Anti-microbial Resistance

Factsheet

Background

Each year, it is estimated that around 700,000 people die as a result of antimicrobial resistance (AMR) and the World Health Organisation (WHO) predicts that we will reach 10 million deaths per year by 2050 if no action is taken[i]. In addition to the human cost of AMR, there is also an economic impact. It is estimated that AMR costs the EU €1.5 billion per year in healthcare costs and productivity losses[ii]. Whilst AMR is a natural phenomenon, it has worsened dramatically over the last decades, triggered by improper use of antibiotics. It is threatening public health and jeopardizing healthcare providers' ability to manage life-threatening infections.

Policy recommendations

To fight AMR while ensuring patient access to life-saving medicines, Medicines for Europe proposes the following reforms that are needed in the antibiotics market:

Incentives for environmentally responsible manufacturing

Like other healthcare challenges, no single actor can address the challenge alone: action needs to be taken by the entire population to reverse the trend on AMR. The pharmaceutical industry has been a pioneer in finding solutions to fight AMR.

Since the improper disposal of antibiotics is a driver of AMR, Medicines for Europe, together with other industries and healthcare stakeholders, jointly developed an online communication campaign http://www.medsdisposal.eu to raise public awareness around the proper disposal of medicines.

Additionally, the AMR Industry Alliance was formed to provide sustainable solutions to AMR by engaging their members to reduce environmental impact and enhance access to and appropriate use of antibiotics, while also promoting innovative responses to infectious diseases. Every 2 years, a progress report is published to show the improvement of the members.

One of the important projects of the AMR Industry Alliance, is also to create a standard manufacturing framework. The board of Medicines for Europe committed to these goals by making compliance with the standards of the Alliance a prerequisite to be a member.

Creating rewards for compliant companies, such as including it as a criterium for tenders, will encourage companies to invest in appropriate effluent management, and create a level playing field for environmentally responsible manufacturing.

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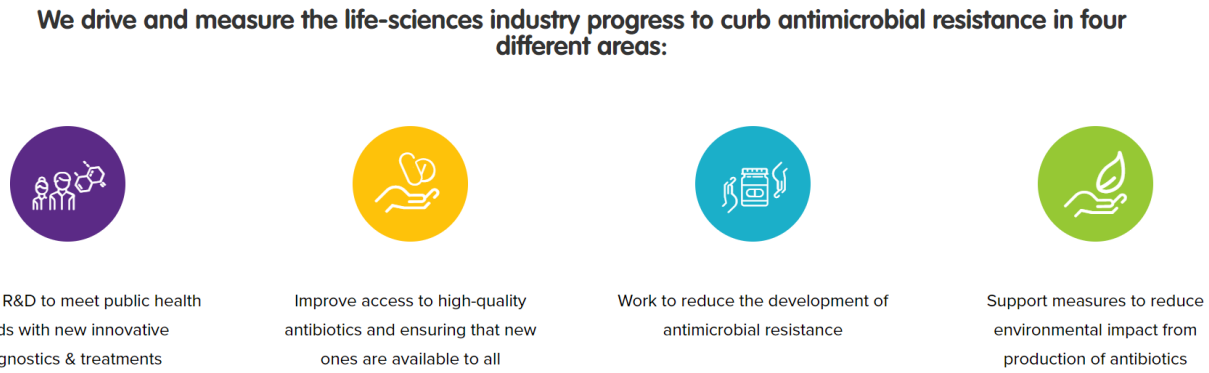

Figure 2: *Objectives of the AMR industry alliance*[iii]

Multi-winner procurement criteria to avoid consolidation and shortages

Notwithstanding the imminent threat of AMR, **antibiotics are often treated as commodities,** instead of the indispensable medical products they are. The **continuous downward price pressure** through cost-containment measures and procurement procedures, have created a tough market environment for older, but essential, antibiotics. In many countries the price policies of antibiotics are unsustainable for manufacturers. This frequently causes shortages of antibiotics, which **leads to delayed and suboptimal treatment**, poorer health outcomes and increased risk of AMR. For example, when a narrow spectrum antibiotic is unavailable, the broader spectrum antibiotic needs to be used to treat the infection, increasing the risk of AMR[iv,v].

The strict pricing rules applied to antibiotics have resulted in European market consolidation by reducing the number of manufacturers that can supply medicines to patients. Pricing policies should ensure healthy market competition and allow patients to continue to have access to a broad range of antibiotics, as well as guaranteeing that generic competition remains healthy over the long term (e.g. allowing for price adjustment when the market becomes too consolidated).

Furthermore, when tenders for essential antibiotics are awarded to a single supplier, the whole supply chain becomes vulnerable to any issues or delays that this one supplier may experience. Tenders should not only focus on the price of the antibiotic but should consider other relevant criteria (MEAT criteria) to ensure best value for money for the benefit of patients and healthcare systems. To address this, tender models should consider **multiple-winner designs to remedy a potential shortage** in a timely manner and to address unexpected demand by having in place appropriate manufacturing capacity. A well-functioning procurement system should support a competitive market environment that benefits patients, healthcare professionals and payers, both short-term and long-term.

