NIMble innovation—a networked model for public antibiotic trials

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Antibiotic research and development is at an inflection point. Faced with ongoing problems with commercial innovation, we argue for a networked public approach to support and coordinate existing research and development initiatives by sustainably moving promising compounds through clinical trials. We propose a global public infrastructure of institutes tasked with (1) conducting all trial stages up to market authorisation, including small-scale compound production; (2) negotiating licensing agreements for global production and distribution by industry partners; and (3) using public purchasing agreements or subscription models to ensure commercially viable drug production at equitable prices. We invite stakeholders to consider our Networked Institute Model's benefits for unblocking the public and private antibiotic pipeline.

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Introduction

Antibiotic resistance is a global crisis. Although risk estimates differ,[1–4] there is an agreement that a globally coordinated response is needed,[5–7] including innovation in research and development (R&D) pipelines to create antibiotics with novel modes of action[8] that target priority pathogens.[9] Responding to market failures caused by low financial returns and stewardship requirements for new drugs,[10] the past 10 years have seen funders try to re-invigorate commercial investment with economic push and pull incentives.[11] Increased funding by governments (eg, Innovative Medicines Initiative: DRIVE-AB[12] and ENABLE; Biomedical Advanced Research and Development Authority[13]), charities (eg, Wellcome Trust), private industry (eg, AMR Impact Fund: REPAIR), and non-governmental bodies (eg, CARB-X and Global Antibiotic Research and Development Partnership) means that early-phase antibiotic R&D has yielded more promising compounds than in nearly 30 years, and some of these compounds are now in late stages of clinical trials.[14,15] This success shows that public incentives can increase R&D activity at this early stage in the pipeline.[16]

Although the preclinical stage was the most tractable area for public stimulus, success throughout later stages of the R&D pipeline has been more limited. Funders' support for individual companies and compounds has led to the licensing of several new antibiotics (eg, plazomicin, eravacycline, sarecycline, omadacycline, pretomanid, lefamulin, and cefiderocol). However, funding and case-by-case support for innovation remain insufficient to address the scale of antibiotic resistance and to halt the loss of private sector investment and expertise.[15,17,18] With inadequate investment from major companies, many compounds developed by universities and small-sized and medium-sized enterprises fail to progress through trials or generate sufficient post-licensing income.[19,20] R&D also continues to disproportionately focus on high-income countries, despite higher disease burdens and antibiotic resistance threats in low-income and middle-income countries.[15,17,18] As already argued in previous publications,[21–23] improving antibiotic innovation therefore depends on creating a system capable of enhancing funder coordination, focusing R&D on priority pathogens, and reliably moving promising compounds through clinical trials to distribution.

In this Personal View, we suggest a solution in the form of internationally networked and publicly funded clinical trial institutes. Complementing and coordinating rather than replacing existing R&D support, our proposed Networked Institute Model (NIM) would create an accessible infrastructure capable of conducting all stages of antibiotic clinical trials, including the small-scale production of promising compounds for those trials, up to market authorisation.

Challenges of the existing R&D ecosystem

Efforts to increase antibiotic innovation have relied on neoclassical economic models favouring stimuli for market-based solutions. Push incentives include investment in, and subsidies for, public and private sector R&D and trials. Pull incentives include profit guarantees for commercial developers that hold financial risk in the public sector.[24] Since 2017, funders have injected over US$ 3 billion into research on new anti-infectives and support for clinical trials[25] (figure 1, panel [accurate as of June 20, 2021]). Since 2019, pull initiatives to incentivise private R&D investment or keep new antibiotics available in small markets include proposals for higher pricing and exclusivity guarantees in the USA, and the adoption of subscription payment models in the UK and Sweden.[20,26]

It is appropriate that the public sector takes on high-risk, high-public reward projects that have not gained commercial traction. In the case of antibiotic R&D, the long-term economic merits, public use, and sustainability of the described private or public–private models remain unclear. According to CARB-X Executive Director and Principal Investigator Kevin Outterson, "of the 18 antibiotics approved in the past decade, the makers of seven have either gone bankrupt or their investors have lost most of their money".[27] A worrying example is that of the publicly supported company Achaogen, which declared bankruptcy in 2019 despite approval from the US Food and Drug Administration of its antibiotic plazomicin.

