KEY FINDING 1

Out of 28 antibiotics in late stages of clinical development, only two have both access and stewardship plans in place

As more microbes develop drug resistance, a robust pipeline of new antimicrobial medicines is critical for replacing less effective medicines.

The pipelines captured in the Benchmark have 175 antimicrobial medicines targeting pathogens seen by WHO and CDC as the biggest AMR threats. Of those, 40 – one quarter – are drug candidates in late stages of clinical development, including 28 antibiotics. Several are novel, with new modes of action, including new classes of antibiotics to treat multidrug-resistant *S. aureus*. In much of the world, more than half of *S. aureus* infections are reported to be resistant to standard treatment with methicillin (known as methicillin-resistant *S. aureus*, or MRSA).[1]

Once a new antibiotic has market approval, AMR response strategies call for it to be used prudently, to slow the emergence of resistance and maximise the antibiotic's useful lifespan. Such stewardship measures must be pursued alongside efforts to ensure appropriate access to antimicrobials. More people die from lack of access to antimicrobials than from drug-resistant microbes. Companies must put access and stewardship plans in place at the same time to ensure they are most effective, and before a new product enters the market.

Of the 28 antibiotics in late-stages of clinical development, only two (eravacycline, Phase III; bedaquiline for paediatrics, Phase II) have both access and stewardship provisions in place. Eravacycline is being developed by Tetraphase to treat complicated intra-abdominal and urinary tract infections caused by a range of pathogens, including *A. baumannii, S. aureus,* and *C. difficile*. To plan for access, Tetraphase is seeking licensing partners to increase access in several regions of the world. For stewardship, it provides hospitals with testing strips that check whether a patient's infection is susceptible to the drug, which is important to ensure its appropriate use.

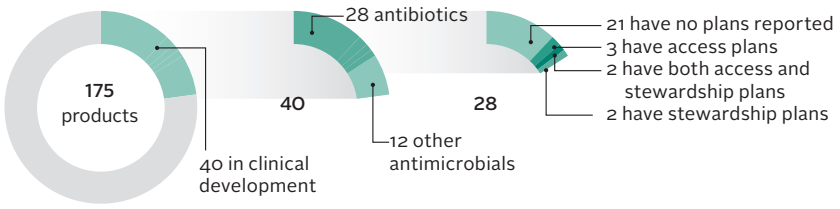
Bedaquiline (Sirturo®), conditionally approved for the treatment of multidrug-resistant tuberculosis (MDR-TB) in adults, is now being developed by Johnson & Johnson for the treatment of MDR-TB in children. The company will use the same access and stewardship provisions that are in place for the adult formulation. These include a managed access programme through the Global Drug Facility (GDF) and with its own subsidiaries. To limit resistance to bedaquiline, the company's stewardship provisions include educational activities for paediatric healthcare professionals that aim to improve knowledge and awareness on the appropriate use of the antibiotic.

Two other antibiotics in the late-stage clinical pipeline have stewardship provisions, but no access plan: GSK's gepotidacin (Phase II) for gonorrhoea; and Pfizer's avibactam/aztreonam (Phase II) for multidrug-resistant gram-negative bacterial infections. Three have an access plan in place, but no stewardship provisions: a second gonorrhoea medicine, an antibiotic for acute skin infections, and a gel for treating umbilical stump infections (being developed by Entasis, Melinta and GSK respectively).

Besides antibiotics, there are 12 other medicines in late-stage clinical development targeting priority pathogens, including five with both access and stewardship provisions. All are antivirals for HIV/AIDS being developed by GSK, either alone (three) or in partnership with Johnson & Johnson (two).

Figure 12. Few late-stage antibiotics with access and stewardship plans.

The Benchmark identified 28 antibiotics in clinical development that target pathogens posing significant threats due to AMR (according to WHO and CDC). Only two have plans in place to ensure they will be accessible, yet used prudently: eravacycline from Tetraphase and paediatric bedaquiline from Johnson & Johnson.



KEY FINDING 2

Nearly half of companies with products on the market are involved in AMR surveillance

Curbing AMR depends on knowing which pathogens are developing resistance and where. Yet there are major gaps in global AMR surveillance, with countries having differing levels of surveillance capacity and a lack of data harmonisation, making it more difficult to use the data that are shared.

The pharmaceutical industry can make an important contribution in this area. Companies that signed the 2016 Industry Roadmap for Progress in Combating Antimicrobial Resistance (including 10 the Benchmark measures) agreed to support efforts to increase AMR surveillance.