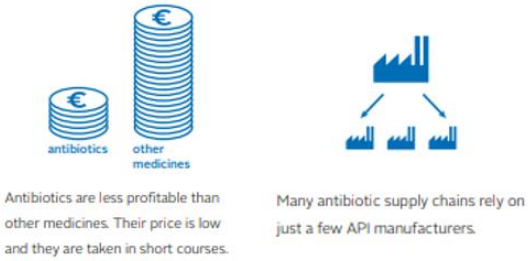

Figure 3: *What is causing antibiotic shortages?*[vi]

Incentivize value-added innovation for fast and cost-effective patient solutions

In addition, there is a large **untapped potential of existing antibiotic molecules** that could be repurposed or reformulated to combat infections. Regrettably, the **EU does not incentivise this kind of innovation** which is essential for combatting AMR.

Research into repurposing and reformulation of existing molecules with anti-microbial activity should complement R&D processes aimed at discovering new antibiotics. The advantage of working with established molecules compared to new chemical entities is that repurposed or **reformulated medicines can reach more patients sooner** because their development processes are faster, require less significant investments and have lower failure rates. When needed, existing medicines with anti-microbial activity can also be optimised and adapted to refine their dosing, which is key to minimising the risk of AMR. The **EU can incentivise this cost-effective innovation by recognising value added innovation** in the EU pharmaceutical legislation and granting proportionate incentives (4 years of data exclusivity). Improvements, leading to better antibiotic stewardship should be encouraged and recognised in pricing and reimbursement decisions.

Risk of introducing transferable exclusivity vouchers in Europe

In regard to post-authorisation incentives currently under discussion, while alternative incentives are coherent with the current review, we strongly oppose novel/additional incentives particularly via transferrable exclusivity vouchers, as they would extend monopolies on more profitable products, dramatically increase costs for healthcare budgets, increase legal uncertainty (incl. on market formation dates) & unduly delay access to generics/biosimilars. It is worth noticing that no jurisdiction worldwide has any transferable exclusivities – the US transferable vouchers relate to priority reviews only.

An **Independent study** in the context of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) concludes that "*[t]he price paid for such a voucher would be high, probably in the range of billions of dollars … they are an inefficient mechanism for promoting innovation*", creating a "*disproportional level of subsidizing one area of healthcare at the expense of another*", with "*negative impact on patient care, by delaying the generic entry (and therefore lower prices) of more widely used medications. The overall cost of this incentive, from both societal and healthcare perspective, may be too great.*"

Medicines for Europe calculated that additional costs for EU healthcare systems with a one-year additional exclusivity on the EU most profitable blockbusters of recent years (adalimumab, trastuzumab, rituximab) would amount to around €2 billion.

Conclusion

Without resolute action now, AMR could undo decades of progress in healthcare and cost millions of lives worldwide. Against this background, I call on the EU and Member states to support sustainable pricing levels, procurement practices and long-term sustainable measures to ensure continued availability of essential antibiotics able to treat bacterial infections in the EU and avoid shortages that can put patients' lives at risk:

- Promote the appropriate use and manufacturing of antibiotic medicines (therapeutic guidelines, prescription-only)
- Ensure that Europe has a secure supply of antibiotic medicine through pricing and procurement reforms

- Incentivise the repurposing and reformulation of off-patent molecules with a known anti-microbial activity

[i] https://ec.europa.eu/research-and-innovation/en/horizon-magazine/more-bacteria-are-becoming-resistant-antibiotics-heres-how-viruses-and-vaccines-could-help

[ii] https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en

[iii] https://www.medicinesforeurope.com/wp-content/uploads/2020/01/AMR-Industry-Alliance-2020-Progress-Report-Prepublication-Copy_embargo-til-16Jan2020.pdf#page=20

[iv] https://www.europarl.europa.eu/doceo/document/A-9-2020-0142_EN.html#title2

[v] https://www.eahp.eu/sites/default/files/report_medicines_shortages2018.pdf

[vi] https://accesstomedicinefoundation.org/media/uploads/downloads/5bea831e16607_Antibiotic-Shortages-Stockouts-and-Scarcity_Access-to-Medicine-Foundation_31-May-2018.pdf

Note on Transferable Vouchers

March 2022

The European Commission has been considering introducing novel rewards to incentivise the development of orphan and/or paediatric medicines, or to better address unmet medical needs, including for antibiotics. In particular, among different options, the EC has been evaluating the possibility of introducing transferable vouchers for priority review or regulatory rewards[1]. The idea is that these specific rewards would potentially complement existing incentives.

A form of transferable vouchers exists in the US and is being referenced in EU policy discussions for the possible introduction of transferable vouchers in the EU. However, **transferable vouchers in the US are allowed ONLY for priority review** (ie. accelerated approval) and **there is NO such voucher extending regulatory or IP exclusivities**.

