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RESEARCH ARTICLE

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'Piloting a framework for analysing the public contributions to R&D: new antibiotics in focus'

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ABSTRACT

Background: Within the context of increasing transparency around public contributions, a framework for reporting and analysing public contributions to research and development (R&D) was previously developed and is piloted here using the example of antibiotics. The aim of this work is to check whether the category system is feasible, to revise and adjust the granularity of the category system where necessary, and to expand the range of sources for detailed analyses.

Methods: All antimicrobial medicinal products in development, discontinued and approved in the last 10 years were identified in the literature. Thereafter clinical trials and company information was searched generating a list of 56 compounds where primarily small to medium-sized enterprises (SMEs) were involved in antibiotics development. Information on clinical trials, university spinouts and public funding for SMEs was then gathered from various sources. The framework for classifying public contributions was then applied.

Results: We found that around one-third of antibiotics are developed by SMEs. We identified numerous public funding sources for SMEs that develop antibiotics. At both early-stage and late-stage development, public research funding is the most common public funding reported by SMEs, ahead of other public sources like public equity funds, private-public partnerships and philanthropic sources. A deep-dive into one antibiotic drug, Venatorx, revealed public funds investment of approximately $655 million, dwarfing private investment funds. We found the classification framework generally practicable and we suggest recommendations to improve its granularity and applicability.

Conclusion: In this paper we piloted and revised a framework that has been developed to classify types of public contributions to pharmaceutical products at different stages of development. The framework, together with work we have done on identifying sources for funding, can be applied to support pharmaceutical price negotiations that reflect the level of public contribution to product development.

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Introduction

The need for new antibacterial agents and the lack of private commercial initiatives to develop them has become obvious in recent decades. Numerous governmental interventions to support innovation in the field of antibiotics are now slowly showing results; however, they also show a market failure due to poorly aligned social and private values and perceived medical needs. Most large pharmaceutical companies have withdrawn from antibiotic research and development (R&D) because antibiotics are less profitable than in other areas, such as cancer. Small and medium-sized enterprises (SMEs) and academic institutions are now the drivers of development (Anderson et al., 2023).

Already in 2009, TATFAR (Transatlantic Taskforce on Antimicrobial Resistance) was founded to address the urgent threat of antimicrobial resistance (AMR). Since then, TATFAR's experts from Canada, the European Union (EU), Norway, the United Kingdom (UK) and the United States (US) have collaborated and shared best practices to strengthen domestic and global efforts. Somewhat later, in 2012, the ND4BB (New Drugs for Bad Bags) initiative was founded in Europe, and in 2015, the CARB-X (Combating Antibiotic-Resistant Bacteria) initiative was founded as well as the BARDA-BSA (Biomedical Advanced R&D Authority – Broad Spectrum Antimicrobial Program) in the US (Eichberg, 2015; Rex & Outterson, 2021). In 2016, GARDP (Global Antibiotic Research & Development Partnership) was founded by the World Health Organization (WHO) and the Drugs for Neglected Disease Initiative (DNDi). It now has several government and philanthropic funders.

These push incentives for funding preclinical and clinical research and development (Theuretzbacher, Bush, et al., 2020; Theuretzbacher, Outterson, et al., 2020) are complemented by pull incentives such as regulatory support (priority review, extended monopoly protection by vouchers) and methodological guidance (e.g. for non-inferiority trials) (So & Shah, 2014). Further incentives such as subscription-, insurance- or premium-price models, joint procurement, and advanced purchasing agreements have been discussed (Anderson et al., 2023; Mullard, 2020; Towse et al., 2017).

In the debate on setting the right incentives for the development of antibiotics, 3Rs are proposed: Sharing Resources, Risks and Rewards (So et al., 2012). The evidence for public contributions (push and pull incentives) to developing new antibacterial agents is strong, and in the media, this observation is referred to as 'the public pays twice' and 'risks are socialised and rewards are privatised' (Vogler et al., 2023). However, even with increasing evidence, corresponding public policies (such as conditionalities) are still lacking. In April 2023, a proposal for a revision of the 'Pharmaceutical Legislation' in the EU (consisting of a new Directive (European Commission (EC), 2023a) and a new Regulation (European Commission (EC), 2023b)) was published and will be negotiated in the coming years. The draft pharmaceutical legislation contains a transparency requirement regarding public financial support received for R&D activities for a medicinal product. Article 57 of the proposed medicines Directive (European Commission (EC), 2023a) will require market authorisation (MA) applicants and MA holders (MAH) to publicly declare any 'direct financial support received from any public authority or publicly funded body' about 'any activities for the research and development of the medical product', without specifying the period during which funding was received. The obligation is not restricted to only EU financial support, so MAHs will also need to consider any funding from public authorities and publicly funded bodies outside the EU. The scope of the provision is very broad and covers direct funding for any R&D activities related to the medicinal product's development. This reporting obligation could, therefore, include funding received during pre-clinical and clinical stages. However, the recitals of the Directive do not stipulate indirect funding, such as regulatory support or tax reductions.

