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(Inter)nationalising the antibiotic research and development pipeline

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Abstract

This paper critically examines the wider context of international efforts to stimulate commercial antibiotic research and development (R&D) via public-private initiatives. Despite these efforts, antibiotics remain a global common without an international support structure that is commensurate to the risks from antibiotic-resistant infections and the long-term nature of required solutions. To protect this common, we propose a two-pronged antibiotic R&D strategy based on: (1) a short-term strengthening of incentives, such as market entry rewards, to maximise the delivery of existing opportunities in the pipeline; and (2) a concurrent medium- to long-term establishment of a global, publicly-funded antibiotic R&D Institute. Designed to sustainably deliver novel and first-in-class antibiotics targeting key human health gaps, the Institute and its staff would become a global resource that, unlike the private pharmaceutical sector, would be managed as an open science platform. Our model of internationalised public R&D would maximise scientific synergy and cross-fertilisation, minimise replication of effort, acquire and preserve existing know-how, and ensure equitable and sustainable access to novel and efficacious antibiotics. Its genuinely global focus would also help counteract tendencies to equate donor with global health priorities. Our proposal is not radical. Historical precedent and developments in other research areas show that sustained international funding of publicly owned research can hasten the delivery of critically-needed drugs and lower access barriers.

Introduction

For over three decades, the scale and trend of research and development (R&D) investment into novel antibiotics has not been proportionate to the global risks and demand. This discrepancy is acknowledged by academia[1–3], World Health Organisation (WHO) member

states[4,5], and by the recent Interagency Coordination Group on Antimicrobial Resistance (IACG)[6]. Initiatives to 'push-pull' the pharmaceutical industry into antibiotic R&D have focused on creating public-private development platforms, which use public money and funds from major health donors to incentivise drug development. Despite significant investment into R&D of promising compounds in pre-clinical stages of development, no new class of antibiotics has been approved, and commercial developers continue to leave the field voluntarily or due to economic necessity. This is in part due to the difficulty in finding promising chemical start points and due to the rigour of stop / go decisions which are linked to the current economic model based on return[7]. The ongoing market weakness and the real risk of losing anti-infectives R&D expertise[8] require a broad analysis of current modes of antibiotic R&D and potential alternatives.

Panel 1

In this interdisciplinary paper, we propose a two-pronged short- and longer-term response to the crisis of antibiotic development: (1) a time-limited short-term expansion of push-pull incentives, e.g., 'market entry rewards' to secure existing public investment in promising compounds and to stem the loss of private sector antibiotic expertise and human capital; and (2) a medium- to long-term solution consisting in the establishment of a publicly owned international R&D Institute to guarantee sustainable and equitable global antimicrobial access. Ultimately, international public ownership of antibiotic research, drug trial capabilities, and licensing powers – an (inter)nationalisation of antibiotic R&D – is the most promising alternative, or Plan B, to the sputtering commercial pipeline.

Existing Responses: from private to public-private

Diagnoses of a broken antibiotic pipeline date back to the 1980s and have acquired ever-increasing urgency due to increasing antimicrobial resistance (AMR) and a greater international focus on (re)emerging infectious diseases[9,10]. Despite high-level warnings[11], difficulties in navigating regulatory pathways, low-profit margins, and the likelihood of

stringent stewardship requirements have deterred commercial investment in antimicrobial R&D and led to companies leaving the field[11–13]. Between 2016 and 2018, pharmaceutical giant AstraZeneca abandoned antibiotic development[14] and both Sanofi and Novartis exited in 2018-19. In April 2019, biopharmaceutical developer Achaogen filed for bankruptcy despite injections of public money to develop its antimicrobial candidate Zemdri (plazomicin) and FDA approval of the drug for complicated urinary tract infections in June 2018[15]. Numerous organisations have proposed ways to respond to ongoing market failures and reinvigorate antibiotic development (Table 1).

