

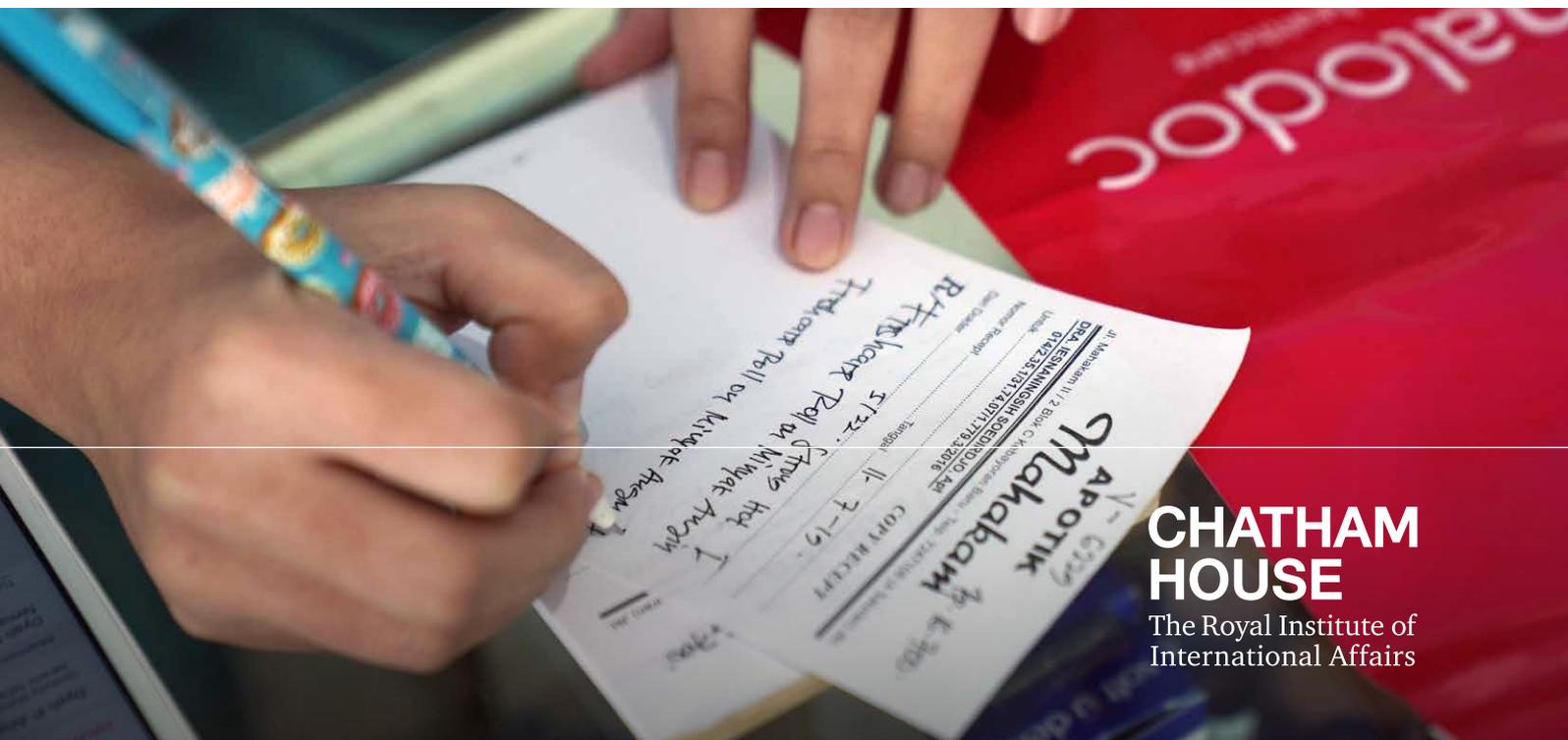
Research Paper

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# Review of Progress on Antimicrobial Resistance: Background and Analysis



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## Summary

- The 2016 Review on Antimicrobial Resistance has had a global impact: as an advocacy tool, in raising the profile of antimicrobial resistance (AMR) on the international agenda, and in helping to stimulate a number of new initiatives, in particular relating to the funding of early-stage research.
- However, there has been very little progress on the review's central and most expensive recommendations for transforming research and development incentives for antibiotics, vaccines and diagnostics.
- There have been significant advances in reducing antibiotic use in agriculture, particularly in high-income countries, but there is a long way to go in low- and middle-income countries (LMICs).
- There has been greater investment in awareness raising but questions remain about its impact and effectiveness in changing behaviour.
- Proposals to restrict over-the-counter sales of antibiotics, as recommended by the Review, have foundered in the face of poor living conditions and access to healthcare in LMICs.
- A major reason for the use of antibiotics in LMICs is the prevalence of unhygienic conditions in the community and in healthcare facilities, which contribute to infection and limit the impact of messages about awareness and infection prevention and control.
- Providing quality healthcare to all and moving towards universal health coverage in LMICs will be crucial in addressing the problems of both adequate access to antibiotics and in restricting over-the-counter sales.
- A greater emphasis on investments in water, sanitation and housing will be central to reducing reliance on antibiotics in LMICs in the longer term. This agenda should inform the operations of governments and funding agencies such as the International Monetary Fund (IMF) and the World Bank.
- Investments have been made in improving surveillance of antibiotic use and resistance, particularly for humans, but more effort is required to create surveillance systems that provide data sufficiently accurate to influence policy and action. This applies also to antibiotics and resistant genes circulating in the environment.
- The emerging innovations in the global governance of AMR need to lead to action rather than more words.

# 1. Introduction

The Review on Antimicrobial Resistance (AMR Review), chaired by Lord Jim O’Neill, was commissioned by the then UK Prime Minister David Cameron, in July 2014, and supported by the UK government and Wellcome. The establishment of the Review reflected a renewed concern at the highest political levels in the UK about antimicrobial resistance (AMR), catalysed by the sustained advocacy of Dame Sally Davies, England’s chief medical officer. The choice of Jim O’Neill, an economist who had spent much of his career at Goldman Sachs, was surprising to some but reflected the view that tackling the AMR crisis was not just a scientific and medical challenge but also an economic and social one that would benefit from someone capable of thinking ‘outside the box’. Moreover, a key factor was the feeling that Jim O’Neill, who had coined the acronym BRIC (for Brazil, Russia, India and China), could be instrumental in building connections with emerging economies, which were perceived as critical players if AMR was to be addressed globally. This perspective is reflected in the Review’s emphasis on the potential leadership role of the G20 group of countries, alongside that of the UN and G7.<sup>1</sup>

The final report of the Review was published in May 2016 and has had a global impact in terms of motivating political leaders and decision-makers to take more seriously the threat posed by AMR.<sup>2</sup>

The Review set out why AMR is such a huge threat as antimicrobial drugs – used to treat bacterial, viral, fungal and parasitic infections – become less effective and too few new ones are developed. It found that not enough was being done to reduce unnecessary use of antimicrobials in human healthcare and in animals and plants, nor to curb their presence in the environment. The Review estimated that if no action is taken AMR could cause the deaths of 10 million people worldwide every year by 2050, with a cumulative economic impact of around \$100 trillion lost from global GDP.

The purpose of this report is to assess progress against the recommendations of the Review and to identify opportunities for further action and key obstacles that need to be overcome. There may be a need to reappraise current priorities – those expressed in the Review and in other policy pronouncements – to reflect, in light of experience to date, what adjustments might be made to current policies. The analysis presented in this research paper is based on a review of the available literature, on interviews with selected experts in their fields, and the views expressed at a Chatham House expert roundtable held in May 2019 (see Annex 1 for the list of participants).

While the framework for this research paper focuses on the recommendations of the Review, it is important to recognize that actions to date in this area have been influenced by outputs from multiple sources. Notably, the World Health Organization’s Global Action Plan on Antimicrobial Resistance, published in 2015 after extensive consultations including with the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE), provided the framework for global actions and the development of national action plans.<sup>3</sup> Prior to that there had been a number of

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<sup>1</sup> O’Neill, J. (2018), ‘Two years on: an update on achievement towards the recommendations of the antimicrobial resistance report’, *Journal of Applied Microbiology* 125(2), pp. 308–312, <https://doi.org/10.1111/jam.13933> (Note: All URLs accessed 10 September 2019).

<sup>2</sup> AMR Review (2016), *Tackling Drug-Resistant Infections Globally: Final report and recommendations*, London: AMR Review, [https://amr-review.org/sites/default/files/160525\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf).

<sup>3</sup> World Health Organization (2015), *Global Action Plan on Antimicrobial Resistance*, Geneva: WHO, <https://www.who.int/antimicrobial-resistance/global-action-plan/en/>.

global, regional and national initiatives beginning in 2009.<sup>4</sup> As far back as 2001, the World Health Organization (WHO) published a global strategy on containing AMR, responding to a 1998 World Health Assembly resolution, which presaged many of the recommendations reflected in subsequent plans and reports, including the AMR Review.<sup>5</sup>

### The Review on Antimicrobial Resistance

The AMR Review made 10 main recommendations covering the broad range of actions it considered were required to address the imminent threat posed by AMR (see Box 1). It also made a total of 29 sub-recommendations (see Annex 2).

Apart from its final report, the Review published eight separate reports in 2014–16 on different aspects of tackling the AMR crisis. These reports were informed by many supporting documents commissioned by the Review.<sup>6</sup>

#### Box 1: AMR Review recommendations

1. A massive global public awareness campaign;
2. Improve hygiene and prevent the spread of infection;
3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination in the environment;
4. Improve global surveillance of drug resistance in humans and animals;
5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics;
6. Promote the development and use of vaccines and alternatives;
7. Improve the numbers, pay and recognition of people working in infectious disease;
8. Establish a Global Innovation Fund for early-stage and non-commercial research;
9. Better incentives to promote investment for new drugs and existing ones; and
10. Build a global coalition for real action – via the G20 and the UN.

### Overall impact

The Review made an impact well before the publication of its final report in May 2016. Its first report in December 2014 contained the estimates of deaths and economic costs noted above, which have since been widely used to justify urgent action to tackle AMR.<sup>7</sup> While the estimates have been queried,<sup>8</sup> the number of times the figures have been quoted is a testament to the large advocacy impact the Review has achieved. For example, a Google search for ‘10 million deaths globally 2050 drug-resistant’ on 30 September 2019 produced 5.92 million results. In its January 2016 declaration on combating AMR the pharmaceutical, biotechnology and diagnostics industries cited the 2014 Review report as a key influence on their initiative.<sup>9</sup> In its major report on the economic impact

<sup>4</sup> World Health Organization (2014), *Additional global, regional and national strategies and plans to address antimicrobial resistance*, Geneva: WHO, [https://www.who.int/antimicrobial-resistance/global-action-plan/General\\_and\\_national\\_plans\\_amr\\_Dec\\_2014.pdf?ua=1](https://www.who.int/antimicrobial-resistance/global-action-plan/General_and_national_plans_amr_Dec_2014.pdf?ua=1).

<sup>5</sup> World Health Organization (2001), *WHO Global Strategy for Containment of Antimicrobial Resistance*, Geneva: WHO, [https://www.who.int/drugresistance/WHO\\_Global\\_Strategy\\_English.pdf](https://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf).

<sup>6</sup> AMR Review (n.d.), ‘Publications’, <https://amr-review.org/Publications.html>.

<sup>7</sup> AMR Review (2014), *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*, London: AMR Review, [https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations\\_1.pdf](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf).

<sup>8</sup> *Independent* (2016), ‘British study’s claim 10 million people a year could die because of antibiotic resistance dismissed as ‘unreliable’ 17 December 2016, <https://www.independent.co.uk/news/science/antimicrobial-resistance-superbugs-death-toll-new-study-flawed-assumptions-british-amr-review-david-a7481396.html>.

<sup>9</sup> AMR Industry Alliance (2016), ‘Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance’, January 2016, <https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf>.

of AMR, the World Bank referred often to the analysis and recommendations in the Review's report and background papers – all of which it described as 'remarkable'.<sup>10</sup> Most recently the report of the UN's Interagency Coordination Group on Antimicrobial Resistance (IACG) referred to the estimates.<sup>11</sup>

While the advocacy impact of the Review's estimates of AMR costs is clear, it is more difficult to trace the relationship between the report, and its recommendations, and subsequent political impact internationally. The commissioning of the Review by the UK government was, in itself, evidence of the already increased political profile of the threat posed by AMR. The advocacy activities of the Review team and chair and its series of reports leading up to its final report performed an important function in mobilizing actors around the world and focusing attention on concrete measures that could or should be taken to address AMR. The Review came in the wake of a series of actions taken nationally and internationally seeking to address the issue. Key events and reports between 2000 and 2016 are noted in Box 2.

### Box 2: Key developments in the fight against AMR since 2000

- 2000** WHO published *Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*.<sup>12</sup>
- 2001** WHO published its *Global Strategy for Containment of Antimicrobial Resistance*.<sup>13</sup>
- 2003** First joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance.<sup>14</sup>
- 2005** ReAct formed in Sweden.<sup>15</sup>
- 2009** Sweden, as president of the European Union (EU), made antimicrobial development a priority and the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) published a technical report on the AMR challenge.<sup>16</sup>
- 2009** The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established by the EU and the US (later including Canada and Norway).
- 2009** The Global Antibiotic Resistance Partnership (GARP) was founded.
- 2011** The European Commission published its first action plan against AMR<sup>17</sup> and established the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), bringing together EU nations to combat AMR.<sup>18</sup>
- 2011** Health ministers in WHO's South-East Asia Region adopted the Jaipur Declaration committing them to tackling AMR.<sup>19</sup>

<sup>10</sup> World Bank (2017), *Drug-Resistant Infections: A Threat to Our Economic Future*, Washington DC: World Bank, <http://documents.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf>.

<sup>11</sup> Interagency Coordination Group on Antimicrobial Resistance (2019), *No Time to Wait: Securing the future from drug-resistant infections*, April 2019, <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/>.

<sup>12</sup> World Health Organization (2000), *Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*, Geneva: WHO, [https://apps.who.int/iris/bitstream/handle/10665/68931/WHO\\_CDS\\_CSRAPH\\_2000.4.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/68931/WHO_CDS_CSRAPH_2000.4.pdf?sequence=1).

<sup>13</sup> World Health Organization (2001), *WHO Global Strategy for Containment of Antimicrobial Resistance*, Geneva: WHO, [https://www.who.int/drugresistance/WHO\\_Global\\_Strategy\\_English.pdf](https://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf).

<sup>14</sup> World Health Organization (2004), 'Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: scientific assessment', Geneva: WHO, <https://apps.who.int/iris/handle/10665/68883>.

<sup>15</sup> ReAct (n.d.), <https://www.reactgroup.org/about-us/>.

<sup>16</sup> ECDC/EMA (2009), *The bacterial challenge: time to react*, Stockholm: ECDC/EMA, [https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf).

<sup>17</sup> European Commission (2011), *Action plan against the rising threats from Antimicrobial Resistance*, COM (2011) 748, [https://ec.europa.eu/health/amr/sites/amr/files/communication\\_amr\\_2011\\_748\\_en.pdf](https://ec.europa.eu/health/amr/sites/amr/files/communication_amr_2011_748_en.pdf).

<sup>18</sup> Joint Programming Initiative on Antimicrobial Resistance (n.d.), <https://www.jpiaamr.eu/about/>.

<sup>19</sup> Jaipur Declaration on Antimicrobial Resistance (2011), Jaipur: SEARO, [http://www.searo.who.int/entity/antimicrobial\\_resistance/rev\\_jaipur\\_declaration\\_2014.pdf?ua=1](http://www.searo.who.int/entity/antimicrobial_resistance/rev_jaipur_declaration_2014.pdf?ua=1).

- 2012** Indian doctors met in Chennai, resulting in the Chennai Declaration, a roadmap for tackling the challenge of AMR.<sup>20</sup>
- 2012** WHO published a report on *The evolving threat of antimicrobial resistance: Options for action*.<sup>21</sup>
- 2012** The European Commission commits funding to the Innovative Medicines Initiative's New Drugs for Bad Bugs project.<sup>22</sup>
- 2013** The UK government published Volume 2 of the Chief Medical Officer's 2011 Annual Report, which called for action in the UK and globally to combat AMR<sup>23</sup> and in the US, the Centers for Disease Control and Prevention (CDC) published a major report on the threat from AMR.<sup>24</sup>
- 2014** The US President's Council of Advisors on Science and Technology published a report on combatting AMR<sup>25</sup> and the US National Strategy for Combating Antibiotic Resistant Bacteria was released.<sup>26</sup>
- 2014** Seven UK research councils launched the AMR cross-council initiative.<sup>27</sup>
- 2015** WHO, OIE and FAO member states agreed on the Global Action Plan on Antimicrobial Resistance.
- 2016** The pharmaceutical, biotechnology and diagnostics Industries signed the Davos Declaration on combating antimicrobial resistance.

In 2013, WHO established the Strategic and Technical Advisory Group on Antimicrobial Resistance, chaired by Dame Sally Davies, which at its first meeting recommended that WHO should lead in developing a global action plan to address AMR.<sup>28</sup> In 2014, the World Health Assembly approved a resolution on AMR that called, *inter alia*, for WHO to develop a draft global action plan to combat AMR.<sup>29</sup> This resolution was based on a draft proposed by the UK and Sweden.<sup>30</sup> All this activity culminated in agreement on the Global Action Plan on Antimicrobial Resistance in 2015.

Against that background, it is difficult to differentiate the influence of the AMR Review on events subsequent to its publication from that of the Global Action Plan or other initiatives. In reality the Review was one element of a collective effort by key players – including the UK and like-minded governments such as Sweden, Wellcome (which co-funded the AMR Review),

<sup>20</sup> Ghafur, A., Mathai, D., Muruganathan, A., Jayalal, J. A., Kant, R., Chaudhary, D., Prabhash, K., Abraham, O. C., Gopalakrishnan, R., Ramasubramanian, V., Shah, S. N., Pardeshi, R., Huilgol, A., Kapil, A., Gill, J., Singh, S., Rissam, H. S., Todi, S., Hegde, B. M. and Parikh, P. (2013), 'The Chennai Declaration: a roadmap to tackle the challenge of antimicrobial resistance', Position Paper, *Indian Journal of Cancer*, 50(1), pp. 71–73, doi: 10.4103/0019-509X.104065.

<sup>21</sup> World Health Organization (2012), *The evolving threat of antimicrobial resistance: options for action*, Geneva: WHO, <https://apps.who.int/iris/handle/10665/44812>.

<sup>22</sup> Kostyanev, T., Bonten, M. J. M., O'Brien, S., Steel, H., Ross, S., François, B., Tacconelli, E., Winterhalter M., Stavenger, R. A., Karlén, A., Harbarth, S., Hackett, J., Jafri, H. S., Vuong, C., MacGowan, A., Witschi, A., Angyalosi, G., Elborn J. S., deWinter, R. and Goossens, H. (2016), 'The Innovative Medicines Initiative's New Drugs for Bad Bugs programme: European public-private partnerships for the development of new strategies to tackle antibiotic resistance', *Journal of Antimicrobial Chemotherapy*, 71(2), pp. 290–295, <https://doi.org/10.1093/jac/dkv339>.

<sup>23</sup> Department of Health (2013), 'Chief Medical Officer annual report 2011: Infections and the rise of antimicrobial resistance', London: Department of Health, <https://www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-2>.

<sup>24</sup> Centers for Disease Control and Prevention (2013), *Antibiotic Resistance Threats in the United States*, Washington D.C.: CDC, <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>.

<sup>25</sup> President's Council of Advisors on Science and Technology (2014), *Combating Antibiotic Resistance*, Washington DC: PCAST, <https://www.cdc.gov/drugresistance/pdf/report-to-the-president-on-combating-antibiotic-resistance.pdf>.

<sup>26</sup> The White House (2014), *National Strategy for Combating Antibiotic Resistant Bacteria*, Washington D.C.: White House, [https://www.cdc.gov/drugresistance/pdf/carb\\_national\\_strategy.pdf](https://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf).

<sup>27</sup> Medical Research Council (n.d.), 'Our strategy for tackling antimicrobial resistance', <https://mrc.ukri.org/research/spotlights/antimicrobial-resistance/how-is-the-mrc-involved/>.

<sup>28</sup> World Health Organization (2013), 'Strategic and Technical Advisory Group on Antimicrobial Resistance (STAG-AMR) Report of the first meeting Geneva, 19-20 September 2013', Geneva: WHO, [https://www.who.int/antimicrobial-resistance/publications/amr\\_stag\\_meetingreport0913.pdf?ua=1](https://www.who.int/antimicrobial-resistance/publications/amr_stag_meetingreport0913.pdf?ua=1).

<sup>29</sup> World Health Organization (2014), 'Antimicrobial resistance' Resolution WHA67.25, [http://apps.who.int/gb/ebwha/pdf\\_files/WHA67/A67\\_R25-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf).

<sup>30</sup> Shallcross, L. and Davies, S. (2014), 'The World Health Assembly resolution on antimicrobial resistance', *Journal of Antimicrobial Chemotherapy*, 69(11), pp. 2833–85, <https://doi.org/10.1093/jac/dku346>.

and many other groups and individuals – who sought to mobilize action at the highest level by influencing governments and others such as the UN, WHO, the European Commission, the G20, G7 and other international organizations.

Therefore, although this paper’s assessment of progress in tackling AMR is framed by the recommendations of the Review it does not necessarily seek to link specific actions to the Review itself.

### Political impact

The Review, and the lobbying efforts of the UK and other governments, certainly played a role in raising the international political profile of AMR. These efforts were reflected in the declaration on AMR from G7 health ministers in October 2015, which specifically referred to the Review’s estimate of 700,000 AMR-related deaths annually,<sup>31</sup> and in the first reference to AMR by the G20 in the Antalya G20 summit communique in November 2015.<sup>32</sup> Following publication of the Review, the UN Political Declaration on AMR was agreed in September 2016.<sup>33</sup> It reflected many of the themes identified in the Review including, for instance, ‘the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales’ and the need to mobilize predictable and sustainable funding to address all aspects of AMR.

As host of the 2017 G20 meeting, Germany made AMR one of its priorities and undertook substantial preparatory work along with others to seek agreement on the appropriate use of antibiotics as well as to coordinate on incentives for improved research and development (R&D).<sup>34</sup> One major input was the commissioning of the Boston Consulting Group (BCG) to make proposals for new incentives and financing for R&D. These proposals drew heavily on many of those in the Review.<sup>35</sup> A second was a report from the Organisation for Economic Co-operation and Development (OECD) and the Tripartite agencies (the FAO, the OIE and WHO) on tackling AMR and ensuring sustainable R&D that drew substantially on the analysis in the AMR Review and the BCG report.<sup>36</sup> G20 health ministers met in Berlin in May 2017 and produced a declaration in which AMR was one of the three key priorities, along with crisis management and health system strengthening.<sup>37</sup>

However, compared with all this comprehensive preparatory work, the G20 leaders’ declaration in July 2017 in Hamburg was decidedly muted. The one concrete proposal was to call for the establishment of an international R&D Collaboration Hub, but when it came to the detailed proposals put forward by BCG and the OECD/Tripartite for stimulating R&D the declaration simply said ‘we will further examine practical market incentive options’.<sup>38</sup>

<sup>31</sup> G7 (2015), ‘Declaration of the G7 Health Ministers’, 8–9 October 2015, Berlin, <http://www.g8.utoronto.ca/healthG8/2015-berlin.pdf>.