Within the context of increasing transparency on public contributions, a framework for reporting and analyzing public contributions to R&D was developed as part of the EC Horizon Europe project HI-PRIX (Health Innovation Next Generation Payment and Pricing Models; Grant Agreement Nr. 101095593). This research aims to pilot the framework for analyzing public contributions to R&D of medical innovations (AdisInsight; Butler et al., 2022, 2023; Walesch et al., 2023; Wild et al., 2024; World Health Organization (WHO), 2021) on a cohort of medicines, namely antibiotics, to check whether the category system is feasible, to possibly adjust the granularity of the category system and to expand the range of sources for detailed analyses. This article does not aim to provide comprehensive data on all individual financial supports (sums) provided.

Methodology

Identification of antibiotics and categorisation by status

Initially, all antimicrobial medicinal products in development, discontinued and approved in the last 10 years (since 2014) were identified in the literature

(sources used for this were: AdisInsight; Butler et al., 2022, 2023; Walesch et al., 2023; World Health Organization (WHO), 2021) and deduplicated, resulting in 152 compounds. The identified compounds were then divided into four categories based on the status of their development or marketing authorisation. The first category comprised approved antibiotics, while the second and third categories included compounds in Phase 3 and Phase 1/2, respectively. The fourth category comprised compounds whose development has been discontinued.

Identification of generic or nonproprietary and proprietary designations

Next, we meticulously searched for product identifiers, including initial numbers and character combinations, generic or nonproprietary names of active ingredients, and trade or brand names. This search was performed in AdisInsight and supplemented with additional alternative names as needed. For products in Phase 3 ($n = 17$), we also searched for clinical trials in clinicaltrials.gov and at the International Clinical Trials Registry Platform (ICTRP), using all identified product names. The relevant study data we collected included the title, trial ID, phase, status, sponsor, number of patients, and study duration.

Categorisation by actors in product development

We conducted a search for company information for the products ($n = 126$) that had already been approved or are in development (source: initial literature references above). These companies were then divided into four groups of actors (big pharma/large companies > 250 staff headcount, small and mid-sized enterprises (SMEs) $\leq$ 249 staff (Organisation for Economic Co-operation and Development (OECD), n.d.), non-profit, and public institutions) based on their number of employees according to OECD business size classification or organisational form. The company size refers to our search date (December 2023) for the approved products. We also made note of products resulting from public-private collaborations. Our sources for this research were data available online on company websites (to obtain up-to-date and accurate information about products, organiaational structure of the company and development pipelines) and company profiles on LinkedIn (to supplement details on company operations, size and organisational form). Other online resources used were industry reports, press releases, investor relations websites and pharmaceutical news pages. Our search results were presented graphically, highlighting the respective proportions of study phases and organisational forms of the companies in colour and displaying the distribution using bars.

Identification of public funding for SME

Using the 126 products identified above as our starting point, we identified 71 of these that had been developed by SMEs (referring to the developer of the last phase reported and not earlier phases). Of the 71 products, we excluded 15 products that were not relevant (delivery technologies, immunomodulators, topical treatments and products for very specific situations, such as anthrax). This left 56 compounds identified for antimicrobial resistance, that had been developed, or were in development, by SMEs. Information on university spinouts and public funding for SMEs was then gathered from various sources, such as company websites, press releases, investors' websites, and pharmaceutical news pages. The amounts and donor details were subsequently extracted from these sources. Funding reported is often for several programmes (portfolio) and not only specific products. The cut-off date for all searches was December 2023.

Application of framework on public funding

Lastly, the framework of public contributions to R&D of medical innovations, recently published elsewhere (Wild & Fabian, 2024), was applied by classifying the identified public contributions for the development of antibiotics according to the phase in which the contributions were provided and the category of contribution (see Table 1). Finally, we complemented the list of sources for identifying the public contributions.

The piloting of the framework was conducted in May 2024.

Results

Actors in product development

Since 2014, 27 new antimicrobials have been approved, 17 by big pharmaceutical companies (63%) and 10 by small and medium-sized enterprises

Table 1. Framework for analyzing public contributions to R&D of medical therapies.

Phase of R&D	Category of public contributions
Discovery	R&D grants by supranational, national research funders global charitable foundations for basic & translational research
Preclinical development	Technology transfer grants for spinout/off companies Technology & innovation support for lifesciences, biotech start-ups and SME
Clinical development	Trial support by supranational, national research funders global charitable foundations
Market authorisation	Regulatory support: scientific advice, fast track etc. RWE data collections/ PLEG

PLEG – post-launch evidence generation, R&D – research and development, RWE – real-world evidence, SME – small and medium-sized enterprise.