Table 1: Major international public-private initiatives

Year	Initiative
2008	As part of the EU-funded Innovative Medicines Initiative (IMI) (2008-2020),[16] the **'New Drugs for Bad Bugs' (ND4BB)** initiative represents an investment of $780 million in antibiotic R&D[17]. Within ND4BB, the EU- and industry-funded COMBACTE-MAGNET project is developing new compounds including a new beta-lactam antibiotic (AIC499, developed by AiCuris) with activity against a broad range of multidrug-resistant Gram-negative bacteria and a monoclonal antibody (MEDI3902, developed by AstraZeneca), with activity against *Pseudomonas aeruginosa* (in clinical trial)[18]. ENABLE (est. 2014) is another ND4BB programme to advance the development of antibiotics against Gram-negative bacteria[19,20]. Universities and small and medium-sized enterprises (SMEs) have been supported by ENABLE to progress potential antibiotics through early stages of drug development. Candidates include: apramycin, dabocillin, and thiophene[19,21].
2015/2018	The second and sixth calls of the EU's **Joint Programming Initiative on Antimicrobial Resistance** (JPIAMR) sponsored academic-industry initiatives for the repurposing of neglected antimicrobials with €4.5 million and novel antimicrobial therapy development with €14.4 million[22].
2016	Established by the WHO and the Drugs for Neglected Diseases Initiative, the **Global Antibiotic Research and Development Partnership (GARDP)** is a not-for-profit R&D organization that develops and delivers new and improved antibiotic treatments while endeavouring to ensure their sustainable access. So far, GARDP has attracted ca. $70 million and is fundraising for more than $200 million[23]. GARDP's Antimicrobial Memory Recovery & Exploratory Programme (AMREP) aims to recover the knowledge, data, and assets of forgotten, abandoned, or withdrawn antibiotics as well as seeking new drugs via an online platform called REVIVE[24,25].

	GARDP's "5 by 25" initiative calls upon the global community to work with it to develop five new treatments by 2025 to address the most urgent public health needs[26]. Within the same timescale, GARDP also aims to have recovered two new antibacterial entities in pre-clinical or clinical development. In 2017, GARDP signed a license agreement with commercial manufacturer Entasis to support the development of a new gonorrhoea drug (zoliflodacin)[27].
2016	**Combatting Antibiotic-Resistant Bacteria-X (CARB-X)** is the largest non-profit public-private R&D initiative. It has attracted over $550 million (US) of investment capital and has supported more than 40 developers in 7 countries – including, until April 2019, Achaogen[28]. CARB-X is funded by the US government's Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID), the Wellcome Trust, the UK government's Department for Health and Social Care, Germany's Bundesministerium für Bildung und Forschung (BMBF), as well as the Bill and Melinda Gates Foundation[29]. BARDA, in particular, supports antibiotic R&D for biodefense, including more than $1B invested in supporting Phase 2 and Phase 3 clinical development, purchases for the US Strategic National Stockpile as well as funding, technical assistance, and access to the Centers for Innovation in Advanced Development and Manufacturing[29]. CARB-X sponsorship is tied to significant commercial investment (cost-share), acceptance of stewardship requirements for new drugs, and support for equitable access to new medicines throughout the world.
2018	Funded and commissioned by the Danish Novo Nordisk Foundation, the **REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund** is a for-profit venture capital effort aimed at discovering and promoting early-stage development of therapies targeting resistant microorganisms with a budget of $165 million[30]. An additional $20-40 million over 3–5 years is planned for investment in ca. 20 projects in Europe and the U.S., to deliver one new therapy to market[30].
2018	Between 2018 and 2028, the German government will invest €500 million in coordinating global AMR research efforts – including support for GARDP and CARB-X. Germany has also facilitated the launch of the Berlin-based **Global AMR R&D Hub**, which aims to improve the coordination of international efforts to tackle AMR while further increasing investments into R&D for AMR.[31]
2019	Britain's **National Health Service (NHS)** will incentivise drug development with the help of a pioneering subscription model, which pays private companies upfront for access to new drugs depending on their usefulness[32].
*Many initiatives have received funds from national governments as well as from AMR-focused programs by the Wellcome Trust (2016-2021), Bill & Melinda Gates Foundation (2018-2022), and US National Institutes of Health (2016-2018); and UKAID (2018-2021).	

