Response to call for public consultation

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14 September 2020

Thank you for the opportunity to comment on the "Pharmaceutical Strategy for Europe."

As experts and stakeholders in antimicrobial research and development (R&D) and antimicrobial resistance (AMR), we limit our comments to these threats.

Europe faces a pair of interlinked crises in antibiotic R&D which require a comprehensive solution.

First, ***the global economic model is fundamentally broken***. New antibiotics don't sell because stewardship puts them on the shelf. A good new antibiotic sells poorly; a great new antibiotic will sell even less due to the entirely appropriate and necessary stewardship efforts to limit use of novel new antibiotics to situations of last resort. Because of this, five of the last 16 antibiotics approved by the US FDA have since April 2019 passed through bankruptcy or been sold for a small fraction of their R&D cost.

Unlike other drugs where paying for them on a per-use basis makes sense, antibiotics have the unique property of being valuable to the community simply by being available in the pharmacy. We believe that antibiotics are properly described as the Fire Extinguisher of Medicine: infections and fires both go quickly and the ability to control the fire (infection) at an early stage requires prompt access to the needed fire extinguisher (antibiotic).

Given their role as fire extinguishers, providing preparedness and protection against bacterial threats calls for a fundamental re-orientation on how antibiotics are reimbursed. Instead of being reimbursed per-use (i.e., on the volume of sales), antibiotics should be reimbursed primarily on their value. The value of antibiotics includes the five "STEDI" elements:

- **Spectrum**: broad-spectrum antibiotics respond to wide-ranging threats, while narrow-spectrum antibiotics are less disruptive to both microbiomes and bacterial evolution;
- **Transmission**: cured patients do not transmit the infection to others;
- **Enablement**: many medical treatments and procedures – from oncology to all surgeries – would be more dangerous without the safety net of antibiotics;
- **Diversity**: evolution to antibiotics is better managed when physicians have a variety of antibiotics to choose from; and
- **Insurance**: being prepared *before* a pandemic is upon us.[3]

Payment systems that focus only on the immediate value to the individual patient will fail to recognize the true value of antibiotics, leading to ongoing bankruptcies, not only from the companies with approved products, but also killing the pipeline of innovative drugs in development from companies in Europe.[4]

Significantly, more than 90% of antibiotic innovation is happening in SMEs, academic groups, or non-profits.[5] In Europe, many of these small companies are members of the BEAM Alliance.[6] These small companies all have very limited resources and will continue to fail unless changes are made to our approach to reimbursing for antibiotics.