<sup>32</sup> G20 (2015), ‘G20 Leaders’ Communiqué Antalya’, 16 November 2015, <http://www.g20.utoronto.ca/2015/151116-communiqué.html#annex>.

<sup>33</sup> United Nations (2016), ‘Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance’, A/71/L.2, 22 September 2016, <https://digitallibrary.un.org/record/842813?ln=en>.

<sup>34</sup> Federal Government (2017), ‘The G20 Presidency 2017 at a glance’, [https://www.g20germany.de/Webs/G20/EN/G20/Agenda/agenda\\_node.html](https://www.g20germany.de/Webs/G20/EN/G20/Agenda/agenda_node.html).

<sup>35</sup> Boston Consulting Group (2017), *Breaking through the Wall A Call for Concerted Action on Antibiotics Research and Development*, Berlin: BCG/Federal Ministry of Health, [https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5\\_Publikationen/Gesundheit/Berichte/GUARD\\_Follow\\_Up\\_Report\\_Full\\_Report\\_final.pdf](https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf).

<sup>36</sup> OECD, WHO, FAO, OIE (2017), *Tackling antimicrobial resistance: Ensuring sustainable R&D*, Final note prepared by OECD, WHO, FAO and OIE, 29 June 2017, <https://www.oecd.org/els/health-systems/G20-AMR-Final-Paper-2017.pdf>.

<sup>37</sup> G20 (2017), ‘Berlin Declaration of the G20 Health Ministers’, 19–20 May 2017, [https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3\\_Downloads/G/G20-Gesundheitsministertreffen/G20\\_Health\\_Ministers\\_Declaration\\_engl.pdf](https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf).

<sup>38</sup> G20 (2017), ‘G20 Leaders’ Declaration. Shaping an interconnected world’, 7–8 July 2017, <https://www.oecd.org/els/health-systems/G20-leaders-declaration.pdf>.

The outcome of the 2017 G20 summit seems to mark a turning point in the global political commitment to take concrete action on AMR. In 2018, the G7 communique contained just one sentence on AMR: ‘We will prioritize and coordinate our global efforts to fight against antimicrobial resistance, in a ‘one health’ approach’.<sup>39</sup> There was no meeting of G7 health ministers at that time. The 2018 G20 communique was similarly brief and repeated the 2017 Hamburg conclusion ‘to further examine practical market incentives’.<sup>40</sup> The G20 health ministers devoted considerable space to AMR but offered no new proposals.<sup>41</sup> In 2019, G7 health ministers made only passing and unspecific reference to AMR.<sup>42</sup> While the G20 summit called for strengthened efforts to combat AMR and for ‘interested G20 members and (the) Global AMR R&D Hub to analyse push and pull mechanisms to identify (the) best models for AMR R&D and to report back to relevant G20 Ministers’.<sup>43</sup>

Overall it can be said that, to the extent that statements made by the G7 and G20 are important in moving things forward, these peaked in 2017 and there was clearly a political impediment in moving, in respect of R&D, from ‘examining practical market incentives’ to actually proposing concrete steps to make these a reality.

**It appears that the threat, in spite of many warnings, is not perceived to be sufficient to merit the exceptional policy action many consider necessary.**

This lack of forward momentum may be compared with the political impetus that resulted in the G7 summit in Okinawa in 2000, which gave birth to the Global Fund to Fight AIDS, Tuberculosis and Malaria.<sup>44</sup> The Global Fund has disbursed to date more than \$40 billion, which is the amount the Review estimated would be needed over a decade to address AMR.<sup>45</sup> Current political and economic circumstances are very different from those that prevailed in 2000 but it is apparent that the pressure arising from civil society, key governments, individuals and WHO, allied with the obvious severity of the AIDS pandemic and millions of lives immediately at risk, is what resulted in effective action at the level of the G7 in 2000 and the mobilization of large-scale financial resources.<sup>46</sup> While many of these elements are present in the case of AMR, they have so far failed to generate financial commitments on the scale that the Review and many others believe is required. It appears that the threat, in spite of many warnings, is not perceived to be sufficient to merit the exceptional policy action many consider necessary.

<sup>39</sup> G7 (2018), ‘The Charlevoix G7 Summit Communique’, 9 June 2018, <https://www.consilium.europa.eu/en/press/press-releases/2018/06/09/the-charlevoix-g7-summit-communique/pdf>.

<sup>40</sup> G20 (2018), ‘G20 Leaders’ declaration: Building consensus for fair and sustainable development’, 1 December 2018, [http://www.g20.utoronto.ca/2018/buenos\\_aires\\_leaders\\_declaration.pdf](http://www.g20.utoronto.ca/2018/buenos_aires_leaders_declaration.pdf).

<sup>41</sup> G20 (2018), ‘Declaration G20 Meeting of Health Ministers’, 4 October 2018, <http://www.g20.utoronto.ca/2018/2018-10-04-health.pdf>.

<sup>42</sup> G7 (2019), ‘G7 Health Ministers’ Declaration’, 16–17 May 2019, <https://www.elysee.fr/en/g7/2019/05/17/g7-ministers-commit-to-improving-access-to-health-care-for-all>.

<sup>43</sup> G20 (2019), ‘G20 Osaka Leaders’ Declaration’, 29 June 2019, <http://www.g20.utoronto.ca/2019/2019-g20-osaka-leaders-declaration.html>.

<sup>44</sup> Global Fund (2017), ‘Japan and the Global Fund’, Geneva: Global Fund, [https://www.theglobalfund.org/media/1493/donor\\_japan\\_report\\_en.pdf?u=636918787320000000](https://www.theglobalfund.org/media/1493/donor_japan_report_en.pdf?u=636918787320000000).

<sup>45</sup> The Global Fund (n.d.), ‘Financials’, <https://www.theglobalfund.org/en/financials/>.

<sup>46</sup> Liden, J. (2013), *The Grand Decade for Global Health: 1998–2008*, Working Group on Governance, Paper 2, London: The Royal Institute of International Affairs, [https://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0413\\_who.pdf](https://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0413_who.pdf).

## Methodology

This paper is based on a review of available literature and other materials documenting developments in the AMR field, particularly since 2016. It is supplemented by the insights of the participants at the May 2019 Chatham House roundtable and interviews with other stakeholders. The draft of this paper was peer reviewed by participants at the roundtable and other experts.

An original objective of this report was to produce a scorecard assessing progress against each of the main recommendations and participants at the roundtable were asked to rate progress on a scale from one to five, where one is ‘poor’ and five is ‘excellent’. The average outcome against all recommendations was 1.8 – between ‘poor’ and ‘fair’. The variation between recommendations was from 1.5 to 2.7. The scores (based on 15 returns) are presented in Table 1.

**Table 1: Roundtable scores**

| Recommendation   | Score      |
|--|------------|
| A massive global public awareness campaign   | 2.5        |
| Improve hygiene and prevent the spread of infection  | 1.7        |
| Reduce unnecessary use of antimicrobials in agriculture and their dissemination in the environment | 2.1        |
| Improve global surveillance of drug resistance in humans and animals                               | 2.1        |
| Promote new, rapid diagnostics to cut unnecessary use of antibiotics                               | 1.6        |
| Promote the development and use of vaccines and alternatives                                       | 1.6        |
| Improve the numbers, pay and recognition of people working in infectious disease                   | 1.5        |
| Establish a Global Innovation Fund for early-stage and non-commercial research                     | 2.5        |
| Better incentives to promote investment for new drugs and existing ones                            | 1.7        |
| Build a global coalition for real action – via the G20 and the UN                                  | 2.7        |
| <i>All</i>   | <i>1.8</i> |

Source: Compiled by the author.

It is clear that roundtable participants rated overall progress as less than ‘fair’. On the other hand, there was some cause for optimism in respect of recommendations one, eight and 10. However, the lack of variation in the average scores for each recommendation, along with the difficulty in assigning scores to diverse sub-recommendations (see Annex 2), limits the value that can be extracted from a scorecard produced by a small group of experts. In most of the very diverse areas covered by the Review there are positive developments of various kinds but, for the most part, these have thus far fallen well short of what the Review recommended. Thus, participants seemed to agree with the conclusion of a recent UN report on the implementation of the 2016 political declaration:

Despite early progress, critical challenges remain in terms of the development of national action plans and the establishment of a coordinated response at the global level.<sup>47</sup>

The following section seeks to document progress in each of the recommendation areas of the Review and to identify the challenges and opportunities for making further progress.

<sup>47</sup> United Nations (2019), *Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*, A/73/869, New York: United Nations, 10 May 2019, <https://undocs.org/en/A/73/869>.

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## 2. Assessment of Progress

### A massive public awareness campaign

The Review recommended that an appropriate global body should establish an internationally coordinated public campaign to improve understanding and support positive behaviour change. Prior to the Review, the EU had already mounted in 2008 an Antibiotic Awareness Day (EAAD) on 18 November. In 2010, the US and Canada synchronized their campaigns with the EU, and in 2012 Australia and WHO Europe joined the EAAD. In 2014 New Zealand joined, and in 2015 WHO initiated the World Antibiotic Awareness Week around the 18 November as part of its Global Action Plan.

Other relevant awareness initiatives include:

- The Antibiotic Guardian campaign, launched in 2014 in the UK, asks health leaders, health professionals and the public to make one simple pledge that they can take forward. It has since been expanded to some European countries.<sup>48</sup>
- The e-Bug project was established in 2006 to educate children and young people across Europe about microbiology, hygiene and the spread, treatment and prevention of disease.<sup>49</sup>
- WHO published guidance in 2018 for a competency framework on health workers' education and training, recognizing the variability in quality and uneven coverage of initiatives to strengthen education and training of health workers on AMR.<sup>50</sup>

While these initiatives all predate the Review, they have developed considerably since 2016. Participation in WHO's campaign increased from 83 countries in 2016 to 131 in 2017 (but fell back to 116 in 2018).<sup>51</sup> The campaign has evolved since 2015 in the use of different messages, media and techniques. A new initiative launched in India is the Superheroes against Superbugs programme (See Box 3).

While the recommendation of the Review did not focus explicitly on non-human use, the WHO campaign now involves the FAO<sup>52</sup> and OIE<sup>53</sup> and an interactive joint platform has been established to share country activities.<sup>54</sup> In agriculture, international organizations, the private sector, civil society and governments have invested significant resources in awareness-raising campaigns directed to the full value chain – from farmers to consumers. In particular, the OIE recognizes World Antibiotics Awareness Week each year with high-profile activities. The OIE has dedicated significant resources to its 'We Need You' campaign that promotes better stewardship and reduction of unnecessary use by all stakeholders in the value chain.

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<sup>48</sup> Antibiotic Guardian (n.d.), <https://antibioticguardian.com/>.

<sup>49</sup> E-Bug (n.d.), <http://www.e-bug.eu/>.

<sup>50</sup> World Health Organization (2018), *WHO competency framework for health workers' education and training on antimicrobial resistance*, Geneva: WHO, <https://apps.who.int/iris/bitstream/handle/10665/272766/WHO-HIS-HWF-AMR-2018.1-eng.pdf?ua=1>.

<sup>51</sup> World Health Organization (2019), *World Antibiotic Awareness Week 2018: Monitoring & Evaluation Report* Geneva: WHO, [http://www.searo.who.int/entity/antimicrobial\\_resistance/waaw-2018-monitoring-and-evaluation-report.pdf?ua=1](http://www.searo.who.int/entity/antimicrobial_resistance/waaw-2018-monitoring-and-evaluation-report.pdf?ua=1).

<sup>52</sup> Food and Agriculture Organization (2018), 'World Antibiotic Awareness Week, 12-18 November 2018', <http://www.fao.org/antimicrobial-resistance/world-antibiotic-awareness-week/en/>.

<sup>53</sup> World Organisation for Animal Health (n.d.), 'We Need You', <https://oie-antimicrobial.com/>.

<sup>54</sup> World Health Organization (2018), <http://apps.who.int/world-antibiotic-awareness-week/activities/en#/grid-content>.

### Box 3: Superheroes against Superbugs<sup>55</sup>

The 'Superheroes against Superbugs' programme is an initiative of India's Department of Biotechnology and Wellcome. It aims to involve schoolchildren as partners in creatively engaging with the public on AMR. In India, about 50 per cent of antibiotic prescriptions are inappropriate and 64 per cent of antibiotics sold are unapproved. Approximately, 58,000 newborns in India die each year because of infections caused by antibiotic-resistant bacteria. The programme aims to create a platform to initiate conversations about the dangers of antibiotic resistance between the children and various community groups.

A pilot programme introduced concepts related to microbes, infections, antibiotics and resistance using interactive games and creative activities. Children were encouraged to explore mediums such as comics and short animated films to initiate and sustain a dialogue on antibiotic resistance. They were encouraged to develop comic-book stories based on different problems related to antibiotic resistance, such as using antibiotics for viral infections or without a doctor's consultation, use of antibiotics in poultry and dairy, and the importance of sanitation and hygiene.

However, the views of participants at the roundtable, as well as other evidence, indicate that there are difficulties in making the connection between undertaking a campaign, the impact on awareness and the link between increased awareness and behaviour change. A recent review of campaigns in 60 countries concluded that:

many questions regarding how best to conduct and evaluate these campaigns remain unanswered. [Awareness campaigns] should move beyond long-standing but problematic messages (e.g. 'complete the course'), towards accurate and locally adapted communication. Involvement of experts in health communication and social marketing seems crucial.<sup>56</sup>

A systematic review of studies of public understanding of AMR in Europe, Asia and North America found an incomplete understanding of antibiotic resistance – most thought it referred to changes in the human body. While many understood that excessive use caused resistance, they thought it was unlikely to affect them. Whereas the public thought that they should trust clinicians to prescribe antibiotics appropriately, clinicians still felt that patients expected to be prescribed antibiotics.<sup>57</sup>

The EU has conducted regular surveys on the impact of awareness campaigns. Findings of the latest survey in 2018 included the following:

- Around one-third of Europeans have taken antibiotics in the last year, ranging from 47 per cent in Italy to 20 per cent in Sweden. This is down from 40 per cent in 2009.
- Nearly half (48 per cent) of Europeans thought that antibiotics kill viruses, varying from 22 per cent in Sweden to 71 per cent in Greece.
- Most Europeans (85 per cent) were aware that using antibiotics unnecessarily makes them become ineffective and that it is necessary to complete the course of treatment (84 per cent), although the validity of this message is now questioned.<sup>58</sup>
- The majority of respondents (66 per cent) did not remember getting any information about not taking antibiotics unnecessarily, for example for a cold.

<sup>55</sup> India Alliance (2018), 'Grassroots Comics for Antibiotic Resistance: Superheroes Against Superbugs', <https://www.indiaalliance.org/news/252>.

<sup>56</sup> Huttner, B., Saam, M., Moja, L., Mah, K., Sprenger, M., Harbarth, S. and Magrini, N. (2019), 'How to improve antibiotic awareness campaigns: findings of a WHO global survey', *BMJ Glob Health*, 4(3), pp. 1–9, doi:10.1136/bmjgh-2018-001239.

<sup>57</sup> McCullough, A. R., Parekh, S., Rathbone, J., Del Mar, C. B. and Hoffmann T. C. (2016), 'A systematic review of the public's knowledge and beliefs about antibiotic resistance', *Journal of Antimicrobial Chemotherapy*, 71(1), pp. 27–33, doi:10.1093/jac/dkv310.

<sup>58</sup> Llewelyn, M. J., Fitzpatrick, J. M., Darwin, E., Tonkin-Crine, S., Gorton, C., Paul, J., Peto, T. E. A., Yardley, L., Hopkins, S. and Walker, A. S. (2017), 'The antibiotic course has had its day', *BMJ*, 358(8118), <https://doi.org/10.1136/bmj.j3418>.

- A doctor was the most likely source of such information, followed by television news or other programmes or a television advertisement. Eighty-six per cent of respondents said they were much more likely to go to a doctor to get trustworthy information on antibiotics than to rely on any other source of information.
- Seven in 10 Europeans said the information that they obtained about the unnecessary use of antibiotics did not change their views about using them.<sup>59</sup>

These findings illustrate the difficulties in establishing the efficacy of public awareness campaigns in reducing unnecessary use of antibiotics, even in high-income countries. It is disappointing also that awareness does not seem to translate easily into changing use behaviour. Evaluations of campaigns in some high-income countries suggest there is some impact on antibiotic prescribing and consumption, although the benefits are likely to be seen in countries that are considered high prescribers and only if campaigns use specific behavioural and social marketing techniques to target specific populations.<sup>60</sup>

There is also a concern that awareness, even if increased, does not readily translate into appropriate behaviour change in the use of antibiotics because of the complexity of the factors that affect use. For example, some studies have highlighted a perverse response where raising awareness among those with little prior knowledge can result in increased demand for antibiotics, for instance in the UK.<sup>61</sup> In low- and middle-income countries (LMICs) such problems are compounded by cultural, language and access issues. This led one study in Laos to conclude:

The continued high level of antibiotic use among participants and villagers with already ‘desirable’ attitudes, together with widespread poverty and the generally low access to public healthcare, even in our peri-urban setting, suggest that solutions to problematic forms of antibiotic use do not necessarily reside in the domain of awareness raising, but rather in more fundamental areas like access to healthcare and medicine. Our case does not render awareness-raising activities obsolete, but it does suggest that they can, at best, be only a small facet of AMR-related behavioural policies.<sup>62</sup>

Similar complexities were revealed in a study in Thailand.<sup>63</sup> A multi-country study in six LMICs found that, despite high levels of AMR awareness among health professionals, antibiotics were nevertheless widely used as ‘band aids’ to protect patients from unhygienic conditions in community and clinical settings. It concluded that ‘simply increasing awareness of AMR will be insufficient to change prescribing and dispensing without local information on which antibiotics do work well, without investment in infrastructure that allows antimicrobials to be released from their “band aid”

<sup>59</sup> Kantar (2018), ‘Special Eurobarometer 478’, Brussels: Kantar, <http://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/survey/getsurveydetail/instruments/special/surveyky/2190>.

<sup>60</sup> Huttner, B., Goossens, H., Verheij, T. and Harbarth, S. (2010), ‘Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries’, *The Lancet Infectious Diseases*, 10(1), pp. 17–31, [https://doi.org/10.1016/S1473-3099\(09\)70305-6](https://doi.org/10.1016/S1473-3099(09)70305-6); Goossens, H., Guillemot, D., Ferech, M., Schlemmer, B., Costers, M., van Breda, M., Baker, L. J., Cars, O. and Davey, P. G. (2006), ‘National campaigns to improve antibiotic use’, *European Journal of Clinical Pharmacology*, 62(5), pp. 73–9, <https://doi.org/10.1007/s00228-005-0094-7>.

<sup>61</sup> Roope, L. S. J., Tonkin-Crine, S., Butler, C. C., Crook, D., Peto, T., Peters, M., Walker, A. S. and Wordsworth, S. (2018), ‘Reducing demand for antibiotic prescriptions: evidence from an online survey of the general public on the interaction between preferences, beliefs and information, United Kingdom, 2015’, *Euro Surveillance*, 23(25), <https://doi.org/10.2807/1560-7917.ES.2018.23.25.1700424>.

<sup>62</sup> Haenssger, M. J., Xayavong, T., Charoenboon, N., Warapikuptanun, P. and Khine Zaw, Y. (2018), ‘The Consequences of AMR Education and Awareness Raising: Outputs, Outcomes, and Behavioural Impacts of an Antibiotic-Related Educational Activity in Lao PDR’, *Antibiotics*, 7(4), 95, <https://doi.org/10.3390/antibiotics7040095>.

<sup>63</sup> Charoenboon, N., Haenssger, M. J., Warapikuptanun, P., Xayavong, T. and Zaw, Y. K. (2019), ‘Translating antimicrobial resistance: a case study of context and consequences of antibiotic-related communication in three northern Thai villages’, *Palgrave Communications*, 5, Article number: 23, <https://doi.org/10.1057/s41599-019-0226-9>.

role, and without active regulation of pharmaceutical representatives.<sup>64</sup> Another study characterizes antibiotic overuse as a quick fix in the absence of effective measures to resolve underlying structural problems in healthcare systems, housing, water and sanitation, and agriculture.<sup>65</sup>

There is more evidence, mainly from high-income countries, that strategies that focus specifically on the clinician–patient relationship in the community where most antibiotics are prescribed have the most success in reducing antibiotic consumption. Such strategies include:

- Shared decision-making between patients and clinicians, which has been shown to have some effect on use;<sup>66</sup>
- Delayed prescribing or reconsultation if symptoms do not resolve;<sup>67</sup>
- Incorporating computerized decision support systems in clinicians' prescribing software;<sup>68</sup>
- Financial incentives for clinicians – the introduction of a Quality Premium in the UK to reward reduced prescribing and apparently reduced consumption overall by 3 per cent and by more in younger patients;<sup>69</sup>
- As used in Australia and the UK, letters sent to high prescribers pointing out that their prescribing greatly exceeded the average for their local area;<sup>70</sup>
- Greater use of diagnostic tests (C-reactive Protein) in conjunction with interactive communication materials.<sup>71</sup>

The Review did not focus in detail on the issue of stewardship – how to reduce unnecessary or inappropriate use in clinical settings. However, it did recommend that regulations be introduced and enforced to prevent the sale of antibiotics without a prescription or, at least, clinical input.

The latest WHO analysis of self-assessment by countries reveals that 123 countries (80 per cent of the sample) have policies in place to regulate the sale of antimicrobials, including the requirement of a prescription for human use, but in low-income countries only 53 per cent of countries have these policies; 102 countries (66 per cent) have developed a plan to do this but only seven countries globally have reached full implementation level. However, nearly 27 per cent of responding countries have guidelines in place to enable appropriate use of antimicrobials or to optimize antibiotic use

<sup>64</sup> Pearson, M. and Chandler, C. (2019), 'Knowing antimicrobial resistance in practice: a multi-country qualitative study with human and animal healthcare professionals', *Global Health Action*, 12(1), <https://doi.org/10.1080/16549716.2019.1599560>.

<sup>65</sup> Denyer, W. L. and Chandler, C. (2019), 'Quick fix for care, productivity, hygiene and inequality: reframing the entrenched problem of antibiotic overuse', *BMJ Global Health*, 4(4), doi:10.1136/bmjgh-2019-001590.

<sup>66</sup> Coxeter, P., Del Mar, C. B., McGregor, L., Beller, E. M. and Hoffmann, T. (2015), 'Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care', *Cochrane Database of Systematic Reviews*, Issue 11, Art. No.: CD010907, <https://doi.org/10.1002/14651858.CD010907.pub2>.