Existing push incentives like grants provided by CARB-X and GARDP or pull incentives like market entry rewards, subscription models like those recently announced by the NHS, or new antibiotic reimbursement models by Medicare in the US may well lead to a new antibiotic class and improved diagnostics. In the short-term, public investment in well-established pharmaceutical knowledge and production infrastructures will also help slow the loss of commercial R&D expertise. However, in the medium- to long-term, it remains doubtful whether existing public-private initiatives will be able to retain this expertise and refill the antibiotic pipeline.

The comparatively low level of international public and private investment is one reason for this. Delivering antibiotic R&D within the commercial framework of drug development is expensive, and although there is room for substantial efficiency improvements,[33] the overall cost of clinical trials remains a significant financial barrier (Table 2).

Table 2: Estimated costs of clinical trials

Clinical Trial Phase	Median cost ($million) from 2017 study [33]
I	3.4
II	8.6
III	21.4
I-III	33.4
Total cost of bringing a new drug to market	
Dates	Cost
1983-2009	$0.802 to 2.2 billion[34]

2013[34]	$2.6 billion

Some public-private initiatives are already trying to overcome this barrier. In the US, CARB-X funds compounds up to the completion of Phase I. It can then 'hand-off' promising compounds to BARDA for evaluation of possible funding of Phase 2 and 3 clinical trials (Kevin Outterson, personal communication). However, even if a compound makes it past Phase I, it remains uncertain whether further commercial investment in it will pay off. According to the PEW Trust, fewer than one in five infectious disease products entering human testing at Phase One will be approved for patients[35]. This means that only ca. 13 antibiotics currently in Phase 1 will likely gain FDA approval– where their sales will probably be subject to strict stewardship requirements[36]. Despite the new public-private partnerships, commercial investment in antibiotic R&D remains a high-cost, low-reward endeavour.

Combined with declining industry investment, the high costs and financial risks of antibiotic R&D make it extremely ambitious to expect the ca. $0.62 billion invested by high-income governments and donors in GARDP and CARB-X between 2016 and 2019 to generate one new antibiotic class. Expecting this scale of investment to sustainably regenerate the commercial antibiotic pipeline in the medium- to long-term is over-ambitious and unlikely to pull-in significant industry reinvolvement. In the case of the EU's ENABLE initiative, €100 million of public funds over six years failed to generate sufficient private involvement by industry partners leading to an end of the initiative in 2020 (personal Communication Kevin Outterson).

While it is difficult to disaggregate pure R&D investment from market-shaping purchasing and rollout pledges, other examples of public-private research efforts indicate relative international underinvestment in new antibiotic development (Table 3).

Table 3: Major R&D funding for vaccines, HIV, tuberculosis, and malaria
The Coalition for Epidemic Preparedness Innovations (CEPI) (est. 2016) focuses primarily on vaccine development. So far, CEPI has established partnership agreements reflecting a potential investment of over $350 million in private vaccine development[37].
The public-private Global Alliance for Vaccination and Innovation (GAVI) (est. 2000) attracted ca. $9 billion between 2016 and 2020 for vaccine development and rollout efforts in GAVI-eligible low-income countries[38]. GAVI is financed by direct public and donor contributions as well as by innovative bond financing, which respectively accounts for 77% and 23% of its funding portfolio[39].
The Global Fund (est. 2002) invests almost $4 billion per year in research, drug procurement, treatment, and prevention of tuberculosis, HIV, and malaria[40]. In the case of malaria, the Global Fund invested over $11.4 billion in control programs in more than 100 countries between 2002 and 2018 (60% of international funding) and aspires to raise a further $14 billion over the next three years to halve the mortality rate from HIV, TB and malaria[41].
As a major sponsor of GAVI, the Gates Foundation spent about $282 million on vaccine R&D in 2017 alone (Personal Communication Gates Foundation).

Since 2000, GAVI and the Global Fund, purchase guarantees, and co-financing mechanisms have played a major role in reinvigorating international R&D for vaccines, drugs, and other technologies for disease prevention, control, and treatment. This is in addition to further substantial private R&D investment by commercial actors, who remain active in the vaccine and antiretroviral fields. International investment in antibiotic R&D remains comparatively weak.

