise the few remaining manufacturers to abandon the market. Improved communication and transparency can lead to weakening of the confidentiality of companies' sensitive financial, proprietary or anti-competitive information; this puts them at risk of being driven out of the market through competitor actions, leading to more consolidation.[185] A multifaceted approach may be required to ensure sustainability is achieved via increased communication, with reforms to procurement (described in policy approach 3) occurring in tandem. API supply knowledge could enable procurement policies to be designed in a way that ensures supply diversity, not just in terms of having multiple finished products but also multiple API sources. By rewarding companies for the strength of their supply chains in the procurement process, there is an incentive for companies to ensure a sustainable supply without incurring the financial risk of price-only tenders that exploit the availability of sensitive commercial information.

Policy approach 7: Joint procurement across countries

To overcome the challenges created by unsuitable price controls and fragmented demand in LMICs, academics have proposed the implementation of an antimicrobial subscription and pooled procurement (ASPP) model.[186] Under this model, a group of countries or states within a county would jointly negotiate a multi-year subscription contract for a portfolio of antibiotics and diagnostics. To enable low-income countries (LICs) to participate, development assistance akin to UNITAID, the Global Fund or Gavi would likely be required, and middle-income countries (MICs) could self-finance.

Authors suggest that the antibiotic market will become more sustainable if demand is aggregated; however, this does not account for the potential impact on price. Pooled procurement of medicines in the public sector in LMICs has been found to result in a 15% price reduction on average.[187] This exacerbates the already unviable price environment that off-patent antibiotic producers must operate in. Pooled procurement can also disincentivise having multiple manufacturers, particularly for drugs with low or uncertain demand.[188] Therefore, if a pooled procurement model is to be designed to ensure access

185 Årdal, C. et al. (2021) Supply chain transparency and the availability of essential medicines. *Bull World Health Organ*. 99(4): 319–320.

186 Berman, D. et al. (2022) Global access to existing and future antimicrobials and diagnostics: antimicrobial subscription and pooled procurement. *Lancet Global Health*. 10: e293–297.

187 Dubois, P., Lefouili, Y. and Straub, S. (2021) Pooled Procurement of Drugs in Low and Middle Income Countries. *European Economic Review*. 132(4): 103655.

188 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

to antibiotics while preventing shortages, as proposed by the Global Antibiotic Research and Development Partnership (GARDP), then it needs to be combined with other interventions (such as sustainable procurement practices) in order to be successful.[189]

Cross-border joint procurement for off-patent antibiotics may not provide additional value to patients, healthcare professionals or payers. Joint procurement across countries has several shortcomings for multi-source medicines, which we highlight below:[190,191]

- Antibiotics have different national licenses, and unless there is a global marketing authorisation it would not be efficient to implement joint procurement policies for antibiotics
- Joint procurement across some countries for generic and biosimilar medicines will not result in additional long-term savings for healthcare budgets, but rather in a concentration of suppliers in the market due to pricing pressure, increasing the risk of medicine shortages and decreasing competition

Policy approach 8: Stockpiling of antibiotics at risk of shortages

Various governments already enforce a requirement for companies to stockpile key antibiotics, either through physical stockpiles at pharmacies or buffer stocks from wholesalers.[192] Having a nationally coordinated security stock of essential off-patent antibiotics can act as a buffer in the system in case of local or national shortages.[193] However, stockpiling can also create misaligned incentives, particularly in LMICs where shortages are often associated with resource constraints and budget management. When stock-outs are used as a negative performance metric along the supply chain, stakeholders are incentivised to keep drugs in stock but not distribute them.[194] Stockpiling may be a viable short-term option in some governments to decrease the likelihood of shortages in pharmacies, but it is unlikely to enable long-term supply sustainability. Extensive and uncoordinated stockpiling requirements will aggravate market concentration, increasing the

189 Balasegaram, M. (2022) Antimicrobial subscription and pooled procurement. *The Lancet Global Health*. 10(5): e624.

190 Mohapatra, P.R. (2022, May 1) Antimicrobial subscription and pooled procurement. *The Lancet Global Health*. Available at: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(22)00091-2/fulltext [Accessed October 2022]

191 Management Sciences for Health. The positives and pitfalls of pooled procurement. (2022, February 11) Available at: https://msh.org/resources/the-positives-and-pitfalls-of-pooled-procurement/ [Accessed October 2022]