(37%). 17 compounds are investigated in phase 3 trials, of which 5 (29%), 11 (65%), and 1 (6%) are led and owned by big pharmaceutical companies, SMEs, and a public institution, respectively. The ratios for the 82 projects currently in phase 1 or phase 2 investigations are 16 (19.5%), 50 (61%), 3 (3.7%), 3 (3.7%), 8 (9.8%) and 2 (2.4%) for big pharmaceutical companies, SMEs, public institutions, non-profit charitable institutions, collaborations, and unknown ownership, respectively (see Figure 1).

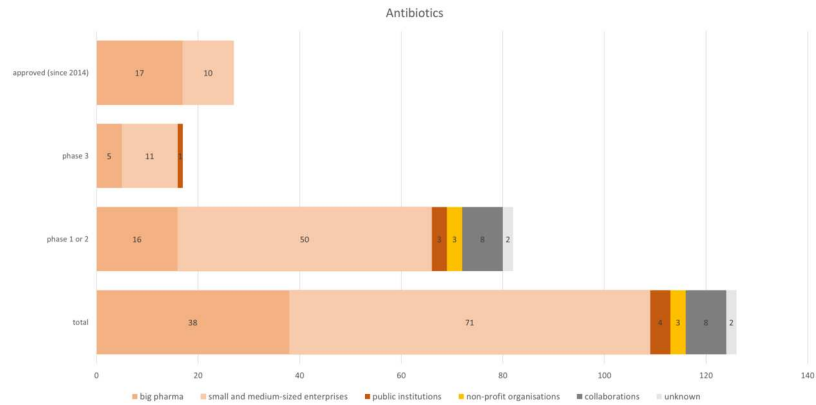

Figure 1. Antibacterial projects in clinical development or approved since 2014, according to organisation type.

Public funding for SME

Applying our search methodology described above, we were able to document a wide range of public funding sources – provided to and accessed by SMEs – in the development of antibiotics. Supplemental Tables S1 and S2 provide details of the public and philanthropic financial support provided at different stages of product development that we could identify after searching our sources.

The search covered additional sources including company websites, industry news reports, investor relations publications and press reports. These sources are particularly useful in identifying funding streams that are not official research funding or are funding grants at an early stage of product development, which would otherwise be difficult to identify.

Figure 2 summarises the type of funding provided to, and accessed by, SMEs at each stage of development. At both early-stage and late-stage development, national and supranational research funding is the most common public funding reported by SMEs. In the discovery and translational stage

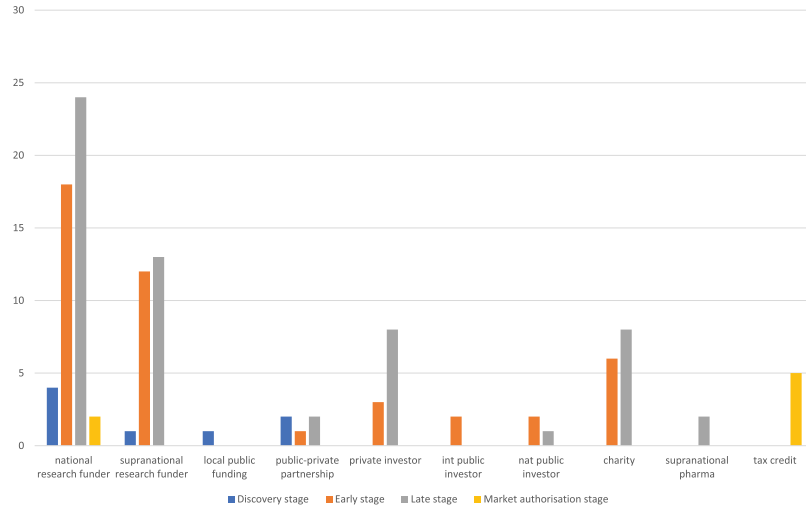

Figure 2. Financial support to SMEs: number of SMEs accessing types of public funding at different stages of development.

of development, the second most accessed funds were public-private partnerships (accounting for 25% of public funding reported by SMEs). For the market authorisation stage, the public funding most often reported by SMEs took the form of tax credits, which accounted for 70% of public contributions reported by SMEs at this stage (although it must be noted that it is difficult to identify the exact stage of development that tax credits relate to due to lack of specific information).

To illustrate, we conducted a deep-dive into the funding streams accessed by one US-based SME (Venatorx Pharmaceuticals) in more detail as an example (see Table 2). Concurring with the analysis above, national public research funders were the funding source most commonly accessed in the discovery/translational research stage and in the preclinical (early-stage development) phases. During clinical (late-stage) development, however, Venatorx was just as likely to access private investment funds (series A through to C funding) as it was national or international public research funding; however, the dollar amounts accessed were vastly different. In terms of the sum of public and private funds we identified for Venatorx, public funding bodies contributed funds of approximately $655 million, an amount dwarfing the amount of private investment funds we were able to identify, which amounted to approximately $45 million. We did not identify any large pharmaceutical companies providing funds to Venatorx, although their website states that they have a licensing or collaboration agreement with Roche (Venatorx Pharmaceuticals, 2021).