<sup>67</sup> Spurling, G. K. P., Del Mar, C. B., Dooley, L., Foxlee, R. and Farley, R. (2017), 'Delayed antibiotic prescriptions for respiratory infections', *Cochrane Database of Systematic Reviews*, Issue 9, Article number:CD004417, doi: 10.1002/14651858.CD004417.pub5.

<sup>68</sup> Gonzales, R., Anderer, T., McCulloch, C. E., Maselli, J. H., Bloom, F. J., Graf, T. R., Stahl, M., Yefko, M., Molecavage, J. and Metlay, J. P. (2013), 'Cluster Randomized Trial of Decision Support Strategies for Reducing Antibiotic Use in Acute Bronchitis', *JAMA Intern Med*, 173(4), pp. 267–273, doi:10.1001/jamainternmed.2013.1589.

<sup>69</sup> Bou-Antoun, S., Costelloe, C., Honeyford, K., Mazidi, M., Hayhoe, B. W. J., Holmes, A., Johnson, A. P. and Aylin, P. (2018), 'Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis', *Journal of Antimicrobial Chemotherapy*, 73(10), pp. 2883–2892, <https://doi.org/10.1093/jac/dky237>.

<sup>70</sup> World Health Organization (2018), 'Nudge vs Superbugs', <https://www.who.int/campaigns/world-antibiotic-awareness-week/world-antibiotic-awareness-week-2018/features-from-around-the-world/nudge-vs-superbugs>.

<sup>71</sup> Little, P., Stuart, B., Francis, N., Douglas, E., Tonkin-Crine, S., Anthierens, S., Cals, J., Melbye, H., Santer, M., Moore, M., Coenen, S., Butler, C., Hood, K., Kelly, M., Godycki-Cwirko, M., Mierzecki, A., Torres, A., Llor, C., Davies, M., Mullee, M., O'Reilly, G., der Velden, A., Geraghty, A., Goossens, H., Verheij, T. and Yardley, L. (2013), 'Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial', *Lancet*, 382(9899), pp. 1175–82. [https://doi.org/10.1016/S0140-6736\(13\)60994-0](https://doi.org/10.1016/S0140-6736(13)60994-0).

in human health facilities.<sup>72</sup> In agriculture, regulatory procedures are much weaker. Just over half of reporting LMICs have laws or regulations in place, and a smaller proportion regulate the use of antibiotics for growth promotion.<sup>73</sup> It should be noted that the two regulatory systems are interrelated. It is difficult to convince farmers to have a veterinarian involved in antibiotic use when they can walk down the street to a pharmacy and buy antibiotics for their personal use.

A recent review of studies in 24 countries found that about three in four antibiotic requests and three in five consultations in community pharmacies resulted in the supply of antibiotics without a prescription.<sup>74</sup> Other studies in Tanzania,<sup>75</sup> China<sup>76</sup> and India<sup>77</sup> give essentially similar results. Even in Europe, a recent study estimates that 7 per cent of antibiotic use in 2016 was without a prescription, with rates up to 20 per cent in one country.<sup>78</sup> A review of studies in the US also found widespread non-prescription use.<sup>79</sup> Box 4 describes the experience of Tanzania in seeking to improve the quality of antimicrobial dispensing.

### Box 4: Accredited drug dispensing outlets in Tanzania

The goal of the accredited drug dispensing outlet (ADDO) programme in Tanzania, instituted in 2003, is to improve access to affordable, quality medicines and pharmaceutical services in retail drug outlets in areas where there are few or no registered pharmacies. To achieve this goal, the ADDO model combines developing the capacity of owners, dispensers and institutions that regulate or work in retail drug shops.

A recent study concluded that the ADDO programme has brought about positive changes in knowledge of dispensing practices. Despite this knowledge, its translation to appropriate dispensing practice was problematic. Dispensers are influenced by customer demand, habit (*'mazoza'*), inappropriate prescriptions from health facilities and the need to make a profit. Although the majority of dispensers reported that they had intervened in situations where customers asked for antibiotics unnecessarily, they tended to give in to clients' requests.<sup>80</sup>

While the programme has increased rural Tanzanian's access to antimicrobials and ADDOs are viewed as an integral part of the healthcare system, overall use of antimicrobials remains suboptimal. This stems not only from poor dispensing practices in ADDOs, but also from poor prescribing and antimicrobial availability in public facilities as well as inappropriate consumer demand that is rooted in poor understanding. To improve how the community uses antimicrobials, multi-pronged interventions to increase appropriate practices in both ADDOs and public health facilities need to be combined with active monitoring of those practices.<sup>81</sup>

<sup>72</sup> World Health Organization (2018), *Monitoring global progress on addressing antimicrobial resistance: analysis report of the second round of results of AMR country self-assessment survey 2018*, Geneva: WHO, <https://www.who.int/antimicrobial-resistance/publications/Analysis-report-of-AMR-country-se/en/>.

<sup>73</sup> United Nations (2019), *Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*.

<sup>74</sup> Auta, A., Hadib, M. A., Ogaa, E., Adewuyic E. O., Abdu-Aguyed, S. N., Davies, A., Strickland-Hodge, B. and Morgang, D. J. (2019), 'Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis', *Journal of Infection*, 78(1), pp. 8–18, <https://doi.org/10.1016/j.jinf.2018.07.001>.

<sup>75</sup> Horumpende, P. G., Sonda, T. B., van Zwetselaar, M., Antony, M. L., Tenu, F. F., Mwanziva, C. E., Shao, E. R., Mshana, S. E., Mmbaga, B. T. and Chilongola, J. O. (2018), 'Prescription and non-prescription antibiotic dispensing practices in part I and part II pharmacies in Moshi Municipality, Kilimanjaro Region in Tanzania: A simulated clients approach', *PLoS One*, 13(11), <https://doi.org/10.1371/journal.pone.0207465>.

<sup>76</sup> Chang, J., Ye, D., Lv, B., Jiang, M., Zhu, S., Yan, K., Tian, Y. and Fang, Y. (2017), 'Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey', *Journal of Antimicrobial Chemotherapy*, 72(4), pp. 1235–1242, <https://doi.org/10.1093/jac/dkw519>.

<sup>77</sup> Jaganathan M., Vallish, B. N., Mayathevar, B. and Mahato, K. (2016), 'Non-prescription sale of antibiotics in pharmacies across Puducherry, India', *International Journal of Basic & Clinical Pharmacology*, 5(6), pp. 2403–2406, <http://dx.doi.org/10.18203/2319-2003.ijbcp20164096>.

<sup>78</sup> European Commission (2017), *Antimicrobial resistance and causes of non-prudent use of antibiotics in human medicine in the EU*, Brussels: European Commission, [https://ec.europa.eu/health/amr/sites/amr/files/amr\\_arna\\_report\\_20170717\\_en.pdf](https://ec.europa.eu/health/amr/sites/amr/files/amr_arna_report_20170717_en.pdf).

<sup>79</sup> Grigoryan, L., Germanos, G., Zoorob, R., Juneja, S., Raphael, J. L., Paasche-Orlow, M. K. and Trautner, B. W. (2019), 'Use of Antibiotics Without a Prescription in the U.S. Population: A Scoping Review', *Ann Intern Med*, 174(4), pp. 257–263, doi: 10.7326/M19-0505.

<sup>80</sup> Dillip, A., Embrey, M., Shekalaghe, E., Ross-Degnan, D., Vialle-Valentin, C., Kimatta, S., Liana, J., Rutta, E., Valimba, R. and Chalker, J. (2015), 'What motivates antibiotic dispensing in accredited drug dispensing outlets in Tanzania? A qualitative study', *Antimicrobial Resistance and Infection Control*, 4(30), <https://doi.org/10.1186/s13756-015-0073-4>.

<sup>81</sup> Chalker, J. C., Vialle-Valentin, C., Liana, J., Mbwasii, R., Semali, I. A., Kihyo, B., Shekalaghe, E., Dillip, A., Kimatta, S., Valimba, R., Embrey, M., Lieber, R., Rutta, E., Johnson, K. and Ross-Degnan, D. (2015), 'What roles do accredited drug dispensing outlets in Tanzania play in facilitating access to antimicrobials? Results of a multi-method analysis', *Antimicrobial Resistance and Infection Control*, 4(33), Doi: 10.1186/s13756-015-0075-2.

### Conclusion

While resources have flowed into awareness campaigns, as recommended by the AMR Review, there is very limited evidence regarding their impact on antibiotic use, in countries at all levels of development. How to tailor messages to local circumstances, and the appropriate content of those messages, is not well established. Participants at the roundtable felt there needs to be a clearer focus on the factors that influence the behaviour of potential and actual patients, doctors and other prescribers and on what interventions could cause changes in behaviours that lead to inappropriate use. People (including health professionals, veterinarians and farmers) need suggestions about specific things they can do to achieve impact such as, for example, the specific recommendations put forward as part of WHO's hand hygiene initiative. Social and behavioural scientists need to be involved as well to help bring about behaviour change. Participants also said more resources need to be put into assessing impact.

Achieving sustainable change requires the involvement of groups in civil society (including, for example, consumers, professional societies and investors) to create the demand and pressure for change. Incorporating more guidance on AMR in general and professional education was also considered very important for sustainable impact.

The analysis also suggests that the realities of access to healthcare in most LMICs makes the enforcement of regulations on prescribing, and the translation of awareness into behaviour change, highly problematic. One reason is the inadequacies of the healthcare systems for much of the population and the consequent incentives for patients and sellers of antibiotics to go outside the system. Another is that antibiotics are often used as a 'quick fix' in the absence of effective measures to resolve underlying structural problems in healthcare systems, housing, water and sanitation, and agriculture that contribute to infections.

This is not just a question of regulating inappropriate use but also of recognizing that lack of access to quality antibiotics is a major concern, responsible for millions of deaths annually. Regulation is therefore important, but it is necessary to address the inadequacies in healthcare systems to bring about sustainable change in appropriate use and access.<sup>82</sup> Providing quality healthcare to all and moving towards universal health coverage will be crucial in addressing both the problems of adequate access to antibiotics and in restricting non-prescription sales.

### Improve hygiene and prevent the spread of infection

The Review recommended that healthcare systems embed infection prevention and control (IPC) as a top priority at all levels, using defined healthcare-associated infection (HCAI) reduction goals as the basis for targets, incentives and other performance management measures.

The latest UN progress report suggests that 97 countries out of 158 for which data are available (i.e. 61 per cent) are implementing infection prevention and control programmes, but the percentages vary from 77 per cent in high-income countries to 44 per cent in low-income countries.<sup>83</sup> WHO analysis of country self-assessments reports that 58 per cent of responding countries say they have taken action to reduce the incidence of infection through sanitation, hygiene and infection prevention measures.

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<sup>82</sup> Bloom, G., Merrett, G. B., Wilkinson, A., Lin, V. and Paulin, S. (2017), 'Antimicrobial resistance and universal health coverage', *BMJ Global Health*, 2(4), <http://dx.doi.org/10.1136/bmjgh-2017-000518>.

<sup>83</sup> United Nations (2019), *Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*.

Of these countries, 25 per cent have reached the highest level of implementation.<sup>84</sup> WHO issued updated guidelines on IPC programmes in healthcare facilities in 2016<sup>85</sup> and specific technical guidelines in 2017 on the prevention and control of emerging threats from resistant bacteria in healthcare facilities.<sup>86</sup>

However, an estimated 900 million people in LMICs still use healthcare facilities with no water service and 1.5 billion use facilities with no sanitation services. It is likely that many more people are served by healthcare centres lacking hand-hygiene facilities and safe waste management. Water and sanitation services are more likely to be available in hospitals than in other types of other healthcare facilities, and in urban areas than in rural areas.<sup>87</sup> In 2019, WHO member states agreed a resolution calling for action on water and sanitation in healthcare facilities.<sup>88</sup> Some countries, such as Tanzania, have produced national guidelines for water and sanitation in healthcare facilities.<sup>89</sup>

### An estimated 900 million people in LMICs still use healthcare facilities with no water service and 1.5 billion use facilities with no sanitation services.

Improving IPC is not just about planning, guidelines and infrastructure. Even in high-income countries compliance with IPC guidelines can be low. There is a large literature base that discusses why simple low-cost hand-hygiene methods are often not complied with, even in healthcare facilities with apparently all the infrastructure and resources necessary. Low compliance is often the result of the pressure on healthcare workers – thus understaffing and overcrowding common in many healthcare systems, but particularly in LMICs, is a major contributor to the spread of infection. Figure 1 shows the results of compliance with IPC practices in a study in Kenya.

The Review recommended improvements in funding of studies demonstrating the effectiveness of novel IPC interventions. A recent review of hand-hygiene studies indicated that much of the evidence is of low quality and that hardly any addressed the subject of cost-effectiveness. It concluded that there was a need to undertake methodologically robust research to explore the effectiveness of multimodal versus simpler interventions to increase hand-hygiene compliance, and to identify which components of multimodal interventions or combinations of strategies are most effective in a particular context.<sup>90</sup> Broadly similar conclusions were reached in a 2017 literature review of studies on a range of IPC interventions in hospitals – that the studies were generally of poor quality and that future attempts to establish the cost-effectiveness of such interventions needed to be underpinned by robust evidence of clinical effectiveness and cost-effectiveness.<sup>91</sup>

<sup>84</sup> World Health Organization (2018), *Monitoring global progress on addressing antimicrobial resistance: analysis report of the second round of results of AMR country self-assessment survey 2018*, Geneva: WHO, <https://www.who.int/antimicrobial-resistance/publications/Analysis-report-of-AMR-country-se/en/>.

<sup>85</sup> World Health Organization (2016), *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level*, Geneva: WHO, <https://apps.who.int/iris/bitstream/handle/10665/251730/9789241549929-eng.pdf?sequence=1>.

<sup>86</sup> World Health Organization (2017), *Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in healthcare facilities*, Geneva: WHO, <https://www.who.int/infection-prevention/publications/guidelines-cre/en/>.

<sup>87</sup> World Health Organization and the United Nations Children's Fund (2019), *WASH in health care facilities: global baseline report 2019*, Geneva: WHO/UNICEF, <https://apps.who.int/iris/bitstream/handle/10665/311620/9789241515504-eng.pdf>.

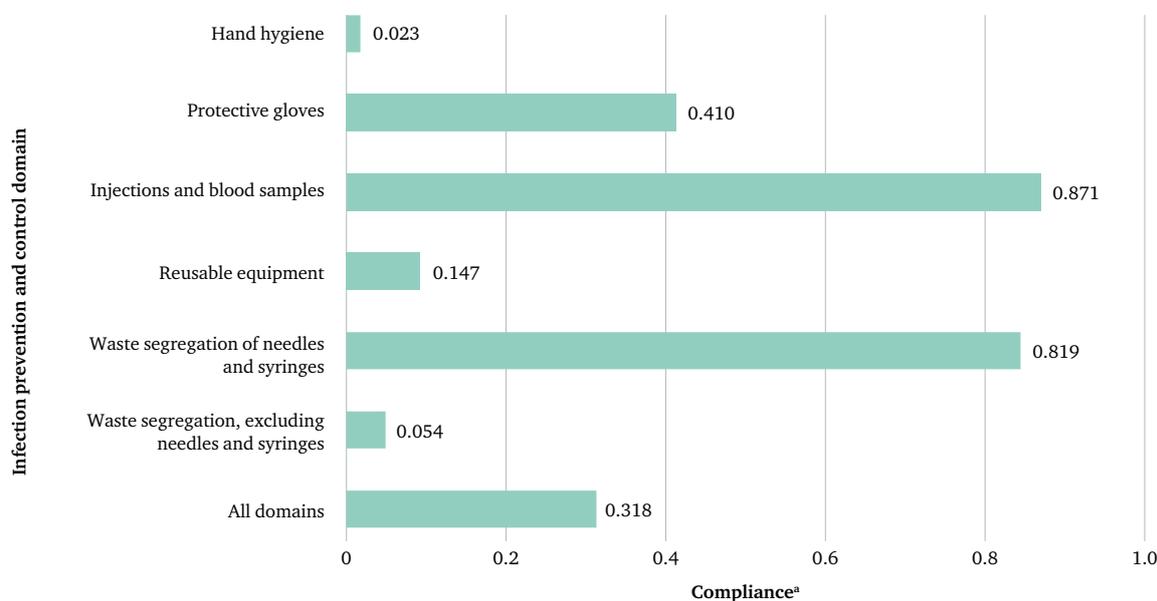
<sup>88</sup> World Health Organization (2019), 'Water, sanitation and hygiene in health care facilities', Resolution WHA72.7., 28 May 2019, [http://apps.who.int/gb/ebwha/pdf\\_files/WHA72/A72\\_R7-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R7-en.pdf).

<sup>89</sup> Ministry of Health (2017), *The national guidelines for water, sanitation and hygiene in health care facilities*, <https://washmatters.wateraid.org/publications/national-guidelines-for-wash-services-in-health-care-facilities-in-tanzania>.

<sup>90</sup> Gould, D. J., Moralejo, D., Drey, N., Chudleigh, J. H. and Taljaard, M. (2017), 'Interventions to improve hand hygiene compliance in patient care', *Cochrane Database of Systematic Reviews*, Issue 9, Article number: CD005186. DOI: 10.1002/14651858.CD005186.pub4.

<sup>91</sup> European Centre for Disease Prevention and Control (2017), *Economic evaluations of interventions to prevent healthcare-associated infections*, Stockholm: ECDC, doi: 10.2900/4617.

**Figure 1: Compliance with infection prevention and control practices, by infection prevention and control domain, Kenya, 2015**



<sup>a</sup> The compliance is the proportion of indications for an infection prevention and control practice for which the corresponding action was taken. Source: Adapted from Bedoya, G. et al. (2017), 'Observations of infection prevention and control practices in primary health care, Kenya'.<sup>92</sup>

The Review also recommended that the benefits from IPC, and the potential for reducing AMR, be factored into decisions about investing in improved water and sanitation. The Sustainable Development Goals (SDGs), agreed in 2015, contain much more comprehensive and ambitious targets for water and sanitation than did the Millennium Development Goals, agreed in 2000. While progress has been made, in 2015, 2.3 billion people still lacked even a basic sanitation service and 2.1 billion lacked access to safe water.<sup>93</sup> In Africa, the proportion of people living in improved housing with adequate water and sanitation doubled between 2000 and 2015 but 50 per cent of the urban and 82 per cent of the rural population live in unimproved housing with inadequate water and sanitation.<sup>94</sup> It is difficult to measure how concerns about AMR might positively influence decisions on investments on water and sanitation. However, a recent study concluded that 'globally, a high prevalence of antimicrobial resistance can be more likely attributed to the dissemination of antimicrobial resistance, especially via poor sanitation and contaminated potable water' than to selection pressure due to high use of antibiotics.<sup>95</sup>

<sup>92</sup> Bedoya, G., Dolinger, A., Rogo, K., Mwaura, N., Wafula, F., Coarasa, J., Goicoechea, A. and Dasa, J. (2017), 'Observations of infection prevention and control practices in primary health care, Kenya', *Bulletin of the World Health Organization*, 95, pp. 503–516, <http://dx.doi.org/10.2471/BLT.16.179499>.

<sup>93</sup> World Health Organization and the United Nations Children's Fund (2017), *Progress on drinking water, sanitation and hygiene: 2017 update and SDG baselines*, Geneva: WHO/UNICEF, <https://washdata.org/sites/default/files/documents/reports/2018-01/JMP-2017-report-final.pdf>.

<sup>94</sup> Tusting, L., Bisanzio, D., Alabaster, G., Cameron, E., Cibulskis, R., Davies, M., Flaxman, S., Gibson, H. S., Knudsen, J., Mbogo, C., Okumu, F. O., von Seidlein, L., Weiss, D. L., Lindsay, S. W., Gething, P. W. and Bhatt, S. (2019), 'Mapping changes in housing in sub-Saharan Africa from 2000 to 2015', *Nature*, 568, pp. 391–394, <https://doi.org/10.1038/s41586-019-1050-5>.

<sup>95</sup> Collignon, P., Beggs, J. J., Walsh, T. R., Gandra, S. and Laxminarayan, R. (2018), 'Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis', *Lancet Planet Health*, 2, pp. 398–405, [https://doi.org/10.1016/S2542-5196\(18\)30186-4](https://doi.org/10.1016/S2542-5196(18)30186-4).

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### Conclusion

IPC measures need to be viewed in terms of their importance for public health rather than just through an AMR lens. IPC is ignored for a variety of reasons, including pressures on health professionals and the absence of basic facilities such as clean water and sanitation. IPC is not an issue just for healthcare facilities but also in the wider community, where the absence of adequate water and sanitation facilities is a primary driver of the spread of infectious diseases and hence antibiotic use. There is therefore a need for a multi-sectoral approach, including addressing the causes of infections in plants and animals, as well as humans. At the roundtable there was also a discussion of whether lenders such as the International Monetary Fund (IMF) and the World Bank should lend weight to the cause of IPC by integrating public health concerns, including combatting AMR, into their agendas and dialogue with countries. Such a dialogue would include investment in water and sanitation.

### Reducing unnecessary use in agriculture

The Review made seven sub-recommendations under this heading. A central theme was to take steps to reduce unnecessary antibiotic use in animals by setting targets at the country level, establishing targets in 2018. European countries have taken the lead in reducing unnecessary use, beginning in 2006 with the banning of the use of antibiotics in animal feed for growth promotion purposes. The latest data show that a standardized measure of antimicrobial use across all species (mg/PCU)<sup>96</sup> showed a decline of 20 per cent between 2011 and 2016 in the 25 countries reporting data. The Netherlands has been conspicuously successful in reducing antimicrobial use – consumption reduced by 64 per cent between 2010 and 2016. But the range in Europe is very wide – from 2.9 mg/PCU in Norway to 453.4 mg/PCU in Cyprus.<sup>97</sup> In the UK, consumption decreased by 48 per cent between 2013 and 2017.<sup>98</sup> These policies have been introduced with aggregate targets playing a role but also with sectoral targets that reflect the very varied characteristics of different sectors – from beef and chickens to crustaceans. One reason for the relative success in Europe is that, with the right policies, the costs to producers of transitioning to low antibiotic use can be relatively small or negligible if compensated by improvements in animal hygiene, professional veterinary advice, herd management and other relevant management activities.

In the US, significant action to reduce the use in livestock of medically important antibiotics occurred with voluntary guidance issued in 2013. This led in January 2017 to these products being withdrawn for growth promotion purposes and only being used under the supervision of a licensed veterinarian.<sup>99</sup> This was one reason why sales of antibiotics fell by 33 per cent in 2017.<sup>100</sup> The fact that such significant results have been obtained in a number of countries in relatively short periods of time suggests that this is quite low-hanging fruit in many, but not all, high-income countries.

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<sup>96</sup> Population Correction Unit: Roughly mg/PCU = mg/kg of animal.

