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Cross-disease spillover from research funding: Evidence from four diseases

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ABSTRACT

There is widespread appreciation for the role of research in addressing health problems. However, there is limited evidence on the extent to which research can be targeted to specific diseases. Analyses highlighting a concentration of research funding towards certain diseases have prompted growing scrutiny over the allocation of research funding. In this paper, we show that research funding targeted to a disease often results in publications relating to other diseases. Using data from the world's largest biomedical research funders, we estimated the frequency and direction of this cross-disease spillover by examining 337,573 grant–publication pairs for four diseases. We found the majority of our grant–publication pairs were cross-disease spillovers. We also found some variation between "rich" and "poor" diseases, in terms of the frequency and direction of cross-disease spillover. These differences are likely to be related to characteristics of the diseases themselves, as well as features of the research environment. One implication of frequent cross-disease spillover is that although more investment in areas of research such as neglected diseases is necessary, it may not be sufficient to improve the alignment between research funding and health needs.

1. Introduction

To what extent does research funding for a disease result in findings related to other diseases? This question is important for medical research policy for at least two reasons.

First, the distribution of research funding across diseases has recently come under scrutiny, with some diseases allocated much less funding than others. These disparities have been characterised as misalignments, with calls to rectify them via greater research funding for specific targeted disease areas (Commission on Health Research for Development, 1990; Policy Cures Research, 2019). However, addressing health disparities by increasing research funding for specific diseases is less straightforward than it appears because of the possibility that the results from funding directed toward research into one disease can spill over to other diseases, an idea we term cross-disease spillover. The recent development of COVID-19 vaccines, rolled out across rich countries, was built on decades of research oriented to diseases in poor countries, such as malaria and Ebola (Yaqub et al., 2022). One implication of such cross-disease spillover is that greater investment in neglected diseases, while necessary, may not be sufficient to improve the alignment between research funding and health needs, if the extra funding also produces results related to less neglected diseases (Coburn et al., 2023). Reducing the disparity in funding may not necessarily reduce the disparity in results to the same extent.

Second, funding for biomedical research has long had broad-based support, but recently there have been concerns that markets and stakeholders are becoming disaggregated into narrow disease constituencies and that the organisation of medical research is increasingly disease-focused. For example, the President of the American Neurological Association criticized an array of specific neuromuscular interest groups for being overly narrow in their focus (Best, 2019, p. 47). Recognition of cross-disease spillover may help us to understand both this fragmentation and also potential collaborations among the groups and markets that support biomedical research. Despite the relevance to policy and theory, however, the notion of cross-disease spillover from research funding has remained largely unexplored.

In this paper, we describe an approach for estimating the frequency and direction of cross-disease spillover. Using data from the world's largest biomedical funders, we examined grants and their linked publications. We focused on four diseases that vary across a range of policy-relevant dimensions, such as funding level, disease burden, and geography of burden. From over 300,000 grant–publication pairs, we found

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that more than half were classed as cross-disease spillovers. We also found some variation between diseases in terms of the frequency and direction of cross-disease spillover. The evidence in this paper raises questions about priority-setting, how and why we evaluate research funding, and to what extent we ought to organize biomedical research by disease area.

2. Addressing disease with research: a framework

Biomedical research, as a foundation for the practice of medicine, has long been recognised. In 1894, one of the founders of the Johns Hopkins School of Medicine and the associated hospital remarked, "The physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practising a sort of popgun pharmacy. … [Laboratories are] as essential to the proper equipment of the hospital as the interns." (Osler, cited in R. Porter, 1997, p. 305 and p. 347). Since then, appreciation for biomedical research has become widespread and has captured popular imagination as a dynamo of medical progress. Biomedical research is often seen as the source of many spectacular advances in therapeutic and preventative healthcare, such as new drugs, devices, and techniques.

Longstanding bipartisan support for the world's largest biomedical research funder, the U.S. National Institutes of Health (NIH), has seen its annual budget grow from less than $1 billion in 1965 to over $45 billion today. However, during this time, there have been increasing efforts to target research funding to specific diseases and basic research funding has decreased as a proportion of total NIH funding. Consequently, targeted research funding has grown faster than non-targeted funding. For example, one mechanism to solicit research in specific diseases and areas (termed "Requests for Applications"), grew from 2% of the NIH's funding in 1985 to over 25% by 2015 (Aslan et al., 2023).

