

Norwegian Institute of Public Health, Division of Infection Control, Case number 3

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Infection Control
Title of case study: Stimulating innovation of and access to new antibiotics – DRIVE-AB
Period when the underpinning research was undertaken: 2014-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2014 to present
Period when the impact occurred: 2016 and ongoing

1. Summary of the impact (indicative maximum 100 words)

Bacteria are becoming increasingly resistant to many antibiotics, and too few antibiotics are developed to combat them. DRIVE-AB provided foundational evidence about how to stimulate the innovation of and access to novel antibiotics through economic incentives. Not only did DRIVE-AB publish (50+) and present (30+) widely, its results informed the implementation of incentives in Sweden and the UK, started in 2019, as well others in progress (Canada, EU, Japan, and US). DRIVE-AB continues to influence European policy with a recent publication in Nov-23. Countries now see the incentives developed by DRIVE-AB as vital to manage the growing threat of AMR.

2. Underpinning research (indicative maximum 500 words)

The key research findings that underpinned the impact were:

- New economic models are needed as incentives for the discovery and development of novel antibiotics, especially for infections with too few patients today to justify private sector research and development (R&D) investments. These models should focus on rewarding the innovation, not the use of the antibiotic since stewardship of the antibiotic make the potential for a profitable business model unlikely. DRIVE-AB recommended the implementation of a delinked pull incentive (where revenues are based on innovation and accessibility rather than consumption). These findings were based upon extensive stakeholder interviews, primary data analyses, and computer simulations.
- New economic models represent potential sizeable public investments. These must be protected to ensure that the resulting antibiotics have a lengthy and positive impact on human health. DRIVE-AB developed stewardship and access requirements based upon extensive stakeholder interviews, then current stewardship policies, timelines regarding the development of resistance, and data on the availability of existing antibiotics.
- Innovation of new antibiotics is important, but it is worthless if the antibiotics are not accessible to the patients who need them. DRIVE-AB found that there is great variation in geographic availability of antibiotics. These findings were based upon analyses of sales data (IQVIA) for antibiotics approved globally between 1999-2014.
- Other technologies (peptides, bacteriophages, etc.) are also being developed to treat antibacterial infections. Yet DRIVE-AB found that whereas these technologies are promising, they will not displace the need for new antibiotics in the short and medium terms. These findings were based on a literature review and a multi-criteria decision analysis exercise.

This research was performed in work package 2 of DRIVE-AB –co-led by John-Arne Røttingen (Director, Division for Infection Control, NIPH, 2014-2016) and Christine Årdal (Senior Researcher, NIPH) with 50 participating researchers from about 10 organizations including pharmaceutical companies. DRIVE-AB was funded by the EC's Innovation Medicines Initiative, meaning that public

sector researchers were funded through the EC and companies were funded through their own financing. NIPH had a team of 11 researchers working on DRIVE-AB (including Røttingen and Årdal): Jostein Johnsen, Cecilia Kållberg, Lene Martinsen (2017-2018), Ejike Nwokoro (2015-2016), Elizabeth Peacocke, Jens Plahte, Miloje Savic (2016-2018), Live Storehagen Dansie (2016-2018), and Dimitrios Gouglas. All contributed to the research on economic models. Kållberg contributed mainly on the areas of access and stewardship, which were the focus of her PhD, financed by DRIVE-AB. NIPH was paid € 919,100 from IMI for DRIVE-AB.

3. References to the research (indicative maximum of six references)

1. Årdal C, Findlay D, Savic M, Carmeli Y, Gyssens I, Laxminarayan R, Outterson K, Rex JH. DRIVE-AB Final Report: Revitalizing the antibiotic pipeline, 2018. <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>
2. Årdal C, Baraldi E, Theuretzbacher U, Outterson K, Plahte J, Ciabuschi F, Røttingen J-A. Insights into early stage antibacterial development in small and medium sized enterprises: a survey of targets, costs, and durations. *Journal of Pharmaceutical Policy and Practice* 2018;11:8. <https://doi.org/10.1186/s40545-018-0135-0>
3. Kållberg C, Årdal C, Salvesen Blix H, Klein E, M. Martinez E, Lindbæk M, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. *PLoS ONE* (2018) 13(10): e0205166. <https://doi.org/10.1371/journal.pone.0205166>.
4. Theuretzbacher U, Årdal C, Harbarth S. Linking sustainable use policies to novel economic incentives to stimulate antibiotic research and development. *ID Reports* 2017;9(1). <https://doi.org/10.4081/idr.2017.6836>
5. Kållberg C, Hudson J, Salvesen Blix H, Årdal C, Klein E, Lindbæk M, Outterson K, Røttingen J-A, Laxminarayan R. The effect of generic market entry on antibiotic prescriptions in the United States. *Nat Commun* **12**, 2937 (2021). <https://doi.org/10.1038/s41467-021-23049-4>
6. Nwokoro E, Leach R, Årdal C, Baraldi E, Ryan K, Plahte J. An assessment of the future impact of alternative technologies on antibiotics markets. *Journal of Pharmaceutical Policy and Practice* 2016;9:34. <https://doi.org/10.1186/s40545-016-0085-3>