<sup>97</sup> European Medicines Agency (2018), *Sales of veterinary antimicrobial agents in 30 European countries in 2016: Trends from 2010 to 2016*, EMA/275982/2018, London: EMA, [https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac\\_en.pdf](https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac_en.pdf).

<sup>98</sup> Veterinary Medicines Directorate (2019), *Erratum to UK Veterinary Antibiotic Resistance and Sales Surveillance Report UK-VARSS 2017*, London: VMD, [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/837180/PCDOCS-\\_1692413-v1-Erratum\\_to\\_UK-VARSS\\_2017.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/837180/PCDOCS-_1692413-v1-Erratum_to_UK-VARSS_2017.pdf) (accessed 9 Oct. 2019).

<sup>99</sup> Food and Drug Administration (n.d.), 'Veterinary Feed Directive Final Rule and Next Steps', <https://www.fda.gov/animal-veterinary/development-approval-process/fact-sheet-veterinary-feed-directive-final-rule-and-next-steps>.

<sup>100</sup> Food and Drug Administration (2018), *2017 Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, Washington DC: FDA, <https://www.fda.gov/media/119332/download>.

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A review of evidence concerning the use of antimicrobial growth promoters suggested that ‘the economic impacts of a ban on AGPs could be limited in high-income industrialized countries but potentially higher in lower-income countries with less-developed hygiene and production practices.’<sup>101</sup>

The situation is different in LMICs. In such less-regulated environments, producers are inclined to resort to antibiotics as they move to more intensive farming methods. Moreover, there is a lack of accurate information on antibiotic use or the level of AMR in animals.<sup>102</sup> One study, which acknowledges the paucity of data on which it is based and the consequently large number of assumptions necessary, has projected that global antimicrobial consumption in agriculture will rise by 67 per cent by 2030 and that it will nearly double in Brazil, Russia, India, China, and South Africa. This would be the case if consumer demand for livestock products in LMICs grows explosively as predicted, with a shift to large-scale farms, and if the routine use of antimicrobials is not further curtailed.<sup>103</sup> One of the Review’s recommendations was that a detailed economic analysis of the transition costs associated with lowering the use of antibiotics in farming should be conducted, but this analysis was not able to find any such studies. In its 2017 major report on drug-resistant infections, the World Bank noted for LMICs that there was ‘little economic research on preventive strategies such as enhanced farm biosecurity and better animal hygiene. No studies were found that assess cost-effectiveness of these different interventions.’<sup>104</sup> Because of the diversity of livestock development business models in LMICs, identifying solutions for cost-effectively reducing antibiotic use is difficult. But research, as suggested by the Review, could certainly open up new policy options. A new initiative in this area is the CGIAR Antimicrobial Resistance Hub, based at the International Livestock Research Institute (ILRI) in Kenya. Its aim is to help countries reduce and refine their antimicrobial use in crop, livestock and fish farming to help stem the rise of drug resistance.<sup>105</sup>

Regarding the recommendation about surveillance as an aid to target-setting, the OIE publishes annual data on the use of antimicrobials in animals. The latest report notes that contributions to its database have continued to grow, with increasing engagement from countries, and that the results from its third round of data collection have demonstrated a growing capacity worldwide for collection of more quantitative and better quality data.<sup>106</sup> The report advises caution in the interpretation and use of quantitative data presented and describes the reasons for uncertainty associated with the estimates presented. It notes that limitations of this analysis include quantitative data source errors, which may lead to overcounting of antimicrobial amounts by some countries new to the process of data collection. It recognizes that the challenges for many of its members in developing their capacity should not be underestimated. The main limitation of the OIE report is therefore that it presents very scarce data on antimicrobial use, often based on imports data that still need corrections. It is therefore not the kind of information that could inform target-setting as recommended by the Review.

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<sup>101</sup> Laxminarayan, R., Van Boeckel, T. and Teillant, A. (2015), ‘The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector’, *OECD Food, Agriculture and Fisheries Papers*, No. 78, Paris: OECD, <https://doi.org/10.1787/5js64kst5wvl-en>.

<sup>102</sup> Grace, D. (2015), ‘Review of evidence on antimicrobial resistance and animal agriculture in developing countries’, UK: Evidence on Demand, [https://dx.doi.org/10.12774/eod\\_cr.june2015.graced](https://dx.doi.org/10.12774/eod_cr.june2015.graced).

<sup>103</sup> Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., Teillant, A. and Laxminarayan, R. (2015), ‘Global trends in antimicrobial use in food animals’, *Proceedings of the National Academy of Sciences*, 112(18), pp. 5649–5654, <https://doi.org/10.1073/pnas.1503141112>.

<sup>104</sup> World Bank (2017), *Drug-Resistant Infections: A Threat to Our Economic Future*, Annex 10.

<sup>105</sup> CGIAR (n.d.), ‘The CGIAR AMR hub’, <https://amr.cgiar.org/about>.

<sup>106</sup> World Organisation for Animal Health (2018), *The Third OIE Annual report on the use of antimicrobial agents in animals*, Paris: OIE, [http://www.oie.int/fileadmin/Home/eng/Our\\_scientific\\_expertise/docs/pdf/AMR/Annual\\_Report\\_AMR\\_3.pdf](http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Annual_Report_AMR_3.pdf).

The Review recommended that experts in human and animal health work together to agree a single, harmonized list of those antibiotics most critical to human health. The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) reviews and updates the WHO list of critically important antimicrobials for human medicine every two years. The latest list was published in 2019.<sup>107</sup> It said that antibiotics used in animals should be selected from those that WHO has listed as being ‘least important’ to human health, and not from those the agency has classified as ‘highest priority, critically important’. Such antibiotics are often the last line, or one of a limited pool, available to treat serious bacterial infections in humans.<sup>108</sup>

WHO introduced to its Essentials Medicines List in 2017 a new classification of antibiotics with categories labelled Access, Watch and Reserve. The last group includes antibiotics that should be treated as ‘last-resort’ options, or tailored to highly specific patients and settings, when other alternatives would be inadequate or have already failed.<sup>109</sup> The OIE also publishes a list of antimicrobials of veterinary importance, following WHO’s recommendation. The latest list recommends that antibiotics of high importance in both animal and human medicine (including fluoroquinolones, third- and fourth-generation cephalosporins and colistin) only be used when strictly necessary and that their use for growth promotion be urgently prohibited.<sup>110</sup> While there has been no formal move by the Tripartite agencies to agree a harmonized list, at the request of the European Commission, the Antimicrobial Advice ad hoc Expert Group (AMEG) of the European Medicines Agency (EMA) is currently finalizing an updated classification, which takes account of the recommendations from WHO and OIE based on four categories – Avoid, Restrict, Caution and Prudence.<sup>111</sup> Although designed to be applicable to EU production conditions, it represents an effort to harmonize advice that can be used by countries to guide their domestic policies. It also needs to be recognized that these lists should be regularly updated to reflect changes in the pattern of resistance and increasing scientific knowledge. For example, the EMA changed its advice on colistin in 2016 following the identification of plasmid-mediated colistin resistance conferred by the *mcr-1* gene in 2015.<sup>112</sup>

The Review called for food producers and retailers to improve transparency regarding the use of antibiotics in food production and for agreement on standards for responsible use. Advocacy and consumer organizations play an important role here in pressuring governments and the food industry to improve the way antibiotics are used in the food chain. Since the Review, organizations such as Red Tractor, an influential quality assurance scheme in farming in the UK, have raised their standards for the use of antibiotics in line with advice from WHO and EMA.<sup>113</sup> In the US the Pew Charitable Trusts have played an important role in influencing governments and producers to reduce the unnecessary

<sup>107</sup> World Health Organization (2019), *Critically Important Antimicrobials for Human Medicine: 6th Revision 2018*, Geneva: WHO, <https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/>.

<sup>108</sup> World Health Organization (2017), *WHO guidelines on use of medically important antimicrobials in food-producing animals*, Geneva: WHO, [https://www.who.int/foodsafety/areas\\_work/antimicrobial-resistance/cia\\_guidelines/en/](https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia_guidelines/en/).

<sup>109</sup> World Health Organization (2017), *The Selection and Use of Essential Medicines*, Geneva: WHO, [https://www.who.int/medicines/publications/essentialmedicines/EML\\_2017\\_ExecutiveSummary.pdf?ua=1](https://www.who.int/medicines/publications/essentialmedicines/EML_2017_ExecutiveSummary.pdf?ua=1).

<sup>110</sup> OIE (2018), *OIE List of Antimicrobial Agents of Veterinary Importance*, Paris: OIE, [http://www.oie.int/fileadmin/Home/eng/Our\\_scientific\\_expertise/docs/pdf/AMR/A\\_OIE\\_List\\_an\\_1371\\_timicrobials\\_May2018.pdf](http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/A_OIE_List_an_1371_timicrobials_May2018.pdf).

<sup>111</sup> European Medicines Agency (2019), *Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals – Categorisation of antimicrobials*, London:EMA, [https://www.ema.europa.eu/en/documents/other/answer-request-european-commission-updating-scientific-advice-impact-public-health-animal-health-use\\_en.pdf](https://www.ema.europa.eu/en/documents/other/answer-request-european-commission-updating-scientific-advice-impact-public-health-animal-health-use_en.pdf).

<sup>112</sup> European Medicines Agency (2016), *Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health*, London: EMA, [https://www.ema.europa.eu/en/documents/scientific-guideline/updated-advice-use-colistin-products-animals-within-european-union-development-resistance-possible\\_en-0.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/updated-advice-use-colistin-products-animals-within-european-union-development-resistance-possible_en-0.pdf).

<sup>113</sup> Red Tractor (2018), ‘Red Tractor Antibiotic standards changes Q&A’, [https://assurance.redtractor.org.uk/contentfiles/Farmers-6935.pdf?\\_=636643269105341095](https://assurance.redtractor.org.uk/contentfiles/Farmers-6935.pdf?_=636643269105341095).

use of antibiotics in agriculture.<sup>114</sup> In Europe the Alliance to Save our Antibiotics brings together health, medical, farming, environmental and civil society organizations to reduce antibiotic use in agriculture.<sup>115</sup> A group of advocacy campaigners in the US has had some success in persuading some food companies to reduce antibiotic use in the food they sell, and they produce an annual report titled *Chain Reaction*. The latest report on burger chains shows there is a long way to go.<sup>116</sup> But their campaigning helped KFC pledge to end the use of medically important antibiotics in its entire US chicken supply<sup>117</sup> and McDonald's has recently announced plans to reduce antibiotic use in its beef supply chain.<sup>118</sup> Pressure from investors has also brought about significant progress in food companies' policies on antibiotics.<sup>119</sup> In the absence of global standards for responsible use, investors have developed best-practice guidance for producers and retailers and a roadmap to establish the necessary steps that food companies need to take to support responsible use.<sup>120</sup>

A group of advocacy campaigners in the US has had some success in persuading some food companies to reduce antibiotic use in the food they sell, and they produce an annual report titled *Chain Reaction*. The latest report on burger chains shows there is a long way to go.

But the progress is patchy and there have been no moves to collectively agree on standards for 'responsible use' or government action to enforce standards. However, there have been positive individual initiatives – notably China's decision to ban the use of colistin in animal feed in 2016<sup>121</sup> and India's recent decision to ban the use of colistin in agriculture.<sup>122</sup>

## Conclusion

The Review's emphasis on aggregate target-setting was criticized by some participants at the roundtable because it failed to take account of the diversity of animal species and of antibiotic use in different species, let alone plants. Moreover, the proposed timescale, with country targets being established in 2018, failed to recognize the lack of species-level data on use, on AMR levels and indeed on production systems in LMICs. Nevertheless, the fact that targets have played a significant role in the successful reduction strategies in a number of European countries suggests they could be an important element in strategies elsewhere.

<sup>114</sup> Pew (2018), 'Comprehensive Framework Is Established for Antibiotic Stewardship in Animal Agriculture', <https://www.pewtrusts.org/en/research-and-analysis/articles/2018/12/17/comprehensive-framework-is-established-for-antibiotic-stewardship-in-animal-agriculture>.

<sup>115</sup> Alliance to Save our Antibiotics (n.d.), <http://saveourantibiotics.org/our-campaign/>.

<sup>116</sup> US Public Interest Research Group (2018), 'Chain Reaction IV. How Top Restaurants Rate on Reducing Antibiotic Use in Their Meat Supply Chains', <https://usp.org/feature/usp/chain-reaction>.

<sup>117</sup> Natural Resource Defense Council (2019), 'KFC: Mission Accomplished on Antibiotics', <https://www.nrdc.org/experts/lena-brook/kfc-mission-accomplished-antibiotics>.

<sup>118</sup> *Guardian* (2018), 'McDonald's to curb use of antibiotics in its beef supply', 12 December 2018, <https://www.theguardian.com/business/2018/dec/12/mcdonalds-to-curb-use-of-antibiotics-in-its-beef-supply>.

<sup>119</sup> FAIRR (2019), 'Improving antibiotics stewardship in livestock supply chains', <https://cdn.fairr.org/2019/05/19194214/FAIRR-antibiotics-engagement-update.pdf>.

<sup>120</sup> FAIRR (2018), 'Best Practice Policy on Antibiotic Stewardship', <https://cdn.fairr.org/wp-content/uploads/sites/5/2018/10/03164107/FAIRR-Template-Antibiotics-Policy-final.pdf>.

<sup>121</sup> Walsh, T. and Wu, Y. (2016), 'China bans colistin as a feed additive for animals', *Lancet Infectious Diseases*, 16(10), pp. 1102–1103, [https://doi.org/10.1016/S1473-3099\(16\)30329-2](https://doi.org/10.1016/S1473-3099(16)30329-2).

<sup>122</sup> Government of India (2019), 'Notification', 19 July 2019, [https://www.greengazette.in/documents/government-gazette-2377-2019-ii3ii-e\\_20190719-232-02377.pdf](https://www.greengazette.in/documents/government-gazette-2377-2019-ii3ii-e_20190719-232-02377.pdf).

A major gap in developing effective strategies to reduce unnecessary use in agriculture is the lack of accurate data on antibiotic use and on AMR, without which target-setting is redundant. Therefore, a priority should be to improve surveillance systems and undertake more research, including on how to promote the transition to lower antibiotic use in LMICs.

Consumer groups and others have played an important role in addressing unnecessary antibiotic use in the food chain.

Where voluntary approaches are inadequate to promote changes on the scale required, governments could play a greater role by setting mandatory standards for antibiotic use in animals and plants. However, standards are only as effective as the enforcement system. The OIE report discussed earlier shows that many LMICs report having insufficient or non-existent regulatory systems to address antibiotic use in agriculture. For those LMICs that are exporters of animal products, regimes in importing countries can be an important influence on production practices and antibiotic use. Namibia, a major beef exporter, banned the use of hormones and antibiotics for growth promotion in the beef industry as long ago as 1991, presumably to bolster its export credentials.<sup>123</sup>

### Reducing dissemination in the environment

The Review referred to the issue of antimicrobials in the environment that come from animal, human and manufacturing waste. It noted that, depending on the antimicrobial class, a significant part of the antimicrobials consumed by humans and animals might be excreted unmetabolized – so measures to reduce unnecessary use needed to be a key factor in reducing contamination of the environment. Effluent from hospitals, as major users of antibiotics, was a particular cause for concern. However, the Review decided to focus its attention on manufacturing waste. It referred to existing research concerning the impact of antibiotic discharges and the possible link to exacerbating AMR.<sup>124</sup> Since then, further research has highlighted the extent of the problem in India as well as elsewhere.<sup>125</sup>

There is little evidence that governments or regulators have sought to introduce measures to enforce limits on discharges. In general, environmental pollution does not feature in regulations relating to Good Manufacturing Practice (GMP) for pharmaceuticals, such as those promoted by WHO. However, in 2019, WHO published for consultation draft guidance on incorporating environmental considerations into GMP procedures, with a specific focus on AMR.<sup>126</sup> The EU considered introducing such regulations in 2018 but appears to have pulled back following pressure from the pharmaceutical industry.<sup>127</sup>

<sup>123</sup> World Health Organization (2017), 'Namibia's ban on antibiotics in healthy animals drives meat exports', 14 November 2017, <https://www.who.int/news-room/feature-stories/detail/namibia-s-ban-on-antibiotics-in-healthy-animals-drives-meat-exports>.

<sup>124</sup> Fick, J., Söderström, H., Lindberg, R. H., Phan, C., Tysklind, M. and Larsson D. G. J. (2009), 'Contamination of surface, ground, and drinking water from pharmaceutical production', *Environ Toxicol Chem*, 28, pp. 2522–2527, doi:10.1897/09-073.1.

<sup>125</sup> Thai, K. P., Ky, L. X., Binh, V. N., Nhung, P. H., Nhan, P. T., Hieu, N. Q., Dang, N. T. T., Tam, N. K. B. and Anh, N. T. K. (2018), 'Occurrence of antibiotic residues and antibiotic-resistant bacteria in effluents of pharmaceutical manufacturers and other sources around Hanoi, Vietnam', *Science of The Total Environment*, 645, pp. 393–400, <https://doi.org/10.1016/j.scitotenv.2018.07.126>.

<sup>126</sup> World Health Organization (2019), *Environmental aspects of Good Manufacturing Practices: Points to consider for manufacturers and inspectors in the prevention of antimicrobial resistance*, Geneva: WHO, [https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/qas19\\_802\\_environmental\\_aspects\\_of\\_GMP.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/qas19_802_environmental_aspects_of_GMP.pdf?ua=1).

<sup>127</sup> *Guardian* (2018), 'Antibiotic apocalypse: EU scraps plans to tackle drug pollution, despite fears of rising resistance', 1 June 2018, <https://www.theguardian.com/environment/2018/jun/01/antibiotic-apocalypse-eu-scraps-plans-to-tackle-drug-pollution-despite-fears-of-rising-resistance>.

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Early in 2018, the AMR Industry Alliance agreed on a voluntary framework that promotes responsible antibiotic manufacturing and in September 2018 published a list of discharge targets to guide environmental risk assessments for the manufacture of antibiotics.<sup>128</sup>

There has therefore been some progress in addressing pharmaceutical discharges on a voluntary basis – notably in the work of the AMR Industry Alliance. A review in 2018 by the Access to Medicines Foundation found that, while 15 out of 18 companies had some form of environmental risk-management strategy aiming to minimize the impact of antibiotics discharged from manufacturing processes, only eight applied limits on factory discharges but none of them made available data on actual discharges. Moreover, only four firms extended these limits to third-party manufacturers (e.g. of active pharmaceutical ingredients (APIs)).

With regard to monitoring, some companies say they monitor discharges, but the data are not made public. In general, industry was not transparent about the measures they were taking (or not taking) in their supply chains to reduce discharges or in revealing the source of their APIs.<sup>129</sup> However, trying to increase transparency requirements on a voluntary basis could discourage companies from joining the Alliance. In the absence of government regulations, the voluntary approach will always have difficulty in recruiting manufacturers who are competing on price in a competitive market. As far as is known, only one country, India, has announced its intention to ‘develop standards for antibiotic residues in industrial effluents’ in its national AMR action plan.<sup>130</sup>

The roundtable concluded that ‘consumers’ – in this case those bodies procuring antibiotics that could appropriately reward (including with higher prices) suppliers who met quality criteria (including on discharges) – could also play a role. On the other hand, there was some concern that because the suppliers of active ingredients (APIs) were highly concentrated in India and, particularly, China, too stringent an application of criteria could cause problems in the fragile supply chain for several antibiotics. However, a procurement system that rewards companies that fulfil given environmental criteria (point system) but does not exclude companies that do not, would mitigate this risk. It was proposed that incentivizing systems could be implemented during the procurement of antibiotics (e.g. by hospitals) and by revising generic substitution systems present in many countries where low cost is usually the main criterion for substitution. It was thought that amending environmental criteria along these lines would reduce the current disincentives for manufacturers to invest in pollution control. Revising the GMP framework to incorporate emission targets is worth pursuing but it would likely be a slow process. Legally binding emission limits should be encouraged based on the actual effluent rather than the impact on the recipient of the discharge.

In terms of the wider impact of environmental sources of AMR there is much that is not known about the relative contributions of different sources of antibiotics and resistant bacteria in the environment; the role of the environment, and human impacts thereon, in the evolution of resistance; the overall human and animal health impacts caused by exposure to environmental resistant bacteria; and the

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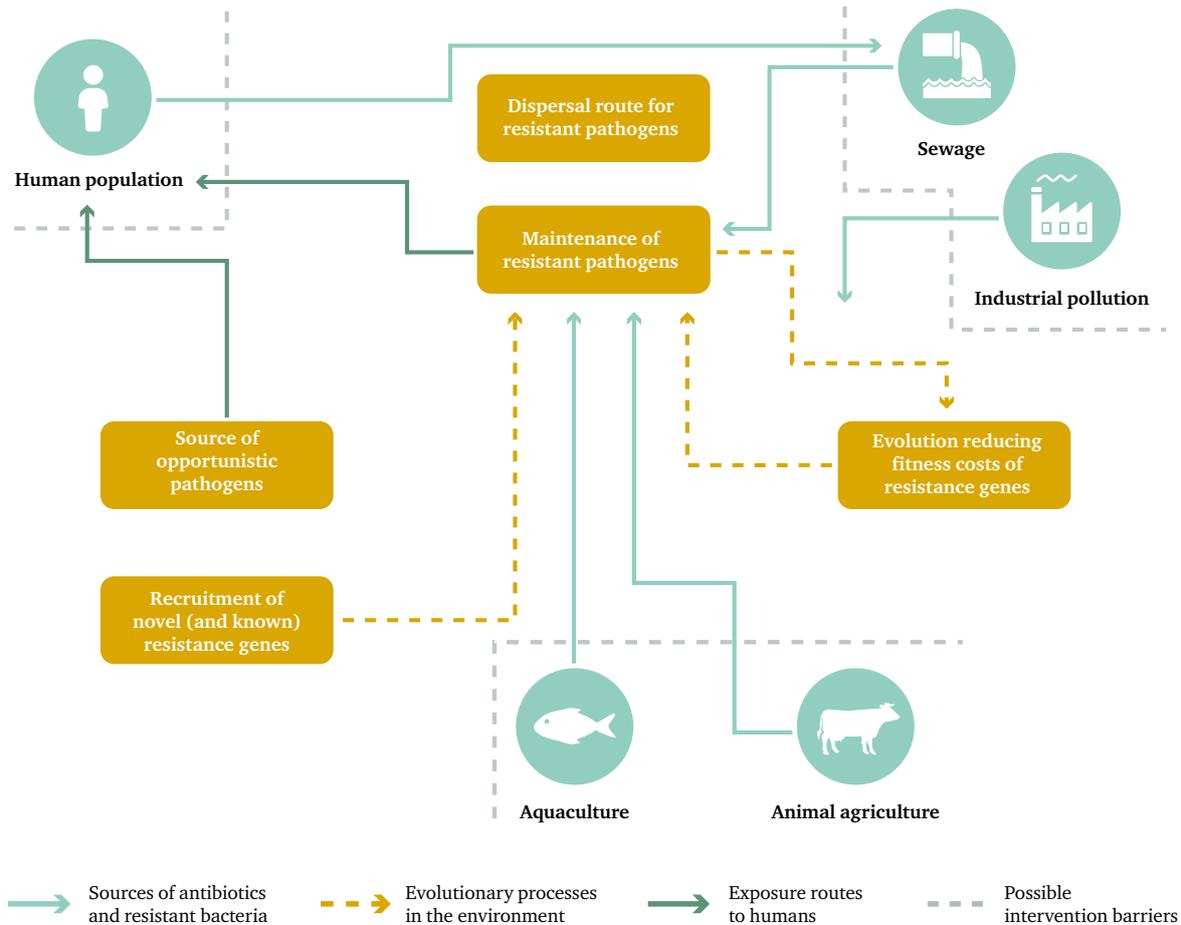
<sup>128</sup> AMR Industry Alliance (2018), ‘AMR Industry Alliance Antibiotic Discharge Targets’, <https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/>.

