FROM WORDS TO ACTION: EXPLORING THE ECOSYSTEM OF ANTIMICROBIAL RESISTANCE

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Antimicrobial resistance (AMR) is the ability of microorganisms to evolve to resist antibiotics, leading to infections becoming increasingly untreatable.

AMR already claims as many as 33,000 lives in the EU every year, but this is set to drastically worsen, with AMR poised to become a bigger killer than cancer by 2050.

But despite the looming threat that AMR presents, research and development in this area has been blocked for many years thanks to a combination of an unpredictable market, lack of incentives and high associated costs.

This has led to the creation of a “toxic” cycle which needs to be broken, but the question is how this can be achieved.

In this Special Report, EURACTIV explores the ecosystem of AMR and concrete proposals for how this deadly threat can be tackled.
MEP: Public-private partnerships needed to face silent threat of AMR

Netflix and pill: Industry subscription service could incentivise antibiotic research, says expert

Heavy use of antibiotics in COVID-19 treatment likely to increase AMR

EU action to turn the AMR tide looks at different incentive models

Superbug pandemic threatens to undo medical progress
The silent threat of antimicrobial resistance (AMR) must be fought with investment in research and development and by encouraging innovative economic models, Swedish centre-right MEP Jessica Polfjärd told EURACTIV in an interview.

Jessica Polfjärd is a Swedish MEP for the Europe People’s Party (EPP). She spoke to EURACTIV’s health reporter Giedre Peseckyte.

Has the pandemic helped to push AMR higher on the agenda in the past year?

The pandemic has put the overall focus on health issues. There have been a lot of discussions going on through the pandemic about health and I didn’t think that we would have so much focus on it.

That is also good for the AMR issue. We can see that it can be a real threat in the future if we don’t manage it well. In documents and files that we have worked on, like the EU4health, we had the possibility to add the issue of AMR and also keep the focus on this issue.

So, I think that if you can see anything good coming out from the pandemic, I would say that this is one example. Of course, there is still much to be done. More focus is needed on prevention, innovation and how we can get support for the pharmaceutical industry.

Has AMR been an important issue at the European Parliament in recent...
Yes, I would say so. I’ve only been elected for two years, but as I recall, it has been an ongoing discussion for many years, both on the human side and the animal side. And there has been a good interest, but of course, it has been highlighted during the past one and a half years. Overall it’s a silent threat and maybe it is a possibility to make it louder.

What still needs to be addressed when talking about AMR at the EU level?

It’s important that we encourage innovation, of course, and also partnerships between the public and private sectors for a long-term perspective. And if we are talking about money and raising money, we could establish a global innovation fund for antibiotics, for example.

There was a fund launched recently to address these issues and they have raised a lot of money. It is also problematic to use the right models for the industry to be encouraged to make investments and innovations.

So, we want to use fewer antibiotics, but how do we keep the businesses running and the revenues independent from sales?

I share your view that we really need sustainable business models for moving forward. As you said, there is a contradiction here. We don’t want to use it but we do need more and new innovative antibiotics on the market.

There is a business model for AMR called the Netflix model. In this model, the public authorities agree to purchase a certain amount of antibiotics for a certain period of time. And then they decide how much is needed and maybe you don’t use it all, but there is an agreement. I think that it is one example of how it could be more sustainable when it comes to the AMR business model.

There is a lack of interest in the industry to invest in the development of novel antibiotics. What are the main factors that keep the investments away from the antibiotic industry?

It is quite an unstable market, there are no lifelong treatments, for example. Also, like we said, the aim is, of course, to reduce the usage of antibiotics and that might give the wrong signals to the market.

But if we can find new models and we can see that it will be more sustainable, it would be a good signal to the market and also to both the investors and to the research groups.

What EU countries offer a good example of how to deal with AMR?

I could give my own country [Sweden] as a good example. When it comes to animals we are one of the countries that use the minimum of antibiotics. But we can also see that prevention is important.

Once again, going back to the pandemic, we can see that how you organise society and organise healthcare can also have an impact on the usage of AMR in the future. So I think there are different aspects to this.

Do you think that the Commission should come up not only with guidelines but with mandatory action for the member states?

In my point of view, the guidelines are the better way. Being a front runner, being guided by examples, is a better way.