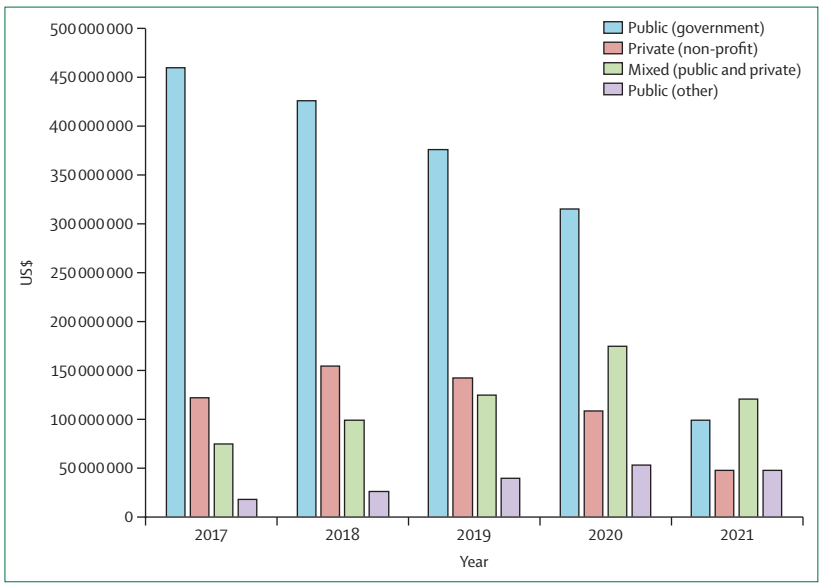

Figure 1: **Total infectious agent product development investments from 2017 to 2021 by type of funder (in US$)[25]**

Until recently, the majority of investment into infectious agent product development was supplied by a government agency or other publicly funded organisations. Total investments across all funding sources have declined or remained unchanged over the past 5 years.

Panel: **Total investment for infectious agent product development by type of research organisation in 2017–21 (in US$)[25]**

- $1 318 904 809 from universities
- $956 183 700 from industry and small-sized and medium-sized enterprises
- $706 401 984 from public research institutions and facilities
- $185 242 950 from industry
- $115 338 452 from other entities
- $32 252 171 from public bodies
- $10 427 738 from private research institutions and facilities

A subsequent attempt by Indian pharmaceutical manufacturer Cipla to gain approval from the European Medicines Agency for plazomicin also failed because of the costs of generating approval and post-approval data.[17] Although some might link this failure to the performance of plazomicin rather than a wider problem, profitability concerns also affect the preclinical pipeline. In April, 2021, US-based company X-Biotix Therapeutics announced it was suspending preclinical antibacterial research due to insufficient funding and market infrastructure.[28] Tellingly, GlaxoSmithKline has continued to streamline its antibiotic business by selling off its cephalosporin production and closing down facilities, despite the announcement of an additional $1 billion industry and philanthropic antibiotic initiative.[29,30] Extending the timelines for funders' goal of developing three to four antibiotics by the end of the decade are already being discussed,[31] and only five large pharmaceutical companies remain in the field.[20,17]

NIM

Although public–private initiatives have long appeared the most politically feasible option to reignite antibiotic innovation and combat market failures, the COVID-19 pandemic has reshaped the willingness of states to consider public, non-profit solutions for health problems. In the absence of a viable unsubsidised market, there are also calls for new open science-based approaches to antibiotic R&D.[32]

Our proposed mission-oriented[33] network of public institutes would address the clinical trial and manufacturing bottleneck by bridging the so-called valley of death of clinical trials for new antimicrobials. The NIM would carry out all stages of clinical testing, including the small-scale production of promising compounds for trials. Intellectual property for successful compounds would rest with the NIM as the market authorisation holder in return for royalties as well as academic credit, or as a result of patent buyouts from academic institutions and small-size and medium-sized enterprises. Global production and distribution could be achieved via long-term licensing and purchasing agreements with industry (figure 2).

The NIM's development route would create a central public offloading point for preclinical compounds and would help coordinate existing efforts by public–private initiatives—some of which are already financing clinical trials on an ad hoc basis. Over time, NIM infrastructure would build public trial expertise and act as an early pull mechanism itself. After successful trials and regulatory approval, institutes would negotiate with industry partners for the commercial manufacture and distribution of antibiotics via licences and agreements mandating equitable pricing and environmentally sound production standards. Similar to subscription or monopoly supply models, pre-agreed, long-term, fixed-volume supply contracts to hospital providers, states, or aid organisations would eliminate the need for marketing and enable profitable production by generic manufacturers. By de-risking clinical trials and maintaining public control over intellectual property, paying for commercial antibiotic production akin to a public service would improve affordable access to innovative drugs, add value to existing pull incentives, and prevent overproduction. Rather than rely on commercial manufacturers, some states and political systems might also want to produce publicly trialled products in publicly owned factories. A NIM would work in both contexts.

Precedents and feasibility

Public R&D and clinical trials have already proven successful. The 20th century saw nation states engage in R&D of vaccines,[34] serum therapy, and chemotherapy:

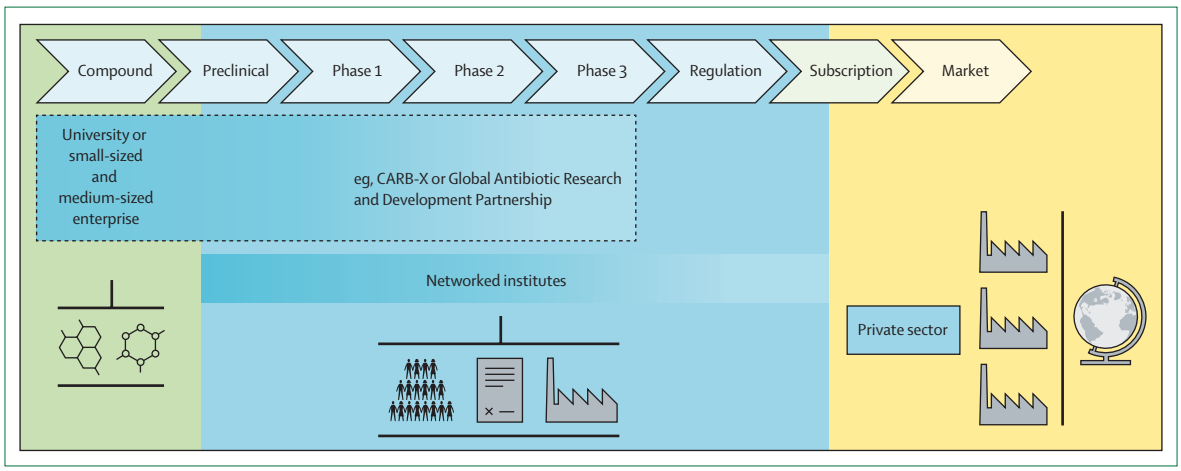

Figure 2: **The Networked Institute Model in relation to the current antibiotic research and development pipeline**
A simplified clinical trials research and development pathway is shown, along with some of the current funding options. Additionally, we have explained where the proposed networked institutes would sit, and what services they could provide in-house. The green section indicates components of the pathway that would remain mixed domain (public and private), the blue section (the networked institutes) indicates where we think the public sector should have a larger role, and the yellow section indicates where the private sector might add the most value in the antibiotic research and development pathway moving forward.

allied research resulted in penicillin,[35] US military research produced antimalarials,[36] and state-run research and trial infrastructures in socialist nations resulted in the discovery and licensing of various novel antibiotics and vaccines.[37–39] Not all non-profit innovation was solely financed by taxpayers. One of the world's oldest biomedical research hubs, the French Pasteur Institute (established in 1887), provides a model for self-sustained non-profit R&D. The main Pasteur Institute in Paris was financed by public subscriptions, state contributions, royalty donations from Pasteurian microbiologists, revenue gained from commercial licensing, and pre-negotiated monopoly supply contracts of serum or vaccine products to the French state.[40,41] Founded in 1936, the British Wellcome Trust similarly reinvested a fixed amount of proceeds from its for-profit Burroughs-Wellcome company (later Wellcome Foundation) into non-profit biomedical research until it divested its company to GlaxoSmithKline in 1995.[42,43]

Recent history illustrates the advantages of combining public trial and limited manufacturing infrastructures for pandemic preparedness and to speed commercial mass production of vital biomedical products. In the UK, the University of Oxford possessed an in-house R&D ecosystem that was able to rapidly respond to COVID-19. The Oxford response rested on the integration of vaccine research at the Jenner Institute, production facilities of the Clinical BioManufacturing Facility, and the expertise of the Oxford Vaccine Group and the Tropical Medicine Department in running clinical trials. As a Good Manufacturing Practice facility, the Clinical BioManufacturing Facility can produce limited amounts of promising compounds and vectors.[44] In early 2020, this ability allowed Oxford researchers to begin moving from bench to proof of concept before partnering with larger manufacturers.[44] A second crucial success factor was the researchers' ability to use pre-existing public infrastructure to organise staggered vaccine trials. Similar to the RECOVERY trial, the UK's National Institute for Health Research and National Health Service provided funds, know-how, and access to nationwide physical trial sites.[45] International contacts enabled additional vaccine trials to take place in South Africa and Brazil. Although these trials benefited from substantial industry investment, success was co-determined by the ability of public researchers to gather and analyse data from multiple public sites.[46,47]

The University of Oxford's handling of vaccine licensing also highlights the challenges of ensuring that public research sustainably serves the public good. Initial plans for a non-exclusive public licence were abandoned in favour of an exclusive licence for AstraZeneca as a result of pressure from funders, industry, and university authorities.[44,48] Although AstraZeneca agreed to non-profit vaccine production during the initial phase of the pandemic, its exclusive licence will allow it to profit from revaccinations—and probably from reformulations.[44] Some resulting income will benefit public research at Oxford, but future for-profit pricing might also limit vaccine access.[49]

Although the licensing decisions of the University of Oxford and its researchers have been criticised by some,[49] the example of ChAdOx1 nCoV-19 highlights the geo-strategic advantages of maintaining national bench-to-bedside capabilities. The UK Government has already decided to upscale this model by investing £93 million in a Vaccines Manufacturing and Innovation Centre at Oxford's Harwell campus.[50] The Institute for Global Change has called for similar integrated centres for antibodies and diagnostics to boost pandemic preparedness.[51]

Economic and geostrategic advantages of a public antibiotic trial infrastructure

Our proposed NIM draws on these precedents to bridge the antibiotic innovation bottleneck for both public and private developers with a permanent public infrastructure for antibiotic trials and small-scale production.