<sup>129</sup> Access to Medicines Foundation (2018), *Antimicrobial Resistance Benchmark 2018*, Amsterdam: ATMF, [https://accessmedicinefoundation.org/media/uploads/downloads/5bc5edd8367eb\\_Antimicrobial-Resistance-Benchmark-2018.pdf](https://accessmedicinefoundation.org/media/uploads/downloads/5bc5edd8367eb_Antimicrobial-Resistance-Benchmark-2018.pdf).

<sup>130</sup> Government of India (2017), *National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017–2021*, [http://www.searo.who.int/india/topics/antimicrobial\\_resistance/nap\\_amr.pdf](http://www.searo.who.int/india/topics/antimicrobial_resistance/nap_amr.pdf).

efficacy and feasibility of different technological, social, economic and behavioural interventions that could mitigate environmental antibiotic resistance.<sup>131</sup> One example of the latter is the challenges in removing antibiotics and resistant bacteria from wastewater and sewage.

Figure 2: The roles of the environment in antibiotic resistance development



Source: Adapted with permission from Larsson, D. G. J. et al. (2018), 'Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance'.

In 2017, UN Environment issued a report highlighting the presence of antimicrobials and resistant bacteria in the environment as one of six issues of major environmental concern.<sup>132</sup> Since then, efforts have been made to include UN Environment more closely in the work of the Tripartite agencies. In 2018 it was announced that UN Environment would formally join the Tripartite (to form what is known as the Tripartite Plus) and the role of the Tripartite plus UN Environment was emphasized in the 2019 IACG report. A joint workplan is reportedly being prepared.<sup>133</sup>

<sup>131</sup> Larsson, D. G. J., Andremont, A., Bengtsson-Palme, J., Brandt, K. K., de Roda Husman, A. M., Fagerstedt, P., Fick, J., Flach, C. F., Gaze, W. H., Kuroda, M., Kvint, K., Laxminarayan, R., Manaia, C. M., Nielsen, K. M., Plant, L., Ploy, M. C., Segovia, C., Simonet, P., Smalla, K., Snape, J., Topp, E., van Hengel, A. J., Verner-Jeffreys, D. W., Virta, M. P. J., Wellington, E. M. and Wernersson, A. S. (2018), 'Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance', *Environment International*, 117, pp. 132–138, DOI: 10.1016/j.envint.2018.04.041.

<sup>132</sup> UN Environment (2017), *Frontiers 2017 Emerging Issues of Environmental Concern*, Nairobi: UNEP, [https://wedocs.unep.org/bitstream/handle/20.500.11822/22255/Frontiers\\_2017\\_EN.pdf?sequence=1&isAllowed=y](https://wedocs.unep.org/bitstream/handle/20.500.11822/22255/Frontiers_2017_EN.pdf?sequence=1&isAllowed=y).

<sup>133</sup> World Health Organization (2018), 'Tripartite Plus: Recent update and Memorandum of Understanding on Antimicrobial Resistance', Presentation: 1 October 2018, [https://www.who.int/antimicrobial-resistance/interagency-coordination-group/Tripartite\\_Plus\\_update\\_info\\_session\\_011018.pdf](https://www.who.int/antimicrobial-resistance/interagency-coordination-group/Tripartite_Plus_update_info_session_011018.pdf).

## Conclusion

There has been some progress in addressing pharmaceutical discharges on a voluntary basis, but the evidence suggests that much more needs to be done to bring about enforceable limits, and that ultimately statutory measures may be necessary.

There is much uncertainty about the impact of antibiotic-resistant bacteria and genes in the environment, the relationship with the development of AMR and therefore the priorities for addressing the problem in ways that would maximize the impact on AMR. Moreover, there is a lack of proven technologies that are known to be feasible and cost-effective in preventing the entry of antibiotics into the environment, and in their removal from the environment. Under these circumstances, it is probably most effective to promote measures that address known hotspots such as hospitals or manufacturing plants and to continue to investigate the complexities of the environmental spread of AMR with a view to identifying the priorities and cost-effective mechanisms for mitigating the threat.

## Improve global surveillance of drug resistance in humans and animals

The Review asked WHO to provide global leadership and coordination to efforts to improve surveillance of drug-resistant infections. Launched in October 2015, the Global Antimicrobial Resistance Surveillance System (GLASS) is being developed to support the global action plan on antimicrobial resistance. The aim is to improve global surveillance of AMR in humans in order to strengthen the evidence base on AMR and to help inform decision-making and drive national, regional and global actions. The first report on its implementation reveals good progress but also many challenges in establishing a global surveillance system to monitor the emergence and spread of drug-resistant infections. As of December 2018, 71 countries were enrolled in GLASS, participation in which is voluntary. According to the UN progress report there are 106 countries with national surveillance systems but only 29 are in LMICs.<sup>134</sup> However, there are many issues concerning the quality and coverage of data and there are methodological as well as practical challenges in generating representative AMR data in ways that could enable comparisons between countries.<sup>135</sup> A recent comprehensive study of surveillance networks in LMICs concluded that case-based surveillance could be implemented in middle-income countries but that obtaining representative data would take time. In low-income countries, it would be many more years before most would have a well-functioning system for routine bacteriological surveillance with high coverage. This raises the risk of generating non-representative data in the short- to medium-term and makes inter-country comparisons difficult.<sup>136</sup>

In Europe, data are collected by the ECDC through the European Antimicrobial Resistance Surveillance Network (EARS-Net). Its latest report indicates that, despite the political prioritization of AMR as a threat to public health and the availability of evidence-based guidance for antimicrobial stewardship and IPC, high levels of resistance remain for several bacterial species–antimicrobial group combinations. Inter-country variations suggest there is scope for significant reductions

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<sup>134</sup> United Nations (2019), *Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*.

<sup>135</sup> World Health Organization (2019), *Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early implementation*, Geneva: WHO, <https://apps.who.int/iris/bitstream/handle/10665/279656/9789241515061-eng.pdf?ua=1>.

<sup>136</sup> Ashley, E., Recht, J., Chua, A., Dance, D., Dhorda, M., Thomas, N. V., Ranganathan, N., Turner, P., Guerin, P. J., White, N. J. and Day, N. P. (2018), 'An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000', *Journal of Antimicrobial Chemotherapy*, 73(7), pp. 1737–1749, <https://doi.org/10.1093/jac/dky026>.

in antimicrobial resistance in many countries through strengthening of current best practice.<sup>137</sup> Another initiative is the epidemiology network (EPI-Net), which brings together diverse expertise to strengthen data collection modelling and analysis and aims to optimize surveillance of resistance and healthcare-associated infections across Europe, covering both humans and animals.<sup>138</sup>

The benefits of adopting a One Health approach to surveillance were frequently noted at the roundtable, including the use of joined-up training for techniques used commonly for surveillance in humans, animals and the environment. It was also noted with respect to AMR surveillance that screening sewage (which contains material from large numbers of people) on a regular basis could also be a cost-effective way of detecting emerging or rare forms of resistance in a region, country, city or hospital.<sup>139</sup>

The Fleming Fund was established in 2015 to support countries generating the data they need to inform policies and practices that will optimize the use of antimicrobial medicines. It funds a range of initiatives in LMICs with the aim of increasing the quantity and quality of data available to better understand the scale and scope of AMR and how to combat it. It is the biggest single funder of surveillance activities in LMICs and is now involved with 24 countries, but building surveillance capacity in LMICs is, as illustrated also by the experience of GLASS, a slow process where both the human and technical infrastructure need to be built up, so it will take considerable time to show results in terms of improved data on AMR.<sup>140</sup>

The Review also recommended that measures be adopted to promote the sharing of data between public and private organizations. The question of how to access and incorporate surveillance data from the private sector is also an important one. Nearly half of pharmaceutical companies with products on the market are involved in AMR surveillance.<sup>141</sup> Wellcome has created an open AMR Register (a pilot study in partnership with the Open Data Institute<sup>142</sup>) that will make data on industry surveillance programmes publicly available and run a data re-use prize competition to promote re-use of industry surveillance data to inform public health activities.<sup>143</sup> Wellcome has also established a consortium, the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC). SEDRIC is a global think-tank with the aim of supporting access to data and fostering coordination between countries and surveillance networks. It has established international working groups to analyse gaps and barriers in data sharing and find potential solutions. It aims to transform the way countries are able to track, share and analyse information about the rise and spread of drug-resistant infections. It seeks to identify the critical gaps in, and barriers to, the surveillance of drug-resistant infections, and how these can be overcome at a national and global level; to provide technical expertise and knowledge to strengthen and support existing surveillance networks and activities, and to improve global co-ordination by

<sup>137</sup> ECDC (2018), *Surveillance of antimicrobial resistance in Europe 2017*, Stockholm: ECDC, <https://www.ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf>.

<sup>138</sup> EPI-Net (n.d.), 'About EPI-Net', <https://epi-net.eu/about/>.

<sup>139</sup> Hendriksen, R. S., Munk, P., Njage, P., van Bunnik, B., McNally, L., Lukjancenko, O., Röder, T., Nieuwenhuijse, D., Pedersen, S. K., Kjeldgaard, J., Kaas, R. S., Clausen, P. T. L. C., Vogt, J. K., Leekitcharoenphon, P., van de Schans, M. G. M., Zuidema, T., de Roda Husman, A. M., Rasmussen, S., Petersen, B., Global Sewage Surveillance project consortium, Amid, C., Cochrane, G., Sicheritz-Ponten, T., Schmitt, H., Alvarez, J. R. M., Aidara-Kane, A., Pamp, S. J., Lund, O., Hald, T., Woolhouse, M., Koopmans, M. P., Vigre, H., Petersen, T. N. and Aarestrup, F. M. (2019), 'Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage', *Nature Communications*, 10: Article Number: 1124, [doi.org/10.1038/s41467-019-08853-3](https://doi.org/10.1038/s41467-019-08853-3).

<sup>140</sup> The Fleming Fund (n.d.), 'About the Fleming Fund', <https://www.flemingfund.org/about-us/>.

<sup>141</sup> Access to Medicines Foundation (2018), *Antimicrobial Resistance Benchmark 2018*.

<sup>142</sup> Open Data Institute (n.d.), 'Antimicrobial resistance and data', <https://theodi.org/project/antimicrobial-resistance/>.

<sup>143</sup> Wellcome (2019), 'New data re-use prizes help unlock the value of research', 25 April 2019, <https://wellcome.ac.uk/news/new-data-re-use-prizes-help-unlock-value-research>.

helping countries adopt common and sustainable best practices and strategies.<sup>144</sup> The consortium includes members from many LMICs spanning all continents.

There is a plan to incorporate AMR data in the Global Burden of Disease programme of the Institute for Health Metrics and Evaluation (IHME).<sup>145</sup> However, a recent review of the data and methodologies used to generate previous estimates of the AMR burden, including the work commissioned by the AMR Review, concluded that a new approach to the estimation of deaths caused by AMR infection was needed and that this would also require the development of much better systematic mechanisms to collect a clinical dataset of substantial breadth and quality to support the accurate assessment of burden.<sup>146</sup>

An area of concern raised at the roundtable was that the difficulties of generating reliable data meant that physicians or veterinarians had little confidence in the data, even where it existed. In light of these difficulties, the view was expressed that surveillance activities focused on antimicrobial consumption were equally important. Surveillance of use could possibly feed more swiftly and cost-effectively into influencing clinical practice and stewardship in the use of AMR.<sup>147</sup>

As noted, the OIE is collecting data on antibiotic use in animals and WHO has begun work on monitoring human consumption. A recent WHO report presents data on consumption in 65 countries where estimated consumption ranged from 4.4 (Burundi) to 64.4 (Mongolia) Defined Daily Doses (DDDs) per 1,000 inhabitants per day. However, the report notes that the data may not include sales in the private or informal sector, which means that consumption may be underestimated and that inter-country comparisons may reflect variations in data capture as much as variations in consumption. There is a long way to go to get reliable standardized information on consumption in LMICs.<sup>148</sup> In Europe, antibiotic consumption has been monitored in humans since 2001 and in animals since 2009 (see earlier). The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) and ECDC publish an annual report on human consumption. In 2017, the average total consumption in 27 countries (community and hospital sector) of antibacterials was 23.4 DDDs per 1,000 inhabitants per day, ranging from 11.0 in the Netherlands to 34.1 in Spain. More than 90 per cent of consumption was in the community rather than in hospitals.<sup>149</sup>

## Conclusion

Building up effective surveillance systems for both humans and animals that provide data relevant to clinical practice and research is a challenge, even in high-income countries.<sup>150</sup> Such efforts

<sup>144</sup> Wellcome (n.d.), 'Surveillance and Epidemiology of Drug-resistant Infections Consortium', <https://wellcome.ac.uk/what-we-do/our-work/surveillance-and-epidemiology-drug-resistant-infections-consortium>.

<sup>145</sup> Hay, S. I., Rao, P. C., Dolecek, C., Day, N. P. J., Stergachis, A., Lopez, A. D. and Murray, C. J. L. (2018), 'Measuring and mapping the global burden of antimicrobial resistance', *BMC Medicine*, 16: Article Number: 78, doi: 10.1186/s12916-018-1073-z.

<sup>146</sup> Limmathurotsakul, D., Dunachie, S., Fukuda, K., Feasey, N. A., Okeke, I. N., Holmes, A. H., Moore, C. E., Dolecek, C., van Doorn, H. R., Shetty, N., Lopez, A. D. and Peacock, S. J., Surveillance and Epidemiology of Drug Resistant Infections Consortium (SEDRIC) (2019), 'Improving the estimation of the global burden of antimicrobial resistant infections', *Lancet Infect Dis*, 16 August 2019, [http://dx.doi.org/10.1016/S1473-3099\(19\)30276-2](http://dx.doi.org/10.1016/S1473-3099(19)30276-2).

<sup>147</sup> Versporten, A., Zarb, P., Caniaux, I., Gros, M. F., Drapier, N., Miller, M., Jarlier, V., Nathwani, D. and Goossens, H., on behalf of the Global-PPS network (2018), 'Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey', *Lancet Glob Health*, 6(6), pp. 619–29, doi.org/10.1016/S2214-109X(18)30186-4; Limmathurotsakul, D., Sandoe, J. A. T., Barrett, D. C., Corley, M., Hsu, L. Y., Mendelson, M., Collignon, P., Laxminarayan, R., Peacock, S. J. and Howard, P. (2019), 'Antibiotic footprint' as a communication tool to aid reduction of antibiotic consumption', *J Antimicrob Chemother*, 74(8), pp. 2122–2127, <https://doi.org/10.1093/jac/dkz185>.

<sup>148</sup> World Health Organization (2018), *WHO Report on Surveillance of Antibiotic Consumption 2016 – 2018: Early implementation*, Geneva: WHO, [https://www.who.int/medicines/areas/rational\\_use/oms-amr-amc-report-2016-2018/en/](https://www.who.int/medicines/areas/rational_use/oms-amr-amc-report-2016-2018/en/).

<sup>149</sup> ECDC (2018), *Antimicrobial consumption Annual Epidemiological Report for 2017*, Stockholm: ECDC, [https://www.ecdc.europa.eu/sites/portal/files/documents/AER\\_for\\_2017-antimicrobial-consumption.pdf](https://www.ecdc.europa.eu/sites/portal/files/documents/AER_for_2017-antimicrobial-consumption.pdf).

<sup>150</sup> Tacconelli, E., Sifakis, F., Harbarth, S., Schrijver, R., van Mourik, M., Voss, A., Sharland, M., Rajendran, N. B. and Rodríguez-Baño, J. on behalf of the EPI-Net COMBACTE-MAGNET Group (2018), 'Surveillance for control of antimicrobial resistance', *The Lancet Infectious Diseases*, 18(3), pp. 99–106. [https://doi.org/10.1016/S1473-3099\(17\)30485-1](https://doi.org/10.1016/S1473-3099(17)30485-1).

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need to continue. Surveillance is critical to the fight against AMR – without surveillance, efforts to combat AMR are essentially flying blind. Surveillance provides data for action. Effective surveillance systems are needed to provide the evidence base upon which treatment guidelines and national, regional and global strategies can be developed. It is also through these systems that the impact of interventions can be measured. Much more effort and funding are needed to address root causes of ineffective surveillance systems, such as the shortage of laboratory professionals and technicians to increase coverage, the lack of quality assurance systems to ensure proficiency, and insufficient use of digital technologies and artificial intelligence to translate surveillance data into clinical decision-support tools for patient management.

There is also a need to strengthen systems for monitoring use in humans and animals. Several monitoring programmes on human antibiotic consumption have been launched in high-income countries and LMICs, by the ECDC, CDC and WHO, but different numerators and denominators are used to express antibiotic use in outpatients and inpatients, and there is a need to standardize the methods and indicators. There is much more work to be done in generating data on antibiotic use in agriculture in LMICs. As noted earlier, much work remains to be done on surveillance and understanding of AMR in the wider environment.

### Promote new rapid diagnostics to cut unnecessary use

The Review recommended that, in high-income countries, incentives should be provided to facilitate the mandatory use by 2020 of diagnostic tests where they are available (or the use of epidemiological data where tests are not available).

The use of diagnostics in primary and secondary care depends on the availability of diagnostics that are affordable and accessible, that can be used at the point of care (POC) and that can rapidly determine antimicrobial susceptibility. A major problem is that, while there has been some progress such as the use of C-reactive protein (CRP) and procalcitonin (PCT) to help distinguish between viral and bacterial infections, for the most part there is no diagnostic test that meets the desirable target product profile that would enable prescribers to avoid empirical prescribing.<sup>151</sup> Therefore, incentives to facilitate mandatory use of tests are secondary to the issue of their availability.

**There is no diagnostic test that meets the desirable target product profile that would enable prescribers to avoid empirical prescribing. Therefore, incentives to facilitate mandatory use of tests are secondary to the issue of their availability.**

There has been a renewed impetus to develop POC rapid diagnostics, which are needed to avoid the unnecessary use of antibiotics. In 2018, the Foundation for Innovative New Diagnostics (FIND) announced a new strategy to combat AMR with a foreword by Jim O'Neill.<sup>152</sup> In 2013, the Longitude

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<sup>151</sup> Dittrich, S., Tadesse, B. T., Moussy, F., Chua, A., Zorzet, A., Tängdén, T., Dolinger, D. L., Page, A. L., Crump, J. A., D'Acremont, V., Bassat, Q., Lubell, Y., Newton, P. N., Heinrich, N., Rodwell, T. J. and González, I. J. (2016), 'Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus', *PLoS ONE*, 11(8), <https://doi.org/10.1371/journal.pone.0161721>; Dailey, P., Osborn, J., Ashley, E. A., Baron, E. J., Dance, D. A. B., Fusco, D., Fanello, C., Manabe, Y. C., Mokomane, M., Newton, P. N., Tessema, B., Isaacs, C. and Dittrich, S. (2019), 'Defining System Requirements for Simplified Blood Culture to Enable Widespread Use in Resource-Limited Settings', *Diagnostics*, 9(10), <https://doi.org/10.3390/diagnostics9010010>.

<sup>152</sup> Foundation for Innovative New Diagnostics (2018), *Accelerating diagnostic use to prevent antimicrobial resistance. AMR Strategy 2018*, Geneva: FIND, <https://www.finddx.org/wp-content/uploads/2018/04/FIND-AMR-Strategy-WEB.pdf>.

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Prize of £10 million was announced in the UK for the development of new diagnostics.<sup>153</sup> In 2014, the US announced a similar \$20 million prize.<sup>154</sup> Neither prize has yet been awarded. The EU Horizon 2020 prize of €1 million for reducing inappropriate use of antibiotics for respiratory infections was awarded in 2017 but the test has still not been commercialized.<sup>155</sup>

A key problem in diagnostics development is the disconnect in the marketplace between the innovators – mainly small and medium enterprises (SMEs) – and the clinicians and payers who constitute the market for diagnostics. Clinicians are reluctant to use diagnostics, even if available, for a number of reasons, including time pressure, mistrust of results, risk aversion and cost.<sup>156</sup> Products are being developed but there is no clear pathway to their use. For example, the recently published UK plan notes:

In the UK, we do not make the best use of available diagnostic tests. For example, our regulatory requirements for diagnostics make it difficult to assess the value of any new diagnostic test to the overall AMR agenda: if a new promising diagnostic came out tomorrow, the NHS is not equipped to get it into front-line use quickly.

The target set for diagnostic use is to 'be able to report on the percentage of prescriptions supported by a diagnostic test or decision-support tool by 2024'.<sup>157</sup>

There is therefore a need to build demand in the healthcare system in ways that would guide developers to produce tests that would be used by clinicians and generate commensurate health benefits as well as revenues. The current access pathway from diagnostics research and development through regulatory approval and policy development for implementation of novel diagnostics in many countries is complex and lengthy, as it is plagued by numerous barriers, duplication and fragmentation. Furthermore, regulatory systems for approval of diagnostic tests are complex, lack clarity and are not harmonized between countries, unlike what has happened to some extent in the regulation of medicines. New paradigms are urgently needed for regulatory authorities, policymakers and experts to jointly assess risks and benefits and determine the value of a novel diagnostic test not only for patient management but for combating the global AMR crisis. Roadmaps should be developed for new technologies that meet real clinical needs as well as educational programmes to teach prescribers when and how to use diagnostics.

The lack of a secure market for new diagnostic tests also affects the ability of developers to attract the funds necessary to bring products to market, for example from venture capital funds. Moreover, purchasing in health systems is often fragmented, making market access even more difficult. Additional pull mechanisms, including new procurement models to support innovative diagnostics that would have an impact on AMR, are urgently required.

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<sup>153</sup> Longitude Prize (n.d.), 'About the prize', <https://longitudeprize.org/about-us/about-prize>.

<sup>154</sup> National Institutes of Health (n.d.), 'Antimicrobial Resistance Diagnostic Challenge', <https://dpcpsi.nih.gov/AMRChallenge>.

