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Systematic analysis of funding awarded for antimicrobial resistance research to institutions in the UK, 1997–2010

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Objectives: To assess the level of research funding awarded to UK institutions specifically for antimicrobial resistance-related research and how closely the topics funded relate to the clinical and public health burden of resistance.

Methods: Databases and web sites were systematically searched for information on how infectious disease research studies were funded for the period 1997–2010. Studies specifically related to antimicrobial resistance, including bacteriology, virology, mycology and parasitology research, were identified and categorized in terms of funding by pathogen and disease and by a research and development value chain describing the type of science.

Results: The overall dataset included 6165 studies receiving a total investment of £2.6 billion, of which £102 million was directed towards antimicrobial resistance research (5.5% of total studies, 3.9% of total spend). Of 337 resistance-related projects, 175 studies focused on bacteriology (40.2% of total resistance-related spending), 42 focused on antiviral resistance (17.2% of funding) and 51 focused on parasitology (27.4% of funding). Mean annual funding ranged from £1.9 million in 1997 to £22.1 million in 2009.

Conclusions: Despite the fact that the emergence of antimicrobial resistance threatens our future ability to treat many infections, the proportion of the UK infection-research spend targeting this important area is small. There are encouraging signs of increased investment in this area, but it is important that this is sustained and targeted at areas of projected greatest burden. Two areas of particular concern requiring more investment are tuberculosis and multidrug-resistant Gram-negative bacteria.

Keywords: antibiotics, antifungal, antiviral, antiparasitic

Introduction

Infections caused by antimicrobial-resistant microorganisms are often associated with poor clinical outcomes, resulting in increased morbidity and mortality. Many factors contribute to the spread of drug-resistant infections, including weak health systems,[1,2] failing public health control,[3] population movements and international travel of people who may be infected or asymptomatically colonized by resistant strains,[4] unregulated use of antibiotics in many parts of the world[5] and inappropriate drug use in countries with tighter regulation.[4,6] There are also biological factors, including spread of resistant strains and spread of mobile genetic elements, that can transfer resistance genes between strains, species and genera. The resistance problems that we now face are exacerbated even further by the dwindling developmental pipeline for new antibiotics.[7]

The burden of resistance changes over time. Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemias in the UK were reduced

from 7790 in 2003/04 to 1481 in 2010/11 and macrolide resistance in pneumococci causing bacteraemias declined from 11%–14% in 2005 to ~5% by 2009.[8] However, also in the UK, there was <2% imipenem resistance in *Acinetobacter* spp. in 2000, rising to 30% by 2008, and while there were no reports of cefixime resistance in *Neisseria gonorrhoeae* in 2005, rates of 12% were reported in 2009.[8] Outside of the UK, in 1997–98, extended-spectrum β-lactamases (ESBLs) were present in 13%–35% of *Escherichia coli* from Chinese centres participating in the SENTRY surveillance,[9] which had increased to 50%–80% by 2007,[10] and the number of cases of multidrug-resistant tuberculosis reported by 27 countries with a high burden of disease almost doubled between 2009 and 2011.[11]

Antimicrobial resistance therefore presents many opportunities and needs for research, ranging from (i) the discovery and development of new agents, through (ii) basic, applied and public health-focused research on resistance mechanisms and the epidemiology of resistant organisms and their resistance elements, to (iii) improved diagnostics for early detection of resistance and clinical trials of different treatment options or influencing usage of antimicrobials, to (iv) social sciences/behavioural/health services/policy research and (v) economic research.

UK research institutions received at least £2.6 billion of public and philanthropic funding to carry out infectious disease research between 1997 and 2010 from a variety of national and international funding sources.[12] These included the Wellcome Trust, Medical Research Council, Department of Health, Bill & Melinda Gates Foundation, European Commission and a range of other bodies, departments and research charities. This funding was spent on all types of science along the research pipeline, from laboratory studies to operational research and translational medicine. We report here the research funding that was awarded to UK institutions specifically for antimicrobial resistance-related research, along with temporal trends and the relative proportions allocated. We assess how closely the topics funded relate to the clinical and public health burden of resistance, seeking to identify potential funding gaps that policy makers and funders can be encouraged to focus on in future, and areas where the UK has clear research strengths.

