Shortages, stockouts and scarcity
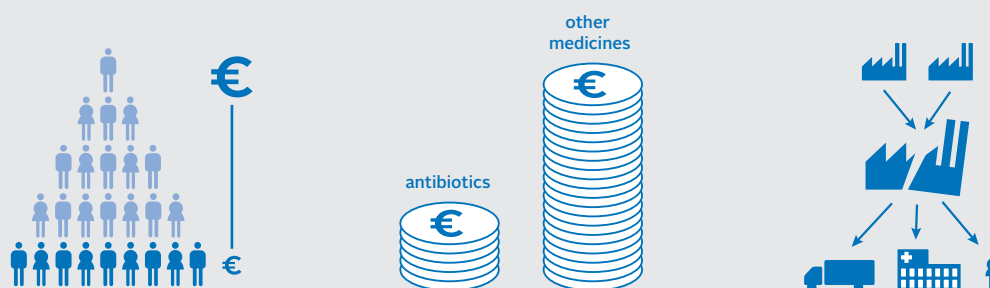
The issues facing the security of antibiotic supply
and the role for pharmaceutical companies

other
medicines

antibiotics

Three of the main issues are: growth comes from the poor, there's low profitability and the supply chain has weak links.

GLOBAL ANTIBIOTIC SUPPLY IS PATCHY, COMPLEX AND AT RISK OF COLLAPSING

This white paper unpacks the systematic factors making antibiotic supply so fragile. For example, a global penicillin shortage now affects 39 countries. The paper links the causes of antibiotic shortages to recommendations for governments, regulators, the pharmaceutical industry and others.

Supply chain collapses lead to antibiotic shortages, which are linked to disease outbreaks and antimicrobial resistance. Commercial incentives underpinning the market are weak: few pharmaceutical companies are willing or able to invest in rebuilding supply chains.

To show where action is possible, the paper identifies examples of how some pharmaceutical companies are already strengthening supply chains. It identifies three further areas where action is needed.

1 Pharmaceutical companies must bring a step change in their practices for antibiotic stock and inventory management, improve their agility, e.g., in response to shortages, and communicate information about their plans and stock data earlier and in more detail to more partners.
2 A unified approach – led by governments and supported by regulators and the industry – is needed to ensure there are multiple suppliers competing at critical links in the chain.
3 Success will depend on the development of stronger incentives for pharmaceutical companies to enter and stay in the market.

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Shortages, stockouts and scarcity

The issues facing the security of antibiotic supply and the role for pharmaceutical companies

ACCESS TO MEDICINE FOUNDATION

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ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine.

For 10 years, the Foundation has been building consensus on the role for the pharmaceutical industry in improving access to medicine and vaccines. It publishes the Access to Medicine Index every two years, with the next Index due in late 2018. The Foundation published the first Access to Vaccines Index in 2017, followed by the first Antimicrobial Resistance Benchmark in 2018.

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# Access to antibiotics — an overlooked piece of the AMR debate

Since the discovery of antibiotics in the early 20th century, these have been an essential tool in treating the massive burden of infectious diseases worldwide. Yet antimicrobial resistance or AMR is increasingly threatening the effectiveness of antibiotics. The rise of AMR is being accelerated by excessive antibiotic use in humans and in the agricultural sector. This issue of *excess* now has the political attention it so desperately deserves, but there is less attention being paid to another vital component, namely *access.*

People living in less developed and resource-limited settings are on the frontlines for AMR. They generally face higher rates of resistance and infectious diseases yet get poor healthcare advice and often struggle to access antibiotics when they need them. In fact, millions of people currently live without reliable access to antibiotics or to good information on how to use them. There are many reasons why communities may not be able to get hold of antibiotics when they need them. Challenges in the public sector include patchy healthcare services, poor infrastructure, affordability, insufficient funding and a lack of universal health coverage. The private sector can also contribute to affordability challenges, while regulatory regimes and government pricing controls can inadvertently constrain the private sector's capacity to improve access.

Many low-and middle-income countries (LMICs) face both excess and access issues. A 2015 study by the Centers for Disease Dynamics and Control found that global antibiotic consumption had increased by 65% in the past 15 years (from 21.1 billion to 34.8 billion defined daily doses).[1] This was driven by rising consumption in LMICs. In India, for example, easy access to the strongest antibiotics is commonplace. In 2015, antibiotic consumption in India reached 4,950 defined daily doses per 1,000 people, up from 2,645 in 2000.[2] Nevertheless, the burden of infectious diseases in India remains extremely high. Lower respiratory infections, diarrhoeal diseases and tuberculosis are among the ten deadliest diseases in India.[3] Out of every 100,000 children aged under five in 2016, 258 died due to pneumonia, diarrhoea or another common infectious disease.[4] Although infectious disease burdens are also linked to safe water, hygiene and sanitation, these numbers also indicate a clear unmet need for access to appropriate antibiotics.

The fragmented supply chain
The causes of both excess and access issues are multiple and complex, and include patchy antibiotic supply and fragmented supply chains. For example, a lack of visibility and accountability across supply chains increases the chances of high quantities of poor-quality medicines reaching pharmacy shelves. The issue of excessive use is being addressed by governments and others, including pharmaceutical companies. The 2018 Antimicrobial Resistance Benchmark identified company activities to promote the appropriate use of antibiotics or to prevent substandard antibiotics making their way onto shelves. These include AMR surveillance programmes,
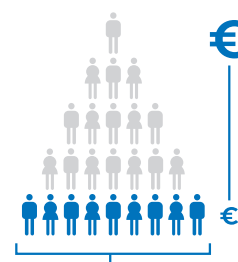

Increasing demand for antibiotics comes largely from poorer populations.
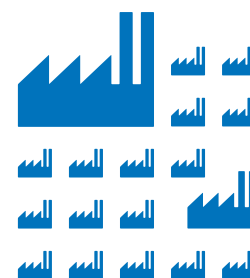
Antibiotics market is fragmented between a few very large companies and many small ones.

education activities targeting healthcare practitioners, and appropriate promotion practices.[5] However, the Benchmark identified fewer actions related to improving access to antibiotics globally.

Global antibiotic supply chains are highly fragmented, consisting of many players at some stages of the chain, and very few at other vital stages. Supply inefficiencies can be caused by: e.g., failures in manufacturing processes, scarcity of active pharmaceutical ingredients (APIs), the concentration of API manufacturing in only a few countries (mainly India and China), pressure on margins, and heavy dependence on only one or a few producers of some antibiotics. To give a real-life example, a global shortage of the key antibiotic piperacillin-tazobactam was caused by an explosion at a Chinese factory – the single producer of the API needed to produce the medication.[6]
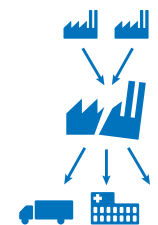
Weak links at key points raises the risk of supply chain collapse.

Antibiotic shortages are worryingly common

Shortages lead to empty shelves in hospitals, pharmacies and community health centres. Shortages of generic antibiotic products have been reported on a global and national scale (see table 1) and many formulations of antibiotics for specific populations, including children, have limited availability.[7]

A 2015 study, for example, found that the commonly prescribed antibiotic benzathine penicillin G (BPG), costing just under USD 2 a vial, was unavailable in 39 out of 114 countries.[8] In 2010, national shortages of injectable streptomycin were reported in 15 countries, with 11 more countries predicting their stocks would run out before they could be replenished.[9] The United States alone encountered 148 national antibiotic shortages between 2001 and 2013, with 22% of drugs experiencing multiple shortages.[10] In other countries, including Croatia, Latvia and Switzerland, the sale of antibiotics such as penicillin V and oxacillin has been discontinued, while a global shortage of piperacillin-tazobactam has forced doctors to hold this once widely-used antibiotic in reserve for only the neediest patients.[6,11] There is significantly less published data on antibiotic shortages in LMICs, yet anecdotal reports suggest that the problem is much worse, particularly for antibiotics such as penicillin, cloxacillin and vancomycin.[7]

WHAT IS CAUSING ANTIBIOTIC SHORTAGES?