Networked public trial facilities allow for new drug development, reduce waste and inefficiencies, retain information in the public sphere, and protect against loss of human capital in terms of R&D expertise. A NIM also maximises academic capital—a value not adequately captured in innovation frameworks—by enabling researchers to publish, take credit for innovations, and generate further grant income. NIM pretrial patent buyouts for promising compounds developed by industry or sponsored by public–private initiatives can also create an attractive offloading point for small-sized and medium-sized enterprises struggling to attract venture capital. Over time, centralised offloading of promising compounds can improve coordination throughout the public and private pipeline, protect public knowledge and promising compounds from commercial failure, and focus R&D on priority pathogens.

The greatest strength of the NIM lies in its ability to streamline and reorientate existing clinical trials and licensing frameworks. After 1962, the randomised clinical trial gradually became the gold standard to satisfy regulatory safety, efficacy, and non-inferiority requirements.[52] As a result of the regulatory focus on a new drug's superiority against an established competitor, trials and licensing of new antibiotics often focus on narrowly circumscribed conditions and generate little data and guidance on how they should be used in the face of new resistance factors.[53,54] A further problem consists in the for-profit nature of most trial networks. Current clinical trial networks often rely on a commercial clinical research organisation taking on risk and outlaying money with the hope of recouping investments once the network is running.[55] The five largest clinical research organisations have a capitalisation ($24·8 billion) that is 40 times smaller than that of the five largest pharmaceutical companies ($1006·9 billion).[55] The relatively small size of clinical research organisations and low proportion of revenue coming from antibiotics pose an inherent hurdle for attracting investment in antibiotic trials.[55] Meanwhile, there is little synergy between different for-profit trial networks in the form of data sharing or shared infrastructure use, which adds to R&D costs. Even if commercial trials of a compound are successful and regulatory approval is granted, gathering post-approval data requires additional capital outlay. The need for financial returns can make developers focus investments on trials and licensing applications for the most lucrative drug applications and markets.[17]

The non-inferiority limitations, duplication of effort, and profitability bias inherent in the current trials and licensing system are well known and many improvements can be made irrespective of whether a public or private model is chosen.[56] In Asia, the Wellcome Trust is already funding multi-site networking of intensive care units to improve critical care delivery.[57] Responding to COVID-19, WHO launched the international solidarity programme to rapidly trial treatments.[58] In the case of antibiotics, the NIM's design as a permanent and specialised public entity for antibiotic trials in multiple locations could build on these examples and break the ad hoc nature and commercial bias of existing clinical trials systems. A networked public infrastructure for trials would maximise synergies and build human expertise in antibiotic design, trials, and licensing. Because financial risks of the clinical and licensing pipeline no longer have to be priced into products or paid by governmental and non-governmental funds, a NIM would enable compounds to be trialled and marketed where they are most needed and not where they will make the most—or any—profit. Trials could also be conducted in an adaptive way that not only looks for new compounds, but identifies safe and efficacious ways of expanding treatment options with existing drugs.[53,54]

Downstream of the trials bottleneck, market elements can be maintained at the nodes where they work best. Transnational corporations have far-reaching and flexible logistical and supply chain networks; these corporations also hold mass production abilities for quality-assured medicines exceeding those of any national or international organisation. Once an effective compound has been successfully trialled by the NIM, this compound could be contracted via a tendering process to companies for production at an agreed price. Similar to models being used by public development partnerships like the Drugs for Neglected Diseases initiative,[59] industry partners could be chosen both in terms of their ability to manufacture and distribute accessibly priced antibiotics and their ability to deliver environmentally sustainable production—a goal that has yet to be achieved.[60]

Licensing antibiotic production would, at the post-licensing stage (figure 2), be akin to paying for a service (ie, scale-up, logistical supply, and delivery). Pre-agreed purchasing guarantees of specific volumes of novel compounds by hospital consortia, states, or international organisations would incentivise bidding and enable profitable production by efficient manufacturers. To improve antibiotic access, licensing profit margins could be capped at, for example, 15–20%. This would probably favour licensing to generic manufacturers. Although commentators have highlighted that profitability issues extend to the generic market,[20,61] fixed purchasing guarantees for essential drugs are already proving successful in the case of the non-profit Civica Rx[20,62] and governments are increasingly willing to consider direct investments in, or subsidies for, onshore production of essential drugs. In the case of antibiotics, existing subscription models and proposed pull incentives (eg, PASTEUR Act[63]) could easily be repurposed or

broadened to fund sustained generic production of NIM-trialled drugs. Although studies show that access to cheaper generic antibiotics does not necessarily jeopardise stewardship,[64] the described purchasing models and NIM intellectual property and market authorisation ownership would also protect against overproduction. Ultimately, the economic and social value of having a predictable supply of innovative and effective antibiotics in terms of avoided mortality and morbidity outweighs the costs of any direct or indirect subsidies for generic production.[65]

Diversifying the locations of trials, manufacturing, and intellectual property ownership also holds geostrategic value and would improve the resilience of global antibiotic supply chains during times of geopolitical tension or other supply chain vulnerabilities. Currently, manufacturing of active pharmaceutical ingredients for antibiotics is largely concentrated in China, which can be problematic; for example, the 2016 explosion at the Chinese factory that produced active pharmaceutical ingredients resulted in a global shortage of piperacillin–tazobactam.[66–68] A NIM and geographically diversified manufacturing could mitigate vulnerabilities. In response to crisis situations like the international spread of a novel pathogen or resistance gene, activities at all NIM sites could be scaled up to ensure rapid trials of promising compounds and production by industry partners. International pathogen biobanks and samples would also ensure comparability within networked activity.