2.1. Disease categories as a focus for targeted research funding

Diseases are important categories. Inquiries and responses to crises have been undertaken in their name; institutes and health programs are oriented towards specific diseases; and wars are even declared against them (Crow, 2011; Fauci and Eisinger, 2018; Rettig, 1977, 1978). In health and medicine, patients are diagnosed into disease categories with repercussions that shape the delivery of healthcare and social welfare (Hacking, 1995; Jutel and Nettleton, 2011; C. Rosenberg, 2002).

More recently, the impact of disease categories on biomedical research funding has become recognised, especially in terms of the prominent role disease categories play in the organisation of resources and activities, and the pressure to fund research into specific diseases. Researchers have highlighted market size (Acemoglu and Linn, 2004; Evans et al., 2014); the emergence of disease advocacy (Best, 2012; Dresser, 1999, 2001; Hegde and Sampat, 2015); the mobilisation of disease constituencies (S. Epstein, 1996; Steven Epstein, 2016); donor programmes that favour targeting multiple aspects of a single disease from diagnosis to treatments, a "vertical" disease focus, over broader strengthening of health systems (Clinton and Sridhar, 2017); and public–private partnerships that focus on specific products such as vaccines for malaria or HIV (Chataway et al., 2010). The growing influence of disease categorisation has resulted in funders pursuing different priorities than previously (Ncube and Chataway, 2019; Zhou, 2019).

Disease advocacy can be viewed as benevolent but imperfect. Disease campaigns draw in new funding (i.e., adding to, rather than competing with, existing funds); however, the resulting funding allocations can seem haphazard. For example, investments in infrastructure and prevention may be neglected. As Best writes, "We're choosing between a large amount of money distributed irrationally and a small[er] amount of money distributed rationally. The former is probably better." (Best, 2019, p. 163). These contingent allocations can develop into research "bandwagons" focused on a particular disease (Fujimura, 1988).

Advocates have sought to construct commensurability between research priorities through a variety of metrics (Espeland and Stevens, 1998; T. Porter, 1995; Power, 1997; Timmermans and Epstein, 2010). These include (1) directly ranking diseases in terms of their research funding; (2) comparing disease burdens in terms of mortality (deaths) and morbidity (lost disability-adjusted life years [DALYs]); (3) comparing the economic costs and geographical distributions of disease mortality and morbidity; and (4) assessing the potential growth of a disease category by emphasising new cases and diagnoses and extrapolating the burdens into the future.

These variations allow advocates to deploy their metric of choice when presenting what a rational distribution of resources might look like. However, some diseases consistently attract much less research funding than others, regardless of which metric is used. By most measures, these diseases disproportionately affect poor populations (see for example Røttingen et al., 2013; von Philipsborn et al., 2015). As such, comparing diseases is not an exercise confined only to disease advocates; it has also drawn the attention of researchers and policymakers working in the areas of development and poverty alleviation. Disease comparison sets in motion an impetus to align illness with investment and deaths with dollars.

2.2. Misalignments in research funding

A growing body of evidence highlights misalignments between biomedical research and societal needs (Evans et al., 2014; see for example Gross et al., 1999; Ràfols and Yegros, 2017; Yegros et al., 2020). Such analyses provide a basis for claims that: a disease or group of diseases are underfunded compared to the funding of others; by accounting for their burden relative to other diseases when making funding comparisons; by estimating economic costs of a disease; or through a combination of all of these. In India, for example, cancer causes around 5% of the disease burden but has a research publication share of nearly 25%, whereas cardiovascular and respiratory diseases cause around 23% the disease burden but have a publication share of only 6% (Kumar et al., 2023).

In response to claims of misalignment, there have been efforts to promote a group of diseases termed the "poverty-related and neglected diseases" (PRNDs), whose disease burdens fall mainly in low- and middle-income countries (LMICs) (Hotez, 2013; Policy Cures Research, 2017, 2018). PRNDs comprise AIDS, tuberculosis, malaria, and a group of neglected tropical diseases. PRNDs have become a prominent organising category for priority setting and evaluation in research funding (Cochrane et al., 2017). Despite these categorical efforts, the extent to which research funding has supported progress outside of PRND research remains unclear, and this is also the case for research targeted towards tackling diseases that are more prevalent in high-income countries (HICs).