Shortages are symptoms of fragile supply chains – because there are few competitors at different stages of the chain, the failure or exit of even one factory, manufacturer or middle-man can lead the entire supply chain to collapse. Fundamentally, the antibiotic market has a financially unstable model with tough market and regulatory conditions. Compared to blockbuster medicines for cancer or heart disease, for example, new antibiotics offer slimmer margins. Where on-patent antibiotics collectively generate USD 4.7 billion in global sales annually, a single cancer medicine can generate twice that revenue in one year.[12] Further, governments with high purchasing power are using increasingly stringent tendering processes focused on price, creating competition among producers that puts further pressure on already

antibiotics   other medicines
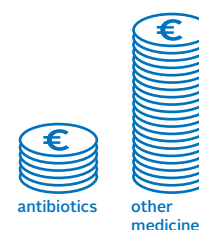
Antibiotics are less profitable than other medicines. Their price is low and they are taken in short courses.

Table 1. Global and national antibiotics shortages have different causes.

	Global Shortage	National Shortage
Definition	A worldwide shortage of an antibiotic with few or no producers.	Specific antibiotics are globally available but specific regions are unable to access them.
Example causes	• Global market failure due to low margins and low profit • Pharmaceutical companies exiting market • Reliance on a few manufacturers	• Prioritisation by companies of profitable markets over smaller markets • Fragile supply chains • Inadequate healthcare financing • Products are unaffordable

slim margins. What's more, when a new antibiotic enters the market, it will be used sparingly due to the risk of AMR, meaning there is little prospect of ensuring the high-volume sales that may be needed to justify the investment in R&D. As a result, there is little commercial incentive to develop new antibiotics.

Several pharmaceutical companies, including large research-based pharmaceutical companies and smaller companies, have left the anti-infectives market in recent years.[11] This has particularly affected the antibiotics market, mainly due to low profit margins, but also to other factors, such as the opportunity cost of using a production line for more profitable products.[13]

Further, for many antibiotics, there are fewer and fewer companies producing the APIs needed.[14] The current API market is led by manufacturing companies in India and China.[15] With increasing cost pressures particularly in Europe, some companies are outsourcing production to the same few markets (i.e., India and China) where the cost of manufacturing is lower.[16] Other companies have left the market entirely.

This concentration in a few API manufacturers means that supply is less able to quickly adapt to meet surges in demand. It also means that failures at one manufacturing plant can quickly lead to shortages that can last months or years. If pharmaceutical companies continue to exit the antibiotic market, API manufacturers are more likely to also exit. If large research-based pharmaceutical companies leave, this will also jeopardise the commercialisation and production of new antibiotics to replace less effective antibiotics.

Many antibiotic supply chains rely on just a few API manufacturers.

Figure 1. Why is there a global penicillin shortage?

Penicillin — a revolutionary antibiotic discovered 80 years ago — is now in scarce supply. 39 countries have reported benzathine penicillin G (BPG) shortages* — putting millions of lives at risk. BPG is the first-line therapy for syphilis and rheumatic heart disease. Worryingly, many countries with BPG shortages are experiencing syphilis outbreaks in parallel.
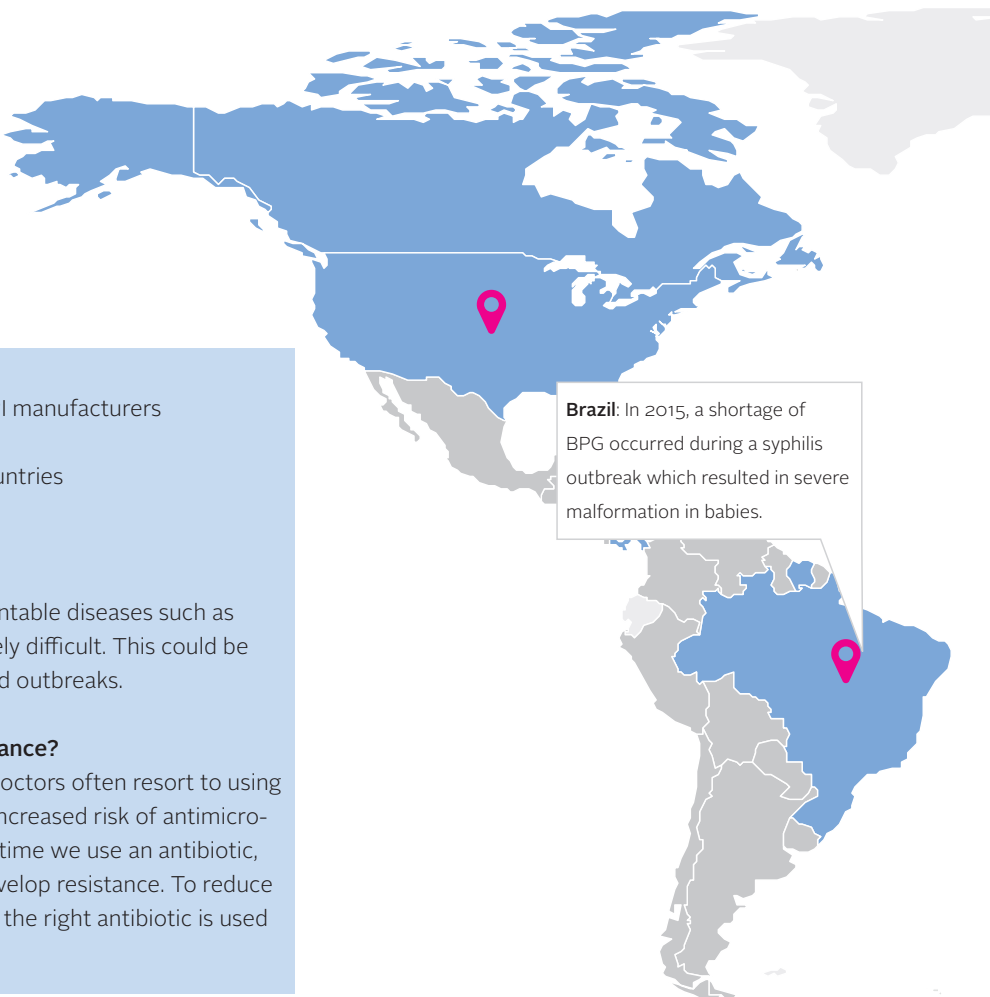
What is causing this BPG shortage?
- Fragile supply chain, reliant on only four API manufacturers
- BPG offers little profit
- Demand is high but largely from poorer countries
- Production levels kept low

What is the effect of this BPG shortage?
Shortages of BPG make treatment for preventable diseases such as syphilis and rheumatic heart disease extremely difficult. This could be contributing to increased rates of disease and outbreaks.

How do shortages fuel antimicrobial resistance?
When demand spikes and shortages occur, doctors often resort to using less optimal treatments. This also brings an increased risk of antimicrobial resistance (AMR). This is because, every time we use an antibiotic, we give bacteria the chance to adapt and develop resistance. To reduce the threat of AMR, doctors must ensure that the right antibiotic is used against the right type of infection.