Methods

The analyses in this paper focused on studies funded in a 14 year period (1997–2010 inclusive) that were relevant to, or had specific mention of, antimicrobial resistance in any of bacteriology, virology, mycology and parasitology research. Antimicrobial resistance studies were defined as those that made specific reference to resistance to one or more antimicrobials or focused on an area of microbiology of clear relevance to resistance (e.g. MRSA). Global health studies were defined as those that investigated diseases not endemic in the UK (such as malaria or schistosomiasis) or where the study had a clear reference to another country (e.g. tuberculosis in South Africa). No private sector funding was included in this analysis, as the publicly available data are very limited from these sources and were considered to be under-representative.

The methods have been described in detail elsewhere,[12] but are reiterated briefly here. The overarching dataset was obtained from several sources of public and charitable funding for infectious disease research studies, including the Wellcome Trust, the Medical Research Council and other research councils, UK government departments, the European Commission and the Bill & Melinda Gates Foundation and other research charities. Data collection was via: (i) downloading all data from the funder web site and manually filtering the infectious disease studies; (ii) searching open access databases on the funder web site for infection-related keyword terms; or (iii) contacting the funder directly and requesting details of their infection studies. Funders were identified through the authors' knowledge of the research and development (R&D) landscape and searches of the Internet. The majority of data extraction was performed by author M. G. H., with support from authors J. R. F., F. B. W. and M. K. C. Each study was assigned to as many primary disease categories as appropriate.[13] Within each category, topic-specific subsections (including specific pathogen or disease) were documented. Studies were also allocated to one of four R&D categories: pre-clinical; Phase 1, 2 or 3; product development; and implementation and operational research (including surveillance, epidemiology and statistical and modelling projects). Funders were either considered in their own right or, for convenience, some were grouped into categories, such as in-house university funding, research charities and government departments. A total of 26 funder categories were used.[13] Studies were excluded if: (i) they were not immediately relevant to infection; (ii) they were veterinary infectious disease research studies; (iii) they concerned the use of viral vectors to investigate non-communicable diseases; (iv) they were grants for symposia or meetings; or (v) they included UK researchers, but with the funding awarded to and administered through a non-UK institution. Studies that made reference to related areas such as antimicrobial stewardship or development of new therapeutics were excluded unless there was specific mention of resistance in the title or abstract. Unfunded studies were also excluded. Grants awarded in a currency other than pounds sterling were converted into UK pounds using the mean exchange rate in the year of the award. All awards were adjusted for inflation and reported in 2010 UK pounds. Analysis was carried out in Microsoft® Excel and Access (versions 2000 and 2007) and Stata (version 11).

Results

We identified 6165 studies funded within the 14 year period and covering all infectious disease research representing a total investment of £2.6 billion (Table 1). Despite the global impact and clinical importance of antimicrobial resistance, by funding volume this research area ranked only 14th out of the 38 primary disease categories.[13] Three hundred and thirty-seven studies were funded for antimicrobial resistance research, comprising 5.5% of total infectious disease research projects. These were awarded £102.0 million; only 3.9% of the total spend, with a median award of ~£120 000 (Table 1). If tuberculosis, HIV and malaria are not included, then the total antimicrobial research spend is £62.5 million (Figure 1).

Of the 337 resistance-related projects, 51.9% ($n=175$) focused on bacteriology (Table 1), but these attracted only 40.2% (£41.0 million) of total resistance-related spending, with a median award of ~£112 000. Studies on antiviral resistance ($n=42$) represented 12.5% of resistance-related projects and were awarded 17.2% of the resistance-related funding (median award ~£121 000). In contrast, parasitology studies ($n=51$) represented 15.1% of resistance-related projects, but were awarded 27.4% of funding with a median award of ~£223 000. Hence, a substantial proportion of the funding awarded to UK institutions for resistance-related research over the 14 year study period was for projects addressing global health issues. In particular, studies on resistance in malaria were awarded £21.3 million across 35 studies (Table 2). Thirty-four percent (£34.8 million) of the total funding for antimicrobial resistance was related to global health.