Table 2. Example of Venatorx Pharmaceuticals (VP) and details (https://venatorx.com/press-releases/).

Year	Characteristics of contribution	Sum
26 June 2010	VP has been awarded an NIH R01 biodefense grant for novel approaches to address resistant category B food and water-borne pathogens.	NIH-grant: $4.3 m
21 August 2011	VP has been awarded a Phase 1 SBIR Grant for novel approaches to address multi-drug resistant gram-negative infections.	SBIR grant: $600,000
22 November 2013	VP has completed a Series A financing round to complement its other sources of funding and help advance its novel discovery and development programmes.	Private investors: appr. $3.5 m
22 October 2013	VP received an investment from the Wellcome Trust to develop novel small molecules for the treatment of antibiotic-resistant bacterial infections.	Wellcome Trust Translation Fund: $8.9 m
16 September 2013	VP was elected to execute a research and development contract around proprietary compounds that address resistant NIAID Category A, B, and C pathogens.	NIAID: $21.2 m
September 2013	VP was awarded a Phase 2 SBIR Grant for novel approaches to address multi-drug resistant gram-negative infections.	SBIR grant: $3 m
7 April 2014	VP has been awarded an NIH R01 Grant for novel approaches to address biodefense-related infections.	NIH-grant: $6 m
27 July 2017	VP receives funds to develop a new class of antibiotic to combat multi-drug resistant bacteria. The funding will be used to support discovery and preclinical development of a new class of antibiotic that circumvents beta-lactam antibiotic resistance, but with the same safe and effective mechanism of action of beta-lactams.	CARB-X: $9.4 m
25 July 2017	VP raises funds in Series B to advance the Venatorx Pharmaceuticals' portfolio, including lead product candidate VNRX-5133 for multi-drug resistant (MDR) gram-negative infections.	Private investors (Versant Ventures, Abingworth and Foresite Capital): $42 m
4 January 2018	VP receives award to develop a novel, first-in-class antibiotic against potential drug-resistant biodefense category A/B Respiratory Pathogens. The funding will support discovery and preclinical development. The project derives from the company's proprietary platform of non-beta-lactam penicillin binding protein inhibitors (PBPi).	DTRA: $16 m
25 November 2019	VP receives funds to support the development of a new class of oral antibiotics to treat multi-drug-resistant gonorrhea. VP receives non-dilutive funding with the possibility of additional funding, if certain project milestones are met, to develop a new class of oral antibiotics to treat infections caused by multi-drug-resistant (MDR) *Neisseria gonorrhoeae.*	CARB-X: $4.1 m non-dilutive funding, $8.9 m milestone payments
22 July 2019	The U.S. Department of Health and Human Services' (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) will	HHS-ASPR, DTRA, VP Collaboration

(*Continued*)

Table 2. Continued.

Year	Characteristics of contribution	Sum
	collaborate with the U.S. Department of Defense's Defense Threat Reduction Agency (DTRA) and VP to develop a novel antibiotic to treat infections caused by bacteria resistant to currently available agents.	
28 February 2019	VP awarded R01 grant to uncover determinants of gram-negative permeability in novel antibacterial agents. The grant will support therapeutic discovery for gram-negative bacterial pathogens, including carbapenem-resistant Enterobacteriaceae, multi-drug resistant *Acinetobacter baumannii* and/or *Pseudomonas aeruginosa*.	NIAID: $1.9 m in first-year funding $7.4 m over 5 years in milestone payments
27 July 2020	VP has been awarded a contract to advance a novel series of Penicillin Binding Protein (PBP) Inhibitors targeting multi-drug resistant (MDR) *Acinetobacter baumannii* through Phase 1 clinical testing.	NIAID: $44 m
29 April 2020	VP and the Global Antibiotic Research and Development Partnership (GARDP) announced a collaboration to accelerate the development of, and access to, cefepime-taniborbactam (formerly cefepime/VNRX-5133), a new antibiotic for hospital acquired Infections.	GARDP: conduct of several Phase 3 trials (up to $35 m) VP collaboration
3 October 2022	VP awarded BARDA Project BioShield Contract for cefepime-taniborbactam against multi-drug resistant infections.	BARDA: up to $318 m $72 M for the development of cefepime-taniborbactam Up to $67 M in milestone payments for further development Up to $179 M for product procurement
4 April 2022	VP raises Series C financing led by the AMR Action Fund with participation from existing investors including Abingworth against shares.	Private investors (Abingworth)
10 October 2023	VP was awarded a 3rd Antibiotic BARDA Contract to support the development of oral ceftibuten-ledaborbactam etzadroxil for the treatment of complicated urinary tract infection (cUTI), including pyelonephritis.	BARDA: Up to $20.3 m initial commitment Up to $167 m over 6 years