The strategic advantages of creating a robust innovation and supply pipeline by financing trials and development of physical infrastructures rather than virtual market incentives mark a logical next step for national preparedness. Governments have previously focused on investing in short-term emergency response capabilities rather than in long-term physical resilience to structural challenges such as antibiotic resistance. Created in 2006, the US Biomedical Advanced Research and Development Authority has financed stockpiling and R&D on diagnostics, therapeutics, and antibiotics.[69] The Biomedical Advanced Research and Development Authority also supported the establishment of CARB-X but initially refrained from creating dedicated production or trial capabilities.[23] However, prioritisation of innovation over manufacturing capabilities is changing. Over the past 2 years, US decision makers have become more supportive of onshoring of large-scale production capabilities (eg, by sponsoring antibiotic manufacturer Paratek Pharmaceuticals).[70,71] Meanwhile, the EU's 2020 pharmaceutical strategy responded to pandemic shortages by trying to protect crucial biomedical production capabilities but contained no explicit commitments to move beyond public–private initiatives in the case of antibiotics.[72] This conservative approach is a missed opportunity to apply COVID-19 experiences of vulnerable biomedical infrastructures to antibiotic resistance and antibiotic innovation.

Establishing the NIM

The costs of obtaining the NIM's described public health and geostrategic advantages pale in comparison with the costs of losing access to effective antibiotics. At the same time, a NIM would consolidate and improve coordination of already existing investments in the antibiotic field. In 2019, we calculated that an investment of $4 billion to 5 billion per year (0·01% gross domestic product contribution by Organisation for Economic Co-operation and Development countries) would generate a sustainable supply of new compounds and buy out large parts of the stalled commercial antibiotic pipeline within 2 years.[23]

A NIM could emerge in a top-down or bottom-up manner. Similar to the international community's success in raising funds to tackle tuberculosis, malaria, and HIV/AIDs (The Global Fund to Fight AIDS, Tuberculosis and Malaria) or reinvigorate vaccine development (GAVI, the Vaccine Alliance),[73] an international clinical trials network for antibiotics could be established by governmental and non-governmental donors in a top-down manner. WHO is already seeking to build more equitable R&D capacity in the form of the mRNA vaccine hub[74] and could act as a convener and adviser of the NIM. The advantages of this approach would lie in creating an integrated global testing infrastructure with likely rapid clinical trial successes and WHO prequalification. This approach would also provide an opportunity to implement international environmental manufacturing standards. Establishing the NIM as a WHO-aligned yet autonomous entity would avoid conflicts of interest resulting from blurring responsibilities for choosing and trialling compounds with those for licensing and authorisation.

The NIM could also emerge through the bottom-up adoption of our matrix by individual nations and funders in different areas worldwide. Costs will vary depending on the location. Although little is yet known about how products will be trialled and licensed, the INEOS Oxford Institute for AMR Research was recently established in the UK with £100 million to develop novel antibiotics.[75] Similar initiatives could just as easily arise in middle-income countries, such as Russia, India, and China, whose success in developing COVID-19 vaccines is testament to vibrant biotechnological R&D and trials networks,[76] or in low-income contexts with emerging or developed pharmaceutical infrastructures, such as Rwanda[77] or Bangladesh.[78] In the case of India, a dedicated NIM infrastructure could build on the Indian Council of Medical Research initiatives to generate networked antibiotic resistance data for treatment guidelines[79,80] and would substantially benefit from proximity to large pharmaceutical manufacturers. Dedicated national and regional NIM infrastructures could also counter the perceived need for companies in low-income and middle-income countries with promising compounds to establish headquarters and seek market authorisation in high-income countries.

The degree of coordination, trial priorities, costs, and access to resulting products will vary depending on whether institutes arise in a top-down or bottom-up fashion.[81] However, the global scale of the antibiotic resistance challenge and WHO's success in creating international consensus on priority pathogens[9] will incentivise collaboration.

Conclusion

We believe that existing attempts to refill the antibiotic pipeline are inadequate to overcome the innovation bottleneck. Our NIM for publicly owned and geographically diversified antibiotic trials addresses market failures without precluding the possibility that industry might wish to re-enter this space. The model does not attempt to nationalise antibiotic R&D but focuses public investment on bridging the crucial trials bottleneck for public and private developers in a permanent way. NIM aligns taxpayer funding and incentive schemes with taxpayer-owned products, maximises academic capital, protects human R&D expertise, reduces replication of effort, and drives down costs. Finally, this model opens up equitable pricing via subscription style licensing and purchasing agreements.