What can be done to speed things up with AMR, with new antibiotics development in the EU? What would be the key points?

We really need cooperation within the EU and it is also about research, innovation and investments. It is also, about sustainable, long-term business models for the industry, for sending a clear signal that it is important for the EU. And if we think it’s important, we need to add money and give the possibility for the research and innovation.
‘Netflix-style’ subscription service, regularly paid from governments to the pharmaceutical industry, could help incentivise the creation of sorely-needed new antibiotics and break the “toxic” environment of antibiotic research and development, according to an expert.

Antimicrobial resistance (AMR) is the ability of microorganisms to evolve to resist antibiotics, leading to infections becoming increasingly untreatable.

AMR claims as many as 33,000 lives in the EU every year, but this is set to drastically worsen, with AMR poised to become a bigger killer than cancer by 2050.

However, despite the looming threat of this so-called ‘silent pandemic’, research and development of new antibiotic treatments is toxic, according to Jeremy Knox, policy and advocacy lead on the drug-resistant infections priority programme of the Wellcome Trust, a charitable foundation focused on health research.

“The market is very unpredictable and delivers very low revenues, which has led decades of disinvestment by pharmaceutical companies,” Knox told EURACTIV, pointing out that, unlike other newly-developed drugs, new antibiotics are not made to be used, but to be kept back only in cases of emergency.

This has left only a small handful of major global pharmaceutical companies still in the AMR game, he said, as others opted instead to shift their business model to focus more on the lower-risk areas.

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“[Companies] are starting with a small market, and then you’re only capturing a fraction of that small market. So it’s a really kind of toxic environment,” he said.

This has created a situation where there are “rising rates of resistance, existing drugs becoming increasingly undermined by those rising rates of resistance, but really far too few products in the pipeline,” Knox said, pointing out that this has been the case since the 1980s.

Breaking this cycle of under-investment and scientific roadblocks will be enormously challenging and require revolutionary new approaches, according to Knox.

Crucially, governments must find a way to deliver a predictable revenue which is large enough to offset the investment costs of all of the late-stage research and development (R&D) and up to being ready to enter the market, he said.

One way in which this could be achieved is via an upfront lump sum payment for products that meet defined criteria.

Another possible avenue that merits exploration is the idea of a ‘Netflix-style’ subscription service, he said, adding that this more “nuanced” approach has been gaining momentum in recent years.

In this way, governments would agree to regularly pay a set amount of money to support the industry, regardless of how many units of the antibiotics are sold.

This kind of subscription can create “stable, dependable revenues regardless of how much or how little of the antibiotic is used,” thus breaking the economic cycle of paying on a per pill basis, he said.

Such contracts could be awarded for 5-10 years, he suggested, with governments committing to pay an annual lump sum linked to the value of an antibiotic.

This can be seen as a “win-win” for all parties, Knox said, as developers would have “certainty around the revenues they’re going to make and the demands they will face” while the governments can “apply proper stewardship, there’s no incentive to overuse the product, and they have certainty that they will have fixed costs on this for years to come”.

While the idea is relatively new, he pointed out that this idea is currently being trialled in the UK, and the US is also moving to consider the possibility of such a subscription service.

There is also increasing interest for such a model in the EU, with Swedish MEP Jessica Polfjärd recently citing it as an example of how AMR business models could be more sustainable.

Translating this to the EU could be a struggle though, as Nathalie Moll, director general of EFPIA, pointed out during a recent event on tackling AMR,

“We see national prescription models, sort of subscription models like Netflix models in the UK and Sweden that seem to work in the US, but we need things that work for us here in Europe, because we’re not a single country,” she warned.

However, one thing all stakeholders were clear about is that there is no time to lose in addressing the issue.

“We can’t wait. We need to address things now,” Moll said, adding that initiatives such as the AMR fund, a $1 billion facility aimed at overcoming technical and funding barriers in antibiotic development and ensuring a sustainable pipeline of new antibiotics to fight superbugs, is simply a “bridge” while waiting for longer-term solutions.
COVID-19 pandemic has helped raise political awareness of health issues but the widespread misuse of antibiotics in COVID patient treatment is likely to result in increased antimicrobial resistance, health experts have warned.