ASPR – Office of the Assistant Secretary for Preparedness and Response, BARDA – Biomedical Advanced Research and Development Authority, CARB-X – Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, DTRA – Defense Threat Reduction Agency, GARDP – Global Antibiotic Research & Development Partnership, HHS-ASPR – Department of Health and Human Services-Administration for Strategic Preparedness and Response, MDR – multi-drug resistant, NIAID – National Institute of Allergy and Infectious Diseases, NIH – National Institutes of Health, PBPI – penicillin binding protein inhibitors, SBIR – Small Business Innovation Research, VP – Venatorx Pharmaceuticals.

Application of framework on public funding

Using the information we had researched on the funding of antibiotics, as reported in Tables S1 and S2, we tested the application of the framework. Testing the application of the framework of public contributions to R&D enabled us to assess whether any amendments to the framework were

needed. The results of the framework applied to antibiotics development is shown in Table 3.

Table 3 shows the updated classification framework (which can be compared with Table 1, which shows the original framework), which was refined to reflect the antibiotics example. The extended framework allowed us to classify and show a wide range of public and philanthropic funding used to support the development of antibiotics at all stages of product development. During discovery/translational research and both preclinical (early) and clinical (late-stage) development, the development of antibiotics was financially supported by supranational research funders (e.g. EC-research programmes such as IMI), national research funders (notably NIH), charities (e.g. the Wellcome Trust), local/regional public support (e.g. local hospital and university), support through public and private partnerships (such as Health Holland, DNDi) and public investments (notably Bpi France – Banque publique d'investissement). It was only for the market authorisation stage that we could not document a wealth of diverse public funding sources. However, even at this stage, we know that regulatory agencies provide in-kind support to pharmaceutical companies, for instance, on clinical trial aspects like trial design, choice of comparator and outcomes. Since this information is not publicly available, we are unable to assign a monetary value to this type of support. Similarly, reductions in tax burdens are likely to be applied, but again, it is difficult to document these through publicly available sources. As a result, we are also unable to determine at which stage of development tax rebates or credits are used to support R&D efforts and the exact amounts of money involved. Hence, although from Table 3 it would appear that there are few public funding sources for the market authorisation stage, we think this reflects a lack of documentation of the support at this stage rather than a lack of support itself.

In Table 3, we have also summarised the sources we used for identifying financial contribution information, which is the product of both this and our earlier work (Schmidt & Wild, 2020). We found 'softer' sources such as press releases, industry journals and investors news to be important sources that enabled us to identify funding 'leads' which we were then able to follow up on the website of the relevant funding agency.

Generally, we found that applying the framework was possible and enabled us to categorise the stage of product development alongside the category of public contributions. Having a framework helped make sense of the range of information that can be found on funding sources and enabled the type and stage of funding to be structured coherently. However, specific aspects of the framework needed to be adjusted for application to the field of antibiotics, which we have summarised in the discussion.

Table 3. Framework for analyzing public contributions to R&D of medical innovations applied on antibiotics R&D.

Phase of R&D	Category of public contributions	Public & philanthropic sponsors (examples)	Sources		Additional category needed?
Discovery	R&D grants by supranational funders, national research funders, global charitable foundations, public-private partnerships, local public funding	*National research funder*: NIH, APC Microbiome Ireland, US Department of Defense, NIAID. *Charity*: Gates Foundation *Public-private partnership*: Health Holland, AMR Action Fund *Regional/Local*: St Vincent's Hospital Melbourne, RMIT University	*Europe*: Cordis Db, IMI/IHI projects, Websites of National research agencies. *US*: NIH, US government agencies. Websites of other national research agencies	STATnews, FiercePharma, Bioworld, Biopharmadive, Pharmaphorum, Pharmatime, Pharmafile, Business Wire, BusinessInsider, PRNewswire, Forbes, Reuters, … Product + News (Google), Homepages (Developer): News, Press releases + IR website (ad-hoc announcements + press releases) Patents: FDA orange book/ US PTO, Health Canada Patent Database, Espacenet patent database, Medicines Patent Pool Patent, Pat-informed database	Yes – category of public-private partnership needed e.g. Health Holland and AMR Action Fund. Also category representing local funding especially where resources are provided for free e.g. hospital settings Generally, more transparent (and harmonised) reporting of national funders is needed
Preclinical development	Technology transfer grants for spinout/-off companies, technology & innovation support for Lifesciences, biotech start-ups and SME, national and supranational research funders, national and international public investors, global charitable foundations	*National research funder*: National Science Foundation, UKRI, Innovate UK, Department of Defense, NIH, NIAID, SBIR, A*Star, BARDA, *Supranational research funder*: CARB-X, UK-China AMR Fund, IMI, EUHorizon 2020, EU Framework 7 *National public investor*: BpiFrance *Supranational public investor*: European Investment Bank *Charity*: Wellcome Trust, CFF, Gates Foundation	*Europe*: EIC, EISMEA, EIT. *US*: SBIR/STTR seed funding. Google searches on Websites of Universities Websites of national support agencies e.g. Innovate UK, A*Star		Yes – Public investment banks whether national or international need adding. Also, research funders and charities are still very active in funding of this stage of product development

(*Continued*)

Table 3. Continued.