The concepts of "poverty-related" and "neglected" are not clear cut (Coburn et al., 2023). For example, many diseases are present in both developed and developing countries, the global distribution and funding of research into diseases can change over time, and there are both rich and poor populations within most countries (Hotez, 2013, 2016; Policy Cures Policy Cures Research, 2019). Nevertheless, attempts have been made to classify diseases according to how poverty-related and neglected they are.

The poverty-relatedness of a disease can be measured by calculating the ratio of the disease burden per person in LMICs divided by the disease burden per person in HICs. A ratio of 1 means that a disease is found equally in LMICs and HICs; and the higher the ratio, the more prevalent the disease is in LMICs relative to HICs. On the basis of this ratio, diseases have been categorised as type I (ratio less than 3), type II (ratio of at least 3 but less than 35), or type III (ratio of 35 or more) (Røttingen et al., 2013).

Similarly, the neglect factor of a disease can be calculated by dividing the global burden of a disease (GBD) (as a percentage of the total GBD) by its global research and development (R&D) expenditure

(as a percentage of total global health-related R&D expenditure). So, the higher the neglect factor, the more neglected the disease (von Philipsborn et al., 2015). These measures can bring into sharp focus the sheer magnitude of the disparity between diseases. According to these measures, malaria and Chagas disease are examples of highly poverty-related and neglected diseases, whereas neoplasms such as breast cancer and cardiometabolic diseases such as diabetes are counterexamples (von Philipsborn et al., 2015). These are the four diseases selected for our study.

2.3. Cross-disease spillover

Comparing diseases in this way creates the potential to address health disparities across populations by directing research funding to specific diseases. Ranking diseases according to specified metrics also challenges reliance on expert opinion and managerial discretion for resource allocations. However, some researchers and funding agencies argue that a disease-focused approach overlooks other concerns.

First, scientific and technical opportunities may not be evenly distributed across diseases. Some problems, regardless of their disease burden or the social imperative to pursue them, may remain intractable, at least in the short term: "It is unlikely that any amount of money devoted to inventive activity in 1800 could have produced modern, wide-spectrum antibiotics, any more than vast sums of money at that time could have produced a satellite capable of orbiting the moon. The supply of certain classes of inventions is, at some times, completely inelastic—zero output at all levels of prices …" (N. Rosenberg, 1974, p. 106). Furthermore, researchers who are not limited to investigating a particular disease can change their lines of enquiry to pursue lower hanging fruit and technical opportunities that cross disease boundaries: "The hope of major advances lies in sustaining broad and free-ranging inquiry into all aspects of the phenomena of life" (NIH director Shannon, cited in Best, 2019, p. 101). Moreover, organising medical research by disease may introduce inefficiencies when particular research capabilities, techniques, instruments, datasets, and approaches could be deployed across multiple disease areas.

Second, cross-disease spillover may reflect fundamental biological or medical characteristics, whereby different diseases share common pathogens, vectors, symptoms, and treatments. Some diseases may therefore show greater propensity for cross-disease spillover than others, depending on how features of the disease are connected to other diseases. For example, infectious diseases such as Chagas disease and malaria have causative pathogens and are well bounded. By contrast, noncommunicable diseases such as diabetes and breast cancer have multifactorial aetiology. In particular, diabetes is closely related to other diseases such as obesity (a risk factor) and atherosclerosis (a possible long-term symptom). Where a disease is less well defined and harder to disambiguate from other diseases, research funding is likely to yield spillover to neighbouring diseases. Because of this, it is useful not just to estimate the frequency of cross-disease spillover, but also to map the direction of the spillover.