Brazil: In 2015, a shortage of BPG occurred during a syphilis outbreak which resulted in severe malformation in babies.

WHO CAN FIX SUPPLY?

The rise of AMR – now a priority for the UN, the World Health Organization (WHO), G20 and G7 – brings new urgency to the problems posed by fragile antibiotic supply. But which parties are in a position to strengthen those supply chains? Antibiotic supply chains are complex and highly interdependent. They involve a multitude of stakeholders, processes and resources needed to transform raw materials into high-quality medicines. Strengthening supply chains will depend on international coordination, commitment and collaboration between a broad range of stakeholder groups. This international effort will require strong action by governments, policymakers, regulators (such as the FDA and EMA, which regularly track shortages), public health authorities, pharmacist associations, pharmaceutical companies and others. According to WHO, 90% of the world's population now lives in a country with a national action plan for AMR.[17] Such plans typically include measures to address supply-chain stability. To track national shortages, WHO has developed a mechanism for the national reporting of stockouts.

Pharmaceutical companies clearly have a vested commercial interest to ensure supply chains are strong and reliable. They also have extensive experience, expertise and capacities in supply chain management and distribution. This gives them the power and responsibility to support the transfer of good practices and promising innovation between supply chains and different actors.

Few API producers: BPG supply now depends on only four API manufacturers. With BPG offering little profit, manufacturers tend to keep production levels low. Such a small number of manufacturers can also increase the risk of substandard medicines, as, in the past, regulators have had to allow poor-quality drugs on the market to prevent shortages of life-saving drugs.

Sub-Saharan Africa: syphilis is endemic here and responsible for almost 20% of perinatal deaths.

- BPG shortage*
- No BPG shortage*
- No BPG data*

High syphilis rates**

API manufacturers for the production of BPG

*Source: WHO. Shortages of benzathine penicillin. How big is the problem? And why it matters. 2017
**Syphilis endemic: Sub-Saharan Africa
Syphilis outbreaks declared: Brazil, Australia
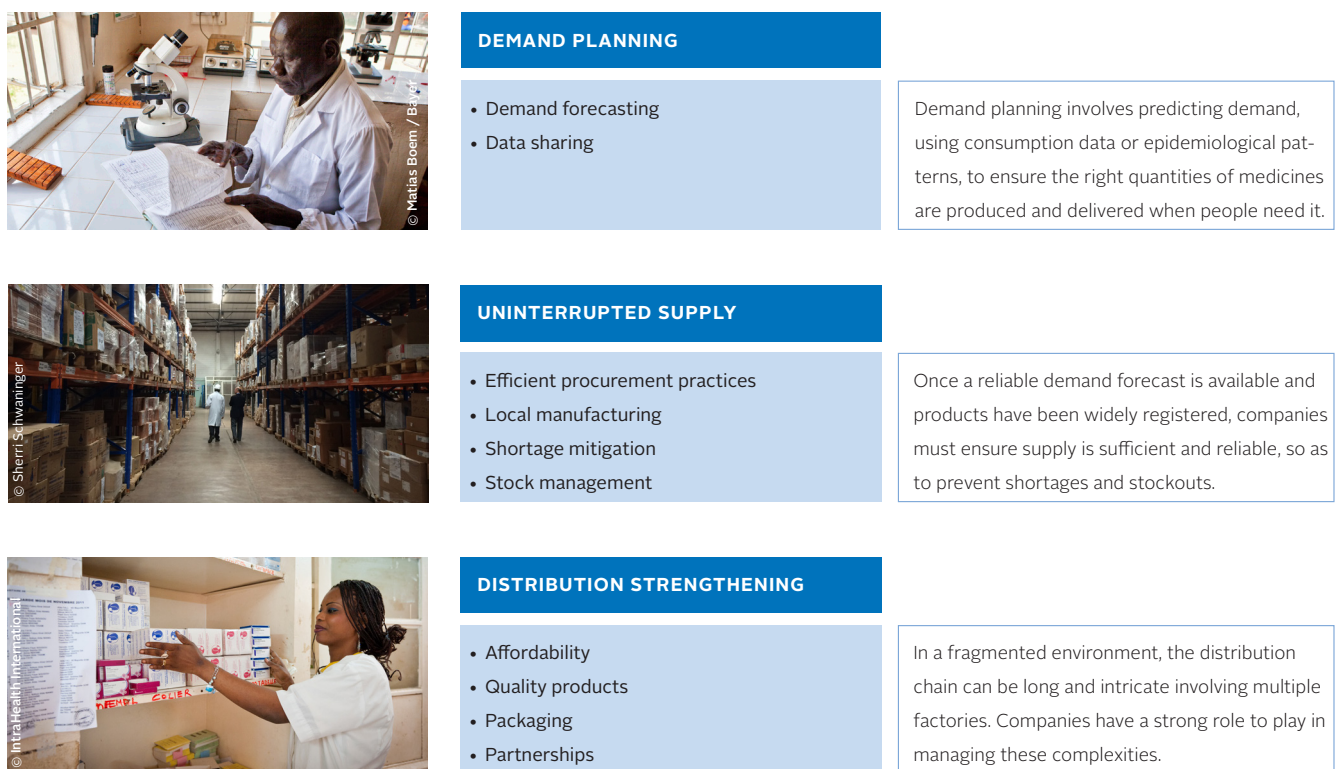Syphilis on the rise: USA, Germany, UK, Netherlands, Spain and France

What are the priorities and where are pharmaceutical companies focusing?

In light of the emerging antibiotic crisis, how can we ensure pharmaceutical companies prioritise this market – for example, by communicating with commercial teams on the importance of antibiotics in the portfolio, by dedicating sufficient capacity to this area, and by investing in multi-product production lines?

For ten years, the Access to Medicine Foundation has been researching whether pharmaceutical companies are working to improve issues relating to access to medicine, such as fragile supply. There are three broad tactics that experts and stakeholders – such as non-governmental organisations (NGOs), governments, academics, and industry representatives – expect pharmaceutical companies to use to improve the effectiveness and efficiency of supply chains in LMICs. These tactics are: (1) demand planning; (2) ensuring sufficient, uninterrupted supply; and (3) strengthening the distribution chain.

The next section of this paper gathers examples of actions corresponding to these tactics as identified in the 2016 Access to Medicine Index, 2017 Access to Vaccines Index and 2018 Antimicrobial Resistance Benchmark.[18,19,5] These examples are primarily drawn from the antibiotics sector, and include practices relating to antivirals and vaccines. We recommend that these practices are applied to antibiotics, particularly those listed on the WHO Model List of Essential Medicines (EML), and with reference to its Access, Watch and Reserve categorisations. It should be noted that, although the examples are grouped under the three tactics named above, many of these can be used to improve other areas of supply chain management as well.

Figure 2. Priority actions for pharmaceutical companies to strengthen supply chains

DEMAND PLANNING

- Demand forecasting
- Data sharing

Demand planning involves predicting demand, using consumption data or epidemiological patterns, to ensure the right quantities of medicines are produced and delivered when people need it.

UNINTERRUPTED SUPPLY

- Efficient procurement practices
- Local manufacturing
- Shortage mitigation
- Stock management

Once a reliable demand forecast is available and products have been widely registered, companies must ensure supply is sufficient and reliable, so as to prevent shortages and stockouts.

DISTRIBUTION STRENGTHENING

- Affordability
- Quality products
- Packaging
- Partnerships

In a fragmented environment, the distribution chain can be long and intricate involving multiple factories. Companies have a strong role to play in managing these complexities.

