Institution: London School of Economics and Political Science

Unit of Assessment: 22: Social Work and Social Policy

Title of case study: Re-igniting R&D for antibiotics

1. Summary of the impact

Millions of cases of multi-drug resistance bacterial infection occur each year. Yet the pharmaceutical industry has all but ceased investing in antibiotic development due to a combination of low profits and lack of appropriate incentives. In her 2011 Annual Report, the Chief Medical Officer called for more attention to be given to an antimicrobial resistance strategy for the UK and worldwide. The Unit's work analysed the nature of the incentives necessary to get antibiotic R&D going again. In particular it served as the basis for an urgent request by the EU Council for action and sparked the formation of the critical 'transatlantic taskforce' (TATFAR): the first major international collaboration to tackle antibiotic resistance. Recommendations from the work served as the foundation for an EU-level public/private partnership and for US regulatory reform.

2. Underpinning research

Research Insights and Outputs: the Unit built up a substantial strand of work from the mid-1990s on possible incentives to promote research on areas of critical unmet medical need [1, 2]. Subsequent work on different ways of stimulating the development of new vaccines for neglected diseases [3] attracted the attention of the Swedish Government, which made the problem of antibiotics one of its priorities for its Presidency of the European Union (in 2009). The Swedish Ministry of Health and Social Affairs asked LSE Health to explore ways of promoting the development of new priority antibiotics (€120,000 grant).

The resulting LSE report [4] explored in depth the market failures in respect of producing new antibiotics and analysed different incentive frameworks to develop them. The report analysed over 20 different incentive frameworks to stimulate the production of new antibiotics, focusing on both 'push' and 'pull' mechanisms. Push mechanisms reduce the costs of the R&D process for research groups or (usually smaller) companies (e.g. via start-up funds). Pull mechanisms promise (usually large) companies a reward if goals regarding a new product are achieved, with the aim of getting companies with experience in antibiotic development to go through the full set of research and development stages. The Unit's research stressed the importance of possible combinations of push and pull incentives, setting out the expected magnitude of impact and overall financial and political feasibility for each incentive, and recommended policy responses at the national and international (e.g. EU) level.

In particular, the Report made specific recommendations on:

(i) The need for new approaches to risk sharing on the part of the key actors - governments and private producers of antibiotics. The Report attached considerable importance to the potential of these public/private partnerships at key stages of the R&D process. On the 'pull' side, these partnerships would specify and reward the development of goals for antibiotic development, while on the 'push' side they would seek to reduce the costs of the R&D process, particularly of clinical trials.

(ii) The importance of regulatory reform that would act as an appropriate incentive, for example, protecting intellectual property for an extended period. This in turn would protect against market competition (something that was particularly important for US companies). The Report called attention to the way in which such extensions are particularly useful for drugs like antibiotics, where greater rewards are needed to spur the full development of the drug (a push factor), but where linking the reward to the long-term efficacy of the drug is also important (a pull factor).

In 2010 and 2013 the research was published in high-impact journals [5,6] and was expanded to include a closer comparative analysis using 20 essential criteria deriving from the various

stakeholder perspectives (long-term public health, regulatory authorities, industry) [7]. In particular this research proposed a new incentive that combined the critical elements inherent in existing (successful) regulatory incentives with those that respond to the specific needs of antibiotics market, that is, incentives intended to limit over-marketing and over-consumption of any new drug in order to slow the growth of resistance over the medium-to-long-term.

Key Researchers: Professor Elias Mossialos has been at LSE from 1992. Research Officers: Chantal Morel at LSE from 2009; Suzanne Edwards at LSE from 2009; and Julia Berenson at LSE from 2009. Research Associate: Marin Gemmill-Toyama has been at LSE from 2003-9.

3. References to the research

[1] Mossialos, E., Kanavos, P., Abel-Smith, B. (1994) *Policy Options for Pharmaceutical Research and Development in the European Community. Brussels: European Parliament* – Science and Technology Options Assessment Programme. Available from LSE.

[2] Mrazek, M., Mossialos, E. (2003) Stimulating pharmaceutical research and development for neglected diseases, *Health Policy* 64 (1). pp. 75-88. LSE Research Online number 20087.

[3] Brogan, D, Mossialos, E (2006) Applying the concepts of financial options to stimulate vaccine development, *Nature Reviews*, 5, 641-647. LSE Research Online number 19345.