Third, whilst there is often emphasis on overall funding levels for a disease, there is less recognition of the different forms that funding can take and the effects this might have for potential cross-disease spillover. For example, the vast majority of funding supports research conducted in HICs, even for diseases which are almost wholly confined to LMICs (Ralaidovy et al., 2020). There is a relative lack of availability of unrestricted institutionalized funding in LMICs, whereas this is typically part of the funding landscape for disease research in HICs via the healthcare organisations, such as hospitals, that physician researchers work for (Bieszczad et al., 2020). With weaker healthcare infrastructure, there may be fewer opportunities to access institutionalized funding in hospitals and connect with clinical research specialties that cross disease areas. Institutionalized funding also provides a "protected space" for researchers to change their research direction if needed, and may thus produce more cross-disease spillover than other forms of funding (Franssen et al., 2018; Gläser et al., 2014; Whitley et al., 2018). Moreover, neglected diseases may suffer reputational disadvantages, such as perceptions of limited future funding or interest from prestigious journals, which leave these researchers relatively isolated from those working in other disease areas. For example, research on diseases of the poor suffers a citation penalty, despite the results being published in the top quartile of journals as often as for other diseases (Yegros et al., 2020). Together, these factors suggest that there is likely to be more spillover from research into well-funded diseases than less well-funded diseases.

Accordingly, we explored three aspects of cross-disease spillover: frequency, direction, and variation. In the next section, we describe the approach we developed to form quantitative and qualitative estimates of these parameters.

3. Methods

3.1. Research design

We aimed to measure and compare the frequency and direction of cross-disease spillover from research funding for Chagas disease, malaria, diabetes, and breast cancer. We limited our comparison to four diseases to enable a more detailed approach, including manually reviewing samples of grants and publications. We examined the same set of funders for each of these diseases. However, the four diseases differ in terms of poverty-relatedness, neglected-ness, and other factors (as noted in section 2 and below).

3.2. Data collection

3.2.1. Selecting diseases and specifying search terms

To guide the selection of diseases for comparison, we collected a range of descriptive statistics. Table 1 shows how the mortality and morbidity (deaths and lost DALYs), geographic distribution (across LMICs and HICs), and research levels (number of grants, USD value) vary across the four diseases.

Chagas disease and malaria are infectious vector-borne diseases, predominantly prevalent in LMICs, whereas diabetes and breast cancer are non-communicable diseases, prevalent worldwide. Using a measure of poverty-relatedness that combines morbidity and geographic

Table 1
Descriptive statistics on global burden of disease, funding, and grants for four diseases.

Disease	Chagas disease	Malaria	Diabetes	Breast cancer
Deaths, annual, millions	0.01	0.64	1.55	0.70
Deaths, annual, as % of all-cause deaths	0.02	1.14	2.74	1.24
DALYs worldwide, annual, millions	0.28	46.44	70.88	20.63
DALYs in LMICs, annual, millions	0.20	45.98	47.09	11.96
DALYs in HICs, annual, millions	0.08	0.44	23.73	8.65
DALYs ratio (DALYS per person LMIC/DALYS per person HIC) (Røttingen et al., 2013)	1,869.10	185.10	0.80	0.45
Disease type (Røttingen et al., 2013)	III	III	I	I
Grants count (2005–2019)	321	2,660	16,203	7225
Value of grants, millions USD, (2005–2019)	583.53	11,778.55	23,137.35	15,757.14

Sources: Web of Science, Dimensions, research funders (NIH, U.K. Research and Innovation (UKRI), European Commission (EC), and the Wellcome Trust), and the Institute for Health Metrics and Evaluation.

distribution (Røttingen et al., 2013), Chagas disease and malaria have a very high DALYs ratio (Type III), whereas diabetes and breast cancer have a low DALYs ratio (Type I).

The level and type of research funding for the selected diseases differs. From 2005 to 2019, Chagas disease received the least amount of funding ($583.5 million) and diabetes received the most ($23,137 million). Although malaria is classified above as poverty related (Type III), funding into malaria was more than 20 times that for Chagas disease. The higher level of R&D investment for malaria is likely to be because of its status as one of the "big three" neglected infectious diseases with the highest mortality (alongside HIV and tuberculosis), which has increased its profile globally (Hotez, 2013). The level of research investment in diabetes and breast cancer research could be even higher than shown in Table 1 owing to institutionalized funding at universities and hospitals.

For each disease, we used search terms that were refined in consultation with medical professionals (Table 2). We also manually verified that the search terms succeeded in gathering grants for the disease in question whilst minimising false positives (where, for example, a grant may not in fact be about the disease of interest) (Table 2) by reviewing a randomly selected sample of 100 grants for each disease. Additionally, we collected the publications linked to our set of grants.

3.2.2. Collecting data on grants and their linked publications

We compiled data on grants and their publications from four major biomedical research funders. We used their individual funder databases, as well as an aggregated database: NIH RePORTER and ExPORTER, UKRI Gateway to Research, EC CORDIS, the Wellcome Trust website, and the Dimensions database.