The proposed NIM is not a magic bullet. Investment in stewardship, antibiotic resistance surveillance, and systems strengthening across all One Health domains (human, animal, and environmental) remains crucial.[82] However, faced with the ongoing innovation crisis and the political paradigm shift created by COVID-19, we believe it is appropriate to think beyond existing initiatives and propose a NIMble alternative for public investment.

Contributors

CK, ACS, APR, and REG co-authored the manuscript. ACS and REG authored the figures. CK was responsible for drafting and editing.

Declaration of interests

We declare no competing interests.

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References

1 Centers for Disease Control and Prevention. Antibiotic resistance threats in the united states. Atlanta, GA: Centers for Disease Control and Prevention, 2019.
2 Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations. New York, NY: Interagency Coordination Group on Antimicrobial Resistance, 2019.
3 European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net). Annual Epidemiological Report for 2019. Stockholm: European Centre for Disease Prevention and Control, 2020.
4 HM Government. Contained and controlled. The UK's 20-year vision for antimicrobial resistance. London: HM Government, 2019.
5 Van Katwyk SR, Balasegaram M, Boriello P, et al. A roadmap for sustainably governing the global antimicrobial commons. *Lancet* 2019; **394:** 1788–89.
6 Rodríguez-Baño J, Rossolini GM, Schultsz C, et al. Key considerations on the potential impacts of the COVID-19 pandemic on antimicrobial resistance research and surveillance. *Trans R Soc Trop Med Hyg* 2021; trab048.
7 Knight GM, Glover RE, McQuaid CF, et al. Antimicrobial resistance and COVID-19: Intersections and implications. *eLife* 2021; **10:** e64139.
8 European Centre for Disease Prevention and Control, European Medicines Agency. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. Stockholm: European Centre for Disease Prevention and Control, European Medicines Agency, 2009.
9 WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization, 2017.
10 Årdal C, Balasegaram M, Laxminarayan R, et al. Antibiotic development—economic, regulatory and societal challenges. *Nat Rev Microbiol* 2020; **18:** 267–74.
11 Dutescu IA, Hillier SA. Encouraging the development of new antibiotics: are financial incentives the right way forward? A systematic review and case study. *Infect Drug Resist* 2021; **14:** 415–34.
12 DRIVE AB. Re-Investment in R&D and responsible antibiotic use. 2014. http://drive-ab.eu/drive-ab-info-package/ (accessed Sept 16, 2021).
13 Sinha G. BARDA to pick and choose next-generation antibiotics. *Nat Biotechnol* 2013; **31:** 665.
14 Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. *Nat Rev Microbiol* 2020; **18:** 275–85.
15 WHO. Antibacterial agents in clinical and preclinical development. An overview and analysis. Geneva: World Health Organization, 2020.
16 Paulin S, Alm RA, Beyer P. A novel pre-clinical antibacterial pipeline database. *PLoS One* 2020; **15:** e0236604.
17 Aagard H, Malpani R, Zorzet A. Ensuring sustainable access to antibiotics for everyone—everywhere. Stockholm: ReAct Europe, 2021.
18 PEW. Antibiotics currently in global clinical development. 2014. https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development (accessed Sept 16, 2021).
19 Mullard A. Achaogen bankruptcy highlights antibacterial development woes. *Nat Rev Drug Discov* 2019; **18:** 411–12.
20 Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Transl Res* 2020; **220:** 182–90.
21 Spellberg B, Nielsen TB, Gilbert DN, Shorr AF, Brass EP. Ensuring sustainability of needed antibiotics: aiming for the DART board. *Ann Intern Med* 2019; **171:** 580–82.
22 Nielsen TB, Brass EP, Gilbert DN, Bartlett JG, Spellberg B. Sustainable discovery and development of antibiotics—is a nonprofit approach the future? *N Engl J Med* 2019; **381:** 503–05.
23 Singer AC, Kirchhelle C, Roberts AP. (Inter)nationalising the antibiotic research and development pipeline. *Lancet Infect Dis* 2020; **20:** e54–62.
24 Cama J, Leszczynski R, Tang PK, et al. To push or to pull? In a post-COVID world, supporting and incentivizing antimicrobial drug development must become a governmental priority. *ACS Infect Dis* 2021; **7:** 2029–42.

25 Global AMR R&D Hub. Dynamic dashboard: investments in AMR R&D. 2021. https://dashboard.globalamrhub.org/reports/investments/product-development (accessed June 20, 2020).

26 Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy* 2021; **125:** 296–306.

27 Mancini DP. Push and pull: funding drugs to be used only sparingly. 2021. https://www.ft.com/content/69edbd0d-da11-4b27-8b73-7aeab34da780 (accessed Sept 16, 2021).

28 Goodwin K. Lack of funding drives biotech to suspend drug-resistant antibiotic pipeline. 2021. https://www.biospace.com/article/lack-of-funding-drives-biotech-to-suspend-drug-resistant-antibiotic-pipeline-/ (accessed Sept 16, 2021).