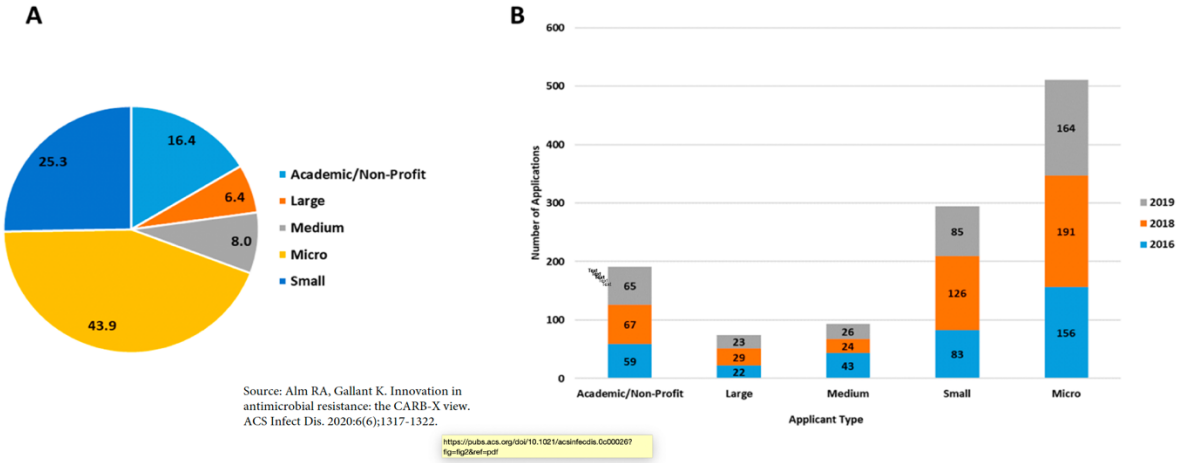


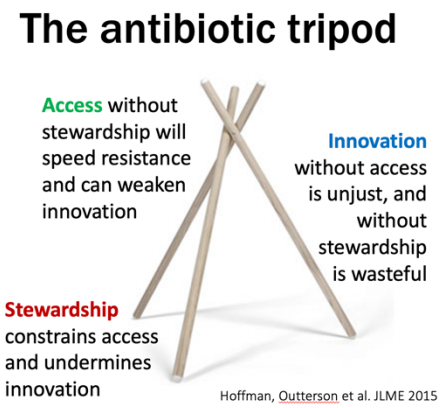
Figure 2. Distribution of applications based on applicant type. (A) The total percentage (%) of applications across all 3 funding rounds based on applicant type. (B) The distribution of application number split by each of the funding rounds. Company sizes limit are as follows: Micro, ≤10 employees; Small, 11−50 employees; Medium, 51−250 employees; Large, >251 employees.

The second crisis is a direct consequence of the first: ***some new antibiotics are not being registered or sold in Europe***. Given the poor economics, these small companies bringing many new antibiotics to market are focusing only on the US market and many of those are going bankrupt. New drugs like omadacycline[7] and plazomicin[8] are not being registered in Europe, and lefamulin still awaits a commercial partner to launch in Europe.[9] Eravacycline, approved by EMA in October 2018, still has not been commercially launched in Europe. We can offer our speculation on drivers, but a full root cause analysis is needed. For at least one of these drugs, a key driver appears to be the that the cost of EU-required pediatric trials exceeded any plausible estimate of sales in Europe, leading to the companies to withdraw from the process. These events suggest that it is likely that new antibiotics from small companies will not be available in Europe, much less the rest of the world.

Roadmap for Solutions

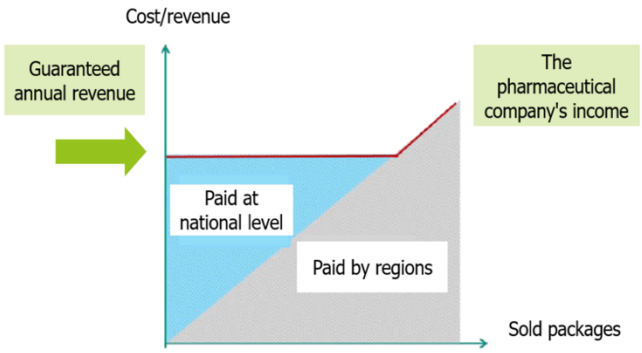
After years of work supported by the European Commission through IMI (see the 2017 DRIVE-AB Final Report[10]), we should be well past the “investigating” phase and moving towards national or EU implementation. Pull incentives must be of sufficient magnitude to both: (i) provide an innovation incentive for work in this area, and (ii) cover the cost of product

maintenance in this area. They should complement the work of key push incentives, and simultaneously support stewardship, access, and innovation.[11] One key finding from DRIVE-AB is that antibiotic pull incentives should be measured by value to society, not the volume of antibiotics sold in any given year, a concept called "delinkage" because rewards to the innovator are delinked from the volume of sales.



As an example of how this might be done, the pilot program at NHS England is very promising if made permanent. The UK NICE created a methodology to calculate the STEDI value of new antibiotics and will offer an incentive payment of up to GBP 10m x 10 years for antibiotics meeting public health criteria. When scaled up by recognizing the UK is approximately 3% of the G20, the UK's proposed "fair share" payment of GBP 100 million over ten years (approximately US$130 million) suggests that the G20 should offer a collective global pull incentive of $3-4 billion for compelling new antibiotics.[12]

The Swedish antibiotic access pilot[13] is an elegant model that could also work in many European national systems. Although, the SEK values in the Swedish pilot were selected with only access in Sweden in mind and are too low to provide a meaningful innovation incentive,[14] the model is conceptually solid and these financial values could readily be adjusted upward to also function as an R&D pull incentive. By leveraging the insights from these pilot programs, the EU can contribute its fair share towards global antibacterial R&D through coordinated national pull incentives.