<sup>155</sup> European Union (n.d.), 'Horizon prize for better use of antibiotics', [https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/prizes/horizon-prizes/better-use-antibiotics\\_en](https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/prizes/horizon-prizes/better-use-antibiotics_en).

<sup>156</sup> Wellcome (2016), *Four diagnostic strategies for better-targeted antibiotic use*, London: Wellcome, <https://wellcome.ac.uk/sites/default/files/diagnostic-strategies-for-better-targeted-antibiotic-use-wellcome-jul15.pdf>.

<sup>157</sup> HM Government (2019), *Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan*, London: HMG, [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/784894/UK\\_AMR\\_5\\_year\\_national\\_action\\_plan.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf).

### Box 5: VALUE-Dx

VALUE-Dx was launched in April 2019 to transform medical practice to achieve more personalized, evidence-based antibiotic prescription and use in community-care settings through the widespread use of clinical and cost-effective innovative diagnostic strategies. VALUE-Dx is co-funded by the European Commission, IMI, Wellcome and diagnostics companies until March 2023. It is a Europe-wide initiative to generate evidence on the medical, economic and public health value of diagnostics in tackling AMR. It will focus on acute respiratory tract infections acquired in community-care settings, as they are the most frequent cause of medical consultation and inappropriate antibiotic use. The outcomes of VALUE-Dx could apply to other common infections such as urinary tract infections, blood stream infections, and hospital-acquired respiratory tract infections.<sup>158</sup>

For LMICs the Review recommended providing a 'diagnostic market stimulus' – a per-unit subsidy to diagnostic test manufacturers upon evidence of their product's purchase or use. This echoes the Advance Market Commitment for pneumococcal vaccines that Gavi, the Vaccine Alliance (Gavi), established in 2008. No attempt has been made to implement such a system. However, CARB-X – the Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator – has recently opened a funding round for new diagnostics.<sup>159</sup>

## Conclusion

There is a multitude of barriers that limit the use of diagnostics and hinder the development of new ones. This applies in countries at all income levels but is particularly acute in the case of LMICs. The problem therefore must be addressed on several different levels if new diagnostics are to be developed and used. An important overriding barrier is the lack of a viable market. Following the model of Gavi or the Global Fund, organizations such as UNITAID, which already works to stimulate the development of diagnostics for tuberculosis and HIV, could extend this work to cover other antimicrobials and antibiotics and help create markets.

## Promote the development and use of vaccines and alternatives

The Review recommended measures to promote the use of existing vaccines in humans and animals and to sustain a viable market for vaccines with the greatest potential for tackling drug resistance. It also recommended that incentives be provided for alternative or non-traditional approaches to infectious disease prevention and treatment.

There has been considerable activity directed at enhancing the role of vaccines in combatting AMR. These include a Chatham House workshop,<sup>160</sup> a Wellcome report,<sup>161</sup> the formation of a working group at WHO (VAC-AMR)<sup>162</sup> as well as contributions from academics and industry.<sup>163</sup>

<sup>158</sup> BioMérieux (2019), 'University of Antwerp, bioMérieux, and Wellcome Trust to coordinate VALUE-Dx, a European Public-Private Partnership to fight antimicrobial resistance through diagnostics', 2 April 2019, <https://www.biomerieux-usa.com/university-antwerp-biomerieux-wellcome-trust-coordinate-value-dx-fight-antimicrobial-resistance-through-diagnostics>.

<sup>159</sup> CARB-X (2019), 'CARB-X launches new funding rounds to support the development of antibiotics, vaccines, diagnostics and other life-saving products that target drug-resistant bacteria', <https://carb-x.org/carb-x-news/carb-x-launches-new-funding-rounds-to-support-the-development-of-antibiotics-vaccines-diagnostics-and-other-life-saving-products-that-target-drug-resistant-bacteria/>.

<sup>160</sup> Clift, C. and Salisbury, D. (2017), 'Enhancing the role of vaccines in combatting antimicrobial resistance', *Vaccine*, 35(48), Part B, pp. 6591–6593, <https://doi.org/10.1016/j.vaccine.2017.09.053>.

<sup>161</sup> Boston Consulting Group, Wellcome (2019), *Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities*, London: BCG/Wellcome, <https://vaccinesforamr.org/read-the-report/>.

<sup>162</sup> World Health Organization (2019), 'Value Attribution Framework for Vaccines against Antimicrobial Resistance', Presentation on 3 July 2019, [https://www.who.int/immunization/research/meetings\\_workshops/5\\_Hasso\\_Prudden\\_AMR\\_PDVAC\\_2019.pdf?ua=1](https://www.who.int/immunization/research/meetings_workshops/5_Hasso_Prudden_AMR_PDVAC_2019.pdf?ua=1).

<sup>163</sup> Bloom, D. E., Black, S., Salisbury, D. and Rappuoli, R. (2018), 'Antimicrobial resistance and the role of vaccines', *Proceedings of the National Academy of Sciences*, 115(51), pp. 12868–12871, <https://doi.org/10.1073/pnas.1717157115>.

Gavi, the Vaccine Alliance, has incorporated the impact on AMR as a criterion in compiling its latest investment strategy.<sup>164</sup> The Review quoted the estimated large reduction of antibiotic use that could occur with universal coverage of pneumococcal conjugate vaccine (PCV). Additional candidates that might have a particular impact on AMR by averting future antibiotic treatment include vaccines for seasonal influenza<sup>165</sup> and typhoid,<sup>166</sup> as well as respiratory syncytial virus<sup>167</sup> and Group A streptococcus.<sup>168</sup> Vaccines might be particularly important for diseases such as gonorrhoea where treatment options are now extremely limited.<sup>169</sup>

The activities of the various groups mentioned have demonstrated the potential of vaccines to combat AMR. However, it has proved extremely difficult to estimate the value of vaccines as a tool to fight AMR in terms of health and economic impact in ways that will influence policymakers. The parameters that determine the extent to which the health and economic benefits that flow from reduced AMR can be attributed to vaccination are extremely complex and the data necessary to elucidate them are scarce.<sup>170</sup>

Thus, while it is self-evident that vaccination should help to reduce AMR, it is a challenge to demonstrate the magnitude and value in ways that would convince policymakers that AMR is a reason to assign a much higher priority to vaccine use and development than they already do. For this reason, Wellcome has recently launched a research programme investigating the impact of vaccines on antibiotic use and/or AMR, with the aim of supporting and informing vaccine decision-makers around the world and tackling AMR.<sup>171</sup> The WHO working group is aiming to create a roadmap that summarizes priority actions for vaccine use and development by creating a value attribution framework that articulates the value of vaccines against AMR.

In respect of the Review's recommendation on 'pull' funding to stimulate development and use, there have been no new initiatives since Gavi's Advance Market Commitment for pneumococcal vaccines. CARB-X's recent funding round also included vaccines and non-traditional approaches to treatment and prevention<sup>172</sup> and the European & Developing Countries Clinical Trials Partnership (EDCTP) has launched a programme to fund clinical trials in Africa for new drugs and vaccines.<sup>173</sup> In the UK, the Global AMR Innovation Fund (GAMRIF) has provided up to £1 million to accelerate the development

<sup>164</sup> Gavi (n.d.), 'Evaluation criteria for vaccines for endemic disease prevention through routine immunisation', <https://www.gavi.org/about/strategy/vis/evaluation-criteria-for-vaccines-for-endemic-disease-prevention-through-routine-immunisation/>.

<sup>165</sup> Knight G. M., Clarkson M. and de Silva, T. I. (2018), 'Potential impact of influenza vaccine roll-out on antibiotic use in Africa', *Journal of Antimicrobial Chemotherapy*, 73(8), pp. 2197–2200, <https://doi.org/10.1093/jac/dky17>.

<sup>166</sup> Andrews, J. R., Baker, S., Marks, F., Alsan, M., Garrett, D., Gellin, B. G., Saha, S. K., Qamar, F. N., Yousafzai, M. T., Bogoch, I. I., Antillon, M., Pitzer, V. E., Kim, J. H., John, J., Gauld, J., Mogasale, V., Ryan, E. T., Luby, S. P. and Lo, N. C. (2019), 'Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance', *Lancet Infect Dis.*, 19(1), pp. 26–30, [https://doi.org/10.1016/S1473-3099\(18\)30350-5](https://doi.org/10.1016/S1473-3099(18)30350-5).

<sup>167</sup> Fleming-Dutra, K. E., Hersh, A. L., Shapiro, D. J., Bartoces, M., Enns, E. A., File, T. M., Finkelstein, J. A., Gerber, J. S., Hyun, D. Y., Linder, J. A., Lynfield, R., Margolis, D. J., May, L. S., Merenstein, D., Metlay, J. P., Newland, J. G., Piccirillo, J. F., Roberts, R. M., Sanchez, G. V., Suda, K. J., Thomas, A., Woo, T. M., Zetts, R. M. and Hicks, L. A. (2016), 'Prevalence of inappropriate antibiotic prescriptions among us ambulatory care visits, 2010–2011', *JAMA*, 315(17), pp. 1864–73, doi:10.1001/jama.2016.4151.

<sup>168</sup> Berkely, S. (2019), 'We're Not Using One of Our Best Weapons against Drug-Resistant Microbes', *Scientific American*, blog, 8 February 2019, <https://blogs.scientificamerican.com/observations/were-not-using-one-of-our-best-weapons-against-drug-resistant-microbes/>.

<sup>169</sup> Edwards, J. L., Jennings, M. P. and Seib, K. L. (2018), 'Neisseria gonorrhoeae vaccine development: hope on the horizon?', *Current Opinion in Infectious Diseases*, 31(3), pp. 246–250, DOI: 10.1097/QCO.0000000000000450.

<sup>170</sup> Atkins, K. E., Lafferty, E., Deeny, S. R., Davies, N. G., Robotham, J. V. and Jit, M. (2018), 'Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance', *Lancet Infect Dis.*, 18(6), pp. 204–213, doi: 10.1016/S1473-3099(17)30478-4.

<sup>171</sup> Wellcome (2019), 'Impact of Vaccines on Antimicrobial Resistance', <https://wellcome.ac.uk/funding/schemes/impact-vaccines-antimicrobial-resistance>.

<sup>172</sup> CARB-X (2019), 'CARB-X launches new funding rounds to support the development of antibiotics, vaccines, diagnostics and other life-saving products that target drug-resistant bacteria'.

<sup>173</sup> EDCTP (2019), 'New drugs and vaccines for priority pathogens in antimicrobial resistance 2019', <http://www.edctp.org/call/new-drugs-and-vaccines-for-priority-pathogens-in-antimicrobial-resistance-2019/>.

of bacterial vaccines to combat AMR<sup>174</sup> and is funding the development of animal vaccines with Canada's International Development Research Centre (IDRC).<sup>175</sup>

Participants at the roundtable also noted that there should be more use of existing vaccines in livestock alongside other measures to reduce the spread of infection and reduce antibiotic use.<sup>176</sup> The OIE has also worked on establishing priorities for diseases where vaccines could reduce antimicrobial use in animals – in chickens, swine and fish<sup>177</sup> as well as cattle, sheep and goats.<sup>178</sup>

### Conclusion

As with diagnostics, a fundamental issue alongside scientific challenges in vaccine development is the absence of an effective market that provides incentives for the development of vaccines relevant to fighting AMR. The WHO working group should establish a list of priorities to guide vaccine R&D on the lines of the priority pathogen list developed to guide R&D on antibiotic development and also develop target product profiles for priority vaccines. Such an effort would need to be supported by funding agencies in order to help create a viable market. The current Global Vaccine Action Plan,<sup>179</sup> which runs from 2011–20, does not mention the role of vaccines in combatting AMR – this highlights the need for international bodies (such as WHO's Strategic Advisory Group of Experts (SAGE) on Immunization) as well as national advisory committees to mainstream AMR as a factor in their decision-making.

### Improve the numbers, pay and recognition of people working in infectious disease

Increases in capacity in healthcare and in R&D are often a by-product of increased investment in, for example, antimicrobial stewardship programmes and in early-stage research. Greater attention to stewardship programmes in recent years has helped to build human capacity in the different elements required in such programmes. Similarly, the greater investment in early-stage R&D has helped to build capacity in the different scientific disciplines required in R&D.

There is evidence that the number of researchers in academia increased as a result of the increased attention and funding for AMR research.<sup>180</sup> The American Society for Microbiology (ASM) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) jointly organize annual

<sup>174</sup> University of Birmingham (2019), 'Up to £1 million funding awarded to develop bacterial vaccines in global fight against antimicrobial resistance', 30 January 2019, <https://www.birmingham.ac.uk/university/colleges/mds/news/2019/01/bactivac-dhsc-funding.aspx>.

<sup>175</sup> HM Government (2018), 'DHSC joins global fight to tackle antimicrobial resistance in animals', 12 April 2018, <https://healthmedia.blog.gov.uk/2018/04/12/dhsc-joins-global-fight-to-tackle-antimicrobial-resistance-in-animals/>.

<sup>176</sup> Health for Animals (2019), *How to Increase Animal Vaccination: 80 Recommendations to Overcome Existing Barriers*, London: Health for Animals, [https://healthforanimals.org/downloads/library/how\\_to\\_increase\\_animal\\_vaccination\\_80\\_recommendations.pdf](https://healthforanimals.org/downloads/library/how_to_increase_animal_vaccination_80_recommendations.pdf).

<sup>177</sup> OIE (2015), *Report of the meeting of the OIE ad hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals*, Paris: OIE, [https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG\\_AMUR\\_Vaccines\\_Apr2015.pdf](https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG_AMUR_Vaccines_Apr2015.pdf).

<sup>178</sup> OIE (2018), *Report of the meeting of the OIE ad hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in cattle, sheep, and goats*, Paris: OIE, [https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG\\_AMUR\\_Vaccines\\_ruminants\\_May2018.pdf](https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG_AMUR_Vaccines_ruminants_May2018.pdf).

<sup>179</sup> World Health Organization (2013), *Global Vaccine Action Plan 2011–2020*, Geneva: WHO, [https://www.who.int/immunization/global\\_vaccine\\_action\\_plan/GVAP\\_doc\\_2011\\_2020/en/](https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/).

<sup>180</sup> Kelly, R., Zoubiane, G., Walsh, D., Ward, R. and Goossens, H. (2016), 'Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systematic observational analysis', *Lancet Infectious Diseases*, 16(4), pp. 431–40, [https://doi.org/10.1016/S1473-3099\(15\)00350-3](https://doi.org/10.1016/S1473-3099(15)00350-3).

meetings, which contribute to information exchange and skill development.<sup>181</sup> However, there is a lack of data concerning the numbers of professionals involved in work on AMR or antimicrobial development, which makes progress difficult to monitor. One proposal at the roundtable was to organize a census to understand better the situation and how it is evolving over time.

While there can be some optimism about the impact of new funding for early-stage R&D, a number of research teams have been sold or disbanded as several large pharmaceutical companies have disposed of their antibiotic research units. In recent years this includes Novartis, AstraZeneca and Sanofi.<sup>182</sup> Smaller biotechs, which now dominate the antibiotic R&D space, have also encountered difficulties – as illustrated by the recent bankruptcy of Achaogen and the sale of all its assets.<sup>183</sup> Several other companies are in danger of going the same way as the revenues generated from antibiotic sales are insufficient to meet the costs incurred in bringing the drugs to market.<sup>184</sup>

**There is a lack of data concerning the numbers of professionals involved in work on AMR or antimicrobial development, which makes progress difficult to monitor.**

Infectious disease specialisms remain a poor relation in terms of popularity among aspiring clinicians. For example, it has proved impossible in the US to fill all the available residency slots with candidates with the right qualifications.<sup>185</sup> And the pay of infectious disease physicians remains near the bottom of all specialisms, as the Review itself noted based on 2012 data (see Figure 3). At the same time, not all infectious disease physicians might actually address issues relevant to AMR such as IPC or stewardship or have a particular interest in them. One problem is that in the absence of a specific career path for professionals specializing in, for instance, IPC, training in these skills might be wasted. Roundtable participants concluded that these specializations need to be developed and that there might be a greater role for professional societies in organizing and promoting training and career paths for those disciplines required to address AMR.

If this is a problem in high-income countries, it is even more so in LMICs. A survey in China found that infectious disease physicians endured more mental stress, smaller salaries and greater dissatisfaction than other physicians in China. Their annual income was the third-lowest among Chinese physicians, very similar to the position in the US. Only one-third of respondents reported that they would again choose to specialize in infectious diseases if given another chance.<sup>186</sup> When it comes to research capacity in LMICs, both China and India have substantial research capacity. Most recently, CARB-X has added an Indian research organization, the Centre for Cellular and Molecular Platforms (C-CAMP), to its global accelerator network, and also funds a C-CAMP startup, Bugworks.<sup>187</sup> In LMICs generally,

<sup>181</sup> American Society for Microbiology (2019), 'ASM/ESCMID Conference on Drug Development', <https://www.asm.org/Events/ASM-ESCMID-2019/Home>.

<sup>182</sup> Hu, C. (2018), 'Pharmaceutical companies are backing away from a growing threat that could kill 10 million people a year by 2050', *Business Insider*, 21 July 2018, <https://www.businessinsider.com/major-pharmaceutical-companies-dropping-antibiotic-projects-superbugs-2018-7?r=US&IR=T>.

<sup>183</sup> Farrar, J. (2019), 'We ignore the disaster in the antibiotics market at our peril', *Financial Times*, 21 April 2019, <https://www.ft.com/content/4da1c6e4-603d-11e9-9300-0becfc937c37>.

<sup>184</sup> Outterson, K. (2018), 'Current Market Conditions for Antibiotics', Presentation, 11 December 2018, <https://www.antibioticresearch.org.uk/wp-content/uploads/2019/04/APPG-Outterson-11-Dec-2018.pptx?x16182>.

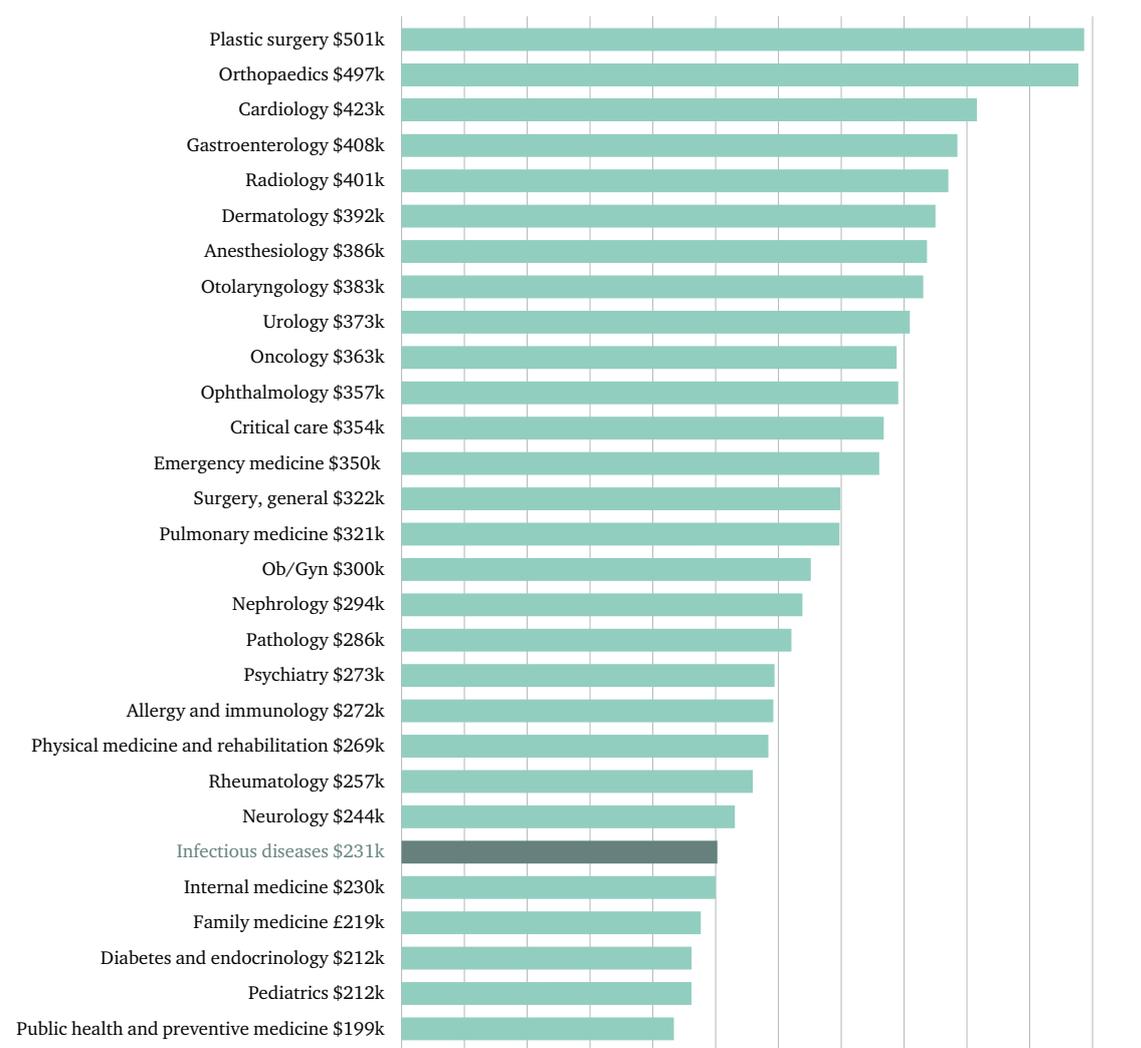
<sup>185</sup> McCarthy, M. (2019), 'The Scary Shortage of Infectious-Disease Doctors', *New York Times*, 9 April 2019, <https://www.nytimes.com/2019/04/09/opinion/doctors-drug-resistant-infections.html>.

<sup>186</sup> Zhang, C., Li, S., Ji, J., Shen, P., Ying, C., Li, L. and Xiao, Y. (2018), 'The professional status of infectious disease physicians in China: a nationwide cross-sectional survey', *Clinical Microbiology and Infection*, 24(1), pp. 5–82, <https://doi.org/10.1016/j.cmi.2017.05.008>.

<sup>187</sup> C-CAMP (n.d.), 'Taking the fight to the superbug's camp – CCAMP startup Bugworks leading India's AMR combat', <http://www.ccamp.res.in/c-camp-innovation-insights-1>.

there is evidence of growing research capacity overall but, particularly in Africa, it is likely that this capacity is predominantly built around the big three diseases – HIV, tuberculosis and malaria.<sup>188</sup>

Figure 3: Relative pay of physicians in the US



Source: Figure reproduced with permission from Medscape (2018), *Infectious Disease Physician Compensation Report 2018*.<sup>189</sup>

## Conclusion

Much would be achieved in improving research capacity if the current enhanced level of push funding directed at early-stage research were maintained or further enhanced and if effective pull mechanisms could be implemented to draw resources into late-stage product development, where there is currently the biggest bottleneck in unlocking the pipeline. Market forces, as modified by public intervention, would naturally improve the numbers, pay and recognition of researchers in the area. Regarding

<sup>188</sup> Franzen, S., Chandler, C. and Lang, T. (2016), 'Health research capacity development in low and middle income countries: reality or rhetoric? A systematic meta-narrative review of the qualitative literature', *BMJ Open*, 7, doi: 10.1136/bmjopen-2016-012332.