Phase of R&D	Category of public contributions	Public & philanthropic sponsors (examples)	Sources	Additional category needed?
Clinical development	Trial Support by supranational, national research funders, global charitable foundations, public-private partnership, local funding	*National research funder*: FMRI, US Department of Defense, US Army Medical R&D Command, US Defense Health Agency, US Navy, US Defense Threat Reduction Agency, BARDA, NIH, NIAID, SBIR, UK Innovation Agency, Wellcome Trust, INSERM, Chinese Academy of Medical Sciences, AIIMS, Australian Research Council, Australian Government. *Supranational research funder:* CARB-X, European & Developing Countries Clinical Trials Partnership, IMI. *Public-private Partnership*: Holland, AMR Action Fund, GARDP, DNDi *Charity*: Gates Foundation, CFF *Regional*: Imperial College, FISEVI	*International*: clinicaltrials.gov, ICTRP *Europe:* EudraCT/ CTIS *Regional* trial registries *US*: Securities & Exchange Commission (SEC-Reports) FDA/EMA submissions	Yes, requires addition of public-private partnerships to this stage of funding also the presence of local or regional public funding

Market authorisation	Regulatory support: Scientific Advice, fast track etc., RWE data collections & PLEG, tax credits	BARDA, tax rebates from Australia and Canada named	*Europe*: EMA, HTA CG – SG JSC, IMI/IHI projects *US*: US Securities & Exchange Commission (SEC-Reports), FDA	Yes, some categories are missing: Advanced purchasing agreements (APA) Manufacturing support Tax reductions. Note, national research funders can still be active in funding of this stage of development, as example of BARDA shows.

A*STAR – Agency for Science, Technology and Research, AIIMS – All India Institute Of Medical Science, AMR – Antimicrobial Resistance, APA – Advanced purchasing agreements, APC – Advanced Propulsion Centre, BARDA – Biomedical Advanced Research and Development Authority, BPI France – Banque publique d'investissement, CARB-X – Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, CFF – Cystic Fibrosis Foundation, CORDIS – Community Research and Development Information Service, CTIS – Clinical Trials Information System, DNDI – Drugs for Neglected Diseases Initiative, DTRA – Defense Threat Reduction Agency, EIC – European Innovation Council, EISMEA – European Innovation Council and SMEs Executive Agency, EIT – European Institute of Innovation & Technology, EMA – European Medicines Agency, EU – European Union, EUDRACT – EU Clinical Trials Register, FDA – Food and Drug Administration, FISEVI – Andalusian Public Foundation for Health Research Management in Seville, FMRI – Future Marine Research Infrastructure, INSERM – Institut national de la santé et de la recherche médicale, GARDP – Global Antibiotic Research & Development Partnership, HTA CG – Member State Coordination Group on HTA, ICTRP – International Clinical Trials Registry Platform, IHI – Innovative Health Initiative, IMI – Innovative Medicines Initiative, IR – Investor Relations, NIAID – National Institute of Allergy and Infectious Diseases, NIH – National Institutes of Health, PLEG – Post Launch Evidence Generation, RMIT – Royal Melbourne Institute of Technology, R&D – research and development, RWE – Real World Evidence, SEC – United States Securities and Exchange Commission, SG JSC – Joint Scientific Consultations, SME – small and medium size enterprise, UK – United Kingdom, UKRI – UK Research and Innovation, US PTO – United States Patent and Trademark Office.

Discussion

Antimicrobial resistance is an urgent and growing global threat (World Health Organization (WHO), 2015), and several public and public-private multinational initiatives have been formed to tackle the challenge it poses. As our earlier work has demonstrated (Schmidt et al., 2021, 2022; Schmidt & Wild, 2020) there is robust evidence for the existence of considerable public and philanthropic contributions made to the development of medical products (medicines and devices), not only but in particular to antibiotics. This paper – complementing our earlier work – looks at the role of SMEs in antibiotics development and the nature of public and philanthropic contributions to research and development of this field to pilot a framework on categories of public contributions to R&D.