We collected publication data from University of Leiden's in-house versions of the NIH PubMed and Clarivate Web of Science (WoS) databases using the unique publication IDs listed in the funder databases as linked to grants. Gathering data from PubMed allowed us to collect the Medical Subject Headings (MeSH) assigned to those publications by the U.S. National Library of Medicine (NLM), and linking to WoS expanded the data fields gathered for each paper to include additional fields such as author details and acknowledgement information.

Table 3 shows that the percentage of grants with links to publications is relatively similar for all four diseases. There are more grant–publication pairs for diabetes and breast cancer than for malaria and Chagas disease, consistent with the difference in their respective funding levels. Table 3 also illustrates that diabetes and breast cancer have higher mean percentages of publications with hospital affiliations, suggesting they may benefit from institutionalized funding via researchers' hospital affiliations.

3.3. Data analysis

3.3.1. Identifying cross-disease spillover publications

To measure and compare the frequency of cross-disease spillover, we categorised grant–publication pairs as "on target" if the title or abstract of the publication contained at least one of the same disease-related search terms used to define the dataset of grants (Table 2). For example, we classified a link as on target if a grant on malaria was linked to a publication also on malaria. We categorised all other grant–publication pairs as cross-disease spillover publications. For example, we categorised a publication on HIV/AIDS from a grant on malaria as a spillover publication. We calculated the frequency of these types of grant–publication pairs for each of the four disease-based datasets.

Table 2
Search terms used to identify grants.

Disease	Search terms
Chagas disease	Chagas OR "American trypanosomiasis" OR "trypanosoma cruzi" OR "t cruzi"
Malaria	malaria OR falciparum OR "plasmodium vivax" OR "p vivax"
Diabetes	diabetes OR "Diabetes Mellitus"
Breast cancer	"breast cancer" OR "breast neoplasm" OR "breast carcinoma" OR "ductal carcinoma in situ" OR "breast tumour" OR "breast tumor"

Table 3
Descriptive statistics on grants and their linked publications for four diseases.

Disease	Chagas disease	Malaria	Diabetes	Breast cancer
Grants with links to publications (%)	66.67	65.26	67.80	66.51
Number of grant–publication pairs	2,092	23,767	218,594	93,120
Mean grant-to-publication links per grant (Links/Grants)	6.52	8.93	13.49	12.89
Publications with hospital affiliation (%)	1.98	3.22	9.36	10.12

Sources: Web of Science, Dimensions and research funders (NIH, UKRI, EC, and the Wellcome Trust).

To check whether the on-target and spillover publication sets were substantively different, and to provide a sense of the extent of any differences, we calculated Salton's cosine similarity between the on-target and spillover publication sets for each disease (Salton, 1989; Yaqub et al., 2023). To compute the cosine similarity scores, we compared a reference vector of the top 50 most frequent MeSH terms found in the on-target publications to a vector of the MeSH terms found in the spillover publications. The vectors consisted of the MeSH terms and their frequencies in the on-target and spillover publications, as shown in Fig. 1.

Additionally, to assess the accuracy of the on-target or spillover classification, 400 grant–publication pairs were manually reviewed (50 on-target and 50 spillover pairs for each disease).

3.3.2. Analysing the distribution of and variation between cross-disease spillover publications

To examine the direction of cross-disease spillover, we identified the most frequently occurring MeSH terms assigned to our publications. We compiled frequency tables to illustrate the variety and balance of diseases most commonly found in both the on-target and spillover datasets.