1 Demand planning

Demand forecasting is the foundation of good supply chain management. It is the discipline of predicting future demand using consumption and stock management data or epidemiological patterns, among other data sets. The resulting forecasts inform manufacturing and supply strategies to ensure the right quantities of medicines are produced and delivered to the right communities at the right time.

Health facilities in LMICs face significant hurdles in collecting and recording consumption and stock-management data. They generally lack adequate inventory systems or logistics management capabilities. They are often also faced with difficulties in identifying APIs or finished products due to a lack of differentiation or tariff codes.

Weak data leads to weak forecasting, which in turn raises the chance of shortages and stockouts. Shortages can be particularly disruptive for diseases such as tuberculosis (TB), where treatment may last several months and patients must complete treatment courses to prevent drug resistance from developing.

The tactic of demand planning relies on two main areas of company practice: 1) forecasting; and 2) data sharing to align supply and demand.

Forecasting

For companies to sustain production, they need to ensure sufficient capacity and financing to keep plants running. Both short-term and long-term forecasting allow companies to accurately schedule production to ensure the continuity of their production and avoid production loss. Short-term forecasting is useful for markets in LMICs where there is a high burden of infection that is relatively stable in terms of incidence and prevalence in the short to medium term: e.g., of TB, HIV/AIDS, syphilis and urinary tract infections (UTI). Companies should be able to accurately predict the volumes needed from country-level or regional-level data, be it for API or finished products.

Both GSK and Pfizer report that they use long-term forecasting. These plans are based on country-level demand data and are continually updated and reviewed. GSK's 10-year plan is based on country-level district demand data and is regularly updated and reviewed by the involved organisations. Pfizer's five-year volume plan is specific to its innovative products and informs the investment decisions of its manufacturing sites. While most companies have forecasting plans in place for their on-patent products, it is important that accurate forecasting is achieved for all products, including older, but nevertheless critical products.

Data sharing to align supply and demand

Data sharing and engagement with stakeholders (such as healthcare workers, government health ministries and public health organisations) to align supply and demand can reduce the uncertainty of future projections. This is especially important in addressing the global supply of products where companies work with institutional procurers and regulators and in local supply with governments. This also helps companies respond appropriately to spikes in demand. Many companies are sharing information on both sides of their supply chains to create a more collaborative environment.[20]

GSK works with WHO and various Ministries of Health to align supply and demand forecasts. The aim is to ensure a continuous exchange of information on, for example, outbreaks. For specific products, Johnson & Johnson also works with stakeholders to align information on supply and demand, including with the Pan American Health Organization (PAHO), the Global Drug Facility, and WHO. Similarly, Mylan engages with the Global Fund, the US President's Emergency Plan for AIDS Relief (PEPFAR) and the South African government and other partners including the United Nations Development Programme (UNDP), the United Nations Children's Fund (UNICEF) and the Kenyan government to align supply and demand forecasting for its HIV/ AIDS medicines.[5] The Global Fund also works with specific companies to align forecasting, allocate volumes and set production plans among other activities.

Pharmaceutical companies also make gains by optimising their internal processes for sharing information — a standard business practice that can often be suboptimal in large research-based pharmaceutical companies. For example, Astellas and Eisai reported that they shape their supply chain management strategies using input from their sales teams, manufacturing teams, local affiliates and

quality assurance teams, among others.[18] Johnson & Johnson has formed a dedicated global public health supply chain team to ensure LMICs are embedded in their overall global enterprise supply chain systems and processes.

Advancements in information technology provide an efficient platform for information to be shared in real-time across a number of users. An example of such a platform is the QuanTB electronic quantification and early warning system. This system was designed to calculate drug quantities

to improve procurement and supply planning for TB treatments, and also to provide an in-depth assessment of a country's current supply management practices. The platform is available to download and has been introduced in a range of countries, through the management of KNCV Tuberculosis Foundation, and the support of United Way Worldwide and Eli Lilly.* Health workers use this downloadable desktop tool to collect and share data on stock management and consumption of TB medicines.

2 Ensuring uninterrupted supply

Once a reliable demand forecast is available, there is a range of actions companies can take to ensure uninterrupted supply and prevent shortages and stockouts. Companies must look both upstream and downstream along the supply chain, and be agile and responsive to the changes they see. This is crucial as heavy dependency on a few API sources has resulted in higher costs, supply insecurity and acute shortages of key antibiotics.[7]

Looking upstream – toward purchasers and suppliers – actions will aim to secure sufficient supply of the ingredients needed, including APIs, at high quality. Looking downstream – toward distributors, healthcare practitioners and patients – measures will aim to track stock consumption as well as surges in demand, to ensure the right products are in the right place, at the right time.

Downstream issues such as poor forecasting and planning and over-reliance on single manufacturers can have a severe impact on the quality of batches and can often result in recalls and withdrawals. Practices to address such over-reliance at both the API level and manufacturing will be covered in this section.

It is also important to note that a product can only be marketed in a country once it has been approved by the country's regulatory authority. Therefore, product registration is the first step in ensuring the supply of products to countries in need. Rapid registration is key for securing market access and growing a strong market share. This is particularly critical for smaller,** less developed markets where institutional procurers such as government and NGOs have limited options (due to less attention from the industry) and potentially weaker health and regulatory systems.[2] Companies can also engage in licensing agreements to ensure that multiple manufacturers can produce a medicine to prevent shortages and over-dependence on a single manufacturer.

The tactic of ensuring uninterrupted supply relies on four main areas of company practice: 1) procurement; 2) local manufacturing; 3) shortage mitigation; and 4) stock management.

Procurement

Procurement involves turning forecasts and supply plans into purchased products such as APIs and intermediates to produce finished products. This section will discuss examples of procurement processes involving companies, governments and pooled procurement initiatives.

As APIs and other raw materials are frequently in short supply, procurement practices must be efficient and effective to avoid global shortages,

national stockouts and the risk of procuring poor quality products. For example, it was recently reported that injectable antibiotics had the highest level of shortages in the United States due to problems with sourcing raw materials and manufacturing difficulties.[13] Recognising this risk, pharmaceutical companies can opt to purchase from multiple sources to keep suppliers active and in business. Procurement practices must also include supplier qualification processes — a crucial step in

*Eli Lilly has left the market for anti-infectives. On doing so, it completed a ten-year technology transfer.
** "Smaller markets" here can refer to markets that are small on the national scale (e.g., the amoxicillin market in specific low-income countries) or to markets that are small on the global scale (e.g., third-line TB medicines).

ensuring quality, safety and efficacy. This process includes site audits, compliance history review, and risk assessments as well as ongoing monitoring and evaluation. Without a quality assurance system in place, companies risk sourcing substandard or con- taminated products leading to major disruptions in the supply chain.

Companies such as Aurobindo, Cipla, Dr. Reddy's, Sandoz (Novartis), Sun Pharma and Teva are among the largest manufacturers of both APIs and of fin- ished generic antibiotic products globally.[21] Looking beyond antibiotics, Mylan produces most of the necessary intermediates, APIs, and finished dosed forms for its HIV/AIDS products in-house, at nine geographically dispersed sites. This dispersion adds the advantage of regional "hubs" allowing for a rapid response to demand coming from different regions. It also ensures companies have other inhouse sources should quality or other issues arise at a spe- cific plant. While this strategy may be only an option for larger companies (that can sustain multiple man- ufacturing sites), other companies are also adopting a similar strategy.