In addition to high costs and relative underinvestment, the fragmentation of publicly funded antibiotic R&D initiatives poses another problem. Although a plurality of initiatives can help avoid monopsony and false negatives (i.e., the elimination of potentially fruitful drugs), the growing number of small- to medium-sized efforts risks fragmenting public funds and limiting individual public-private initiatives' scope of investment. Despite actors' best intentions, a fragmented R&D scene also risks the unnecessary duplication of bureaucracies, creating competing public research portfolios, and incentivising free-riding by actors, who may not support R&D but will still profit once new drugs emerge.

It is moreover questionable whether proprietary developers are the most effective vessel for public R&D money. Although they can incentivise early stage antimicrobial research and facilitate knowledge sharing, the new public-private initiatives continue to rely on pre-existing proprietary infrastructures to conduct trials, upscale production, and rollout drugs. This management approach to publicly sponsored drug development has several downsides. While organisations like CARB-X or major funders like the EU and Wellcome Trust can mandate that 'knowledge' be made public beyond the mandatory patent disclosure, the expertise required for bringing a new drug to market remains within the private enterprises. This means that antibiotic pricing and market incentives will still have to satisfy private companies' need to generate profit and shareholder value. It also entails that publicly funded knowledge will remain vulnerable to commercial failure and bankruptcy.

Finally, any public-private, commercial, or public initiative will face a problem of regional bias if it mostly targets high-income countries (HICs) and markets. In developmental aid, there is a history of equating donor with international health priorities and occasionally using aid to indirectly subsidise the domestic companies and sectors tasked with providing it[42–44]. In the case of antibiotics, one of the key challenges is to tackle the dearth of effective and affordable drugs in low- and medium-income countries (LMIC)[45,46]. While Britain's new

subscription model may well kick-start a new form of delinked drug marketing, it is reasonable to assume that the NHS will define a drug's usefulness with respect to needs identified within the United Kingdom and only secondarily in relation to LMICs and the WHO's global list of priority pathogens[47]. Push incentives primarily targeting companies in HIC markets can lead to similar R&D biases. Achaogen's publicly subsidised drug plazomicin was effective against extensively-drug resistant Gram-negative bacilli, which are commonly recognized as a prime area of need for new antimicrobials[48,49]. However, Achaogen was forced to declare bankruptcy because there was a mismatch between identified global health needs and actual sales in the US market. In the US, gram-negative infections represent only a relatively small market (£115 million, in 2018) as compared to gram-positive pathogens (£215 million, in 2018)[50]. Profit outlooks for plazomicin were further compromised by short treatment durations and its use as an antibiotic of last resort. Plazomicin's ultimate failure was thus not because it did not meet global health priorities, but because it did not sufficiently satisfy the for-profit logic of one HIC market. Only initiatives that are truly global in their ambition and sponsoring will solve the global AMR crisis.

Solutions: from public-private to public

Developing a more robust, equitable, and international antibiotic pipeline entails the dual recognition of the short-term advantages and mid- to long-term disadvantages of public-private initiatives. It would be counterproductive to abruptly stop financing public-private antimicrobial R&D and jeopardize existing investments in promising compounds, infrastructures, and expertise. However, in the mid-to-long-term, a more sustainable, integrated, cost-effective, and equitable use of public money will most likely be achieved by a targeted (inter-)nationalisation of publicly financed antibiotic R&D.

155

156 Short-term: protecting public investment by shoring up the market

157 In the short-term, push-pull incentivisation is a necessary response to the pharmaceutical
158 industry's failure to adequately react to the global antibiotic crisis. Despite decades of
159 underinvestment, the pharmaceutical industry continues to represent the most equipped
160 'body' to undertake antibiotic innovation. Companies possess the infrastructure for R&D and
161 physical manufacturing of drugs and decades of proprietary knowledge about promising
162 avenues of research within their laboratories, databases, and staff that can be leveraged to
163 immediate effect. Short-term support of push-pull incentives, thus maximises society's multi-
164 decadal investment in industrial research and protects existing proprietary antibiotic R&D
165 knowledge before it is lost by the discontinuation of commercial research efforts[14,51–53].

Panel 2

According to the IMI's DRIVE-AB (Driving reinvestment in research and development for antibiotics and advocating their responsible use) initiative, public-private programs should be multi-faceted and comprise:

(1) push-incentives like grants (i.e., non-repayable funds for R&D given to academic institutions, companies, etc.);
(2) pipeline coordinators (i.e., non-profit/government bodies that track gaps in the pipeline and support R&D to fill them);
(3) pull incentives, like market entry rewards (payments to antibiotic developer for meeting a defined public health need); and
(4) long-term supply continuity models (i.e., delinked payment to ensure a supply of generic antibiotics).

