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OPINION ARTICLE

Reinventing the antimicrobial pipeline in response to the global crisis of antimicrobial-resistant infections [version 1; referees: 2 approved]

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The pipeline for new antibiotics is dry. Despite the creation of public/private initiatives like Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (Carb-X) and the Antimicrobial Resistance (AMR) Centre, the current focus on 'push-pull' incentives for the pharmaceutical industry still relies on economic return. We propose a joint, internationally-funded antimicrobial development institute that would fund permanent staff to take on roles previously assigned to pharmaceutical companies. This institute would receive ring-fenced, long-term, core funding from participating countries as well as charities, with the aim to focus on transforming the largely dormant antimicrobial pipeline. Resulting drugs would be sold globally and according to a principle of shared burdens. Our proposed model for antimicrobial development aims to maximise society's investment, through open science, investment in people, and the sharing of intellectual property.

Keywords

antibiotics, antibiotic resistance, antimicrobial, drug pipeline,

Open Peer Review

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	1	2
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EHESS - Université Paris Descartes, France

2 **Dean Baker**, Center for Economic and Policy Research (CEPR), USA

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Singer AC:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Kirchhelle C:** Writing – Original Draft Preparation, Writing – Review & Editing; **Roberts AP:** Writing – Original Draft Preparation, Writing – Review & Editing

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The UK's new five-year national antimicrobial resistance (AMR) action plan highlights that society is at a tipping point: not only are we running out of effective antibiotics, but the pipeline for new drugs is dry and novel diagnostics are slow to come to market (HM Government, 2019). Over the past two decades, decision-makers have tried to overcome this dry spell by relying on the market and creating 'push-pull' incentives for the pharmaceutical industry (Renwick *et al.*, 2016). The fundamental premise of 'push-pull' incentives, is to make it economically attractive for major pharmaceutical companies to invest their infrastructure, staff and skills into the research, development and manufacture of novel antibiotics. The reality for pharmaceutical companies is that there is too little money to be made with antibiotics: any new antibiotic will be reserved as a 'last-line defence', which means it will (hopefully) be an infrequently used antibiotic and as such, a poor source of income.

While recent public-private initiatives like Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (Carb-X) and the AMR Centre (UK), are important steps in the right direction, we strongly contend that using public funds to support private venture and profit is not the only way to refill the antibiotic pipeline. In the current model for drug development, the tax payer pays for everything up to the point where the pharmaceutical companies may invest in later stages of development (Galkina Cleary *et al.*, 2018). Society invests in the students, post-docs, and professors through public funding of the university and/or the research grant that pays their salaries and equipment. However, at the point where knowledge becomes patentable, it quickly disappears down pharmaceutical pipelines.

Commercial pipelines are not always efficient producers of new drugs. Potentially promising drugs are abandoned when commercial or global health priorities change. In some cases, patents are only filed to deter competitors from developing them further. Not only are society's investments in antimicrobial innovation wasted, but the intellectual property associated with a drug's development, i.e., the countless serendipitous leads as well as dropped, yet promising, antimicrobials, remain locked-up within the private pharmaceutical company—inaccessible to the public who invested in the initial development. Ultimately, the current mode of subsidised antibiotic development means that society pays for 100% of all the drugs that are developed and not developed, but, importantly, owns and controls nothing (discussed here (Anon, 2019)). It is this obvious disconnect in societal investment, which needs to be reformed.

We propose a radical change to the current paradigm of antimicrobial development and manufacture—one that reflects humanity's shared interests and global health challenges. We propose a joint, internationally-funded antimicrobial development Institute that would fund permanent staff to take on the role previously assigned to pharmaceutical companies. This institute would receive ring-fenced, long-term, core funding from participating countries as well as charities, with the aim to focus on transforming the largely dormant antimicrobial pipeline.

The international centre would aim to sustainably develop a breadth of new antimicrobials to address both immediate and emerging global health challenges, respond to needs across organisms, i.e., viral, bacteria, fungal, protist, and develop novel modes of action. Prospective antimicrobials submitted to the centre would be developed in an open and transparent manner, so that innovation can be immediately shared and serendipitous findings can be leveraged by the wider research community. The centre would also conduct clinical trials on prospective drug candidates, manufacture all antimicrobials through existing generic drug manufacturers, and contract research organisations.

Resulting drugs would be sold globally and according to a principle of shared burdens. This would mean that high-income countries would pay more for research and the drugs themselves than low-income countries facing ongoing access problems. Signing up to enforceable stewardship requirements would be a precondition to receiving new drugs. Since no development costs need recouping and no share holder incentives need to be satisfied, most drugs could be sold at the cost of manufacture. Nearly 40 years of lacking commercial interest in new antibiotic development means that our 'not-for-profit' antibiotic pipeline would not compete with established manufacturers.

A look back at the 20th century shows that our proposed approach is not as far-fetched as it may sound. While a turn to more profitable 'lifestyle' drugs ended pharmaceutical investment in antibiotic development from the late 1970s onwards (Gradmann, 2016), the 1940s saw many of the same companies work hand-in-hand with nation states and universities to screen antimicrobial compounds, test them in clinical settings, and upscale production. There was no patent on penicillin – only on the process developed to mass-produce it (Bud, 2009). In the case of antimalarials, military interests led to a long history of state-directed and subsidized development (Lezaun, 2018).

Our proposed model for antimicrobial development aims to maximise society's investment, through open science, investment in people, and the sharing of intellectual property. Antimicrobial resistant infections pose a global challenge. It is time to realise that the challenge of solving the global problem of AMR exceeds the capacity of commercial actors. We are already financing the development of antibiotics, why not collectively own and manage the resulting drugs?

Data availability

No data are associated with this article

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Version 1

Referee Report 19 March 2019

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Dean Baker

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This article proposes to establish an international center for antimicrobial research and development. The center would develop and then sell drugs to according to a principle of "shared burden." There is a need for such a center, since the private pharmaceutical industry has largely abandoned research in this area since it sees little prospect for profit.

While this is an innovate idea, it would be helpful to see it flushed out a bit more in two directions. First, while it seems the authors' intentions that all research findings be open, a slightly clearer statement on this principle would be helpful. For example, do they envision something like the Bermuda Principle, where results are posted to the web, if not nightly, as quickly as practical.

The second area that could benefit from clarification is the meaning of the principle of "shared burden." Since the research costs are being paid upfront, it is unclear why there would be any reason to charge a price above the marginal cost. (There could an issue where countries that did not contribute to research costs get charged more, but that should be explicitly stated.)

Anyhow, this is a worthwhile proposal which should advance the debate on the best way to finance the development of prescription drugs.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am economist that has been researching drug development for two decades.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 13 March 2019

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The authors have written a bold, interesting and well argued opinion piece. It discusses alternatives to reviving antibiotics drug development beyond the 'push-pull' incentives offered to pharmaceutical industry. They would essentially result in making novel antibiotics a public commodity. This should trigger much needed debate.

I have two comments. One is in detail. In the opening of the third last paragraph we find the sentence "Resulting drugs would be sold globally ...". Is that consistent with the approach. After all selling could again make the invented drugs private property and prohibit keeping their further development in open areas. Would not licensing be better?

My second question is about comparable stories. I am no great expert in vaccines but it seems to me that in this case we have seen rather successful cases of public-private partnerships in the last decades. Maybe worth considering. Historical reading could start from "Galambos, Louis, and Jane Eliot Sewell. Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995. Cambridge: Cambridge University Press, 1996."

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: History of medicine

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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