192 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

193 Söderlund Leifler, K. (2020) Are security stores the answer to antibiotics shortages? Available at: https://liu.se/en/news-item/sakerhetslager-mot-brist-pa-antibiotika [Accessed August 2022]

194 Frost, I. et al. (2019) Access Barriers to Antibiotics. Washington, DC: Center for Disease Dynamics, Economics & Policy. Available at: https://cddep.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf [Accessed August 2022]

risk of shortages and threatening patient access to medicines. Some of the risks of stockpiling are listed below: [195, 196]

- Stockpiling would result in significant waste and subsequent degradation of medicines, particularly for products with a short shelf life.
- The geographical availability of the stockpile may differ from the location of shortages, threatening patient access to medicines. Stockpiling on a national or regional scale limits the flexibility of supply chains to allocate medicines to markets in need.
- Demand forecasts may be inaccurate, preventing stockpiling to meet needs by over- or underestimating the amount of buffer stock required, resulting in either shortages or waste.
- Stockpiling can be expensive for pharmaceutical companies, limiting their ability to invest in other important activities to support public health and patients.

Policy approach 9: Global coordination of off-patent antibiotic supply and distribution

Many of the root causes described in this report are transnational problems, suggesting there may be a benefit from addressing these challenges at a global level, under the governance of a relevant multilateral agency. Global regulation of supply, production and distribution is not entirely unprecedented; mechanisms exist for controlled substances such as narcotics.[197] Recent stakeholder surveys aimed at gathering perceptions on the need for a new antibiotic purchasing mechanism did not gather any support for a single purchasing global system, instead emphasising the need for international agreement on the goals and principles for such a system and coordination among countries, including between LMICs and HICs, which could eventually result in support for a single global purchasing system.[198] It may be that this is an approach only needed for antibiotics at

195 Wosinska, M. (2012, May 2) Drug shortages: Why a government stockpile falls short as a solution. Health Affairs Forefront. Available at:https://www.healthaffairs.org/do/10.1377/forefront.20120502.019195 [Accessed October 2022]

196 Kamba, P.F., Ireeta, M.E., Balikuna, S. and Kaggwa, B. (2017) Threats posed by stockpiles of expired pharmaceuticals in low- and middle-income countries: a Ugandan perspective. Bulletin of the World Health Organization. 95(8): 594–598. https://doi.org/10.2471/BLT.16.186650

197 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

198 McDonnell, A. et al. (2022) Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation. Available at: https://www.cgdev.org/sites/default/files/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.pdf [Accessed August 2022]

particularly high risk of widespread shortages, such as antibiotics in the WHO's Reserve category, where demand is kept low through enforced regulation.[199]

Policy approach 10: Local manufacturing of off-patent antibiotics

A frequently proposed solution to the low diversity of API supply and failures in distribution of medicines is for government to take on a role in the manufacturing of essential off-patent medicines.[200] However, previous such efforts have typically failed to gain momentum.[201] The WHO recognises that such a model would require significant political commitment and investment relative to other alternative solutions,[202] and academic analysis points out that public sector production may be unviable due to the complexity of antibiotic manufacturing.[203] Evidence of success in avoiding antibiotic shortages is also weak: in Brazil, in 2019, a state laboratory linked to the government of São Paulo announced failure to fulfil a 2017 contract for the supply of BPG as a result of quality issues in production.[204] State-led local production is susceptible to the same challenges as private company-led production, but lacks the legacy of experience and expertise available to private companies that have been developing and refining the production process over the years.

Another, more balanced, alternative is the incentivisation of local production. In India, the government announced in July 2020 that the local production of key starting materials (KSMs) and APIs of 53 medicines, including several antibiotics, would be incentivised. The aim is to avoid future supply disruptions.[205] This trend is also mirrored in several HICs, with the EU for example now considering the reshoring of API production for essential drugs,

199 Access to Medicine Foundation (2018) Shortages, stockouts and scarcity: The issues facing the security of antibiotic supply and the role for pharmaceutical companies. Available at: https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies [Accessed August 2022]

200 ReAct Europe (2021) Ensuring sustainable access to effective antibiotics for EVERYONE – EVERYWHERE. Available at: https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf [Accessed August 2022]

201 Kumar Kakkar, A., Shafiq, N. and Malhotra, S. (2019) Ensuring access to 'access' antibiotics: an imminent consideration for sustainable antimicrobial stewardship in the developing world. *Infectious Diseases*, 51(5): 395–398.