166 Several examples of 'push-pull' incentives are already being supported by BARDA, the EC,
167 the IMI, and – most recently – Britain's NHS (see Table 1), and have been endorsed in expert
168 reports from Chatham House[54], the AMR Review,[45] the Margolis Centre for Health Policy[55].
169 According to the EU's DRIVE-AB initiative (Panel 2), pull-incentives, like market entry
170 rewards, could be made available to manufacturers of antibiotics that fill a public health gap
171 and could amount to approximately €170 million per antibiotic over five years after

regulatory approval[56]. Short-term push incentives could also include grants for non-BARDA eligible Phase 2 and Phase 3 clinical trials outside the US.

These efforts offer the possibility of using public money to secure a short-term 'win' by leveraging the existing pharmaceutical pipeline for compounds and protecting valuable commercial R&D expertise from being lost. However, it is questionable whether public-private initiatives offer a viable long-term solution. Although a limited number of new compounds will likely be marketed in the near future, public-private efforts have so far failed to rejuvenate the antibiotic pipeline.

Medium- Long-term: ensuring sustainability via public ownership

Antibiotic effectiveness is a global commons resource[57], hence, the global common must ensure this resource is produced efficiently, maintained sustainably, and distributed equitably. Rather than indefinitely subsidising a dry commercial pipeline, these goals can best be achieved through core public funding and a wider transformation of the pharmaceutical R&D pipeline.

Rather than using limited funds to manage fragmented research efforts, which would still be subject to commercial profit incentives and proprietary knowledge retention, participating nations would form a ring-fenced, pool-funded infectious disease R&D Institute that would fund permanent staff to take on the role previously assigned to pharmaceutical companies in the production of novel antimicrobials. The formation of such an Institute would create a permanent, integrated, open, and transparent 'home' for the two key resources produced during pharmaceutical R&D: knowledge and skill. Protecting human capital within drug discovery and development is essential if we are to avoid having to relearn the trade and repeat mistakes at the exact time when we cannot afford to do so[49]. Novel antibiotics would

196 be a public commodity that could be developed according to a prioritisation process of
197 greatest need rather than greatest profit and disseminated according to a principle of "shared
198 burden." Nations would only need to cover the costs of manufacture, as the cost of R&D
199 would already be covered by long-term core funding. Differentiated financing with higher
200 HIC contributions would also lead to ‘at cost’ provision of generic antimicrobials in LMICs,
201 where access to safe and affordable medicines remains unsatisfactory.

202 The proposed (inter)nationalised antibiotic R&D pipeline would be open and transparent in
203 its methods, data, and expertise. The Bermuda Principles offer a model for how shared
204 financial burdens can be converted into a shared knowledge resource[58,59]. Competing with
205 Craig Venter’s commercial sequencing project, the Bermuda Principles stipulated that large-
206 scale publicly-funded human genome sequencing would be “freely available and in the public
207 domain in order to encourage research and development and to maximise its benefit to
208 society”[60]. Such transparency and openness hastened knowledge of much more than just the
209 human genome (e.g., mouse and *C. elegans*), while also protecting against the patenting of
210 every sequencing effort[58].

211 Just like the Human Genome Project, the proposed Institute can offer a networking role for
212 academic and non-academic antimicrobials’ research. The Institute can be a nucleating point
213 for antibiotic R&D researchers to declare their research intentions, thereby minimising
214 replication of effort, leveraging existing knowledge, and sparking collaboration. It would also
215 greatly facilitate the efficient horizontal integration of drug development efforts with equally
216 important R&D on improved bacterial diagnostics and antibiotic alternatives, including
217 vaccines. This effort would be open-ended to ensure sustainable and equitable development
218 of a steady stream of new drugs for generations and not just as a stopgap to ensure antibiotic
219 availability for the immediate future.