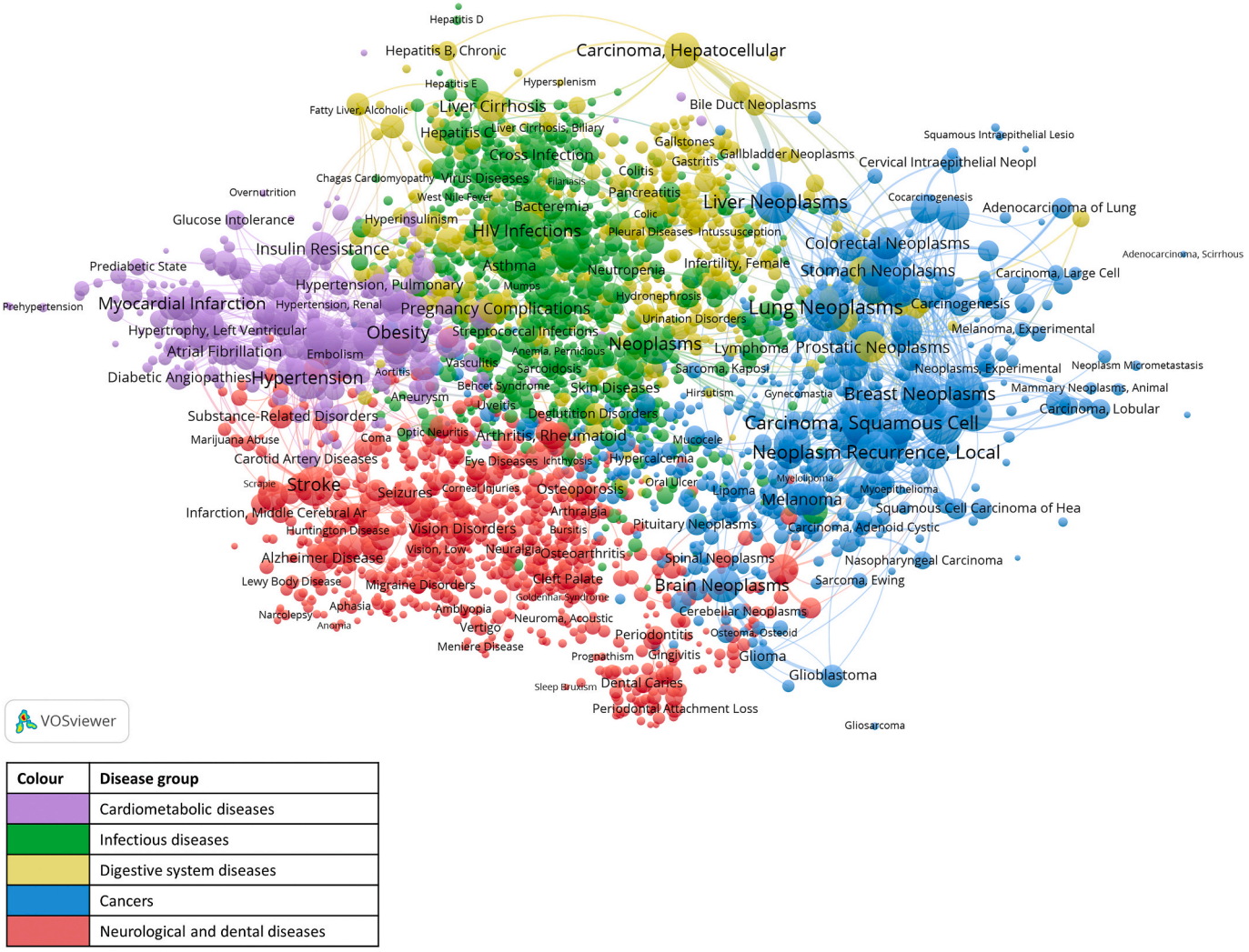
Data visualisations were produced in the form of overlay maps (Carley et al., 2017; Ràfols et al., 2010) for each disease dataset, overlaying the grant, on-target publication and spillover publication datasets onto a MeSH co-occurrence network base map to visualise the distribution of and variation between the datasets. The overlay maps provide another way to visualise variety and balance and also give a sense of the cognitive distance of the cross-disease spillover publications. They show the distances between the disease-based MeSH terms associated with grants and those associated with on-target and spillover publications, as defined by the distribution of the MeSH terms, and where they are located on the MeSH co-occurrence network base map depicted in Fig. 2.

Fig. 2 shows a network map of the co-occurrence of disease-based MeSH terms assigned to all publications in the PubMed database from the time period used in this study (2005–2019). The base map was produced with VOSviewer software, which uses the visualisation of similarities (VOS) distance-based mapping technique (van Eck and Waltman, 2010). The location of each node in the network is dependent on the strength of the co-occurrence of the MeSH terms across millions of publications. Frequently co-occurring terms are placed next to each other and can be interpreted as being more similar or related than those that are further away from each other. The location of the nodes remains the same between the base map in Fig. 2 and the overlay maps in Fig. 4 – Fig. 7 in section 4.2.