We identified numerous public funding sources for SMEs developing antibiotics in this analysis. Large supranational pharmaceutical companies no longer dominate antibiotics development, with around one-third of antibiotics being developed by small and medium-sized enterprises. As our analysis across SMEs shows, public research funding bodies – both national and international organisations – account for the most accessed type of funding across all stages of product development, except for the post-market authorisation stage. Where multinational pharmaceutical companies get involved in antibiotics development, this tends to occur in the late stages of product development. Our in-depth analysis of Venatorx Pharmaceuticals shows that public funding dwarfed the value of the private investments, which we were able to identify and document.

Since we aimed at piloting the framework developed as part of the EC Horizon Europe project HI PRIX (Grant Agreement Nr. 101095593), the following specific recommendations are made to improve the feasibility and usability of the framework:

- More explicit reflection of stage of clinical research in the framework and alignment of Table 1 more closely to phases of discovery, preclinical, clinical and market authorisation. Pre-clinical research best describes activities carried out in the early-stage development in SME and biotech companies, whilst clinical trials phases 1–3 reflect activities performed in a product's late-stage development.
- Investment funding, which can be public and/or private, needs more explicit inclusion in the framework, and we have included this category in the revised framework in Table 3. As well as private investment, this can be investments from public investment authorities or public-private partnerships. We were able to document instances of public bank investment (e.g. European Investment Bank (EIB) and Bpi France) for antibiotic developments. Also, public-private partnerships provide capital for antibiotics

development, such as Health Holland or the AMR Action Fund. Public-private partnerships are an interesting phenomenon as they often contribute in-kind contributions, which is difficult to track. It is difficult to establish whether private companies actually contribute funds to the partnership or whether private companies simply have a role in the distribution of funds managed by the partnership, with the funds themselves coming from public sources. Seed round financing for the early stages of a startup, such as paying for initial costs, developing a prototype, or hiring a small team, can be provided publicly (e.g. through SBIR, the Small Business Innovation Research programme in the US) or privately (through private venture capital investments), can be considered an investment in the discovery (early stage of product development). Series A, B and C funding is more associated with clinical (late-stage product development) activities. The framework needs to take account of these types of investments.

- At the discovery and clinical stages of development, we found local support (such as providing hospital facilities) or regional funding for development. This is an important nuance to the national funding picture as it represents a different type of funding body. For this reason, we have added the category 'regional/local' to the framework in Table 3.
- For some funding bodies, such as national/supranational research funders and charities, we found evidence of their financial support at all stages of product development, not just the discovery/translational stage, and we amended the framework to reflect this.
- Tax breaks occur not just at the market authorisation stage, but also at early-stage product development by SMEs and biotech companies. Unfortunately, the information on tax deductions reported by SMEs is generally insufficient to classify the exact stage of product development. Regarding recommendations for selecting sources for identifying financial contributions, it is clear that any tax credits are difficult to identify. We suggest that the next stage of work around literature sources involves a deep dive into tax advantages using one country as an example.
- It is interesting to note that regulatory support – both formal and informal – was not mentioned in any of the sources considered. We know this occurs (e.g. regulatory authorities provide scientific advice around clinical trial design), though it is likely not documented publicly. In further work, we will consider the feasibility of establishing the extent of this support through, for instance, interviews with regulatory bodies.

At the end of the HI PRIX project 2025, we will not only provide payers and price negotiators with this structured approach to seek public input and/or ask companies to provide information in a structured format, but generic contract clauses will also be presented for mandatory disclosure of this same public input.

Greater transparency around R&D costs is essential for analysts and policymakers to address the current information imbalance on actual costs and transactions in the market. Policymakers throughout the world are calling for more transparency on actual costs and expenditures for R&D, as can be seen in the European Commission's newly proposed revision of the pharmaceutical legislation (European Commission (EC), 2023b) and the World Health Assembly's (WHA) 2019 resolution WHA72.8 on 'Improving the transparency of markets for medicines, vaccines, and other health products' (World Health Organization (WHO), 2019). At present, high development costs are cited as the reason for high prices [25], but in the absence of reliable information on the contributions made by the public sector and charitable organisations, it is unclear whether pharmaceutical companies have borne all those development costs themselves. In this paper, a case study analysis of the contribution of public and philanthropic funding to one SME pursuing antibiotic development, Venatorx, estimated the value of these contributions from the public purse to be around $655 million, which dwarfs estimates we previously made for other pharmaceuticals (Schmidt et al., 2021, 2022).