29 Bulik BS. GlaxoSmithKline to shut down antibiotics production, cut 300 jobs in wake of Novartis buyout. 2021. https://www.fiercepharma.com/pharma/gsk-set-to-close-u-k-antibiotics-business-after-novartis-sandoz-sale (accessed Sept 16, 2021).

30 AMR Action Fund. About us. 2020. https://amractionfund.com/about-us/ (accessed Sept 16, 2021).

31 Jinks T. We're backing the AMR Action Fund—this is what it means for antibiotic innovation. 2021. https://wellcome.org/news/were-backing-amr-action-fund-what-it-means-antibiotic-innovation (accessed Sept 30, 2021).

32 Klug DM, Idiris FIM, Blaskovich MAT, et al. There is no market for new antibiotics: this allows an open approach to research and development. *Wellcome Open Res* 2021; **6:** 146.

33 Mazzucato M. Mission-oriented research & innovation in the European Union. Brussels: European Commission, 2018.

34 Blume S. Immunization: how vaccines became controversial. London: Reaktion Books, 2017.

35 Bud R. Penicillin: triumph and tragedy. Oxford: Oxford University Press, 2007.

36 Lezaun J. The deferred promise of radical cure: pharmaceutical conjugations of malaria in the global health era. *Econ Soc* 2018; **47:** 547–71.

37 Vargha D. Between East and West: polio vaccination across the Iron Curtain in Cold War Hungary. *Bull Hist Med* 2014; **88:** 319–43.

38 Kirchhelle C. Pharming animals: a global history of antibiotics in food production (1935–2017). *Palgrave Commun* 2018; **4:** 96.

39 Schramm M. Wirtschaft und Wissenschaft in DDR und BRD. Die Kategorie Vertrauen in Innovationsprozessen. Köln: Böhlau Verlag, 2008.

40 Hage J, Mote J. Transformational organizations and institutional change: the case of the Institut Pasteur and French science. *Socio-economic Rev* 2008; **6:** 313–36.

41 Velmet A. Pasteur's empire: bacteriology and politics in France, its colonies, and the world. Oxford: Oxford University Press, 2020.

42 Wellcome Trust. History of Wellcome. 2020. https://wellcome.org/about-us/history-wellcome (accessed Sept 16, 2021).

43 Dougan G. How we lost our vaccine manufacturing industry and why we should get it back; a personal perspective. 2021. https://gordondougan.blog/2021/01/28/how-we-lost-our-vaccine-manufacturing-industry-and-why-we-should-get-it-back-a-personal-perspective (accessed Sept 16, 2021).

44 Garrison C. How the 'Oxford' Covid-19 vaccine became the 'AstraZeneca' Covid-19 vaccine. London: Medicines Law & Policy, 2020.

45 Wvt H. The future of clinical research: building on success. 2021. https://www.nihr.ac.uk/blog/the-future-of-clinical-research-building-on-success/27329 (accessed Sept 16, 2021).

46 Oxford Vaccine Group. Trial of Oxford COVID-19 vaccine in South Africa begins. 2020. https://www.ox.ac.uk/news/2020-06-23-trial-oxford-covid-19-vaccine-south-africa-begins (accessed Sept 16, 2021).

47 Oxford Vaccine Group. Trial of Oxford COVID-19 vaccine starts in Brazil. 2020. https://www.ox.ac.uk/news/2020-06-28-trial-oxford-covid-19-vaccine-starts-brazil (accessed Sept 16, 2021).

48 Strasburg J, Woo S. Oxford developed covid vaccine, then scholars clashed over money. 2020. https://www.wsj.com/articles/oxford-developed-covid-vaccine-then-scholars-clashed-over-money-11603300412 (accessed Sept 16, 2021).

49 Hancock J. Oxford's COVID vaccine deal with AstraZeneca raises concerns about access and pricing. 2020. https://fortune.com/2020/08/24/oxford-astrazeneca-covid-vaccine-deal-pricing-profit-concerns/ (accessed Sept 16, 2021).

50 Vaccines Manufacturing & Innovation Centre. About us. 2020. https://www.vmicuk.com /about-us (accessed Sept 16, 2021).

51 Dace H, Miller B, Ramli R, Sleat D, Thorne E, Wain R. The new necessary: how we future-proof for the next pandemic. London: Tony Blair Institute For Global Change, 2021.

52 Podolsky SH. The antibiotic era. Reform, resistance and the pursuit of a rational therapeutics. Baltimore: Johns Hopkins Press, 2015.

53 Lanini S, Ioannidis JPA, Vairo F, et al. Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: the case for post-marketing, adaptive randomised controlled trials. *Lancet Infect Dis* 2019; **19:** e444–51.

54 DiNubile MJ. Noninferior antibiotics: When Is "not bad" "good enough"? *Open Forum Infect Dis* 2016; **3:** ofw110.

55 Wellcome Trust . Clinical trial networks for antibiotic development. Why they're important and how they should be developed. London: Wellcome Trust, 2016.