Implementation of an 'Open Source Pharma' system (Panel 3), could be greatly hastened by the wholesale public purchase of existing commercial antibiotic pipelines, thereby (inter)nationalising efforts, removing ineffective forms of proprietary development, and publicly pooling decades of knowledge about promising compounds[61]. At an estimated cost of less than $5 billion (K. Outterson, personal communication), existing antibiotic pipelines would also cost considerably less than what would be required to finance current pull incentives[62].

Panel 3

In accordance with the principles of the Open Source Pharma (OSP) movement and the April 2019 UN IACG call for governmental production and supply of strategic antimicrobials[6,75], two interconnected solutions emerge to reinvent the antibiotic pipeline: (1) pooling national resources to create a ring-fenced (protected/guaranteed) long-term international R&D Institute to manage, actively develop, and roll out new antibiotics as well as secure existing human capital and expertise (see Singer, Kirchhelle & Roberts 2019)[76]; (2) using public money to acquire existing on-patent and prospective antibiotics, antibiotic development infrastructures, compound libraries, and research platforms[77].

Viability

There is clear evidence that not-for-profit public drug development and production can be effective and equitable. State financing, management, and – in several cases – ownership of the infrastructures used to discover, trial, and rollout promising compounds underpinned important phases of antimalarial and antibiotic development on both sides of the Iron Curtain. In the case of penicillin, the Allies pooled national resources to develop, upscale, and rollout a promising novel and unpatented compound. Within half a decade of basic research starting

in Oxford, UK, the Allies were producing enough penicillin to supply the entire D-Day landing force. A large part of modern vaccine development was also driven not by private, but by state institutes or institutes funded by public subscription. In the case of antimalarials, state-funded military research produced important current compounds[63–67].

Examples of successful not-for-profit funding also encompass the present. Although it does not develop new compounds, Civica Rx has emerged as a novel not-for-profit generic drug company in response to medication shortages and high prices in the U.S.[68,69]. Civica Rx is made up of seven healthcare organizations, representing about 500 U.S. hospitals. It will either directly manufacture generic drugs or sub-contract manufacturing to contract manufacturing organizations, giving Civica Rx members reliable access to affordable generic medication.

Our proposed model of ring-fenced international funding for drug development is already working in other fields. International partnerships such as the Climate Investment Fund, the Global Environment Facility, the Green Climate Fund, and the Multilateral Fund for the Implementation of the Montreal Protocol have successfully harnessed multi-lateral resources to protect global commons[54].

Recent large-scale international science projects also demonstrate the capacity of the global community to generate significant long-term funding for basic and applied research as well as the ability to coordinate work effectively across a wide range of countries (Table 4)[54]. It is not far-fetched to think that similar ring-fenced funding systems would work effectively for international public antibiotic development and ownership.

Table 4. International funding of large-scale collaborative science projects	
Project	**Cost (US$)**
Square Kilometre Array radio telescope	$1.5-2 billion
Human Genome Project	$3 billion
Large Hadron Collider	$4.4 billion
International Thermonuclear Experimental Reactor	$50 billion
International Space Station	$150 billion

There are multiple ways of financing internationalised antibiotic R&D. The most traditional way consists of fixed government contributions to finance internationalised R&D efforts. In 2012, the WHO's Consultative Expert Working Group recommended a commitment of 0.01% of GDP from WHO member states, which would already raise $4-5 billion per year if only OECD countries participated[54] In recent years, other reports have proposed additional models of co-financed antibiotic R&D. In 2015, a Chatham House Report suggested a range of possible funding sources and mechanisms including an airline tax[54]. UNITAID, for example, raised $1.408 billion through an airline tax for the treatment of HIV/AIDS, malaria, and tuberculosis. An additional Chatham House proposal was to allocate 10-20% of national antibiotic expenditures as a kind of 'insurance' towards the future of antibiotics. An equivalent investment by the U.S. would be approx. $6 per resident and yield $2 billion; when combined with EU investments, this insurance could amount to $3 billion per year[54]. Other authors have proposed a fee on nonhuman antibiotic use to minimise global drug consumption and subsidise antibiotic R&D efforts[7071].