Pre-clinical research received £58.0 million across 191 studies, Phase 1–3 studies received £1.2 million across 3 studies, product development research received £4.2 million across 20 studies

Table 1. Funding awarded to UK institutions for research on infectious disease ranked by numbers of awards for antimicrobial resistance-related projects

	Total research funding awarded			Antimicrobial resistance-related funding		
Microbiological subject area	number of studies (%)	total investment, £ millions (%)	median grant award, £	number of studies (%)	total investment, £ millions (%)	median grant award, £
Bacteriology	1995 (32.8)	588.3 (22.6)	162281	175 (51.9)	41.0 (40.2)	112152
Parasitology	1067 (17.6)	666.9 (25.7)	216260	51 (15.1)	27.9 (27.4)	222912
Virology	2147 (35.4)	1027.4 (39.5)	160555	42 (12.5)	17.5 (17.2)	120926
Mycology	171 (2.8)	48.4 (1.9)	138258	14 (4.2)	1.5 (1.5)	91761
Prion	48 (0.8)	33.5 (1.3)	381587	—	—	—
Not specified	914 (15.1)	329 (12.7)	126179	55 (16.3)	14.5 (14.2)	115120
Overall	6165 (100)	2600.0 (100)	158055	337 (5.5)	102.0 (3.9)	119685

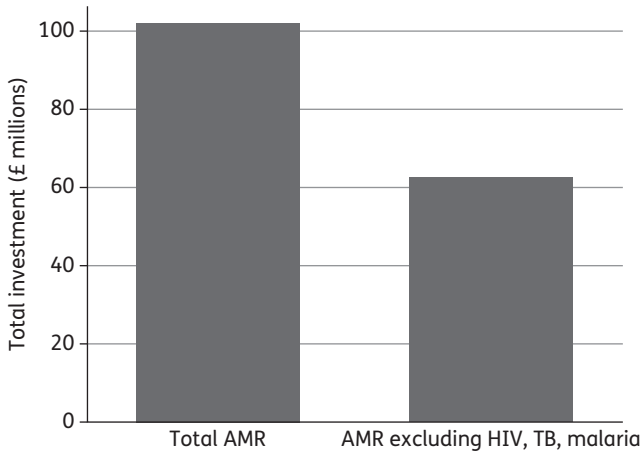

Figure 1. Sum of funding awarded for antimicrobial research (AMR) studies, 1997–2010, with and without inclusion of the 'big three' of tuberculosis (TB), malaria and HIV.

and implementation and operational research received £38.6 million across 123 studies.

Studies related to resistance in staphylococci received £15.9 million across 76 studies, of which 28 were pre-clinical and 41 were implementation and operational research. Twelve studies, totalling £9.1 million, looked specifically at resistance and tuberculosis and were a mixture of implementation research (7 studies) and pre-clinical science (5 studies). Two of the implementation studies were related to work in Africa and two to Asia. There were just two studies specifically on *E. coli* resistance and one more looking at ESBLs generally. There were 30 HIV studies receiving £20.7 million, of which 16 were pre-clinical and 10 were implementation and operational research. Modelling and economics research was limited to nine studies (total funding £1.1 million, median funding £130219).

There were no clear temporal trends in the levels of overall funding (although it appears that funding may be increasing overall) or in awards made by particular funding bodies (Figure 2). The mean funding for resistance-related research was £7.2 million per annum, but ranged from £1.9 million in 1997 to £22.1 million in 2009. The mean funding awarded per study was £302731 (SD £752544), with median funding per study considerably lower at £119685 (IQR £31889–254591), demonstrating the skewed distribution of the awards (there were 146 awards of less than £100000 and 9 awards of more than £1 million).

Discussion

This study is the first systematic analysis of research funding for antimicrobial resistance. Over the 14 year study period analysed, 337 studies were identified that related to antimicrobial resistance where public and philanthropic funding had been awarded to a UK institution. The majority of projects (51.9%; £41.0 million) focused on bacteriology. There was also a focus on pre-clinical science (57%; £58.0 million). Nevertheless, bacteriology-focused resistance projects did not attract pro rata levels of funding, accounting for 52% of funded projects, but only 40% of the total spend; virology- and, especially, parasitology-focused resistance projects attracted larger awards. Two hundred and nine studies investigated resistance, usually in bacteria, but did not specify a pathogen.