Local procurement can help reduce over-reliance on a few manufacturers and improve regional supply chains. However, quality must be guaranteed. When companies procure from local suppliers in LMICs, they are expected to check that local staff have the skills and technology necessary to 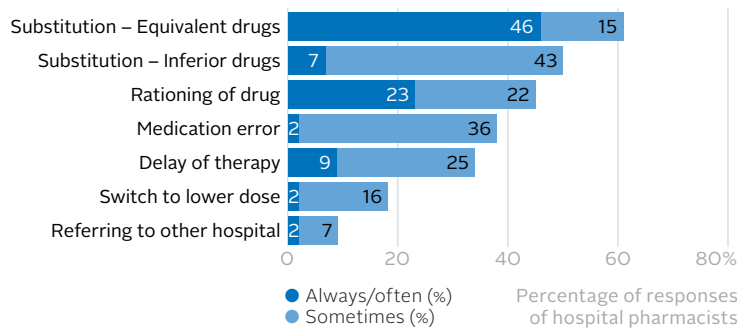meet the require- ments of good manufacturing practices (GMP). By engaging with local suppliers to build capacity in quality manufacturing for more than their own products, companies can embed long-term sustain- able solutions to ensure quality assurance and man- agement. This can be achieved through specialised training courses, establishing centres of excellence and investment in infrastructure (the cluster devel- opment approach). Resulting infrastructure can be leveraged by many companies.

Pooled procurement mechanisms are also a way to improve the procurement outcomes for indi- vidual group members or countries. Pooled pro- curement is done by one procurement office on behalf of a group of organisations, facilities, health systems, or countries. Successfully imple- mented pooled-procurement mechanisms can help
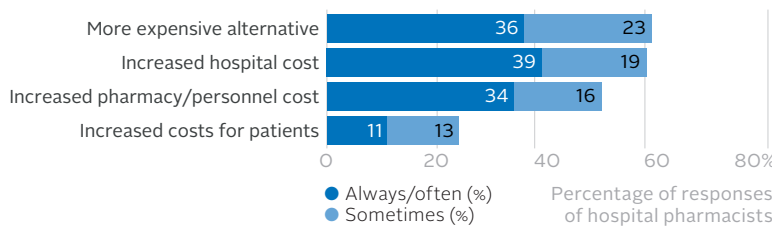

Figure 3. What happens when a doctor cannot prescribe the right antibiotic?

There is little information available about the exact consequences of antibiotic shortages on patients' outcomes, but the mortality rates due to treatable infectious diseases give some indication. According to a 2015 Europe-based survey, half of the hospital pharmacists respondents reported that patients were given inferior drugs during shortages, while more than a third said stockouts led to medication errors.[22] National agencies have also reported that some patients experienced negative outcomes because of a less effective or more toxic alternative. Less effective or more toxic treatment alternatives can contribute to AMR because every time we use an antibiotic, we give bacteria the chance to adapt and develop resistance. To reduce the threat of AMR, doctors must ensure appropriate prescribing, where the right antibiotic is used against the right organism.

What clinical impact has a drug shortage already caused?

	Always/often (%)	Sometimes (%)
Substitution – Equivalent drugs	46	15
Substitution – Inferior drugs	7	43
Rationing of drug	23	22
Medication error	2	36
Delay of therapy	9	25
Switch to lower dose	2	16
Referring to other hospital	2	7

● Always/often (%)
● Sometimes (%)

Percentage of responses of hospital pharmacists

What financial consequences has a drug shortage already caused?

	Always/often (%)	Sometimes (%)
More expensive alternative	36	23
Increased hospital cost	39	19
Increased pharmacy/personnel cost	34	16
Increased costs for patients	11	13

● Always/often (%)
● Sometimes (%)

Percentage of responses of hospital pharmacists

Source: Insights into European Drug Shortages: A survey of hospital pharma- cists. PLoS ONE, 2015.

countries access a sustainable supply of quality medicines (in particular vaccines), achieve greater demand predictability, reduce transaction costs, and reduce the total price paid for products. There are three main multilateral organisations involved in such systems, all related to vaccines: UNICEF and the PAHO Revolving Fund (both procure vaccines on behalf of countries), while Gavi, the Vaccine Alliance, provides funding for immunisation in the world's poorest countries and plays a market shaping role.

For antibiotics, however, the absence of institutional procurers (with the exception of the STOP TB partnership by the Global Drug Facility) makes demand generation and supply security more complex, due to lack of financing and global solidarity. Pooled procurement practices that include antibiotics are being done on a regional level by, for example, Gulf Coordination Council (GCC), the Organisation of the Eastern Caribbean States (OECS). However, global pooled-procurement systems in the area of antibiotics could give manufacturers more predictable demand to cover costs of maintaining a production facility and ensure access to products that are small in volume or difficult to purchase.

Local manufacturing

The local production of medicines can lead to improved supply by reducing lead times and costs.[23] However, the feasibility of local manufacturing depends on a range of activities, such as adequate regulation, funding, technology transfer and procurement capabilities. Companies can take action in this regard and support local manufacturing by transferring their knowledge and expertise to local manufacturers in LMICs.

The 2016 Access to Medicine Index found that 18 out of 20 of large research-based pharmaceutical companies were engaged in a number of activities to help facilitate local manufacturing in LMICs.[18] This included training, workshops and technology transfer activities. Twelve companies specifically committed to assessing skills gaps and supporting in-house and/or third-party manufacturers to meet high-quality manufacturing standards. Until at least 2016, GSK supported local manufacturing and owned 30 manufacturing facilities in 15 LMICs where access to medicine is likely limited.

Merck KGaA also undertakes manufacturing initiatives to support local production, through its training partnership with the Developing Countries Vaccine Manufacturers Network (DCVMN). This partnership, a voluntary public-health driven alliance, provides educational grants and enables Merck KGaA to share its expertise to support local vaccine development. The focus of the partnership

is improving the safety and quality of biologic manufacturing in developing countries.

Merck KGaA, in collaboration with Ridge Management Solutions, is currently developing plans for a vaccine manufacturing facility in Ghana, helping to address health challenges in a continent that imports 99% of its vaccines. The Ebola epidemic illustrated that improved global response mechanisms are needed for outbreaks. By developing a vaccine manufacturing plant in Ghana and other neighbouring countries, Merck KGaA would be able to reduce lead times and locally produce and supply vaccines.

It should be noted that when local production is not feasible, whether economically, commercially or financially, companies must maintain: a) local supply; b) buffer stocks; c) and be agile in response to specific needs, for example from a specific region such as sub-Saharan Africa.

Shortage mitigation

When issues arise in the supply chain, companies' responses and processes should be agile and quick to adapt. Where issues with quality in the manufacturing process may lead to interrupted supply, procedures for reporting and escalating issues are critical. Companies should have communication processes in place to ensure timely escalation of any issues. In the event of a shortage, companies can have systems in place to help avoid stockouts and ensure access to those in need.

GSK has established mechanisms for responding to stockouts in LMICs. These include mechanisms to move stock quickly within a country, and to prioritise supply to populations in need when stocks are limited. Johnson & Johnson keeps buffer stock in reserve for three of its products including bedaquiline (Sirturo®) — the long-awaited treatment for multidrug-resistant TB (MDR-TB) – darunavir (Prezista®) and simeprevir (Olysio®). Johnson & Jonhson also qualifies alternative (dual or multiple) sources of supply and inventory locations. Mylan has response mechanisms for its HIV/AIDS medicines that are designed to enable it to anticipate and respond to competing suppliers' stockouts. Mylan also maintains Vendor Managed Inventory (VMI) to cater to emergency orders and stockouts in various countries through a partnership with the Global Fund. The company is also working with USAID-funded projects under which goods are supplied to various distribution centres in, for example, Belgium, Dubai, Ghana, Kenya and South Africa. To ensure supplies can reach countries quickly and to promote local manufacturing capacity development, Mylan is setting up packaging and manufacturing facilities in sub-Saharan Africa, starting with Zambia and Kenya and evaluating options in South Africa.