202 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

203 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6(11): e006961

204 Cordão, M. (2019) [In Portuguese] Brasil atravessa crise no fornecimento de penicilina para tratar sífilis. Available at: https://www.brasildefato.com.br/2019/06/11/brasil-tem-crise-no-fornecimento-de-penicilina-que-trata-sifilis/ [Accessed August 2022]

205 Government of India (n.d.) Production Linked Incentive (PLI) scheme for Pharmaceuticals. Available at: https://pharmaceuticals.gov.in/schemes/guidelines-production-linked-incentive-pli-scheme-promotion-domestic-manufacturing-critical [Accessed August 2022]

including antibiotics, to Europe.[206] However, given that every country globally requires sustainable access to off-patent antibiotics, and manufacturers' profit margins are low, it is unrealistic to assume that sustainability can be achieved through establishment of local production capabilities in every country. This is particularly challenging, given that many LMICs have small populations and lower, more fragmented demand.[207] Such a model may also not be relevant for the antibiotics at particularly high vulnerability to shortages, namely those with the lowest profit margins, as there is a disincentive to manufacture these at a large scale.[208] Establishment of regional manufacturing hubs may be a more viable approach; however, it cannot be achieved without first addressing the underlying commercial environment of the market, thus creating more resources that companies can invest into expanding manufacturing capacity in each region. A 2018 study analysed the potential for establishing antibiotic API production in Germany to supply the European market and deemed it economically unviable, with an estimated annual loss of €78m incurred by the producer as a result of high costs and low revenue potential.[209] For local production to become economically viable, health systems would likely need to accept higher prices for those antibiotics.

4.2. Overarching success factors

Given the complexity of the problem, successfully tackling the issue and achieving supply sustainability will require a number of overarching elements:

- *A holistic approach that considers interconnectivity*: As set out in Chapter 3, it is not enough to look at the surface-level cause of a reported shortage. For example, if a shortage results from disruption occurring at the sole API supplier for an antibiotic (as was the case with piperacillin-tazobactam in 2017), it is important to evaluate why only one API supplier remains, by looking at the commercial environment, procurement practices and regulation of competition, and resources available to invest in manufacturing infrastructure. Therefore, any effective solution aimed at improving supply sustainability must account for the relation between the different interconnected steps along the supply chain (**Figure 4**).
- *Improved communication and collaboration across the supply chain*: It is possible that the lack of progress towards improving the sustainability of the off-patent antibiotic supply chain is attributable in part to siloes that exist along the value chain. It is unlikely that any solution is the responsibility of one stakeholder alone;

206 European Commission (2020) A Pharmaceutical Strategy for Europe. Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en [Accessed August 2022]

207 Access to Medicine Foundation (2022) Lack of access to medicine is a major driver of drug resistance. How can pharma take action? Available at: https://accesstomedicinefoundation.org/resource/lack-of-access-to-medicine-is-a-major-driver-of-drug-resistance-how-can-pharma-take-action [Accessed August 2022]

208 Shafiq, N. et al. (2021) Shortage of essential antimicrobials: a major challenge to global health security. *BMJ Global Health*. 6(11): e006961

209 Roland Berger (2018) Study on the security of antibiotics supply: Pathways towards a production of antibiotic APIs in Germany and the EU. Available at: https://progenerika.de/app/uploads/2020/09/20181213_ProGenerika_Antibiotics-study-2018_vf-1.pdf [Accessed August 2022]

for example, correcting unsustainable procurement is not solely in the hands of procurement authorities, but likely relies on collaboration with industry, to understand the supply-side dynamics, and with healthcare providers, to understand demand and ensure appropriate use. A key starting point for implementing sustainable solutions will be improving the communication and collaboration across different types of stakeholders.

- *Tailoring solutions for different health systems*: As described in Chapter 3, supply challenges can materialise differently in different country, depending on the structure of the health system and supply chain. There is no one-size-fits-all solution. In Chapter 4 we set out a menu of potential solutions that would require tailoring to fit the specific needs of any individual country. There may also be a role for global coordination.
- *Improving understanding of the market failure:* Through many years of analyses and growing attention and support from policymakers, the general market failure experienced by innovative antibiotics is a well-understood phenomenon. New antibiotics will only be used in last-resort settings, minimising the sales volumes and subsequent commercial return for investors, and thus limiting the incentive for developers to make the large investment required to successfully develop a new drug.[210] Clear articulation of the economic problem has led to a range of innovative solutions being proposed to fix the market for novel antibiotics, some of which are beginning to be implemented.[211,212] While this report and many others describe the commercial unviability of the market for off-patent antibiotics,[213,214] there is a lack of dedicated policymaker-driven analysis focused on the economics of the off-patent market, equivalent to, for example, the O'Neill Review on Antimicrobial Resistance commissioned by the UK government in 2014.[215] While the review rightly concluded that the demand for existing antimicrobials must be reduced to conserve their efficacy, it did not propose concrete solutions to account for the impact this has on sustainability of the market. An important catalyst for implementing future solutions could be the development of a targeted evidence-