The Chief Medical Officer (CMO) for England made antimicrobial resistance, especially in bacteria, a priority area in her annual report, published in 2013,[14,15] and the Department of Health later issued an e-mail bulletin highlighting a call for research in this area, to be released in the autumn of 2013 across the major funding streams of the National Institute for Health Research.[16] Thus there has been a clear acknowledgement within the UK political arena that there are significant challenges in this area that need to be met. The scientific community has repeatedly highlighted the threats posed by the emergence and spread of antibacterial resistance nationally and globally,[17] and the lack of new antimicrobials being developed,[18–20] but this study suggests that the research portfolio in this area of antimicrobial resistance appears to be relatively small.

There are now large international collaborative schemes, such as the National Institutes of Health Public–Private Partnership programme and the Innovative Medicines Initiative (IMI) supported jointly by the European Union and the European Federation of Pharmaceutical Industries and Associations.[21] Part of the IMI has a mission to identify novel lead molecules for antibiotic

Table 2. Breakdown of investments directed to specific infection

		Total research funding awarded			Antimicrobial resistance-related funding		
Topic area	Specific infection	number of studies (%)	total investment, £ millions (%)	median grant award, £	number of studies (%)	total investment, £ millions (%)	median grant award, £
Bacteriology	*Campylobacter*	87 (1.4)	24.1 (0.9)	221532	0	0	0
	chlamydia	112 (1.8)	21.7 (0.8)	50469	1 (0.3)	0.2 (0.8)	165260
	Clostridium	78 (1.3)	35.4 (1.4)	204389	2 (0.6)	0.6 (2.1)	315676
	diphtheria	2 (0)	0.1 (0)	69931	0	0	0
	E. coli	107 (1.7)	26.3 (1.0)	206784	2 (0.6)	0.2 (0.7)	89448
	gonorrhoea	18 (0.3)	0.9 (0)	7548	1 (0.3)	0.01 (0.8)	7441
	Helicobacter	101 (1.6)	15.1 (0.6)	83986	2 (0.6)	0.02 (0.1)	8310
	leprosy	2 (0.0)	0.6 (0.0)	311540	0	0	0
	Listeria	11 (0.2)	4.9 (0.2)	239595	0	0	0