Stock management

End-to-end visibility and adequate information flow in supply chains are vital for ensuring the uninterrupted supply of high-quality medicines. This is particularly the case for supply chains in LMICs with limited resources where multiple players in the supply chain have different information on resources. In recent years, there has been increased investment and activity in technology to overcome fragmented information flows. This has led to the development of projects such as India's electronic vaccine intelligence network (e-VIN) that aims to digitise vaccine stocks and Project Optimize in Senegal.[24,25] Project Optimize is a five-year partnership with WHO and the Program for Appropriate Technology in Health (PATH) for the identification and development of technology systems and interventions to improve immunisation logistics. Some companies have adopted similar technology solutions, mostly in the area of vaccines. However, this approach could also prove to be beneficial for the antibiotic supply chain.

GSK's mVacciNation programme, launched in 2012, is a mobile technology-based supply chain management programme, aiming to increase childhood immunisation in Mozambique, Nigeria and Tanzania. The programme uses mobile technology to support health workers, facilitate record keeping, and improve vaccine stock management. Similarly, Novartis' SMS for Life 2.0 programme is a public-private partnership that aims to keep pharmacy shelves in sub-Saharan Africa well stocked. It enables healthcare workers at public health facilities to use mobile phones to track stock levels and help prevent stockouts, as well as sending an automated reminder to caregivers if a vaccination appointment is missed. The data collected belongs to the relevant national ministry of health.

Importantly, investments to improve stock management are not the sole responsibility of a single company. Improving stock management requires strong collaboration between all groups and individual initiatives. Stock systems are needed for all medicines so that governments, health workers etc. can use them effectively. Many global agencies are investing in large scale systems for collecting stock data. New technology led-companies such as mPharma and mClinica work with pharmaceutical companies, payers and governments to improve access, by providing platforms that help monitor shortages, stockouts and track real-time health and demand information.[26,27]

Countries can opt to partner with private sector logistic providers that perform forecasting, logistics and data management on behalf of health facility staff. Logistic providers can then deliver medicines directly to health facilities based on real-time inventory and consumption data. For example, Senegal has recently adopted the informed push model (IPM) which helps to consolidate several supply chains into one by including the private sector. This means that private third-party logistics (3PL) are involved in last-mile deliveries between district warehouses to individual health facilities, improving the flow of products, financing and information while reducing costs. While this model was initially focused on contraceptives (MSD for Mothers) — it now includes at least 90 essential medicines including antibiotics. Using this method Senegal have drastically reduced the number of shortages.[28]

3 Strengthening the distribution chain

The pharmaceutical distribution chain can be long and intricate, involving multiple territories, factories and warehouses. In LMICs that have limited resources, the chain is particularly complex, encompassing private, public and NGO market sectors. This fragmentation can lead to higher costs, longer lead times and issues with quality.

While managing these complexities is the core responsibility of governments, companies also have a strong role to play, with a focus on strengthening the distribution chain. The main objective is to ensure that the right medicine is given to the right patient, at the right time and at the right price. The four main areas of company practice in this regard are: 1) information sharing through partnerships; 2) ensuring affordability; 3) ensuring quality; and 4) product/packaging adaption.

Information sharing through partnerships

To overcome challenges in the distribution chain, particularly in resource-limited settings, companies are opting to engage in various partnerships with both the public and private sector, including logistics companies, to overcome logistical obstacles and manage the supply chain responsibly and more effectively.

One such initiative was established following the World Economic Forum in 2015 to improve coordination and global response to pandemics: the Pandemic Supply Chain Network (PSCN), a public-private partnership that brings several global players together to enhance, align and test supply chain capabilities in preparation for a pandemic. Up to 10 private sector organisations, including pharmaceutical companies such as Johnson & Johnson, are current members of this network.[29]

GSK, Johnson & Johnson, Merck & Co. Inc., and Pfizer, along with Eisai, are involved in the Neglected Tropical Disease Supply Chain Forum (NTD SCF), a collaborative working group including WHO, the Bill & Melinda Gates Foundation, global NGOs, government donor organisations and DHL (logistics provider). This public-private partnership was established by GSK and WHO in 2012 to enable the partners to share expertise and create a more flexible and efficient approach to the delivery of donated medicines to endemic countries. The NTD SCF considers each step in the supply chain from the 'first mile' to the 'last mile' including planning and forecasting, sourcing APIs, tablet production and packaging, logistics and regulatory requirements. This process aims to maximise the efficiency, security and cost effectiveness of donation deliveries. The Forum is engaging with additional partners such as the NTD support center, Ministries of Health, European Society for Clinical Nutrition and Metabolism (ESPEN), Standard Code (software development company) and others to improve visibility of associated activities. Partners have jointly developed NTDeliver, a supply chain management tool for preventative chemotherapy supply, which helps improve the visibility of all steps of the process. It also established key performance indicators (KPIs) to increase transparency and engagement in supply chain performance for the NTD programmes.[30]

Eli Lilly has also established an information-sharing partnership with Advanced Access & Delivery, a collaborative non-profit organisation working to improve the delivery of MDR-TB therapies. This partnership was developed to create an interactive online 'atlas' of the major investments underway to address the supply and accessibility of quality-assured MDR-TB medicines. The platform is used by funders, governments and technical experts to identify gaps, prevent overlaps in work and to inform future funding for market shaping efforts.

In May 2014, Merck KGaA launched the Accessibility Platform, an informal, pharmaceutical industry-led, multi-stakeholder initiative to promote information exchange, best practice sharing and foster multi-stakeholder dialogue. Currently, there are 13 industry partners, including Novartis, Roche and Sanofi, and other interested stakeholders, such as Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis & Malaria (GFATM), Rx360, and People that Deliver. The platform brings together pharmaceutical expertise and knowledge from the supply chain and global health sectors, to tackle supply chain and delivery challenges from the 'first mile' (upstream) to the 'last mile' (downstream) and 'second mile' (capacity-building). Furthermore, the platform is in discussions with the association of central medical stores in West Africa, known as ACAME (Association Africaine des Centrales d'Achats de Medicaments Essentiels) to collaborate in developing a capacity-building programme that will aim to build core skills in supply-chain strengthening, as well as peripheral skills such as stock management and reporting.

Multiple companies have partnered with the Africa Resource Centre for Supply Chain Management, in a project that involves the secondment of staff to help improve supply chains in West Africa, Southern Africa and Nigeria. Other activities in sub-Saharan Africa include Sanofi's partnership with ACAME. Since 2010, Sanofi has developed and piloted a training programme on pharmaceutical supply chain management for national purchasing centres, in response to specific logistics issues. The company scaled up and adapted the training programme in partnership with ACAME, to address the needs of ACAME member countries. The programme has now been rolled out in several countries including Liberia, Niger and Togo.

Information-sharing can also promote responsible supply chain management and better business conditions, including among API producers. For example, the Pharmaceutical Supply Chain Initiative (PSCI), a non-profit organisation, provides members with industry principles that guide ethics, labour, health and safety, sustainability and management practices to improve suppliers' capabilities.[31] Members include AbbVie, AstraZeneca, Bayer, Eli Lilly, GSK, Johnson & Johnson, Merck & Co., Inc., Novartis, Novo Nordisk, Pfizer, Sanofi, Shionogi, Roche, Takeda and Teva, among others.