The AMR threat has long been well known in expert circles, “but that has not always translated into political momentum or societal recognition of the magnitude of the problem,” Cristina Pricop, a policy officer for a healthy recovery at the European public health alliance (EPHA), told EURACTIV.

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The pandemic, despite first redirecting resources away from AMR, exposed the need for collaboration and “the weakness of European and global health systems when faced with cross-border health crises,” Pricop said.

As a result, she added, “we now see AMR featuring more prominently on the political agenda”.

The 2021 Declaration of the AMR European Patient Group states that the pandemic had underlined the need to understand the complex connections between bacterial and viral infections, as the heavy use of antibiotics in COVID-19 patient treatment might result in increasing AMR.

Furthermore, it is likely that some might have been taking antibiotics to fight the virus even though antibiotics do not kill viruses.

Laura Cigolot, coordinator of the health first Europe AMR Patient Group at the EU level, told EURACTIV that “people sometimes do not realise that antibiotics only cure when there is a bacterial infection, not the virus”.

A 2018 Eurobarometer survey on AMR showed that the majority of EU citizens know that antibiotics do not treat colds, that unnecessary use of antibiotics makes them ineffective, that taking them has side effects and, finally, that treatment must be in line with the doctor’s recommendations.

However, almost half of the
respondents incorrectly replied that antibiotics kill viruses.

For EPHA’s Pricop, the findings of the latest Eurobarometer show virtually no improvement on the previous one on the same theme.

**THE ‘SILENT TSUNAMI’**

AMR has been on the radar of the EU and G7 for years, but antibiotics misuse, together with insufficient infection prevention and control in hospitals, continues to be the main cause of the development of AMR, ECDC reports.

AMR is particularly dangerous for patients with lowered immune defences as it involves the ability of microorganisms to evolve and resist antibiotics, leading to increasingly untreatable infections.

Pricop highlighted that it is often forgotten that AMR is not only a scientifically and financially complex issue. “[It] is, at its core, about lived human experience and struggle. Patients may go to the hospital prepared for a battle against a certain disease but then discover they were completely unprepared and uninformed about the dangers of AMR,” she said.

Cancer patients, in particular, rely on antimicrobials as a key element in their treatment and are therefore particularly threatened by the rise of AMR.

ECDC reports that each year, more than 670,000 infections due to bacteria with AMR occur in the EU/EEA, taking as many as 33,000 lives and incurring costs of about €1.1 billion to health care systems. But this is set to drastically worsen, with AMR poised to become a bigger killer than cancer by 2050.

To fight the antimicrobial resistance, the AMR patient group urged in their declaration European and national authorities to act in three “macro-areas”: education, prevention, and investment.

“There is already enough heavy evidence that AMR is the silent tsunami, which will also be the next pandemic by 2030. We really need to educate more, not only patients but also in schools, among the general population, and also, of course, within the hospital settings as well,” Cigolot said.
HEADING DIFFERENCES ACROSS SOUTH AND NORTH

The situation with AMR varies across the bloc.

Eurobarometer data shows that almost half of those polled in Italy have taken antibiotics in the last 12 months, compared to around a quarter in Germany, the Netherlands, and Sweden. [Please see the chart on the following page.]

"In Europe’s South, in Italy, in Greece, in Spain, we have a huge consumption of end-use antibiotics. And so this ultimately increases the phenomenon of AMR," said Cigolot.

She gave an example of patients choosing to treat tonsillitis with antibiotics while “a simple paracetamol can treat this viral infection, unless, of course, it’s a bacterial infection”.

ECDC report on Antimicrobial resistance in the EU/EEA in 2019 has revealed higher percentages of AMR in Southern and Eastern Europe. Pricop explained that this "may be a result of the capacity challenges they face, including screening procedures for patients who carry resistant bacteria and ability to isolate them".

Another issue can be the availability of new antibiotics, as "in many countries across the continent some antibiotics are simply not commercially launched even despite and after being approved by the authorities because it is not considered lucrative for companies," Pricop said.

The situation is much better in Nordic countries, according to Cigolot. She added that AMR is in the limelight for the health professionals community, who "prefer to use different types of treatments, but not antibiotics".

Despite the changes across the EU, Pricop highlighted that AMR is a cross-border threat at a global scale therefore “While local challenges may need tailored solutions, European vision and coordinated action remain essential".