	meningitis	222 (3.6)	54.0 (2.1)	146153	6 (1.8)	1.1 (2.0)	137022
	pertussis	9 (0.1)	2.4 (0.1)	299840	0	0	0
	Pseudomonas	43 (0.7)	6.5 (0.2)	81793	3 (0.9)	0.5 (7.8)	243667
	Salmonella	145 (2.4)	55.7 (2.1)	256185	7 (2.1)	3.0 (5.4)	384998
	Shigella	9 (0.1)	3.3 (0.1)	211456	0	0	0
	Staphylococcus	139 (2.3)	31.6 (1.2)	114502	76 (22.6)	15.9 (50.2)	81927
	Streptococcus	70 (1.1)	16.7 (0.6)	161869	5 (1.5)	0.6 (3.4)	101876
	syphilis	5 (0.1)	1.1 (0.0)	207346	0	0	0
	tetanus	5 (0.1)	5.1 (0.2)		0	0	0
	trachoma	2 (0.0)	3.7 (0.1)	1859286	0	0	0
	tuberculosis	329 (5.3)	155.3 (6.0)	190467	12 (3.7)	9.1 (6.1)	260866
Parasitology	African trypanosomiasis	76 (1.2)	42.8 (1.6)	262145	4 (1.2)	1.9 (4.0)	323869
	Chagas disease	18 (0.2)	4.9 (0.2)	215639	0	0	0
	helminths	150 (2.4)	67.9 (2.6)	233772	5 (4.4)	1.3 (2.8)	248586
	leishmaniasis	78 (1.3)	41.8 (1.6)	289354	4 (5.3)	2.9 (8.1)	452751
	lymphatic filariasis	7 (0.1)	47.0 (1.8)	551459	0	0	0
	malaria	504 (8.1)	352.9 (13.6)	203348	35 (7.0)	21.3 (6.2)	219834
	onchocerciasis	5 (0.1)	1.7 (0.1)	35769	0	0	0
	schistosomiasis	47 (0.7)	40.8 (1.6)	197557	0	0	0
Virology	CMV	68 (1.1)	28.4 (1.1)	188607	2 (2.9)	0.2 (0.6)	90093
	dengue	29 (0.5)	43.8 (1.7)	269824	1 (3.6)	0.1 (0.2)	95888
	EBV	146 (2.4)	44.6 (1.7)	156697	2 (1.4)	1.1 (2.4)	548026
	hepatitis B	68 (1.1)	11.8 (0.5)	65624	3 (4.4)	0.1 (0.9)	11794
	hepatitis C	235 (3.8)	59.7 (2.3)	116883	1 (0.4)	0.1 (0.1)	64706
	HIV	764 (12.4)	477.6 (18.4)	147404	30 (3.9)	20.7 (4.5)	155583
	HPV	147 (2.4)	52.2 (2.0)	92143	0	0	0
	HSV	48 (0.8)	22.1 (0.8)	202564	0	0	0
	influenza	141 (2.3)	80.0 (3.1)	299988	2 (1.4)	0.6 (0.8)	303676
	measles	12 (0.2)	5.0 (0.2)	284882	0	0	0
	norovirus	12 (0.2)	5.1 (0.2)	200621	0	0	0
	polio	4 (0.1)	1.2 (0.0)	164849	0	0	0
	rotavirus	19 (0.3)	6.1 (0.2)	164690	0	0	0
	RSV	45 (0.7)	16.9 (0.6)	184292	0	0	0
	VZV	20 (0.3)	4.2 (0.2)	145505	0	0	0
Mycology	*Aspergillus*	26 (0.4)	4.9 (0.2)	47948	1 (3.8)	0.1 (2.3)	112397
	Candida	71 (1.2)	19.1 (0.8)	253498	6 (8.5)	0.8 (4.2)	98641
Other or pathogen not specified		2572 (41.7)	935.7 (36.0)	153330	220 (8.6)	50.4 (5.4)	101258
Overall		6165	2600.0	158055	337 (5.5)	102.0 (3.9)	119685