[4] Mossialos, E; Morel, C; Edwards, S; Berenson, J; Gemmill-Toyama, M; Brogan D (2010) *Policies and Incentives for Promoting Innovation in Antibiotic Research*, WHO and European Observatory on Health Systems and Policies. LSE Research Online number 28751.

[5] Morel C, Mossialos E (2010) Stoking the antibiotic pipeline. *British Medical Journal*, 340, 115-118. LSE Research Online number 28555.

[6] Brogan D, Mossialos E. (2013) Incentives for New Antibiotics: The Options Market for Antibiotics (OMA) Model, *Globalization and Health 9* (58). DOI: 10.1186/1744-8603-9-58. Available at: http://www.globalizationandhealth.com/content/pdf/1744-8603-9-58.pdf.

[7] Morel, C and Mossialos,E 'Incentives for promoting R&D in novel antibiotics: How do proposed incentive mechanisms compare according to key criteria?' 23 May 2011, ReAct conference on Collaboration for Innovation – The Urgent Need for New Antibiotics, Brussels. Available from LSE.

Evidence of quality: References [2], [3], [5] and [6] are peer-reviewed journal articles. Grant awarded to LSE Health (€120,000) for the antibiotics project by the Government of Sweden: *Study on antibiotics resistance and incentives to develop new medicines*, October 2008 - November 2009.

4. Details of the impact

Nature of the Impact: As the sole contribution to 2009 "The Stockholm Conference" of the Swedish Presidency, the LSE's Report [4] served as the basis for extensive discussion that led to the EU Council request that the Commission "within 24 months, develop a comprehensive action plan, with concrete proposals concerning incentives to develop new effective antibiotics" [A]. From this stage on there was extensive engagement with a wide variety of stakeholders. The LSE Report served as a pre-conference document for review by leading US academics, industry representatives from both small and large companies and associations (including AstraZeneca, Basilea Pharmaceutica, and the European Federation of Pharmaceutical Industries and Associations), government and regulatory officials (including those from DG Enterprise at the EC; UK Health Protection Agency), and key representatives of international and non-governmental organizations (including the WHO). The importance of the report was acknowledged by the Swedish Ministry for Health and Social Affairs [B], and was officially presented by the Swedish Presidency of the Council of the European Union in the latter half of the Stockholm conference. It was published in 2010 by the WHO as a book [2].

Following the Conference, the Swedish Prime Minister proposed to the US President the formation of a Transatlantic Taskforce with the European Union (Transatlantic Taskforce on Antimicrobial Resistance – TATFAR) to encourage global research and development of new antibiotics, to address antimicrobial resistance, and to push for legislation. The formation of this taskforce – signed into effect by Swedish Prime Minister Reinfeldt of Sweden and US President Obama – was explicitly intended to build on the LSE Report [C]. The LSE work was also cited extensively in the TATFAR's findings [D].

Further evidence of engagement with the recommendations of the LSE Report comes from Professor Otto Cars, Director of the Swedish Strategic Programme Against Antibiotic Resistance, who in 2010 described the work as "pioneering" and emphasized that it would have "a marked influence on future development in the field"[E]. In 2009 and 2010 the LSE work also received further significant international media coverage [F, G]. And in the April 2011 edition of the journal *Nature*, the authors of a paper on the need for action in re-igniting antibiotic research concluded that the LSE recommendations for a "push-pull" response are a "clear front-runner" in the possible courses of action." [H]

Two of the LSE's specific recommendations have been implemented. First, the LSE research was presented on more than ten occasions to key stakeholders in Sweden, London, Washington DC and Brussels over the period 2009-2011, focusing on the need for public-private risk-sharing at critical stages of antibiotic research and development, particularly that of clinical trials. In early 2012 the public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) – the Innovative Medical Initiative (IMI) – announced an (equally) shared commitment of €220 million for the development of new antibiotics, intended to facilitate partnerships between academic and industry researchers focused on new antibiotics and to share the risks of clinical trials [I].

Second, the recommendation for regulatory reform to increase the rewards to the industry by giving a greater measure of market protection via intellectual property extensions was discussed and cited in expert testimony given in the United States Congress in 2010 and again in 2012 [J]. Such testimonies were crucial to the passing of bipartisan legislation in mid-2012, which established greater market protection for vital new antibiotics reaching the market via intellectual property extensions for data generated. (The "GAIN Act" of S. 3187, 112th Cong., 2nd Sess.)