This is the first time the framework of public contributions to R&D of medical innovations, recently published elsewhere (Wild et al., 2024), has been applied in practice. The framework is based on a systematic literature synthesis on the categories of public contributions reported in earlier publications, complemented by detailed data analysis of primary information from public sponsors of research, technology transfer support etc (Wild & Fabian, 2024). The framework for classifying the phase and the categories of public contributions to pharmaceutical research funding was found to be applicable in practice and has been extended in key places to reflect the antibiotics pilot. Furthermore, this and our previous work have documented available ways of identifying sources of funding, which we consider to be robust and comprehensive. Our sources include U.S. Food and Drug Administration (FDA) Database for information on approvals, the FDA´s Orange Book for patents, patent citation data, citation analyses on acknowledged funding and grants, employment information of authors and the National Institutes of Health NIH RePORTER for NIH funds per drug and per target. Additionally, we look at pharmacological and historical information on chemicals, drugs and biologicals (Merck Index or Therapeutic Target Db (TTD)), clinical trials, safety, commercial deals and patents (AdisInsight) and on change of ownership (Technology Transfer Websites from universities on spin-out/offs, U.S. Securities and Exchange Commission (SEC)filings for royalty, mode of agreements such as licensing agreements or acquisitions and payments in FiercePharma, FierceBiotech, STAT Health). Information on public sponsorship of clinical trials is mainly accessed via two databases (ICTRP and ClinicalTrials.gov), but also requests to market authorisation holders (MAH) and investigating institutions are used.

Despite our advances in detailing sources for identifying contributions and finding a way to classify contributions, the problem remains that there is no standardised reporting. Though there is a convention on how to define phases in R&D – discovery (discovery, hit stage, lead stage, lead optimisation, preclinical candidate), preclinical development (formal preclinical development according to the regulatory rules), clinical development (Phase 1–3), market authorisation application (market authorisation application (MAA) in Europe or new drug application (NDA) in the United States) and approval – these terms are not used in the reporting of funding, which further complicates any attempt to conduct a detailed analysis of R&D funding. Even though we used a plethora of sources in our investigations, it remains the case that identifying and valuing contributions made by public and philanthropic organisations is time-consuming and difficult. However, this varies according to the stage and type of contribution. For instance, although time-consuming, it is possible to identify funding from many supranational and national funding bodies since (i) many journals now require authors to declare funding support and (ii) national/international funding bodies often provide searchable databases for identifying project support. However, this is not the case for charitable organisations. Furthermore, there is no standardised way of identifying universities' support for discovery research. Subsequently, the role of public institutions like universities, university spin-outs, and publicly funded biotech start-ups is not widely understood. Late-stage public financial support provided to pharmaceutical companies in the form of research grants, tax incentives, and use of clinical infrastructure or regulatory measures such as scientific assistance or fast-track approvals probably have a considerable impact yet are very difficult to identify and value. A spotlight is rarely put on the public contributions to market authorisation and post-market launch, mainly because sources documenting this support are few and far between.

Limitations

Some limitations need to be mentioned: There are private funds such as the REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund, established by the Novo Nordisk Foundation, providing $20 million to $40 million per year, which invests in companies involved in discovery and early-stage development of therapies targeting resistant microorganisms. Though dilutive and non-dilutive, our searches have not covered these private funds. Additionally, due to the dependency on published sources, we cannot claim to provide an exhaustive picture either of financial support or supporting institutions. This is particularly the case at the market authorisation stage and for financial incentives like tax breaks, as well as charitable funding.

The framework we applied needs further revision and refinement to adequately capture all the sources and stages of public and philanthropic contributions that we identified.

Conclusion

We piloted a framework for analyzing public contributions to R&D of medical innovations on a cohort of medicines, namely antibiotics, to check whether the category system is feasible, recommend refinements to the granularity of the category system, and check the range of sources for detailed analyses.

Our analysis across SMEs shows that public research funding bodies – both national and international organisations – account for the most accessed type of funding across all stages of product development, except for the post-market authorisation stage. It is at the latter stage that multinational pharmaceutical companies most often get involved with antibiotic products. Difficulties remain with estimating public and philanthropic contributions, in particular, the role of universities at the discovery stage and the role of public financial incentives at late-stage development.

If public funds are invested in R&D, it is fair to insist on sharing some of the rewards and profits. Public-private product development partnerships may ensure both fairer returns on public investments and more affordable prices (So et al., 2012). Several recommendations are made in this paper considering the further refinement of this category system for classifying public contributions. Implementing these recommendations will be the focus of future activities so that the framework can be applied to advanced therapy medicinal products (ATMPs) before their approval in 2025. This will enable timely information on public and philanthropic contributions to be available for price negotiations. Conditions for pricing need to be included in major funding contracts at all stages.

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Authors' contributions

Louise Schmidt (LS) piloted and revised the framework and wrote most parts of the first draft. Ozren Sehic (OS) supported the data collection. Ursula Theuretzbacher (UT) contributed detailed information on the development of antibiotics. Claudia Wild (CW) supervised the research and wrote parts of the manuscript. Daniel Fabian (DF) contributed comments on the draft. The final version of the manuscript was agreed upon by all authors.

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Ethics approval and consent to participate

Not applicable.

Availability of data and materials

All data supporting the results can be found in the main article or supplementary material.

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