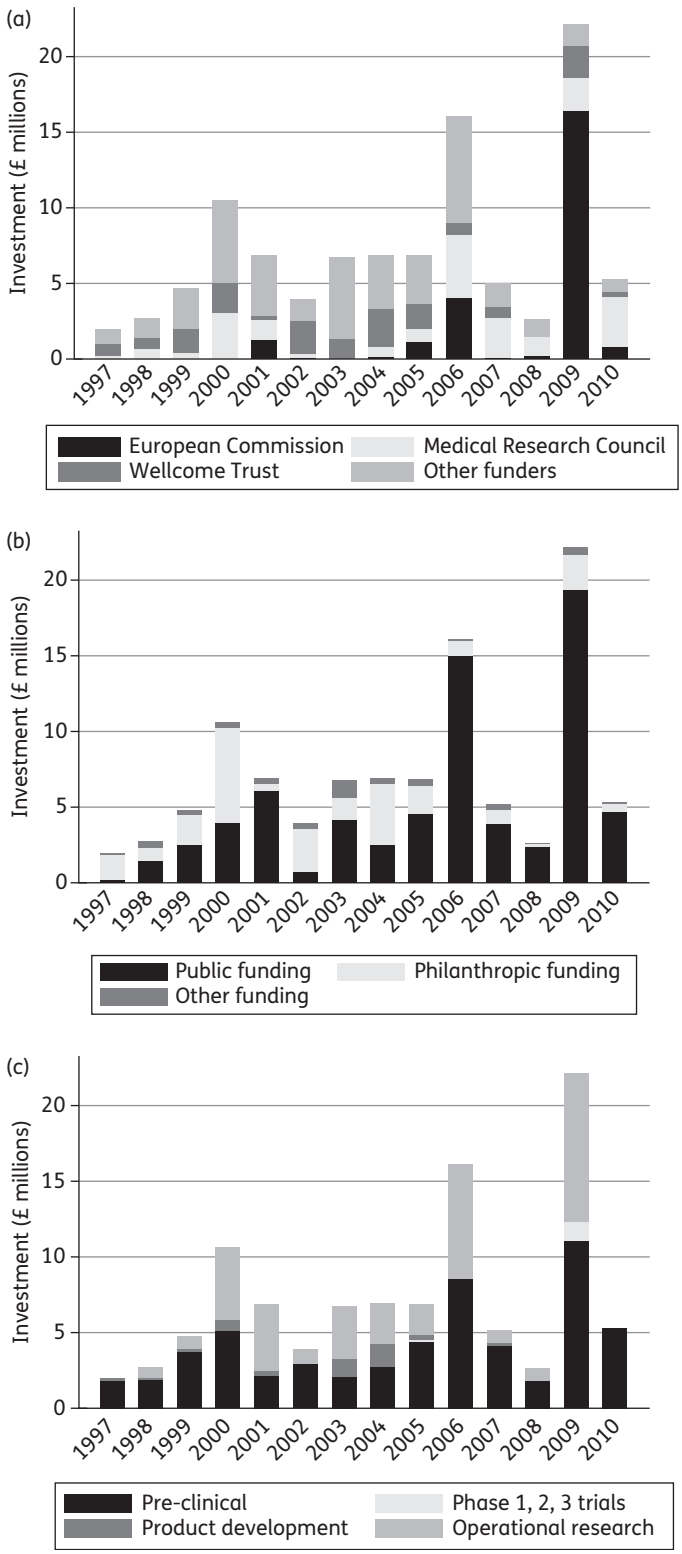

Figure 2. Sum of funding awarded for antimicrobial research studies, 1997–2010, according to (a) top funders, (b) type of funding and (c) stage of research pipeline.

development and this collaboration could be particularly important, in terms of highlighting the best direction for efficient antibiotic development R&D programmes and appropriate models of how the private and public sectors can best work together.

The time period analysed for this study broadly coincides with what has been described as the 'rise and fall' of one of the UK's highest-profile resistance problems, that of MRSA.[8] From a peak in 2003, there has been a general decline in the rate of MRSA bacteraemia in England since 2006.[22] Just 19 MRSA research studies were funded from 1997 to 2002, increasing to 57 from 2003 to 2010. Given that much of this was translational work and hospital focused, it is possible that research has made a timely contribution to the declines in recorded bacteraemias. However, despite success with reducing MRSA, new problems have gained prominence. Resistance rates in many Gram-negative bacteria have increased throughout the period analysed.[23,24] They represent a growing public health threat and indicate the most pressing need for new antibiotics. These bacteria now also have a raised political profile, with the CMO for England highlighting concerns over multidrug-resistant strains of *N. gonorrhoeae* and strains of Enterobacteriaceae, particularly *E. coli* and *Klebsiella pneumoniae*, in both community and healthcare settings with ESBLs and carbapenemases.[14,15] Awards to UK institutions to undertake research in this particular area appeared to be minimal, though some of the studies may have had a tangential focus here and the analysis may have excluded antimicrobial resistance studies involving UK collaborators but led elsewhere. Also, awards were analysed only up to and including 2010. Subsequent to this period, a report by the Joint Working Group of DARC (Defra Antimicrobial Resistance Coordination) and ARHAI (Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections), entitled *ESBLs: A Threat to Human and Animal Health?*,[25] was followed by a specific funding call by the Department of Health in England to address the research and evidence gap surrounding this particular resistance.[26] The spread of carbapenemases, however, remains a topic for greater focus by funders and researchers.

The worldwide burden of drug-resistant tuberculosis is increasing, with WHO estimates of 630000 cases of multidrug-resistant tuberculosis worldwide, great variation between countries and emergence over the last decade of extensively drug-resistant cases.[27] With the highlighted difficulties in the development of an improved vaccine,[28] research into effective tuberculosis treatments becomes even more important. The UK arguably should sustain greater activity in this R&D, with a focus both in the UK and internationally, directing research resources to areas of current and projected future high burden of tuberculosis resistance.