The Benchmark found that nine of the 19 companies reporting such efforts are running or supporting 19 AMR surveillance programmes across 147 countries. These are seven of the eight large research-based companies in scope, one of the 10 generic medicine manufacturers, and one of the 12 biopharmaceutical companies.

The activities are diverse in terms of scale, focus and duration. For instance, GSK periodically monitors international resistance trends in community-acquired respiratory infections; Wockhardt collects data from a representative sample of the entire healthcare infrastructure in India; and Pfizer's ATLAS project tracks susceptibility and resistance patterns for a variety of pathogens and medicines across more than 60 countries.

Pneumonia gets the most attention, followed by other respiratory infections, including tuberculosis. Resistance is also being tracked in a variety of pathogens considered a priority for monitoring, including *S. aureus, E. coli* and *H. influenzae*. Some programmes track a single pathogen (e.g., Johnson & Johnson's DREAM programme, focused on *M. tuberculosis*), while others monitor several pathogens and medicines in the same project (e.g., GSK's SOAR and Merck & Co., Inc.'s SMART programmes).

Sharing the surveillance data with third-party initiatives that track AMR trends is a fundamental next step. At least eight companies reported their data are presented at public conferences or published in journals, while two – Merck & Co., Inc. and Pfizer – publish their surveillance data on the Internet. GSK reported plans to publish all its surveillance data on the Internet and to collaborate with other organisations aiming to publish an online database conglomerating pharmaceutical industry AMR surveillance data.

Key challenges for ensuring that industry AMR surveillance efforts have maximum impact include increasing involvement, harmonising data, converting prevalence studies into long-term monitoring programmes and increasing collaboration with public health bodies coordinating surveillance.

Figure 13a. Nine out of 19 companies support AMR surveillance.

The Benchmark found that nine of the 19 companies evaluated in this area are running or supporting 19 AMR surveillance programmes, spanning 147 countries.

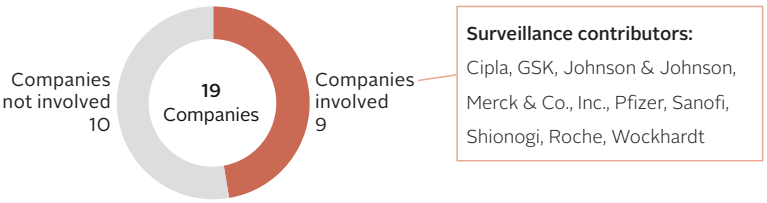
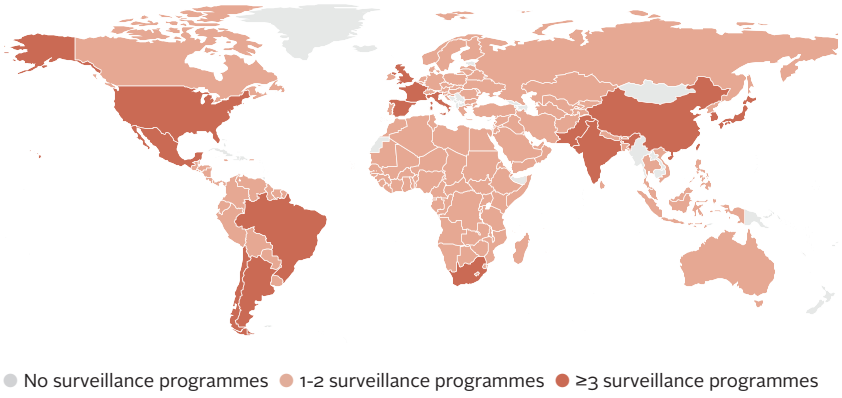


Figure 13b. AMR surveillance programmes are being conducted in 147 countries worldwide.

Nine companies assessed by the Benchmark in this area are engaged in surveillance programmes, active in 75% of countries in the world.



KEY FINDING 3

Eight companies are setting limits on antibiotic wastewater discharge

Antibiotics released into the environment in factory wastewaters are increasingly thought to be contributing to AMR. The exposure of bacteria in soil and water to discharged antibiotic ingredients can trigger the emergence of resistance genes.[2] Large volumes of antibiotics are manufactured in some countries where local populations often rely on untreated groundwater for their household water supplies.[3] Significantly curtailing the release of antibiotics into the environment is seen as an important measure for slowing AMR. Consensus around safe limits for antibiotic discharge has yet to emerge.