MeSH terms were also assigned to the grants by applying the NIH NLM Medical Text Indexer (MTI) tool (Moore et al., 2024; Mork et al.,

MeSH	Malaria, Falciparum	Malaria	Parasitemia	HIV Infections	Insect Bites and Stings	Toxoplasmosis	...
On-target publication frequency	3820	3653	547	177	56	41	...
Spillover publication frequency	0	0	14	1924	10	111	...

Fig. 1. Example of MeSH term frequencies used to calculate cosine similarity between on-target and spillover publications for malaria.



Colour	Disease group
	Cardiometabolic diseases
	Infectious diseases
	Digestive system diseases
	Cancers
	Neurological and dental diseases

Fig. 2. MeSH co-occurrence network base map. The colours of the node clusters represent different groups of diseases, as specified in the key. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2013) to the grant titles and abstracts, so that the spread of diseases associated with grants could be compared with the spread associated with publications.

3.3.3. *Examining types of cross-disease spillover*

For each disease, 100 grant-publication pairs were manually reviewed, 50 on target and 50 spillovers, to examine the accuracy of their classification as on target or spillover, and to explore possible reasons for the spillovers, such as shared instrumentation between the grant and the publication. Categories were derived by thematically coding types based on reading the titles and abstracts of the grants and publications.

4. Results

4.1. *Frequency of cross-disease spillover*

Table 4 shows that cross-disease spillover occurred frequently. For all four diseases, the majority of the grant–publication pairs were classed

Table 4
Descriptive statistics for grant–publication pairs.

Disease	On-target pairs (%)	Spillover pairs (%)	Cosine similarity
Chagas disease	798 (38%)	1,294 (62%)	0.05
Malaria	9,515 (40%)	14,252 (60%)	0.08
Diabetes	49,892 (23%)	168,702 (77%)	0.42
Breast cancer	25,181 (27%)	67,939 (73%)	0.34

as spillovers. Fig. 3 shows higher proportions of spillover publications for diabetes and breast cancer (77% and 73%) than for Chagas disease and malaria (62% and 60%).

These results suggest some degree of variation in the propensity for spillover by disease area. In particular, the results suggest that well-funded diseases may have a slightly higher propensity for cross-disease spillover than neglected and poverty-related diseases. These differences may be related to the biological or medical nature of the diseases themselves; research funding (amount, geographical location, and orientation, e.g., basic versus applied); other features of the research environment such as the nature of scientific publishing or research evaluation; and/or characteristics of the wider social environment within which the research takes place.

To check whether the on-target and spillover publication sets were substantively different, and to provide a sense of the extent of any difference, we calculated the cosine similarity between the MeSH terms associated with two publication sets for each disease (as described in section 3.3 on data analysis). A score of one indicates complete similarity (i.e. no difference between the on-target and spillover publications) whereas a score of zero would indicate complete dissimilarity (i.e., the on-target and spillover publications are completely different).

The cosine similarities shown in Table 4 provide evidence that the on-target and spillover publications are appreciatively different from each other, and that the difference is greater for some diseases than for others. In particular, the cosine similarity is higher for diabetes than for the other diseases, indicating that its on-target and spillover publication sets are not quite as different from each other as they are for the other diseases. This suggests that the cognitive distances “travelled” by these spillover publications is not as far. This could be at least partially due to the nature of the disease. Diabetes has multifactorial aetiology, so the boundaries of the disease may be blurry compared with those of the other diseases. This may also contribute to the high level of spillover publications for diabetes (77%).

4.2. Direction of cross-disease spillover

4.2.1. MeSH co-occurrence maps

Figs. 4–7 show grants, spillover publications, and on-target publications layered on to the MeSH co-occurrence network base map shown in Fig. 2. The location of each node remains the same for all of the maps and is determined by the underlying base map. Node size reflects the frequency of publications in that MeSH category and node colour reflects the proportions in each of the respective maps (i.e. proportion of spillovers in the spillover map, and proportion of non-spillover publications in the on target maps).

For all four selected diseases, the maps (Figs. 4–7) confirm that the on-target publications have MeSH categories that relate very tightly to the focal disease, and also that the on-target and spillover datasets are different from each other. The maps also show that spillover publications are found in non-focal disease categories and in some cases are dispersed widely across the map. The maps add a sense of how far away from the focal disease the spillovers are located.