Within parasitology-related resistance research, the main focus (both funding and study numbers) was on malaria with the rest being distributed relatively thinly amongst leishmaniasis, trypanosomiasis and helminth infections. Resistance of the malaria parasite *Plasmodium falciparum* to antiparasitic drugs is well known, with the WHO launching the Global Plan for Artemisinin Resistance Containment.[29] The malaria out put of this dataset was predominantly basic science, with fewer studies focusing on implementation and operational research. Malaria research generally has been a strength of UK institutions[12] and the number of studies investigating this area of resistance is encouraging. Within neglected tropical

diseases (NTDs, as defined by WHO[30]), the work is almost entirely pre-clinical apart from one study on implementation research and another on product development. Although NTDs are well funded generally, relative to the overall dataset,[12] the few projects on resistance may actually reflect a poorer knowledge base (than malaria). If so, then strengthening surveillance systems in countries of endemic infection to quickly identify any emerging patterns of resistance and using the surveillance data for research could be an interesting area to prioritize.

Of the 30 studies related to HIV, just three studies—each awarded more than £1 million and with two focused on interventions in Africa—were collectively awarded >50% of the total HIV funding. The median award for HIV research was substantially less than the malaria resistance portfolio (£155 583 versus £219 834) and there was a balance between pre-clinical and implementation research, perhaps illustrating the more advanced pool of knowledge within HIV compared with, for example, NTDs.

The study has several limitations, which have been highlighted and discussed in detail elsewhere.[12] One particularly important caveat arises from the difficulty in obtaining details, and hence the exclusion here, of private sector research funding. For the true picture to emerge, private sector data must be analysed to the same level of detail achieved here for data obtained from public sector and charitable foundations. The success of the Policy Cures initiative[31] to obtain industry data is encouraging for future analyses. Another limitation arises because it is difficult to assess associations with other areas of research that are not directly related to resistance, but which nonetheless have an impact, e.g. preventative measures such as vaccine development and enhancing treatment adherence. Also, it was not feasible to assess how much funding was distributed from the lead institution to their collaborative partners, nor was it possible to quantify what proportion of a grant should be allocated to each of the allocated disease categories.

With an increasing globalization in both the transmission of infectious diseases and also the opportunities for institutions to collaborate across borders, there is an increasing need for global data. The Global Burden of Disease Study[32] illustrates the usefulness of such collaborations and Policy Cures shows how an international approach to obtaining neglected disease funding can be applied. There is a need for funders from other countries to provide similarly detailed information of funded studies, in order to build a global database of projects. This would be of great help in identifying true research gaps, reducing unnecessary duplication of research, pinpointing where there is infrastructure and capacity for specific types of research requiring technology or skills, and aiding in assessing global priorities.

To conclude, political leadership, sustained funding and the implementation of global and regional action plans have been highlighted as important facets of any attempt to reduce and combat antimicrobial resistance.[27] The stimulation of new partnerships between the public and private sectors may give new stimulus to the development of new antimicrobials, but there appears to be broad neglect of resistance generally from public and philanthropic funding in the UK, when compared with funding awarded to other infectious disease-related topics. Therefore, there must be consideration of increased funding for research into areas such as epidemiology, modelling, economics, policy and behavioural research, intervention studies aimed at reducing resistance and further pre-clinical research using new technologies such as whole genome sequencing.[33] Tuberculosis and multidrug-resistant Gram-negative bacteria are arguably the two areas of potentially greatest future burden. The UK shows a good example in carrying out research across all areas of infection that is categorized as global health and thus of primary benefit to other countries, and this should continue to be reflected in resistance-related R&D. However, the somewhat reactive nature of the response to the problem indicates that lessons should be learned in setting aside future funding for emerging issues within infectious diseases generally and specifically here within antimicrobial resistance. Researchers should be encouraged to develop high-quality bids and funders encouraged to consider their possible impact in reducing future disease and economic burdens. Funders based in other countries should also be encouraged to release their funding data for similar systematic analyses, to allow the construction of a global database of previous and current antimicrobial resistance projects.

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Author contributions

M. G. H. designed the study and collated the dataset. J. R. F., F. B. W. and M. K. C. checked and refined the dataset. J. R. F. undertook data analysis and created the graphs and figures (with input from M. G. H. and R. A.). M. G. H., N. W. and A. P. J. interpreted the data and wrote the draft

and final versions. A. C. H., A. H. and R. A. commented on the dataset, draft paper and final version. All authors reviewed and approved the final version. M. G. H. is guarantor of the paper.

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