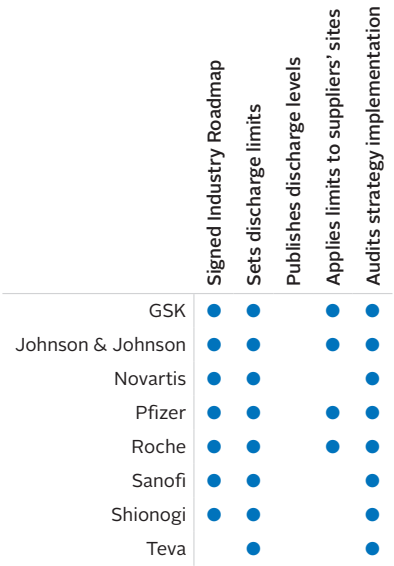
On this issue, the Benchmark questioned the 18 companies in scope with significant manufacturing presence.* Of these, 15 reported having some form of an environmental risk-management strategy in place, with eight also reporting that they have set factory discharge limits for antibiotics. In a further step, four said they also require their suppliers of antibiotic active ingredients and drug products to adhere to the same limits. All eight also disclosed that they audit the implementation of their environmental risk-management strategies. However, no company publishes its environmental audit results, or its discharge levels.

For the remaining ten companies, four reported they do not set limits and four did not respond to the question. The Benchmark was unable to find independent information on the performance in this area for the four companies who declined to answer the question. The two remaining companies, Aurobindo and Dr. Reddy's, report that they do not set limits as they do not release wastewater. Instead they vaporise the waste and dispose of the residual solids by other means.

Ten of the companies included in this Benchmark have signed the 2016 Industry Roadmap for Combatting Antimicrobial Resistance, thereby committing to establishing a common framework for managing antibiotic factory discharges, to developing a mechanism to demonstrate their supply chains meet the standards set, and to agreeing, by 2020, on targets for antibiotic levels released in waste discharge. They also committed to reviewing their actions to identify good practice. Seven of the eight companies that reported setting limits were signatories of this Roadmap.

Figure 14. Eight companies set discharge limits. No company publishes discharge levels.

Eight of 18 companies evaluated in this research area reported that they have set discharge limits for antibiotics. Four of these companies also require upstream suppliers of antibiotic APIs and drug products to adhere to the same limits. Yet no company publishes its discharge levels. All eight companies reported that they audit the implementation of their environmental risk-management strategies at their own manufacturing sites.



*In its analysis of Manufacturing & Production practices, the Benchmark uses global antibiotic sales volumes to inform its selection of companies to analyse.

KEY FINDING 4

Four companies move to decouple antibiotic sales volumes from sales agents' bonuses

The more that antibiotics are used, the faster they become ineffective.[4] One of the strategic pillars of the global effort to address antimicrobial resistance is therefore to ensure that antibiotics are used appropriately, only when needed, to prolong their effectiveness.

The more antibiotics that are sold, the more that are available, and this is thought to contribute to the problem of overuse.[5] The Benchmark has found that four companies are changing the way they remunerate sales staff in ways that should remove the incentive to oversell antibiotics: GSK, Shionogi, Pfizer and Novartis report that bonuses are fully decoupled or that the company has taken steps towards adjusting incentives for its sales teams' bonuses from the volume of antibiotics they sell.

Figure 15. Decoupling sales volumes from sales agents' bonuses: four companies are taking action

GSK, Novartis, Pfizer and Shionogi report that bonuses are fully decoupled from the volume of antibiotics they sell or that the company has taken steps towards adjusting incentives for its sales teams' bonuses.

GSK

- Full decoupling
- All bonuses decoupled from sales volume
- Applies to all sales staff globally
- Changes made in 2013

Shionogi

- Full decoupling
- Bonuses decoupled from antibiotic sales volume for all sales staff

Pfizer

- Pilot
- All bonuses decoupled from sales volume
- Applies to sales staff in selected geographies
- Starts in 2018

Novartis

- Adjusting incentives
- Lowering % of bonuses linked to sales volume

GSK has led in this area, having since 2013 separated pay from antibiotics sales volume for all its sales staff in every country in which it sells antibiotics. Shionogi also reports that it does not remunerate its sales teams based on antibiotic sales volume. Pfizer and Novartis are now following. In 2018, Pfizer will start working on pilots that aim to decouple the remuneration of its sales teams from sales volume. Novartis is starting to increase the weight of fixed pay in overall compensation for sales staff, while reducing the variable component.

At least one other company is taking a different approach at the product level. Johnson & Johnson's new anti-tuberculosis drug, bedaquiline (Sirturo®), is provided solely through national tuberculosis programmes and therefore does not require any marketing materials. The company reports that it does not deploy any sales organisations for the sale of Sirturo® in countries in scope.

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