<sup>189</sup> Medscape (2018), *Infectious Disease Physician Compensation Report 2018*, <https://www.medscape.com/slideshow/2018-compensation-infectious-disease-6009658#2>.

clinicians and other health workers, the need is for the incorporation of AMR-relevant training at all levels of professional education and for creating paths for career progression in those specialisms most relevant to stewardship of antibiotics.

### Funding for early-stage and non-commercial innovation

The Review recommended the establishment of a Global Innovation Fund (GIF) with an endowment of \$2 billion over five years to fund early-stage and non-commercial research. While there has been no move to establish such a fund, and the Review chair apparently felt a fund, as such, was not necessary to achieve the objectives, the latest calculations suggest that current annual funding of such research is approaching \$500 million a year, close to the level implied by the recommendation. However, the Review itself appears to have envisaged that funding from the GIF would be additional to the existing initiatives on AMR and those it identified as in the process of implementation. The Review noted recent improvements in funding to support company efforts including:

- The programmes of the Biomedical Advanced Research and Development Authority (BARDA) in the US, which were initiated in 2010.<sup>190</sup>
- The ‘New Drugs for Bad Bugs’ (ND4BB) programme of the European Union’s Innovative Medicines Initiative (IMI), which was launched in 2012.<sup>191</sup>

The Review also recognized the important role of the US National Institutes of Health and the JPIAMR in supporting research relevant to AMR. A recent study commissioned by Wellcome identified 1,243 AMR research projects with a total public investment of €1.3 billion, mostly on therapeutics across JPIAMR countries and at the European Union-level from 2007 to 2013.<sup>192</sup> Membership of the JPIAMR has extended beyond Europe to include Argentina, Canada, Egypt, Israel, India, Japan, South Africa, South Korea and Turkey.

The Review also identified three imminent initiatives. CARB-X – was established in July 2016 and has now secured funding of \$550 million from the US, UK and German governments and two charitable foundations, Wellcome and the Bill & Melinda Gates Foundation. Another initiative mentioned was the Global Antibiotic Research & Development Partnership (GARDP), which was launched in May 2016. Its business plan envisages funding of €270 million in 2017–23.<sup>193</sup> The third initiative was GAMRIF in the UK, which was launched in October 2015 in association with China<sup>194</sup> and subsequently envisaged a commitment of £50 million over five years.<sup>195</sup> Funds from GAMRIF have been committed to a variety of projects, including cooperation with China, Canada and Argentina as well as funding of CARB-X and GARDP.<sup>196</sup>

<sup>190</sup> Houchens, C. and Larsen, J. (2017), ‘The Role of the Biomedical Advanced Research and Development Authority (BARDA) in Promoting Innovation in Antibacterial Product Development’, 2 August 2017, <http://resistancecontrol.info/2017/the-role-of-the-biomedical-advanced-research-and-development-authority-barda-in-promoting-innovation-in-antibacterial-product-development/>.

<sup>191</sup> Kostyanov, T. et al. (2016), ‘The Innovative Medicines Initiative’s New Drugs for Bad Bugs programme: European public-private partnerships for the development of new strategies to tackle antibiotic resistance’.

<sup>192</sup> Kelly, R. et al. (2016), ‘Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systematic observational analysis’.

<sup>193</sup> GARDP (2017), ‘Business Plan 2017-2023’, [https://www.gardp.org/wp-content/uploads/2017/05/GARDP\\_Business\\_Plan\\_2017-2023.pdf](https://www.gardp.org/wp-content/uploads/2017/05/GARDP_Business_Plan_2017-2023.pdf).

<sup>194</sup> HM Government (2015), ‘UK and China start global fund to tackle drug resistant infections’, 23 October 2015, <https://www.gov.uk/government/news/uk-and-china-start-global-fund-to-tackle-drug-resistant-infections>.

<sup>195</sup> HM Government (2016), ‘Expert advisory board to support the Global AMR Innovation Fund’, 29 November 2016, <https://www.gov.uk/government/news/expert-advisory-board-to-support-the-global-amr-innovation-fund>.

<sup>196</sup> AMR Centre (2018), *New Drugs for Anti-Microbial Resistance: Maximising the AMR Opportunity for the UK*, London: AMR Centre, [https://www.amrcentre.com/wp-content/uploads/New\\_Drugs\\_for\\_Anti-Microbial\\_Resistance\\_Maximising\\_the\\_AMR\\_Opportunity\\_for\\_the\\_UK\\_report.pdf](https://www.amrcentre.com/wp-content/uploads/New_Drugs_for_Anti-Microbial_Resistance_Maximising_the_AMR_Opportunity_for_the_UK_report.pdf).

A more recent development is the REPAIR Impact Fund, established by Novo Holdings in February 2018 with a total budget of \$165 million to invest in companies involved in the discovery and early-stage development of antimicrobial therapies. The fund is expected to invest \$20–\$40 million annually over 3–5 years in about 20 projects in Europe and the US, with the aim of bringing at least one new therapy to the market.<sup>197</sup> Unlike CARB-X and GARDP, REPAIR is a for-profit social impact fund, making equity investments.

Table 2 shows a summary of recent initiatives and their actual or potential funding, but it should be noted that it involves some double counting because it includes amounts allocated by funders (such as BARDA) to recipients (such as CARB-X).

**Table 2: Recent AMR initiatives**

|  |   |
|--|---|
| <b>BARDA</b>                                       | <b>US\$1.2bn (2010–19)</b><br>Phase 2 and 3 product development against 21st Century Health Threats, including drug-resistant bacteria, and CARB-X.   |
| <b>Bill &amp; Melinda Gates Foundation</b>         | <b>US\$124m (2018–22)</b><br>Targets prevention of drug-resistant infections in low- and middle-income countries (LMICs). Disease surveillance, vaccine development, economic modeling, and CARB-X. Global.   |
| <b>CARB-X</b>                                      | <b>US\$550m (2016–21)</b><br>Hit-to-lead to Phase 1 product development of therapeutics, diagnostics, and preventatives against WHO and CDC priority drug-resistant bacteria. Non-dilutive. Global.   |
| <b>GARDP</b>                                       | <b>€270m (2017–23)</b><br>Product development from discovery to delivery including novel therapeutics, optimizing antibiotics, developing combinations. WHO priority pathogen list. Non-dilutive. Global.   |
| <b>UKaid</b>                                       | <b>£315m (2018–21)</b><br>Funded through Global AMR Innovation Fund (GAMRIF) and the Fleming Fund to help LMICs tackle AMR. Fleming Fund (surveillance capacity) and GAMRIF (Innovation R&D) both have a 'One Health' focus.                              |
| <b>Federal Ministry of Education and Research</b>  | <b>€500m (2018–28)</b><br>Support of national research programmes as well as contributions to international initiatives like CARB-X, GARDP and JPIAMR.  |
| <b>ND4BB   IMI Innovative Medicines Initiative</b> | <b>€700m (2014–20)</b><br>Basic science, novel therapeutics, diagnostics, economic models. Priority pathogens including pathogens on WHO priority list. Member states only.   |
| <b>JPIAMR</b>                                      | <b>€234m (2012–24)</b><br>Novel therapeutics, diagnostics, surveillance, prevention, stewardship. WHO priority pathogens. Member states only.   |
| <b>NIH</b>   | <b>US\$1.4bn (2016–18)*</b><br>Basic research, SBIRs, pre-clinical services and other R&D against bacterial threats, for vaccines therapeutics and diagnostics.<br><i>*Mostly antibacterial, but also includes viral, fungal and parasite resistance.</i> |
| <b>REPAIR Impact Fund, Novo Holdings</b>           | <b>US\$1.65m (2018–23)</b><br>Lead optimization to Phase 1 development of therapeutics & diagnostics against priority drug-resistant bacteria defined by WHO and CDC. Dilutive. US and European companies.  |
| <b>Wellcome</b>                                    | <b>£175m (2016–21)</b><br>Drug-resistant infections programme focused on policy, strengthening evidence for action, clinical trial capabilities and innovative product development including CARB-X.  |

Source: Compiled by Kevin Outterson, associate fellow, Centre on Global Health Security, Chatham House.

<sup>197</sup> REPAIR Impact Fund (n.d.), <https://www.repair-impact-fund.com/about/>.

While not a financial input, WHO published in early 2017 a priority list of pathogens to guide R&D for new antibiotics.<sup>198</sup> Later in 2017 it published the full report along with an analysis for tuberculosis, which had been omitted from the earlier report.<sup>199</sup> Also in 2017, WHO produced a report on the pipeline of products in clinical development and concluded that the current clinical pipeline was insufficient to mitigate the AMR threat and that more investment was needed in basic science, drug discovery and clinical development.<sup>200</sup>

Because of the time drug development takes, and the high risk of failure, it is difficult to assess whether progress is being made in the course of a few years. However, CARB-X reports awards to preclinical products that represent more than a dozen new classes of antibiotics against priority Gram-negative bacteria and a greater number of products with new molecular targets, in addition to a growing list of products that are not traditional antibiotics, such as phages and microbiome therapeutics. These preclinical products should begin to have an impact on the clinical pipeline in the coming years.

An updated list of products in the clinical pipeline compiled by the Pew Charitable Trusts in 2019 concluded that there were still too few drugs in development to meet current and anticipated patient needs, particularly for the priority Gram-negative pathogens.<sup>201</sup> The Pew data indicate that since 2014, 14 new antibiotics have been approved for marketing in the US, of which seven tackle Gram-negative bacteria. Of the latter, three are on the CDC list of priority pathogens – two belong to novel classes of antibiotic. During that time, the clinical development of 21 antibiotics has been discontinued: eight in Phase I, nine in Phase II, and four in Phase III. The positive features are the marked increase in antibiotics in Phase I clinical trials and the larger number that have reached Phase III. See Table 3.

**Table 3: Pipeline of antibiotics in development since 2014**

| Phase   | I  | II | III | Approved | Discontinued |
|---------|----|----|-----|----------|--------------|
| 2014    | 8  | 17 | 8   | 4        | 6            |
| 2015    | 8  | 16 | 12  | 5        | 6            |
| 2016    | 13 | 12 | 11  | 0        | 4            |
| 2017    | 16 | 14 | 15  | 2        | 1            |
| 2018    | 15 | 11 | 13  | 3        | 4            |
| 2014–18 |    |    |     | 14       | 21           |

Source: Adapted from Pew Charitable Trusts, 2019.<sup>202</sup>

<sup>198</sup> World Health Organization (2017), *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*, Geneva: WHO, [https://www.who.int/medicines/publications/WHO-PPL-Short\\_Summary\\_25Feb-ET\\_NM\\_WHO.pdf](https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf).

<sup>199</sup> World Health Organization (2017), *Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis*, Geneva: WHO, [https://www.who.int/medicines/areas/rational\\_use/PPLreport\\_2017\\_09\\_19.pdf?ua=1](https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1).

<sup>200</sup> World Health Organization (2017), *Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline*, Geneva: WHO, [https://www.who.int/medicines/areas/rational\\_use/antibacterial\\_agents\\_clinical\\_development/en/](https://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/).

<sup>201</sup> Pew Charitable Trusts (2019), 'Tracking the Global Pipeline of Antibiotics in Development', 5 March 2019, <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/03/tracking-the-global-pipeline-of-antibiotics-in-development>.

<sup>202</sup> Pew Charitable Trusts (2019), 'Five-Year Analysis Shows Continued Deficiencies in Antibiotic Development', 22 July 2019, <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development>.

### Conclusion

It can be concluded that there have been positive developments in the funding of early-stage research and significantly more funding from a variety of sources has been attracted into the field, if not quite on the scale envisaged by the Review. However, there is limited evidence that the pipeline of products in development has significantly improved, particularly with respect to new classes of antibiotics needed to address identified priority pathogens. Moreover, as discussed in the next section, there remains a massive problem in financing later-stage development and in bringing promising products to marketing approval and beyond.

### Better incentives to promote investment in new drugs and existing ones

The Review called for a new system of ‘market entry rewards’ to provide lump-sum payments to successful developers of new antibiotics that meet a specified medical need and recommended that such a system be supra-national. It highlighted the particular need to incentivize new treatment regimens for tuberculosis. It also recommended harmonization and simplification of regulatory systems and the development of ‘clinical trial networks’ to reduce the time and cost of bringing new drugs to market.

It appears that the Review report was the first report to coin the phrase ‘market entry rewards’ as a way to describe a reward system that delinked the recovery of R&D costs from the volume of sales of the product. However, the idea behind it had been developed several years earlier in a different context – as a means to incentivize R&D while also facilitating access to new medicines, particularly in developing countries. In 2008, WHO member states endorsed consideration of ‘a range of incentive schemes for research and development, including ... the delinking of the costs of research and development and the price of health products ... with the objective of addressing diseases that disproportionately affect developing countries.’<sup>203</sup> In the context of AMR, the idea is similar in that public money would be used to reward R&D, thus providing incentives to the private sector to develop new antibiotics while also removing the incentive for companies to promote sales of antibiotics (in ways that might promote AMR) in order to recover R&D costs. Various authors prior to the Review analysed the different pull (and push) options to stimulate R&D on new antibiotics.<sup>204</sup> In 2015, a working group at Chatham House produced a report that called for a new business model for antibiotics where the return on investment in R&D is delinked from the volume of sales and offered ideas as to how such a global effort could be implemented.<sup>205</sup>

Since the Review, the 2017 Boston Consulting Group (BCG) report referred to earlier in this paper made a number of detailed proposals for funding and incentive schemes that drew on and extensively referenced the work of the Review. In 2018, DRIVE-AB, a project established under the EU’s Innovative Medicines Initiative, *inter alia*, to develop and cost new economic models to promote antibiotic

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<sup>203</sup> World Health Organization (2011), *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, Geneva: WHO, [https://www.who.int/phi/publications/Global\\_Strategy\\_Plan\\_Action.pdf](https://www.who.int/phi/publications/Global_Strategy_Plan_Action.pdf).

<sup>204</sup> Mossialos, E., Morel, C. M., Edwards, S., Berenson, J., Gemmill-Toyama, M. and Brogan, D. (2010), *Policies and incentives for promoting innovation in antibiotic research*, Copenhagen: European Observatory on Health Systems and Policies, [http://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0011/120143/E94241.pdf](http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf); Towse, A. and Sharma, P. (2011), *Incentives for R&D for New Antimicrobial Drugs*, London: Office of Health Economics, <https://www.ohe.org/publications/incentives-rd-new-antimicrobial-drugs#>.

<sup>205</sup> Clift, C., Gopinathan, U., Morel, C., Outtersson, K., Røttingen, J-A. and So, A. (2015), *Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales*, Chatham House Report, London: Royal Institute of International Affairs, <https://www.chathamhouse.org/publication/towards-new-global-business-model-antibiotics-delinking-revenues-sales>.

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innovation and sustainable use, published its final report.<sup>206</sup> DRIVE-AB mainly focused on the ways in which a ‘market entry reward’ system could work and also extensively referenced the work of the Review.

As noted, the problem with the Review’s recommendations on market entry rewards, as subsequently elaborated in different ways by BCG and DRIVE-AB, is that they have not been taken forward politically, at the level of the G20 or G7, in any meaningful sense. There seems to be a lack of collective political will to take the first concrete step towards establishing global mechanisms for managing and financing a new business model along the lines proposed by the Review and others. A concrete step would, for instance, be a high-level group tasked with establishing the parameters of such a scheme and consulting widely with interested countries and other stakeholders to generate a degree of consensus on ways forward. There was hope that the Global AMR R&D Hub might be such a vehicle, but this has not yet proved to be the case. It remains to be seen whether there will be a positive response from the latest G20 suggestion that interested G20 members and the Global AMR R&D Hub should analyse push and pull mechanisms to identify the best models for AMR R&D and report back to relevant G20 ministers.

In the absence of positive movement at the global level, there have been a number of relevant initiatives at the national level. The UK is currently in the process of developing a new system of paying for antibiotics based on subscription – the so-called Netflix model where payments are unrelated to actual use.<sup>207</sup> This is seen as a first step towards a system that would stimulate R&D, as it potentially allows companies to make a return on their investments in R&D irrespective of use. The UK government emphasizes that this is an important first step but notes that it will only address global market failure if other countries are prepared to do the same.<sup>208</sup> The system therefore could act as a market entry reward whereby payments are made annually for new antibiotics that meet specified criteria. But exactly how it will work with existing products and at what level payments are set will be critical factors in determining its likely impact on R&D investment. The model resembles existing schemes introduced in Australia and some US states that are rather differently designed to maximize access to expensive hepatitis C drugs.<sup>209</sup>

**The UK is currently in the process of developing a new system of paying for antibiotics based on subscription – the so-called Netflix model where payments are unrelated to actual use.**

Similar ideas were proposed in 2018 by the US Commissioner of Food and Drugs – the head of the US Food and Drug Administration (FDA) – to incentivize product development and stewardship by delinking revenues from use.<sup>210</sup> In August 2019, the US announced new rules for rewarding antibiotic producers. The rules for an existing scheme (New Technology Add-on Payments) were liberalized

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<sup>206</sup> DRIVE-AB (2018), *Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access*, London: Drive-AB, <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>.

<sup>207</sup> *Economist* (2019), ‘The antibiotic industry is broken’, 4 May 2019, <https://www.economist.com/leaders/2019/05/04/the-antibiotic-industry-is-broken>.

<sup>208</sup> Department of Health and Social Care (2019), ‘Development of new antibiotics encouraged with new pharmaceutical payment system’, 9 July 2019, <https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system>.

<sup>209</sup> Rosenberg, T. (2019), ‘Treat Medicines Like Netflix Treats Shows’, *New York Times*, 5 March 2019, <https://www.nytimes.com/2019/03/05/opinion/can-netflix-show-americans-how-to-cut-the-cost-of-drugs.html>.

<sup>210</sup> Food and Drug Administration (2018), ‘Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA’s efforts to foster discovery and development of new tools to fight antimicrobial-resistant infections’, 12 June 2018, <https://www.fda.gov/newsevents/newsroom/pressAnnouncements/ucm610503.htm>.

to increase the price supplement offered to new innovations (from 50 per cent to 75 per cent) and replace the restriction on products that could not demonstrate superiority over existing treatments provided they are registered as qualified infectious disease products (QIDPs) under the 2012 Generating Antibiotic Incentives Now (GAIN) Act. The classification of 18 infectious disease conditions (ICD-10 codes) was also altered to allow higher payments to hospitals for treating patients affected by resistance.<sup>211</sup> The US government also asked for input for the following year's rulemaking process, with a view to removing hospital-administered antibiotics from the Diagnosis-Related-Group bundled payment. Legislation to that effect has also been introduced in Congress in the DISARM Act.<sup>212</sup> But it should be noted that these US changes are reimbursement reforms, not a delinked market entry reward. They still depend on volume to drive revenues, which is difficult in an environment with strong antimicrobial stewardship. US legislation is currently being prepared to create a robust market entry reward fully congruent with the goals of the Review, but the political outlook for such legislation is unclear.

In addition to its main recommendations on R&D incentives, the Review also made proposals for complementary fundraising measures:

- An antibiotic investment charge for pharmaceutical companies ('pay or play') whereby all companies would be obliged either to have antibiotic R&D programmes or pay the charge;<sup>213</sup>
- A tax on antibiotics;<sup>214</sup>
- A scheme that would entitle companies that developed specified antibiotics to a marketable voucher either to claim priority regulatory review on another product (as is the case in the US for products for specified tropical diseases) or an entitlement to extended market exclusivity on another product.<sup>215</sup>

The Review acknowledged a number of challenges in implementing all of these proposals. None of these ideas have come to fruition. The Review did not mention the GAIN Act in the US, which provides an extra five years of market exclusivity for QIDPs. A review by the FDA found that many products that qualified for QIDP designation were approved drugs being developed with modifications, such as a new dosage form or new indication, rather than novel classes of antibiotics and that new incentives were required to address this issue.<sup>216</sup>

It needs to be noted that there is not consensus among experts of different shades of opinion that market entry rewards – offering billion-dollar rewards to pharmaceutical companies – are the right answer.<sup>217</sup> Rather than try to recreate through large-scale public funding a 'market' for antibiotics that incentivizes private sector R&D in ways that will compete with, for instance, the returns on products for cancer or hepatitis C, some argue that non-profit organizations should be tasked with

<sup>211</sup> Verma, S. (2019), 'Aligning Payment And Prevention To Drive Antibiotic Innovation For Medicare Beneficiaries', *Health Affairs*, blog, 2 August 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190802.505113/full/>.

<sup>212</sup> US Congress (2018), 'S.3787 – DISARM Act of 2018', 19 December 2018, <https://www.congress.gov/bills/115th-congress/senate-bill/3787/text>.

<sup>213</sup> O'Neill, J. (2018), 'Pay-or-Play Capitalism', *Project Syndicate*, 8 February 2018, <https://www.project-syndicate.org/commentary/pay-or-play-capitalism-corporate-levies-by-jim-o-neill-2018-02?barrier=accesspaylog>.

<sup>214</sup> Hollis, A. and Ahmed, Z. (2013), 'Preserving Antibiotics, Rationally', *N Engl J Med.*, 369, pp. 2474–2476, DOI: 10.1056/NEJMp1311479.

<sup>215</sup> Outterson, K. and Hollis, A. (2016), 'Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy', *Health Affairs*, 35(5), pp. 784–790, doi:10.1377/hlthaff.2015.1139.

<sup>216</sup> Department of Health and Human Services (n.d.), 'Required by Section 805 of the Food and Drug Administration Safety and Innovation Act Public Law 112-144', <https://www.fda.gov/media/110982/download>.