Despite the promise of these national projects, the small companies with antibiotics approaching approval would greatly benefit from a single "one and done" reimbursement access to EU markets, with valuations set by the principles of STEDI, rather than the existing variety of national valuation approaches. These companies lack the teams of people to navigate these myriad national schemes, leading some to abandon European markets altogether or significantly delay commercial launch. EU member countries should focus on sustainable solutions across Europe, not piecemeal solutions which could further fragment the European market. Unless a truly pan-European strategy is implemented, both access to current antibiotics and innovation for the future will be threatened.

As an example of the impact of pan-EU actions, EMA has worked steadily to update its guidance documents for evaluation of medicinal products indicated for treatment of bacterial infections, and it is encouraging to see that a 3rd revision of this document is now underway.[15] The ongoing efforts of EMA to align with requirements from FDA (USA) and PMDA (Japan) are also noted with appreciation[16] as such efforts are fundamental to the design of the trials that can support approval in jurisdictions around the world.

These substantial efforts noted and acknowledged, works remains to be done on strategies to support the varied needs of developers in this area. A conference focused on enhancing the antibacterial trial process in the US was hosted 18-19 Nov 2019 by FDA, IDSA, NIH, and the Pew Charitable Trusts.[17] This conference highlighted potential actions for all stakeholders and a similar discussion in Europe involving such global and European stakeholders as the BEAM Alliance, CARB-X, the Novo REPAIR fund, GARDP, the Global AMR R&D Hub, and ESCMID would be informative and timely.[18] In addition to the topics already raised, other topics to be covered should include strategies for products focused on rare pathogens, strategies for products focused on prevention, as well as other areas of concern raised in conversation with these stakeholders.

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[3] Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Transl Res*. 2020;220:182-190. doi:10.1016/j.trsl.2020.02.006 (adapted from C Rothery, B Woods, L Schmitt, K Claxton, S Palmer, M Sculpher. Framework for Value Assessment of New Antimicrobials (2018) (available at: http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf)).

[4] BEAM Alliance 10 July 2020 https://beam-alliance.eu/beam-alliance-reflexion-paper-on-the-eu-pharmaceutical-strategy-roadmap/.

[5] Alm RA, Gallant K. Innovation in antimicrobial resistance: the CARB-X view. ACS Infect Dis. 2020;6(6):1317-1322.

[6] https://beam-alliance.eu/.

[7] https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/nuzyra.

[8] https://amr.solutions/2020/07/11/plazomicin-eu-marketing-application-is-withdrawn-near-zero-market-value-of-newly-approved-antibacterials/ and https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/zemdri.

[9] Nabriva Therapeutics plc 10Q (June 30, 2020) https://www.sec.gov/ix?doc=/Archives/edgar/data/1641640/000155837020009653/nbrv-20200630x10q.htm.

[10] http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/.

[11] Hoffman SJ, Outterson K. What will it take to address the global threat of antibiotic resistance? Journal of Law, Medicine & Ethics. 2015;43(2):363-8.

[12] https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/.

[13] https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/.

[14] SEK 4 million, approximately US$460,000 per year. The Swedish pilot was explicitly designed to facilitate access in Sweden, not support global R&D as a pull incentive.

[15] https://www.ema.europa.eu/en/evaluation-medicinal-products-indicated-treatment-bacterial-infections.

[16] https://www.ema.europa.eu/en/documents/minutes/meeting-summary-tripartite-meeting-held-between-pmda-ema-fda-kyoto-japan-discuss-convergence_en.pdf.
[17] https://amr.solutions/2019/11/27/18-19-nov-2019-fda-idsa-nih-pew-workshop-enhancing-antibacterial-trials-in-the-us/.
[18] https://beam-alliance.eu/, https://carb-x.org/, https://www.repair-impact-fund.com/, https://globalamrhub.org/, and https://www.escmid.org/.