In addition to taxation, antibiotic usage fees, and insurance payments, the 2016 AMR Review proposed a 'pay or play' model. Since a large part of medical procedures and treatments rely on antibiotic efficacy, the pharmaceutical sector as a whole should contribute to the development of new antibiotics[49]. The international community and individual governments

could mandate an 'antibiotic charge' for firms selling healthcare products and pool resulting revenues to finance R&D and push-pull incentives like market entry rewards. Charges could be reduced for companies already investing in antibiotic R&D. Ideally, 'pay or play' models could simultaneously finance public R&D efforts and stimulate private re-investment without burdening tax payers[49].

$4-5 billion per year resulting from a 0.01% GDP contribution by OECD countries would not only be sufficient to significantly boost R&D into new compounds but could also buy out large parts of the stalled commercial antibiotic pipeline within two years. According to the 2016 O'Neill Report, $1.6 – 3.7 billion per year for 10 years could already deliver a comprehensive package of interventions to radically overhaul the antibiotics pipeline[49].

The required investments in antibiotic R&D are remarkably small when compared to other recent public interventions into failing market mechanisms. In 2008, the US government's Troubled Asset Relief Program (TARP) mobilised $426.4 billion of taxpayers' money to 'bail out the banks' [72]. More recently, Ofwat, the economic regulator of the water sector in England and Wales, called for extra investment by the water industry of £6 million a day for five years to improve the environment and provide services for a growing population[73]. This equates to £11 billion ($13.73 billion US) over five years, all of which, ultimately, comes from the relatively small English and Welsh publics. In comparison to the funds mobilised to maintain banking and water services, the volume of public funding required to maintain basic chemotherapeutic services during a time of antimicrobial crisis is relatively minor.

Public investment in publicly-owned antimicrobial commons would also yield measurable financial and health returns. Recuperation of initial investments can be quantified through shared ownership of the pipeline and the value associated with serendipitous discoveries that would otherwise be patented by the private sector. The investment in skills and knowledge are hard to quantify, but the capacity to sustainably deliver efficacious drugs into the future

will have societal value through higher quality of life, reduced hospital stays, and medical bills. Perhaps most importantly, the not-for-profit nature of the Institute and the at-cost provision of drugs to members would significantly reduce expenditure on antimicrobials in high- and medium-income countries, create strong membership incentives, deter attempts to free-ride, and enable affordable antibiotic access programs for the poorest parts of the world – in perpetuity.

While the urgency of the AMR crisis and decades of failed commercial solutions underline the need for an (inter)nationalisation of R&D, reinventing the international antibiotic pipeline should, however, not lead to a research monoculture. There are advantages in maintaining a diverse research portfolio, which can also comprise commercial components. Building on existing entities like CARB-X, public funds could still be used to incentivise bottom-up private antibiotic R&D via market entry rewards or patent buyouts. Limited competition between non-profit organisations or public utilities over antibiotic development and production might also be useful in maintaining pressure for efficient public R&D. We are similarly not against private companies re-entering the antibiotic marketplace. Our proposed publicly-funded R&D Institute is a response to lacking commercial interest and the use of public money to subsidise for-profit development – not a condemnation of private innovation *per se*. There are many opportunities in novel antibiotic development , particularly in HICs– that preclude direct competition.

However, after three decades of stalled development, unequal drug access, and rising AMR, it is time to rethink for-profit R&D as a default of antibiotic policy. Following Lord O'Neill's recent appeal to the G20,[74] the time for action is now. Our proposed R&D Institute might not be the most expensive international call to action, but it can arguably make a critical contribution to maintaining global control of infectious disease.

Conclusion

Our proposals here are focused on developing new broad and long-term approaches to international antibiotic development. The cost of research efforts, the global scale of AMR, and ongoing access issues necessitate an internationalised, integrated, and equitable approach to drug research, ownership, and stewardship. While a short-term intensification of public-private sponsorship is necessary to protect existing investments and prevent a global loss of antibiotic R&D expertise, we believe that public ownership of antibiotic R&D is a more attractive, sustainable and equitable medium- to long-term solution to refilling the stalling antibiotic pipeline. Boosting public investment and (inter)nationalising antibiotic development infrastructures will improve health outcomes and maximise the societal yield of spending on antibiotic compounds and expertise. Antimicrobials remain essential workhorses for the functioning of global health care and food production systems. Ensuring that humanity retains access to a sustainable pipeline for new drugs requires us to think beyond conventional models of proprietary development.

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