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Antibiotic use by European Country

Source: ECDC (2018)
EU policymakers are being urged to consider the full range of new incentive systems and pilot innovative approaches to tackle antimicrobial resistance (AMR), including Netflix-style subscription services and pull incentives.

Misuse and overuse of antibiotics in recent years has led some microorganisms, also called superbugs, to develop antimicrobial resistance, meaning that medicines become less effective and infections persist in the body, increasing the risk of spread to others.

The development of novel antibiotics is seen as a solution to cope with this ‘silent pandemic’ that decreases the capability to treat infectious diseases and threatens the ability to perform routine surgery.

However, the availability of new antibiotics in many countries across the EU has proved to be particularly problematic as some of them are not commercially launched even despite and after being approved by the authorities.

Remko van Leeuwen, CEO of the biotech company Madam Therapeutics, which is active in the field of AMR, started his company in 2011 when this particular area of development was commercially not lucrative.

“I’ve started because the medical need [to fight AMR], but the world has changed since 2011 and [... AMR] is far less attractive than 10 years ago,” he said at a recent event.

Van Leeuwen, who is also a board member of the BEAM (Biotech companies in Europe combating antimicrobial Resistance) Alliance, said that the fight against this new potential pandemic needs to be supported as returning investment by sales alone will not work.

According to him, the cost of bringing and keeping antimicrobials to the market is too high to offer an incentive for a private company to invest.

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One year ago, the global pharmaceutical industry invested nearly $1 billion US dollars in the AMR Action Fund with the aim of bringing two to four new antibiotics to patent by 2030.

Global charitable organisations and development banks were also behind the initiative and contributed.

But the problems do not stop at the costs for the development, explained Kevin Outterson, executive director at CARB-X and professor of law. He pointed out that there are drugs approved by the European medicine agency (EMA) and not yet launched in other EU countries because the additional cost of launching is not worth it, compared to the reimbursement they receive.

“We also noticed that the dramatically lower number of launches in Japan and in Canada, which should be a serious issue for concern: if this is difficult in high-income imagine launching in places like Nigeria, South Africa, or India,” he added.

**NOT JUST ONE MODEL**

AMR is listed as one of the top priorities in both the recently proposed pharmaceutical strategy and the EU4Health Programme designed to strengthen the resilience of health systems.

The rotating EU presidency currently held by Slovenia has also listed improving accessibility to and availability of medicines, especially where there may be a lack of commercial interest – such as in the case of antimicrobials – as one of their health priorities.

In particular, the EU executive wants to address the problem by reducing the use of antibiotics and incentivising the development of innovative antimicrobials.

Promoting investments and coordinating the research and manufacturing of novel antibiotics will be also in the mandate of the newly established EU Health Emergency Response Authority (HERA), tasked with strengthening the coordination of operations across the entire health value chain.

Since the One Health approach launched in 2017 is seen as a reference as it highlights interlinks across humans, animals and the environment where they live, the hopes for positive development in this field also fall on the implementation of veterinary medicinal products and medicated feed regulations starting from January next year.

According to Yannis Natsis, policy manager at European Public Health Alliance (EPHA), this is the signal that the EU is steering meaningful innovation instead of writing a blank check to industry.

“Pharmaceutical companies have dropped the ball on AMR for decades now. No new class of antibiotics has been discovered in over 30 years using the usual market-based business model of the pharmaceutical industry,” he said.

A ‘Netflix-style’ subscription service, regularly paid from governments to the pharmaceutical industry, has been recently proposed and experimented in the UK to help incentivise the creation of novel antibiotics.

For BEAM’s van Leeuwen, the subscription system brings the advantage that makes investments attractive for people who are involved in product development because they have guaranteed revenues.

However, the subscription system alone is not enough predictable for investors, according to the director-general of the pharmaceutical EU’s trade association Nathalie Moll.

“We also need that overarching European ‘pull’ incentive, that really reassures investors,” she said.

The ‘pull’ mechanism pay for results rather than for the effort on the part of researchers, creating incentives for private sector engagement by creating viable market demand.

With the aim of providing these ‘pull’ incentives for novel antimicrobials by the end of 2021, the Commission is mulling over whether to pilot innovative approaches to research and development (R&D) and public procurement for antimicrobials and their alternatives.