<sup>217</sup> Torreele, E. (2019), 'The search for new antibiotics—market based solutions are not the answer', *BMJ*, blog, 11 July 2019, <https://blogs.bmj.com/bmj/2019/07/11/els-torreele-fixing-the-wrong-problem-in-the-search-for-new-antibiotics-market-based-solutions-are-not-the-answer/>.

the development of new products to fight AMR.<sup>218</sup> Others have proposed that state-run companies should undertake antibiotic R&D.<sup>219</sup> Yet it is not clear that these approaches, which seek an alternative to reliance on the traditional business model of the pharmaceutical industry, will prove more politically attractive than the market entry rewards proposal. Further work would be required to assess their feasibility, cost and effectiveness and to generate political support. Others argue that the emphasis on stimulating new antibiotic development is misplaced – its primacy in the discourse on AMR risks diverting both resources and attention from social and structural solutions that would reduce infections, antibiotic use and, in the long term, AMR.<sup>220</sup>

Regarding its recommendations for tuberculosis, the Review highlighted the proposal by Médecins Sans Frontières (MSF) of the 3P Project (Pull, Pool and Push), which aimed to combine a *pull* incentive, by rewarding research through prizes, with the *pooling* of intellectual property and data and the use of *push* incentives through research grants.<sup>221</sup> The 3P Project was subsequently renamed the Life Prize and was mentioned in the 2018 UN political declaration on the fight against tuberculosis, which noted an estimated \$1.3 billion dollar gap in funding annually for tuberculosis research.<sup>222</sup> However, the latest assessment of funding for tuberculosis research notes that ‘no governments have yet been willing to put up the money to test alternative innovation models’.<sup>223</sup>

In relation to regulation, there is considerable activity between key regulatory agencies to improve global harmonization of regulatory pathways for new antibiotics. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), a collaboration between the US, EU, Canada and Norway, has a workstream on ‘Strategies for improving the pipeline of new antimicrobial drugs’. This includes an action whereby ‘regulatory agencies will continue sharing approaches regarding antibacterial drug development to ensure that convergence in the requirements and in the regulation of antibacterial agents is maximized’.<sup>224</sup> The European Medicines Agency (EMA) published earlier this year for consultation new guidelines on the evaluation of antibiotics that reflect discussions between regulators in the EU, US and Japan.<sup>225</sup>

Regarding the Review’s recommendations on strengthening clinical trials networks, a business plan is currently being developed with European Commission funding to establish a private-public platform, the European Clinical Research Alliance on Infectious Diseases (ECRAID). ECRAID aims to create a clinical trial network for infectious diseases in hospital care and primary care for adults and children that is focused on carrying out high-quality phase II/III trials on a European scale, but globally connected. ECRAID’s vision is to establish a coordinated and permanent European clinical research infrastructure for clinical research on infectious diseases. Built on the foundations laid by the European Commission-funded Combatting Bacterial Resistance in Europe (COMBACTE)<sup>226</sup> and the

<sup>218</sup> Neilsen, T., Brass, E. P., Gilbert, D. N., Bartlett, J. G., Spellberg, B. (2019), ‘Sustainable Discovery and Development of Antibiotics — Is a Nonprofit Approach the Future?’, *New England Journal of Medicine*, 381(6), pp. 503–505, DOI: 10.1056/NEJMp1905589.

<sup>219</sup> *Guardian* (2019), ‘Nationalised drug companies may be needed to ‘fix antibiotics market’’, 27 March 2019, <https://www.theguardian.com/business/2019/mar/27/nationalised-drug-companies-may-be-needed-to-fix-antibiotics-market>.

<sup>220</sup> Glover, R., Manton, J., Willcocks, S., Stabler, R. (2019), ‘Subscription model for antibiotic development: An unlikely answer to the global crisis in antibiotic resistance’, *BMJ*, 366, <https://doi.org/10.1136/bmj.l5364>.

<sup>221</sup> MSF Access Campaign (2014), ‘Out of Step: Deadly implementation gaps in the TB response’, October 2014, [https://msfaccess.org/sites/default/files/MSF\\_assets/TB/Docs/TB\\_report\\_OutofstepReport\\_ENG\\_2014.pdf](https://msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_OutofstepReport_ENG_2014.pdf).

<sup>222</sup> United Nations (2016), ‘Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis’.

<sup>223</sup> Treatment Action Group (2018), *Tuberculosis Research Funding Trends 2005-2017*, New York: Treatment Action Group, [http://www.treatmentactiongroup.org/sites/default/files/tb\\_funding\\_2018\\_final.pdf](http://www.treatmentactiongroup.org/sites/default/files/tb_funding_2018_final.pdf).

<sup>224</sup> TATFAR (2019), ‘Actions & Recommendations’, <https://www.cdc.gov/drugresistance/tatfar/tatfar-recomendations.html>.

<sup>225</sup> European Medicines Agency (2019), *Revised guideline aims to strengthen global approach to development of new antibacterial medicines*, London: EMA, <https://www.ema.europa.eu/en/news/revised-guideline-aims-strengthen-global-approach-development-new-antibacterial-medicines>.

<sup>226</sup> COMBACTE (n.d.), ‘How it works’, <https://www.combacte.com/about/>.

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Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE),<sup>227</sup> ECRAID will be able to conduct clinical research faster and more easily.<sup>228</sup> The Antibacterial Resistance Leadership Group (ARLG) in the US aims to advance research by building transformational trials that will change clinical practice and reduce the impact of antibacterial resistance and AMR.<sup>229</sup>

### Conclusion

On the key issue of market entry rewards it is now becoming clear, following the recent G20 meeting in Osaka, that there is little, if any, progress being made towards a substantive outcome while the problems with the market for antibiotics continue to deteriorate, as illustrated by the travails of Achaogen and other biopharmaceutical companies. In the words of Jim O'Neill, 'what the world needs now is action, not empty words'.<sup>230</sup> As noted earlier, this applies equally to vaccines and diagnostics, for which companies face similar challenges.

That being the case there is a need to look for, and develop, alternative ways to address the problem of insufficient investment in R&D.

### Build a global coalition for real action via the G20 and the UN

The Review recommended that the G20 take the lead on defined aspects of the AMR agenda, particularly on incentives for the development of new antibiotics, vaccines and diagnostics. As noted earlier, the response overall at the level of the G20 has been disappointing.

The Review also recommended that the UN, the Tripartite and governments consider the 'global coordinated structures' required to oversee the development, implementation and operation of global systems of financial support for fighting AMR.

The main activity in this area has been the establishment of the ad hoc Interagency Coordination Group (IACG), which was called for in the UN's 2016 Political Declaration of the High-level Meeting on Antimicrobial Resistance. The IACG published discussion papers in six areas, covering much of the same ground as the AMR Review. In January 2019, it published its draft recommendations for public discussion and its final report was published in April 2019.<sup>231</sup> It made 14 recommendations for action but with respect to governance its main recommendation was the urgent establishment of a 'One Health Global Leadership Group on Antimicrobial Resistance' supported by a small secretariat. The Group would consist of past and present political leaders, heads of UN and international agencies and the regional banks, and other prominent global leaders in relevant fields. This group would be complemented by an Independent Panel on Evidence for Action against Antimicrobial Resistance, along the lines of the Intergovernmental Panel on Climate Change (IPCC). Finally, it recommended that work on the Global Development and Stewardship Framework to Combat Antimicrobial Resistance be expedited.<sup>232</sup> This had been called for in the 2015 World Health Assembly resolution

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<sup>227</sup> Platform for European Preparedness Against (Re-)emerging Epidemics (n.d.), <https://www.prepare-europe.eu/>.

<sup>228</sup> European Clinical Research Alliance on Infectious Diseases (n.d.), <https://www.ecraid.eu/>.

<sup>229</sup> Antibacterial Resistance Leadership Group (n.d.), 'About the ARLG', <https://arlg.org/about-the-arlg>.

<sup>230</sup> O'Neill, J. (2019), 'Does the G20 Still Matter?', *Project Syndicate*, 16 July 2019, <https://www.chathamhouse.org/expert/comment/does-g20-still-matter>.

<sup>231</sup> Interagency Coordination Group on Antimicrobial Resistance (2019), *No Time to Wait: Securing the future from drug-resistant infections*, <https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/>.

<sup>232</sup> World Health Organization (2018), *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance*, Geneva: WHO, [https://www.who.int/phi/news/WHO\\_OIE\\_FAO\\_UNEP\\_Working\\_paper\\_of\\_the\\_framework\\_FINAL.pdf?ua=1](https://www.who.int/phi/news/WHO_OIE_FAO_UNEP_Working_paper_of_the_framework_FINAL.pdf?ua=1).

adopting the Global Action Plan and reiterated by the 2016 UN Political Declaration. The IACG said consideration should be given to the need for new binding or non-binding international instruments, while also noting that debates on the issue should not detract from addressing already agreed priorities for action.

The Review also recommended that stakeholders work together to identify sustainable funding mechanisms to finance a long-term global response to AMR – including hypothecated revenues from new sources such as taxes on antibiotic use or healthcare products. A recent, possibly significant, development is the establishment of an AMR Multi-Partner Trust Fund, with an initial funding of \$5 million from the Netherlands. It aims to scale up efforts to support countries to counter the immediate threat of AMR.<sup>233</sup>

### Conclusion

The UN Secretary-General has thus far not responded publicly to the recommendations of the IACG report. One possible concern is that both the new bodies proposed – the Leadership Group and the Independent Panel – sound, as described, rather unwieldy. There is a danger that they might become a forum for more talk rather than action. It is also not encouraging that discussions on the Global Development and Stewardship Framework that was originally called for in the 2016 UN Declaration have so far been inconclusive. Furthermore, the Global AMR R&D Hub, the only concrete innovation in global AMR governance, appears to have failed to find an effective role.

However, there are signs that the Tripartite agencies are mobilizing. A secretariat has been formally established, based in WHO but including staff designated by the FAO and OIE in Rome and Paris. The hope is that it can become the driving force for converting words into action and have a much greater operational role and impact than hitherto.

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<sup>233</sup> World Health Organization (2019), 'New Multi-Partner Trust Fund launched to combat antimicrobial resistance globally', 19 June 2019, <https://www.who.int/news-room/detail/19-06-2019-new-multi-partner-trust-fund-launched-to-combat-antimicrobial-resistance-globally>.

### 3. Final Comments

The Review on Antimicrobial Resistance has had a global impact: as an advocacy tool, in raising the profile of AMR on the international agenda, and in helping to stimulate a number of new initiatives, in particular relating to funding early-stage research and the numbers of researchers involved in it. But there has been very little progress in its central and most expensive recommendations for transforming R&D incentives for antibiotics, vaccines and diagnostics.

There has been significant progress in reducing antibiotic use in agriculture, particularly in high-income countries, but there is a long way to go in LMICs. There has been progress in awareness raising but questions remain about its impact and effectiveness in changing behaviour. Proposals to restrict over-the-counter sales of antibiotics, as recommended by the Review, have foundered in the face of the realities of living conditions and access to healthcare in LMICs.

A major reason for the use of antibiotics in LMICs is the prevalence of unhygienic conditions, in the community and in healthcare facilities. These conditions contribute to infection and limit the impact of messages about awareness and infection prevention and control. A greater emphasis on investments in water, sanitation and housing will be central to reducing reliance on antibiotics in LMICs in the longer term. This agenda should inform the operations of governments and funding agencies such as the IMF and the World Bank. Providing quality healthcare to all and moving towards universal health coverage in LMICs will be crucial in addressing both adequate access to antibiotics and restricting over-the-counter sales.

Investments have been made in improving surveillance of antibiotic use and resistance, particularly for humans, but much more effort is required to create surveillance systems that provide data sufficiently accurate to influence policy and action. This applies also to antibiotics and resistant genes circulating in the environment.

The innovations being introduced in the global governance of AMR need to lead to action rather than more words.

# Annex 1

## Participants at the Roundtable held at the Wellcome Trust on 2 May 2019

- Jim O'Neill (Chatham House)
- James Anderson (GSK)
- Manica Balasegaram (GARDP)
- Hanan Balkhy (WHO)
- Peter Borriello (UK Veterinary Medicines Directorate)
- Charles Clift (Chatham House)
- Thomas Cueni (IFPMA)
- Sally Davies (IACG Co-Convenor)
- Elisabeth Erlacher-Vindel (OIE)
- Alyson Fox (Wellcome Trust)
- Haileyesus Getahun (WHO)
- Herman Goossens (University of Antwerp)
- Nina Grundmann (IFPMA)
- David Heymann (Chatham House)
- Tim Jinks (Wellcome)
- Cassandra Kelly (FIND)
- Jeremy Knox (Wellcome)
- Nana Kuo (UN)
- Marlieke de Kraker (HUG)
- Joakim Larsson (University of Gothenburg)
- Maria Lettini (FAIRR Initiative)
- Juan Lubroth (FAO)
- Estelle Mbadiwe (GARP, CDDEP, Nigeria)
- Donal Murphy (NOAH)
- Louise Norton-Smith (UK DHSC)
- Kevin Outterson (CARB-X, Boston University)
- Jo Raven (FAIRR Initiative)
- John H Rex (AMR Solutions)
- Jay Varma (Africa CDC)
- Ed Whiting (Wellcome)
- Ghada Zoubiane (Wellcome)

## Annex 2

### Recommendations of the Review on Antimicrobial Resistance

#### 1. A massive global public awareness campaign

- 1.1 With leadership from an appropriate global body, establish an internationally-coordinated public awareness campaign to improve public understanding of the problems of drug resistance and support positive behaviour change regarding antibiotic use. Whilst globally consistent in its overall message, this should be delivered at country or regional level, with the message and the medium (e.g. social media, broadcast advertising, celebrity endorsement) tailored to local and regional norms.
- 1.2 At a country level, establish robust regulations to prevent the sale of antibiotics and other antimicrobials ‘over-the-counter’ (OTC) without a prescription, and ensure that these are properly enforced. Such policies to be locally-tailored to recognise instances where OTC sales may be only means of accessing antimicrobials – but where this is the case, provision of proper, clinician-led access should be a priority.
- 1.3 Global organisations (including the WHO, INTERPOL and World Customs Organization) to ensure a robust and internationally-coordinated effort to prevent cross-border sales of antimicrobials over the internet without prescription. This should be supported by outright bans on non-prescription internet sales at country level.

#### 2. Improve hygiene and prevent the spread of infection

- 2.1 Governments, insurers, regulators and other healthcare system leaders should embed infection prevention and control (IPC) as a top priority at all levels within healthcare systems, using defined healthcare-associated infection (HCAI) reduction goals as the basis for targets, incentives and other performance management measures.
- 2.2 Public and philanthropic funding bodies to support improvements in funding for studies that demonstrate the effectiveness and cost-effectiveness of novel IPC interventions in health and care settings, and measures to induce positive behaviour change by clinicians and other healthcare workers.
- 2.3 Governments of low and middle-income countries should ensure that the benefits of improved public health and reduced antimicrobial resistance are properly factored into investment decisions about improved access to water and sanitation infrastructure.

### 3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination in the environment

- 3.1 The G20 and UN, with input from the WHO, FAO and OIE, should lead urgent global efforts to improve the collection and use of surveillance data regarding the use of antibiotics in agriculture, and the emergence and spread of drug-resistant microbes amongst animals. This should be prioritised over the next two years to inform targets to reduce unnecessary use of antibiotics starting in 2018.
- 3.2 International institutions with the relevant experience should undertake now a detailed economic analysis of the transition costs associated with lowering the use of antibiotics in farming across different regions and countries – particularly those in low and middle-income settings, where less analysis has been done to date.
- 3.3 The WHO, FAO and OIE should, as a matter of urgency, convene a global group of experts, working across the relevant regulatory bodies and international organisations, to agree a single, harmonised list of those antibiotics most critical to human health. This would help to inform those antibiotics that should be banned or restricted from use in agriculture.
- 3.4 Food producers and retailers to take steps should improve transparency for consumers regarding the use of antibiotics in the meat that we eat, to enable better informed decision-making by customers. As part of this we call on major producers, retailers and regulators to agree standards for ‘responsible use’, to be used as the basis for an internationally-recognised label, or used by existing certification bodies.
- 3.5 In 2018, defined targets should be established at the country level to reduce unnecessary use of antibiotics in agriculture. There will not be a one-size-fits-all target, but all countries need to play their part in reducing use. An international panel of experts will be needed to guide the design of these targets and help countries implement them, alongside support from the WHO, FAO and OIE. Our suggestions on how they could be formulated: targets could be set over 10 years, with milestones to ensure regular progress, for reductions in total agricultural usage of antibiotics. These could be defined on the basis of milligrams of antibiotic used per kilogram of meat or fish production, with consideration given to appropriate variation by species. 50 mg/kg would be a reasonable objective for many high-income countries, but each country will need to have and regularly review their own ambitious targets.
- 3.6 Global bodies/national governments and regulators should establish evidence-based, enforceable targets for maximum levels of antimicrobial active pharmaceutical ingredient (API) discharge associated with the manufacture of pharmaceutical products.
- 3.7 Pharmaceutical companies should improve monitoring of API emissions from directly-operated manufacturing facilities as well as those of third party suppliers, and support the installation of proper waste processing facilities to reduce or eliminate API discharge. Such efforts should be based in voluntary, transparent and auditable commitments, with a globally-consistent ‘quality mark’ applied to end products produced on ‘environmentally responsible’ basis.

#### 4. Improve global surveillance of drug resistance in humans and animals

- 4.1 WHO to provide global leadership and coordination to efforts – supported from governments, regional organisations, and philanthropic organisations – to establish a global surveillance system to monitor the emergence and spread of drug-resistant infections.
- 4.2 National governments/regulators and globally-representative bodies to initiate work to incentivise and remove barriers to the safe, secure and appropriate sharing of data of use to global surveillance efforts between public and private organisations on a large scale, with a particular view to unleashing the potential of advances in ‘big data’, cloud computing and machine learning in the coming years.

#### 5 Promote new, rapid diagnostics to cut unnecessary use of antibiotics

- 5.1 In high-income countries, governments, regulators and other health system leaders to support the uptake and use of rapid point-of-care diagnostics in primary and secondary care. Incentives should be considered in high-income countries to facilitate the mandatory use of such tests to support clinical decision-making, where they are available, or the use of up-to-date epidemiological data where they are not, by 2020.
- 5.2 In low and middle-income countries, the uptake and use of rapid point-of-care diagnostics to guide the use of antimicrobials should be supported via a globally-administered ‘diagnostic market stimulus’ system, providing a direct per unit subsidy to diagnostic test manufacturers upon evidence of their product’s purchase or use.

#### 6 Promote the development and use of vaccines and alternatives

- 6.1 Promote the uptake and use of existing vaccines more widely in humans and animals to save lives and reduce unnecessary antibiotic use, including through the work of Gavi or by initiating comparable new initiatives.
- 6.2 Sustain a viable market for vaccines with the greatest potential in tackling drug resistance. Depending on the characteristics of the vaccines in question, this might be through ‘pull’ funding using a similar form to existing Advanced Market Commitments (to promote broad uptake in mid to large-sized populations), or as market entry rewards (to ensure availability for smaller populations at high risk).
- 6.3 Some alternatives aim to prevent infection, as vaccines do, others to replace antibiotics as treatment, and still others to make antibiotics more effective or reduce the likelihood of resistance arising by being taken alongside them. We believe that alternatives should be eligible for the same incentives as vaccines or antibiotics, where they fulfill the same role in combating AMR.

## 7 Improve the numbers, pay and recognition of people working in infectious disease

- 7.1 Governments, healthcare system leaders and private actors (such as clinical professional bodies and academic institutions), should work together to expand funding and training opportunities to increase the number and capacity of healthcare workers on the frontline of fighting resistance, and of academic scientists working in the field. These efforts should extend to considering the pay, recognition and standing of professionals working in fields relevant to AMR within the healthcare, academic, and commercial communities.

## 8 Establish a Global Innovation Fund for early-stage and non-commercial research

- 8.1 Governments, and public and philanthropic research funding organisations, to collaborate on a global basis to develop a Global Innovation Fund for R&D into new antimicrobials and other related products (including vaccines and diagnostics.) This fund should build on existing bilateral and multilateral arrangements for pooling and coordinating the spending of research funds, but do more to ensure that AMR-related research is properly funded and more proactively targeted towards neglected areas (e.g. re-purposing of older products.)

## 9 Better incentives to promote investment for new drugs and existing ones

- 9.1 Institute a system of ‘market entry rewards’ to provide lump-sum payments to the successful developers of new antibiotics that meet a specified unmet medical need. In principle, this should be administered and funded on a supra-national basis, with support for global, affordable, and responsible access to antibiotics at its heart. Detailed work on the design and implementation of such a system should be picked up as a matter of urgency by the appropriate international partners.
- 9.2 Consider the role that such a system of market entry rewards can play in supporting the development of complete treatment regimens for tuberculosis (TB), as a means of ‘supercharging’ systems of support for TB product development.
- 9.3 Key regulatory agencies should work together to improve the global harmonisation of regulatory pathways for new antibiotics, and explore the possibilities for mutual recognition of regulatory approval across multiple jurisdictions.
- 9.4 Pharmaceutical companies, regulators and healthcare system leaders to work together to institute national and regional ‘clinical trial networks’ for antibiotics, to streamline the clinical trial process and reduce the costs and duration of antibiotic development.

## 10 Build a global coalition for real action – via the G20 and the UN

- 10.1 The G20 group of countries should take leadership on defined aspects of the global response to AMR, particularly work to develop and implement new incentive models to support the development of new antibiotics, diagnostics and vaccines. This should be complementary to wider discussions on the global response to AMR as part of the UN General Assembly, and the continuing efforts of the WHO, FAO and OIE in their respective sectors.
- 10.2 Governments and relevant global bodies to initiate rapid work to consider in detail the global coordinated structures which would be required to oversee the development, implementation, and operation of global systems of financial support for antibiotic and diagnostic development and use.
- 10.3 Governments, industry and relevant global bodies should continue to work together to identify adequate and sustainable global, national and local funding mechanisms for raising the money required to finance a long-term global response to AMR. This should include the exploration of – amongst other options – mechanisms to raise revenue from new sources and on a hypothecated basis, for instance through modest and targeted levies on antibiotic use and/or on the global pharmaceutical, healthcare products, and medical device industries.

## About the Author

**Charles Clift** is a board member of the Medicines Patent Pool, a Swiss charitable foundation seeking to increase access to medicines for people living with HIV and other diseases in developing countries. For a large part of his career he worked as an economist in the UK Department for International Development with experience of working in Kenya, India and the Caribbean.

From 2004 to 2006 he was a staff member of WHO. In addition to his work for Chatham House, he has been a consultant to WHO, UNITAID, the World Intellectual Property Organization, Wellcome and the Access to Medicine Foundation.

His research interests at Chatham House include counterfeit medicines, global health governance and financing, and antimicrobial resistance.

## Acknowledgments

Covering all the aspects of the Review and all aspects of the AMR issue was a challenge and could not have been done without the help of, and inputs from, many people. Special thanks are due to:

- Wellcome for funding this work and sharing their extensive expertise in the Drug-resistant Infections Programme team – in particular Jeremy Knox and Rebecca Sugden, who provided help and advice throughout.
- Colleagues at Chatham House for their help and assistance in producing and editing this report.
- Participants at the roundtable (listed in Annex 1), many of whom also commented on the draft of this report.
- Further experts who also provided valuable peer review comments on the draft of this report.

Finally, it was a pleasure to work with Jim O'Neill. He largely left me to my own devices and did not attempt to steer the report in any particular direction while clearly having his own views, as he has expressed in the foreword to the companion research paper and elsewhere!

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Cover image: An employee writes on a prescription pad for a patient of Halodoc's online healthcare platform at an Apotik Mahakam pharmacy in Jakarta.

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ISBN 978 1 78413 369 6

This publication is printed on FSC-certified paper.



Typeset by Soapbox, [www.soapbox.co.uk](http://www.soapbox.co.uk)

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