Ensuring affordability along the chain

First and foremost, companies need to ensure their products are affordable through, for example, equitable pricing strategies. However, other parties along the distribution chain can affect the price that patients pay. Their mark-ups can have a significant effect on the product's affordability and consequences in the distribution supply chain. Companies have limited ability to influence mark-ups — due to the number of steps between

them and the patient, and by local laws and regulations that guard against price fixing. For example, in countries where there is a free market for medicines, it is not possible for companies to legally control the resale price charged by distributors. In regulated markets, prices are monitored by governmental authorities, and maximum retail prices are set by regulation. Nevertheless, companies may be able to monitor mark-ups across the distribution chain. They can provide pricing guidelines, and monitor the usage of these guidelines, as well as with other contractual obligations and applicable local laws. They can also contractually agree on certain provisions and requirements with distributors, and monitor the activity of their products along the chain. Gilead monitors the selling price and mark-ups of its HIV/AIDS medicines in all applicable countries. In 2014, GSK, Barclays, CARE International and Living Goods, began exploring new ways of tackling affordability, healthcare access and sustainability in Zambia; in 2015, this led to the social enterprise 'Live Well', with the objective of supporting affordable access to medicine through, for example, training community health workers, working in partnership with communities, civil society, the private sector and government.

Ensuring quality

Firstly, it is important to note that every manufacturer of antibiotics should be GMP certified and products should be WHO prequalified where possible. Companies distribution practices must ensure high-quality products throughout the distribution chain.

Many LMICs have a long distribution chain for products. As a result, product diversion or the introduction of expired, substandard and falsified products into the distribution chain become relatively easy. The issue of substandard and counterfeit medicines is now high on the global health agenda with WHO highlighting that one in ten products in developing countries are substandard or counterfeit. Pharmaceutical companies can engage in a range of activities to combat the issue of substandard medicines, including the reporting of identified cases to national authorities and WHO Rapid Alert.

Merck KGaA's Minilabs initiative has provided over 840 portable quality-testing laboratories and related training to healthcare professionals in more than 97 countries via the Global Health Pharma Fund. Minilabs can currently be used to help authenticate 90 active ingredients, including medicines for TB, malaria, HIV/ AIDS and other medicines for transmissible and non-transmissible diseases. The company is currently working on test methods for 10 further APIs usually found in priority medicines. This will bring the number of Minilab test protocols to 100.

Product/packaging adaptation

All medicines need to be protected and packaged in containers that conform to prescribed standards to ensure the safe arrival of the product to the patient. This involves an understanding of the local market context and constraints in order to adapt formulation and packaging to suit local needs and conditions. However, LMICs with limited resources, the infrastructure required for the proper transportation, delivery and storage of medicines is often lacking. For example, an estimated 465 million people in sub-Saharan Africa lack access to electricity.[32] This poses significant challenges for medicines that require a complete cold chain, such as vaccines and some antibiotics. Due to the tropical conditions in some settings, healthcare professionals often face issues surrounding vaccine stability, which can lead to wastage and potential treatment failure.

Some companies, alongside WHO, are carrying out thermal stability studies to qualify vaccines for 'extended controlled temperature chain' prior to use thus facilitating usability in difficult last mile conditions. Johnson & Johnson has achieved high coverage rates for its hepatitis B vaccine Hepavaxgene® to reduce child and adult mortality from hepatitis B and its complications. Another product feature adopted by Johnson & Johnson, Merck & Co., Inc, and Sanofi, includes the use of temperature sensitive vaccine vial monitors (VVMs). These enable healthcare professionals to check whether individual vaccine vials have been exposed to temperatures higher than the permitted maximum during delivery from a regional store to immunisation locations. WHO, UNICEF and Gavi, the Vaccine Alliance, urge all countries that self-procure vaccines to include this feature among the minimum requirements for vaccine purchase agreements.[33] Since their introduction, VVMs have contributed to the preservation, safety and potency of the vaccines deployed in hard-to-reach communities and in areas with cold chain challenges.

Controlled Temperature Chain (CTC) is an innovative approach to vaccine distribution management that allows vaccines to be kept at temperatures outside of the traditional cold chain (+2°C to +8°C) for a limited period of time under monitored and controlled conditions. In 2017, Sanofi was granted a CTC indication for its Shanchol™ cholera vaccine by WHO after a review of specific stability data. The Shanchol™ vaccine can now be kept for up to 14 days at 40°C immediately prior to administration, making the last mile delivery of the Shanchol™ cholera vaccine in hard-to-reach endemic or outbreak areas less costly and more flexible.

How can we fix the supply of antibiotics?

There is a market failure in the antibiotic sector: while there is growing demand, it comes largely from the poor. With little money to be made, more companies are exiting the market. While there are still some large companies active in this space, the majority that remain committed to producing these low-margin but crucial medicines are much smaller players. Smaller players may not be in a position to meet high demand, increasing the risk of shortages and adverse quality outcomes.

Without a competitive market, there will not only be more frequent shortages and quality issues, but the last few companies left in the market will have greater power to dictate prices. This applies to all kinds of medicines, branded (on-patent) and generic alike. Between 2010 and 2015, nearly a quarter of all generic medicines including antibiotics saw at least one price increase of 100% or more, and some saw increases of 1,000% or more.[34] Something similar is happening in the API market. In the past two months, the prices of some APIs have increased between 30% to 50%.[35] To prevent further price hikes, it is critical that we – as a global society – invest in the development of a healthy market, with multiple players at key points of the supply chain. This will mean reaching agreements between antibiotic manufacturers and governments that ensure supply can meet global demand. In fact, society may already be faced with two choices: invest in new mechanisms and/or incentives today that means we may pay a little more — without compromising affordability – or take no action and enable the remaining few players to drive prices up tomorrow.

We need affordable, quality assured antibiotics in order to safeguard public health. Making this happen is a core responsibility of governments, supported by regulators and the industry. Securing sufficient global supply as well as national supply of antibiotics require different ways of working. The first half of the challenge is to secure sufficient global supply. Once a product is globally available, governments, companies and others can strengthen regional and national supply chains to bring sufficient supply into communities in a timely fashion. Securing global supply will require working with a global governance system to align production with multiple manufacturers, and to conduct API sourcing and forecasting on a global scale. As a next step, identifying and reaching countries with limited availability of specific products must be prioritised. With this in place, companies and local governments can work to secure sufficient national and local supply, strengthening downstream supply chains, working with multiple, local producers and by building local capacities in, e.g., inventory management.

The path ahead
When you look at the examples first identified in the Foundation's research and provided in this paper, most practices relate to vaccines. This is unsurprising given vaccines' role in protecting billions from diseases. These are followed by practices related to HIV/AIDS, malaria and then TB — again unsurprising given the heavy burden these diseases place on governments and society and the prolonged period of treatment needed (lifelong for people living with HIV/AIDS) thus predicting supply. These diseases also have the highest levels of international intervention and prioritisation. International interventions for controlling HIV/AIDS, malaria and TB emerged during a period in which the link between health and human rights had

ADVERSE QUALITY OUTCOMES
An increasing number of poor-quality medicines have been left on the market to prevent shortages due to no available alternatives.