“We put additional funds to R&D budget of the European Union, but still we don’t see results,” said Andrzej Rys, director for medical products and innovation at the Commission’s DG Sante, adding that this difficulty led the EU executive to a reflection on the pull model.
Superbug pandemic threatens to undo medical progress

By Nathalie Moll | EFPIA

It’s never easy to focus on more than one crisis at a time. But, as vaccines begin to point the way out of the COVID-19 pandemic, there is another global health threat lurking in the background which needs our attention: antimicrobial resistance (AMR).

Nathalie Moll is the Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Its impact on our health systems, our social lives and our economies could be just as profound as the COVID-19 crisis from which we are slowly emerging.

The scale of the AMR challenge is so great that it can be hard to take in. A world without antibiotics is one in which everything from tooth extraction and prostate surgery to Caesarean sections and chemotherapy carry unpalatable risks. In short, it...
would represent an unprecedented leap backwards.

According to the World Bank, an estimated 10 million people could die annually by 2050 if solutions – new antimicrobials – are not found. For context, this is more than twice the estimated number of deaths from COVID-19 in 2020 and 2021 to date.

Of course, AMR was a significant threat long before any of us had heard of SARS-CoV-2. It was simmering in the background and we are gradually losing an arms race against bacterial and fungal infections capable of evolving to evade our arsenal of antibacterial weapons. So, while COVID-19 may have taken the world by surprise, the potential impact of AMR can be foreseen. We need to take action before it is too late.

**A MARKET LIKE NO OTHER**

The comparisons with COVID-19 must not be lost on us. The battle between vaccines and coronavirus variants should increase our collective understanding of how new bacterial strains can evolve to evade antimicrobial medicines. There is one important difference: increasing vaccination will reduce opportunities for new COVID-19 variants to emerge. In contrast, inappropriate use of antibiotics contributes to antimicrobial resistance – the more of any antibiotic that is used, the greater the risk of resistance.

This takes us to the nub of the problem. Antibiotic stewardship – the cautious use of the antibiotics we have today – is an important piece of the puzzle in our shared fight against AMR. However, it leaves us with a paradox that makes the antibiotic market like no other: any new antimicrobial medicine will be held in reserve, so that superbugs do not develop resistance to that newest line of defence. From a medical perspective, this makes sense and is well understood by research-based pharmaceutical companies. However, from a commercial perspective it poses problems. Developing new medicines is costly and, for investors, success is far from certain.

If new antibiotics are approved by regulators, they are used sparingly to preserve effectiveness. In recent years, a number of antibiotic-focused biotechnology companies have declared bankruptcy or exited this space due to the lack of commercial sustainability. The consequence is a huge public health need for new antibiotics but a lack of funding available for antibiotic R&D, particularly in the later stages of clinical research.

In addition, this essential area of research is scientifically complex. As bacteria are constantly evolving, they are a moving target for researchers developing new treatments. Furthermore, resistance to antimicrobials can be difficult to predict and clinical trials are complex.

**WANTED: INNOVATIVE INCENTIVES**

Industry is committed to working with others to overcome these challenges. The task now is to create a sustainable innovation ecosystem for antimicrobial R&D and commercialisation.

The AMR Action Fund, an initiative from over 20 leading biopharmaceutical companies, developed in cooperation with the World Health Organization, the European Investment Bank, and the Wellcome Trust has committed over $1 billion to strengthen and accelerate antibiotic development, and ensure there is a sustainable pipeline of new antibiotics to fight the highest priority bacterial threats. Its goal is to harness the investment, expertise and political will needed to bring between two and four new antibiotics to patients by 2030.

Even if the Action Fund successfully delivers novel antibiotics, it will be wasted unless the economics are fixed by policy-makers. At the heart of this fix will be adapted market-based policy changes, including reimbursement reforms and new ‘pull’ incentives needed to create a sustainable R&D environment. The successful development of antimicrobials should be rewarded for the insurance value they hold for society, thus attracting investment to this vital cause without encouraging the use of precious new products.

There may not be a single simple solution to the threat of AMR. However, by working together, stakeholders can agree a suite of measures that would support investment in antimicrobial R&D.
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