In addition, in 2011 the research provoked discussion in the arena of national defence in the US [K, L]. It was presented within an expert panel at the US Institute of Medicine's workshop on medical counter measures to terrorism that is generally accepted to have opened the door for the U.S. Biomedical Advanced Research and Development Authority (BARDA) – best known for developing vaccines and therapies as medical countermeasures to bioterrorism threats – to award a series of contracts for antibiotic research. The work was also picked up by major industry players who had not been part of the original "Stockholm" group – demonstrating wider industry acceptance of report findings and recommendations [M].

Today the debate over a new incentive structure to promote research on and development of new antibiotics is still underway in the US and within the European institutions. The work of the Unit has been the first to explore how this might be done and continues to lead the debate. It is undertaking new research funded by the Pew Charitable Trust in late 2012 ($150,000) on how to disentangle the supply- and demand-side bottlenecks currently preventing badly needed diagnostics for bacterial infections from making it to the market.

Wider Implications: Millions of cases of resistance to antibiotics occur each year, adding to the burden of disease. It is estimated that annual hospital deaths from antibiotic resistant pathogens already tops 25,000 patients in the EU alone. The Unit's work has helped to overcome some of the traditional market failures associated with the development of new antibiotics and has contributed to important policy changes in Europe and the USA. By improving incentives to R&D in new antibiotics, the Unit's research should assist with reducing levels of both morbidity and mortality in

Europe and beyond.

5. Sources to corroborate the impact

All Sources listed below can also be seen at: https://apps.lse.ac.uk/impact/case-study/view/60

[A] Council of the European Union, 'Council Conclusions on innovative incentives for effective Antibiotics', 1 December 2009, para 13 acknowledges the LSE Report. Source file: https://apps.lse.ac.uk/impact/download/file/1411

[B] Corroborating letter from the Swedish Secretary of State. This source is confidential.

[C] Memorandum from the Swedish Presidency of the European Union on Antimicrobial Resistance, 23 September 2009. Communication cable: http://www.cablegatesearch.net/cable.php?id=09STOCKHOLM604

[D] Transatlantic Taskforce on Antimicrobial Resistance: Recommendations for future collaboration between the U.S. and EU, 2011. http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf

[E] Burki, T. (2010) Push and pull of antibiotic development, *The Lancet Infectious Diseases*, 10, 1, 12-13. http://www.sciencedirect.com/science/article/pii/S1473309909703421

[F] Harrell, E. (2009) The desperate need for new antibiotics, *TIME*, 1 October 2009. http://content.time.com/time/health/article/0,8599,1926853,00.html

[G] Tutton, M. (2009) New research warns penicillin 'becoming obsolete'. CNN, 26 January 2010, published on 1 October, 2009.

[H] Cooper, M. and Shlaes D. (2011) Fix the antibiotics in pipelines, *Nature*, 472, 32. http://www.nature.com/nature/journal/v472/n7341/full/472032a.html

[I] 'EFPIA contributes to IMI €223.7 million programme to tackle Antibiotic resistance'. Brussels: European Federation of Pharmaceutical Industries and Associations, 24 May 2012. http://www.efpia.eu/mediaroom/67/43/EFPIA-contributes-to-IMI-223-7-million-programme-to-tackle-Antibiotic-resistance

[J] Expert testimony. US Congress House Committee on Energy and Commerce Subcommittee on Health. Washington DC: US Congress; 9 June 2010 and 8 March 2012 (B. Spellberg, Infectious Disease Society of America, expert testimony and B. Eistenstein Senior Vice President, Scientific Affairs, Cubist Pharmaceuticals Inc.) Source file: https://apps.lse.ac.uk/impact/download/file/1416 https://apps.lse.ac.uk/impact/download/file/1417

[K] Institute of Medicine workshop on Countermeasures Enterprise, held in Washington DC (presented by teleconference), 23 February 2010. Source file: https://apps.lse.ac.uk/impact/download/file/1418

[L] Platsis G (Director of the Research Center at the National Defense Foundation) & Kavanagh S. (2011) Keeping Pace: Protecting Our Troops and Our Population by Incentivizing Antimicrobial Research and Development. Washington DC: National Defense Foundation. Source file: https://apps.lse.ac.uk/impact/download/file/1420

[M] Merck & Co., Inc. Public Policy Statement: Antimicrobial Resistance, September 2011. Source file: https://apps.lse.ac.uk/impact/download/file/1421