210 The Review on Antimicrobial Resistance Chaired by Jim O'Neill (2016) Tackling drug-resistant infections globally: final report and recommendations. Available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf [Accessed August 2022]

211 Gotham, D. et al. (2021) Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*. 125(3): 296–306.

212 Årdal, C. et al. (2018) DRIVE-AB Report: Revitalising the antibiotic pipeline. Available at: http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf [Accessed August 2022]

213 Access to Medicine Foundation (2018) Shortages, stockouts and scarcity: the issues facing the security of antibiotic supply and the role for pharmaceutical companies. Available at: https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies [Accessed August 2022]

214 WHO (2019) Meeting Report: Antibiotic Shortages: Magnitude, Causes and Possible Solutions. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?ua=1 [Accessed August 2022]

215 https://amr-review.org/ [Accessed August 2022]

based review of the off-patent antibiotic market by a government or group of governments. Improving political awareness of the problem was recommended by the WHO in 2019 as a short-term action to prompt further action to tackle the fundamental root causes of shortages.[216]

4.3. Summary

There is no singular solution to achieving antibiotic supply chain sustainability, as no approach can address all the root causes of unsustainability. The policy approach needed is likely to differ between countries, and particularly between HICs and LMICs.

Prioritised solutions for HICs

The onus of addressing the underlying economic failure in the off-patent antibiotic market likely lies with HICs, where health systems can afford to pay prices that reflect the value of a sustainable supply of essential antibiotics. Potential priority solutions would be those that provide commercial incentives and encouragement of more sustainable competition and stronger supply, including:

- **Solution (1):** Pricing approaches to recognise the value of off-patent antibiotics
- **Solution (2):** De-linked subscription payment models to guarantee minimum revenues
- **Solution (3):** Sustainable tender policies requiring supply security and multiple winners

Prioritised solutions for LMICs

In LMICs, increasing healthy competition may be more achievable through removing disincentives that prevent manufacturers from establishing or maintaining their presence in the market, and through improving regulation and predictability of demand. Differences between priority solutions in HICs versus LMICs are largely driven by the difference in feasibility, as described in **Figure 8**. This leads to a more targeted focus in LMICs on:

- **Solution (3):** Sustainable tender policies requiring supply security and multiple winners
- **Solution (4):** Reducing the financial disincentives to market entry for new suppliers *(note: also applicable in HICs, but not prioritised)*

Prioritised solutions for both HICs and LMICs

Across countries, there would likely be a positive impact on sustainability if **solutions (5) and (6)** were prioritised: improving forecasting through better use of diagnostic and surveillance data, and improving communication on supply chain structures. Although all of the solutions described in this report are likely to require some up-front investment, the anticipated costs to patient outcomes, healthcare budgets and public health from the increased occurrence of antibiotic shortages and their contribution to mortality, morbidity

216 WHO (2019) Meeting report: antibiotic shortages: magnitude, causes and possible solutions. Available at: https://www.who.int/publications/i/item/meeting-report-antibiotic-shortages-magnitude-causes-and-possible-solutions [Accessed August 2022]

and the spread of AMR, are significant. A holistic approach that leverages communication and collaboration across the supply chain will be required to build from the current global understanding of this problem and move towards implementation of impactful solutions.

Figure 8: Prioritisation of policy solutions in high-income and low- and middle-income countries

Source: CRA analysis of primary and secondary research

In conclusion, given the unique nature of health systems, we hope that the policy solutions proposed in the previous section will be valuable to countries as they consider solutions to the issue of off-patent antibiotic supply sustainability. As the occurrence of antibiotic shortages increases around the world, countries must take action to ensure a sustainable supply of off-patent antibiotics. AMR is one of the most serious health threats confronting the world today, and policy solutions ranging from pricing reform to improved forecasting systems can result in a more sustainable market dynamic and a stronger supply of off-patent antibiotics.