As explained below and demonstrated in independent studies, the introduction of transferable exclusivity vouchers in the EU would

- **extend monopolies on more profitable products that would not otherwise qualify for that extension**
- **unduly delay access to generic and biosimilar medicines for patients**
- **dramatically increase costs for healthcare budgets**
- **be unfair towards those patient categories that would bear the financial burden for an innovation they do not use**
- **increase legal uncertainty & unnecessary litigation**

The US Approach

Transferable vouchers exist in the US under the FD&C Act, section 529. According to the United States FDA guidance for industry on "Rare Pediatric Disease Priority Review Vouchers", an applicant for a rare paediatric disease product application may be eligible to receive a transferable voucher. **However, the specific voucher is well defined as a priority review voucher and therefore, could be used exclusively to accelerate the FDA review process. It does NOT apply to regulatory nor IP exclusivities extension**.

The European Union Approach

The European Commission has been assessing the possibility of amending the pharmaceutical legislation as well as Regulation for rare diseases and Regulation for medicines for children. In particular, for addressing unmet medical needs, including for antibiotics, medicines for children and for rare diseases, the Commission is exploring different options[2] that would include "novel rewards" comprising transferable data and market protections or potentially other forms of exclusivities.

Such approach would take distance from the US model, whereby transferable vouchers just allow a priority review. **The Commission's proposal does NOT reflect the FDA approach and suggests that these vouchers may also extend the regulatory exclusivity of a specific product on the market[3]**, not excluding that the vouchers could complement the existing exclusivities. This approach proposing additional protections to the already existing ones rather than alternative incentives would certainly present serious concerns around timely and equitable access to treatments for patients and would negatively impact healthcare budgets.

[1] European Commission, Inception Impact Assessment – Medicines for children & rare diseases
[2] Ibid
[3] Ibid footnote 1

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What independent studies say

A study by the Slovenian Presidency of the EU and the EU-JAMRAI, quoted in the EPSCO Conclusions on strengthening the European Health Union, includes transferable exclusivity vouchers among the "***discarded pull incentives***", since whereas they "*may be straightforward to implement, in the end,* ***the cost of these vouchers to healthcare systems is anticipated to far exceed the cost of revenue guarantees***"[4].

Another study, "Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance"[5], analysed the best possible incentives for novel antibiotics, stressing that "***a tradable exclusivity voucher would be used to extend the exclusivity period of the most profitable drugs*** *in the market.* ***The price paid for such a voucher would be high, probably in the range of billions of dollars***", concluding that "*they are an* ***inefficient mechanism for promoting innovation***", as it "*would be funded by the purchasers of the drug whose monopoly period is extended*", representing "***a disproportional level of subsidizing one area of healthcare at the expense of another***". It would have a "***negative impact on patient care, by delaying the generic entry (and therefore lower prices) of more widely used medications***. *The* ***overall cost of this incentive, from both societal and healthcare perspective, may be too great***. *Finally, tradable exclusivity vouchers do nothing to ensure appropriate use, because the return on investment of the antibiotic remains directly proportional to its volume sold and/or used.*"

What it would mean in practice

Taking some of the EU most profitable blockbusters of the recent years, an additional period of exclusivity on these products (*eg*. 1 year) **would translate in the following additional costs for EU healthcare systems**:[6]

- ✓ **Adalimumab** (Humira®):
  Costs in 2018: €3.8 billion – Costs in 2019(after biosimilar competition):€2.8 billion→ **€1 billion lost savings**
- ✓ **Trastuzumab** (Herceptin®):
  Costs in 2018: €1.6 billion – Costs in 2019 (after biosimilar competition): €1 billion→ **€600 mln lost savings**
- ✓ **Rituximab** (MabThera®):
  Costs in 2018: €965 mln – Costs in 2019 (after biosimilar competition): €632 mln→ **€333 mln lost savings**

Conclusion

While Medicines for Europe supports incentives for medicines for children and rare diseases, the introduction of transferable vouchers extending the regulatory or IP exclusivity of (the most remunerative) products on the market would:

i) hinder timely access to market for generic and biosimilar medicines for the most expensive products;
ii) dramatically increase healthcare systems expenditures;
iii) be unfair towards the patient categories that would bear the financial burden for an innovation they do not use;
iv) increase legal uncertainty and unnecessary litigation in relation to IP and regulatory exclusivities.

Therefore, it is of utmost importance that the European Commission would consciously evaluate all the different aspects and potential downsides of the introduction of transferable vouchers extending IP/regulatory exclusivities.

[4] *Improving Access to Essential Antibiotics*, by the Slovenian Presidency of the EU and the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), available here.
[5] *Clinical Infectious Diseases*, Volume 65, Issue 8, 15 October 2017, Pages 1378–1382, https://doi.org/10.1093/cid/cix526. The study concludes that the best solutions would be market entry rewards, like delinkages or new pricing models.
[6] Considering available data for 2018. MIDAS Quarterly Audit from Q2/2018 to Q1/2021