56 WHO. WHO-ICMRA joint statement on the need for improved global regulatory alignment on COVID-19 medicines and vaccines. Geneva: World Health Organization, 2020.

57 Wellcome Trust. Innovations flagships: funded projects. 2021. https://wellcome.org/what-we-do/our-work/innovations-flagships/funded-projects (accessed Sept 16, 2021).

58 WHO. WHO COVID-19 solidarity therapeutics trial. 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (accessed Sept 16, 2021).

59 DNDi. Treatments Delivered. Geneva: Drugs for Neglected Diseases Initiative, 2021.

60 Access to Medicine Foundation. Antimicrobial resistance benchmark 2020. Amsterdam: Access to Medicine Foundation, 2020.

61 Pulcini C, Beovic B, Béraud G, et al. Ensuring universal access to old antibiotics: a critical but neglected priority. *Clin Microbiol Infect* 2017; **23:** 590–92.

62 CIVICA. Chronic drug shortages impact patient care across the United States. 2018. https://civicarx.org/ (accessed Sept 16, 2021).

63 Congress.Gov. H.R. 8920—The PASTEUR Act. 116th Congress (2019–2020). 2020. https://www.congress.gov/bill/116th-congress/house-bill/8920 (accessed Sept 16, 2021).

64 Kållberg C, Hudson J, Salvesen Blix H, et al. The effect of generic market entry on antibiotic prescriptions in the United States. *Nat Commun* 2021; **12:** 2937.

65 Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; **19:** 56–66.

66 ECA Academy. Explosion of an API manufacturing site: supply of medicinal products endangered. 2017. https://www.gmp-compliance.org/gmp-news/explosion-of-an-api-manufacturing-site-supply-of-medicinal-products-endangered (accessed Sept 16, 2021).

67 Nurse-Findlay S, Taylor MM, Savage M, et al. Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: an evaluation from multi-country surveys and stakeholder interviews. *PLoS Med* 2017; **14:** e1002473.

68 US Food and Drugs Administration. Safeguarding pharmaceutical supply chains in a global economy. 2019. https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019 (accessed Sept 16, 2021).

69 Rosner D, Markowitz G. Are we ready? Public health since 9/11. Los Angeles, CA: University of California Press, 2006.

70 Fierce Pharma. As US calls for stateside manufacturing, antibiotic maker Paratek gambles on 'onshoring' effort. 2020. https://www.fiercepharma.com/manufacturing/as-u-s-calls-for-stateside-manufacturing-antibiotic-maker-paratek-gambles-onshoring (accessed Sept 16, 2021).

71 Eversana. US Onshoring Essential Antibiotics Act Seeks to Re-Localize Production of Essential Antibiotics. 2021. https://www.eversana.com/2021/04/28/us-onshoring-essential-antibiotics-act-seeks-to-re-localize-production-of-essential-antibiotics/ (accessed Sept 16, 2021).

72 European Commission. A pharmaceutical Strategy for Europe. Brussels: European Commission, 2020.

73 Packard R. A History of global health: interventions into the lives of other peoples. Baltimore, MD: Johns Hopkins Press, 2016.

74 WHO. Establishment of a COVID-19 mRNA vaccine technology transfer hub to scale up global manufacturing. Geneva: World Health Organisation, 2021.

75 University of Oxford. 100 million donation from Ineos to create new institute to fight antimicrobial resistance. Oxford: University of Oxford, 2021.

76 Buss PM, Hoirisch C, Alcázar S. BRICS and the global vaccine barbarism. Rio de Janeiro: Oswaldo Cruz Foundation Center for Global Health and Health Diplomacy, 2021.

77 Fitch Solutions. Rwanda pharmaceutical exports to increase as domestic industry expands. 2020. http://www.fitchsolutions.com/pharma-healthcare/rwanda-pharmaceutical-exports-increase-domestic-industry-expands-09-09-2020 (accessed Sept 16, 2021).

78 Chakma J. Bangladesh on track to becoming a $6b pharma market by 2025. 2020. https://www.thedailystar.net/business/news/bangladesh-track-becoming-6b-pharma-market-2025-1995741 (accessed Sept 16, 2021).

79 Swaminathan S, Walia K. Strengthening research and innovation to address the challenge of antimicrobial resistance. 2016. http://resistancecontrol.info/rd-innovation/strengthening-research-and-innovation-to-address-the-challenge-of-antimicrobial-resistance/ (accessed Sept 16, 2021).

80 Government of India. National action plan on antimicrobial resistance 2017–2021. New Delhi: Government of India, 2017.

81 Moon S, Vieira M, Kimmitt R. Do costs, timeframes and attrition rates differ between non-commercial and commercial biomedical R&D? A study of neglected diseases R&D and the P2I model. 2021. https://repository.graduateinstitute.ch/record/298834?ln=en (accessed Sept 16, 2021).

82 Kirchhelle C, Atkinson P, Broom A, et al. Setting the standard: multidisciplinary hallmarks for structural, equitable and tracked antibiotic policy. *BMJ Glob Health* 2020; **5:** e003091.