4. Details of the impact (indicative maximum 750 words)

The research of DRIVE-AB has paved the way to today's situation where countries are rapidly implementing delinked pull incentives, as DRIVE-AB recommended. Both the UK and Sweden have already implemented delinked pull incentives. Canada, EU, Japan, Switzerland, US, and others are in the process of implementation. All have used evidence from DRIVE-AB as well as other sources where DRIVE-AB collaborated closely including the UK AMR Review (led by Lord Jim O'Neill). Our results have been recognized in several G7 and G20 communiqués calling for new incentives, starting in 2017 after DRIVE-AB published a call in *The Lancet Infectious Diseases*.

DRIVE-AB academic authors continue to contribute to the discussion, including with a *Lancet* editorial in 2023 advising the EU to rethink an alternative incentive. We recently published a policy brief in November 2023 taking account of the EU Council recommendations from June 2023 and suggesting a detailed pan-European pull incentive. This policy brief was presented on December 14, 2023, at the Swedish Mission in Brussels to Member State representatives.

DRIVE-AB has led to new leadership roles and financing for NIPH. It directly led to the next project and role within the EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI-1)

where NIPH co-led the work package on access and innovation as well as the work package on stewardship (2017-2021). In this Joint Action the next step of DRIVE-AB was pursued – to work with Member State stakeholders to understand the barriers to implementation of pull incentives for antibiotics, allowing for continuity of the implementation of DRIVE-AB recommendations. Feedback from Member States demonstrated the need to include older antibiotics with vulnerable supply in the mandate of pull incentives, since shortages of older antibiotics are common and create problems for healthcare systems. DRIVE-AB's incentives were thus adjusted to improve accessibility for both old and new antibiotics.

NIPH will continue to lead on accessibility in EU-JAMRAI-2 (2024-2027), including working with DG HERA as a discussion forum for countries and relevant European organizations regarding access to new technologies and implementation of incentives.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Årdal C, Baraldi E, Ciabuschi F, Outtersson K, Rex JH, Piddock LJV, Findlay D. To the G20: incentivising antibacterial research and development. *The Lancet Infectious Diseases*, Volume 2017, Issue 8, 799 – 801.
https://drive.google.com/file/d/15dX3DY4R0_mgoGHtAbGaeQmFoRmAfKFc/view
2. Årdal C, Lacotte Y, Ploy M-C. Financing pull mechanisms for antibiotic-related innovation: Opportunities for Europe. *Clinical Infection Diseases* (2020).
<https://doi.org/10.1093/cid/ciaa153>
3. Årdal, C.; Lacotte, Y.; Edwards, S.; Ploy, M.-C.; on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections. National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics* 2021, 10, 749. <https://doi.org/10.3390/antibiotics10060749>
4. Årdal C, Baraldi E, Beyer P, Cooke E, Lacotte Y, Larsson DGJ, Ploy M-C, Røttingen J-A, Smith I. Supply chain transparency needed to enable sustainable and continuous supply of essential medicines. *Bull World Health Organ* 2021 March 10 <https://doi:10.2471/BLT.20.267724>
5. Årdal C, Baraldi E, Busse R, Castro R, Ciabuschi F, Cisneros JM, Gyssens IC, Harbarth S, Kostyanev T, Lacotte Y, Magrini N, McDonnell A, Monnier AA, Moon S, Mossialos E, Peñalva G, Ploy M-C, Radulović M, Alonso Ruiz A, Røttingen J-R, Sharland M, Tacconelli E, Theuretzbacher U, Vogler S, Wolff Sönksen U, Åkerfeldt K, Cars O, O'Neill J. Transferable exclusivity voucher: a flawed incentive to stimulate antibiotic innovation. *The Lancet*, Feb 8, 2023,
[https://doi.org/10.1016/S0140-6736\(23\)00282-9](https://doi.org/10.1016/S0140-6736(23)00282-9)
6. Årdal C, Baraldi E, Bettioli E, Ciabuschi F, Colson A, Gyssens I, Monnier A, Morel C, Outtersson K, Røttingen J-A, Tacconelli E, Harbarth S. Policy Brief: A Pan-EU/EEA Pull Incentive for Antimicrobial Innovation and Access, <https://drive-ab.eu/news/drive-ab-policy-brief-a-pan-eu-eea-pull-incentive-for-antimicrobial-innovation-and-access/>