HUMAN RIGHTS
"HIV is no longer just a disease. It is a human rights issue," Nelson Mandela, 46664 concert.

established itself as a distinct area of public health practice. As a result, governments and multilateral agents came together to greatly expand access to medicine for these high-burden diseases — and to great effect. For example, 22 million lives have been saved through the Global Fund Partnership, a partnership of governments, the private sector, and civil society.[36] Such collaborations have helped solve challenges relating to policies and strategies, coordination mechanisms, procurement and supply management including logistics, monitoring and infection control. The antibiotic crisis now needs this level of unity. After years of neglect, antibiotic resistance and dry antibiotic R&D pipelines are now top of global health agendas — a unified approach will ensure the fragile antibiotic supply chain tops the agenda too.

A unified approach

The existence of ongoing shortages of antibiotics demands that communication and coordination between the industry, procurers and other stakeholders be improved. Coordination with stakeholders who understand local needs and can put incentives in place for private-sector involvement are crucial. This will lead to the establishment of new models that can help shape the market, foster increased competition and build resilience in the supply chain. Providers and doctors also have a major role to play to ensure quality products are being prescribed appropriately.

Such a unified approach — which is no small feat — to creating a healthy market with multiple players will require: new strategies for demand planning and forecasting, new approaches to procurement and tender procedures, market entry awards for new products and other targeted economic incentives to encourage the development of antibiotics and their commercial availability, as well as investment to incentivise the production of older antibiotics that benefit a wide range of players and countries. What is also needed are new proposals to facilitate the registration of antibiotics for sale in countries where they are particularly needed.

However, governments cannot do it alone — improving public health is achieved by collaboration and unity including with the pharmaceutical industry. Such a unified and collaborative approach to strengthening fragile antibiotic supply chains is needed now.

Similar measures have already been proven to work in other areas of public health. UNICEF, in collaboration with WHO and the Bill & Melinda Gates Foundation,

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Table 2. Pharmaceutical company strategies to strengthen supply depend on antibiotic category.

The table shows how company strategies for improving antibiotic supply should vary according to the category of the antibiotic. The WHO has grouped the antibiotics on its Model List of Essential Medicines into Access, Watch and Reserve categories. The groupings are linked to the risk of antimicrobial resistance. Note: the examples provided have been simplified for purposes of this discussion. Exceptions may occur. These are not exhaustive lists.

	Access: always on the shelf	Watch: a balancing act	Reserve: the last resort
Treatment line and stewardship advice	First- and second-line treatments that should be widely available. e.g., amoxicillin.	Second-line treatments that should be prescribed only for specific indications, since they are at higher risk of bacterial resistance, e.g., quinolones and fluoroquinolones.	Last resort or third-line treatments e.g., aztreonam, colistin, that should be used to treat only the most severe cases, in order to limit the risk of resistance.
Market at a glance	Commercially attractive	Commercially viable	Small global market
Governance approach needed	Local governance: requires collaboration between pharmaceutical companies, governments and local organisations.	Local governance: requires collaboration between pharmaceutical companies, governments and local organisations.	Global governance: requires the expertise and efforts of governments, multilateral organisations such as WHO, regulators and pharmaceutical companies.
Company strategy needed	Broad strategies are needed to improve access to these antibiotics in countries where health systems are weak. Key elements include plans for widely registering antibiotics, affordability, strengthening supply chain and stewardship practices. An agile approach is necessary for responding to shortages and stockouts.	To manage antibiotics in this group, companies must take a nuanced and weighted approach, developing suitable access plans that are integrated with stewardship practices that limit excessive use and predict emerging resistance trends.	Antibiotics in the Reserve group are essential treatments against the most resistant pathogens. It is vital that companies engage in stewardship activities that facilitate the appropriate use of these antibiotics, while rigorously monitoring demand and growing threat of their resistance. Global strategies must include mechanisms to reserve stock, and facilitate an agile and rapid response to need.

uses its procurement process to promote the uninterrupted and sustainable supply of vaccines — to counter an increasingly consolidated market. UNICEF issues tenders based on several selection criteria including pricing and WHO prequalification, and makes a point of procuring each vaccine presentation from several manufacturers, including manufacturers from both developing and industrialised countries. UNICEF also provides manufacturers with accurate and long-term forecasts. This approach is essential to help ensure a healthier market with multiple players, one that governments can replicate in their procurement processes. While, some governments have started to maintain a shortlist of multiple qualified suppliers, decisions are often based on 'lowest-price' tendering, so if a contractual issue occurs or demand is not met, governments often opt for the next lowest bidder — leading to a financially unstable model.

Ensuring last resort but crucial antibiotics

Different categories of antibiotics will need different approaches to develop healthy markets (see table 2), particularly for antibiotics in the WHO's Reserve category. In 2017, the WHO Model List of Essential Medicines (EML) categorised antibiotics into three groups– Access, Watch and Reserve – to reduce the use of certain antibiotics as part of their ongoing efforts to reduce resistance.[37] The three groups describe which antibiotics should be used more readily and which ones need to be carefully conserved (see table 2). WHO advises that antibiotics in its Reserve category are used only to treat the most resistant pathogens, when all alternative treatments have failed. This is essential to minimise the chances of resistant strains from emerging. Such tight control will keep demand low. Nevertheless, it is critical that adequate supplies of quality-assured Reserve antibiotics are always available.

A unified and active response to supply issues, as demonstrated by UNICEF, could mitigate unintended consequences of the WHO EML's antibiotic categories.These categories will likely influence demand from national governments and therefore, will also have an impact on antibiotic supply chains. For instance, as antibiotics listed in the Access group are first- and second-line treatments that should 'always be on the shelf,' the appeal for companies to remain in this market is high. In contrast, antibiotics listed in the Reserve group are 'medicines of last resort' and can only to be used against the most resistant pathogens. This restriction will have consequences on the market due to the economic impact for those companies with antibiotics in this group, potentially increasing the likelihood these companies will leave the market especially.

Reserve antibiotics are at an increased risk of severe global shortages as they can only be used in the most severe circumstances when all other alternative antibiotics have failed. Global coordination and mechanisms to reserve stock are needed to help keep manufacturers of critical Reserve antibiotics in the market and ensure their supply when needed. However, how governments, global health agencies and pharmaceutical companies respond to the demand of both Access and Reserve antibiotics to ensure sufficient supply, will require different approaches (see table 2).

Access must be sustainable long term

A unified approach could have a major impact on access to antibiotics, but it needs time and resources to implement market shaping options. Moreover, the consensus view is that access must be sustainable in the long-term. This means governments working with pharmaceutical companies to establish plans to ensure recipient populations can continue to access treatments for as long as they are needed – thanks in part to an uninterrupted supply of high-quality antibiotics they can rely upon. For now, there is much more that companies can do.

What can pharmaceutical companies do now?

There is no simple model for rebuilding a healthy antibiotic market – new incentives are needed for pharmaceutical companies to commit to producing antibiotics. Even so, pharmaceutical companies themselves can now take a range of steps – set out below – to build long-term positions in the market and help to secure the long-term future of the market itself. Implementing the six steps below will take pharmaceutical companies forward in strengthening fragmented antibiotic supply chains and improving access to these critical medicines.

1 Think long-term and bring a step change in processes for inventory, stock and risk management.

2 Incentivise staff and country distributors to develop distribution reach beyond urban areas.

3 Improve agility vis-à-vis public health needs, e.g., hold local inventory in regional buffer stocks in response to shortages.

4 Communicate plans in response to challenges, opportunities and innovations; earlier and in more detail to those who understand local needs.

5 Invest in capacity building for supply chain strengthening (this includes technology transfers, training workshops, conducting audits, maintaining strong contracts downstream).

6 Consider multiple sourcing (to avoid market consolidation) and use multiple, even shared, production sites to avoid supply issues.

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