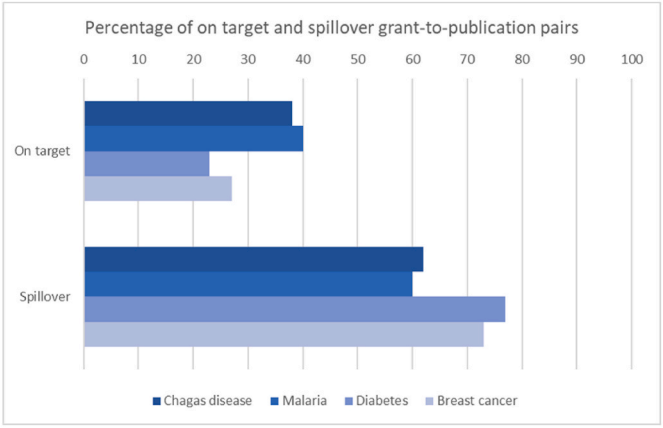


Fig. 3. Frequency of cross-disease spillover publications varies by disease.

Comparing the four diseases, as the number of cross-disease spillover publications increases, the tendency for some of them to be further away from the focal disease also increases. For example, spillover publications for breast cancer are widespread across the map (Fig. 7), whereas those for Chagas disease are more limited in spread (Fig. 4). This suggests that the nature of cross-disease spillover varies both *within* each disease-based dataset (with some spillover publications located nearby and others far away) and *between* different diseases (with some diseases showing clustered spillovers and others more dispersed across the map).

4.2.2. Frequency tables

In this section, for each disease, we explore the spillover publications in more detail using the MeSH categories assigned to them. We compared MeSH categories by measuring the spillover publications in a particular category as a proportion of all outputs in that category. We present the top 10 most frequent MeSH terms, as ranked by spillover proportion.

For Chagas disease, many of the spillover MeSH terms are for other insect-borne infectious diseases that cause fevers, for example Zika, dengue, Lyme disease and Chikungunya (Table 5). There is also a high spillover proportion for diseases that are related to immunodeficiency, such as primary immunodeficiency diseases, immunologic deficiency syndromes, warts and papillomavirus infections. This may be because Chagas disease can be reactivated in people with suppressed immune systems. Additionally, Chagas disease can cause inflammation of the heart or brain and this may provide a link to atherosclerosis and cerebral malaria.

Similarly to Chagas disease, for malaria, many of the spillover diseases are infectious, febrile diseases, for example TB, Orthomyxoviridae infections, Hepatitis C, influenza, pneumococcal infections and Zika (Table 6). Some diseases are common co-infections, such as HIV/AIDS, TB and malaria, sometimes referred to as the "big three” (Hotez, 2013). Research funding is also sometimes directed towards this group of diseases.

For diabetes, vitamin D deficiency may be related to insulin resistance and type 2 diabetes, and diabetes has been linked to osteoporosis because it affects bone metabolism (Table 7). Almost all of the top 10 spillovers are towards other noncommunicable diseases, such as cancers, asthma and Alzheimer’s disease. The exception is HIV infections, a spillover category that features for all of the selected diseases except Chagas disease. Evidence suggests that there are spillovers away from HIV infections as well as spillovers towards the disease (Yaqub et al., 2022).

Finally, for breast cancer, we see other types of cancer such as kidney neoplasms and skin neoplasms featuring in the spillover publications (Table 8). The majority of the spillover publications are in non-communicable diseases, but HIV is again found in the top 10 diseases by spillover proportion.

These categorizations suggest that while some spillovers come from seemingly unrelated diseases, others come from diseases that are related in a variety of ways. Some are closely related, e.g. the spillover diseases from Chagas disease that are also infectious, febrile, insect-borne diseases. Others belong to more general shared categories of disease such as infectious diseases or cancers. Some are related in other ways, such as being common co-infections (e.g. HIV, TB and malaria), or being related in a disease progression pathway (e.g. vitamin D deficiency is related to insulin resistance and type 2 diabetes).

4.2.3. Manual review for possible types of spillover

According to our manual review of grant-publication pairs, spillovers may involve a different disease topic in the publication compared to the

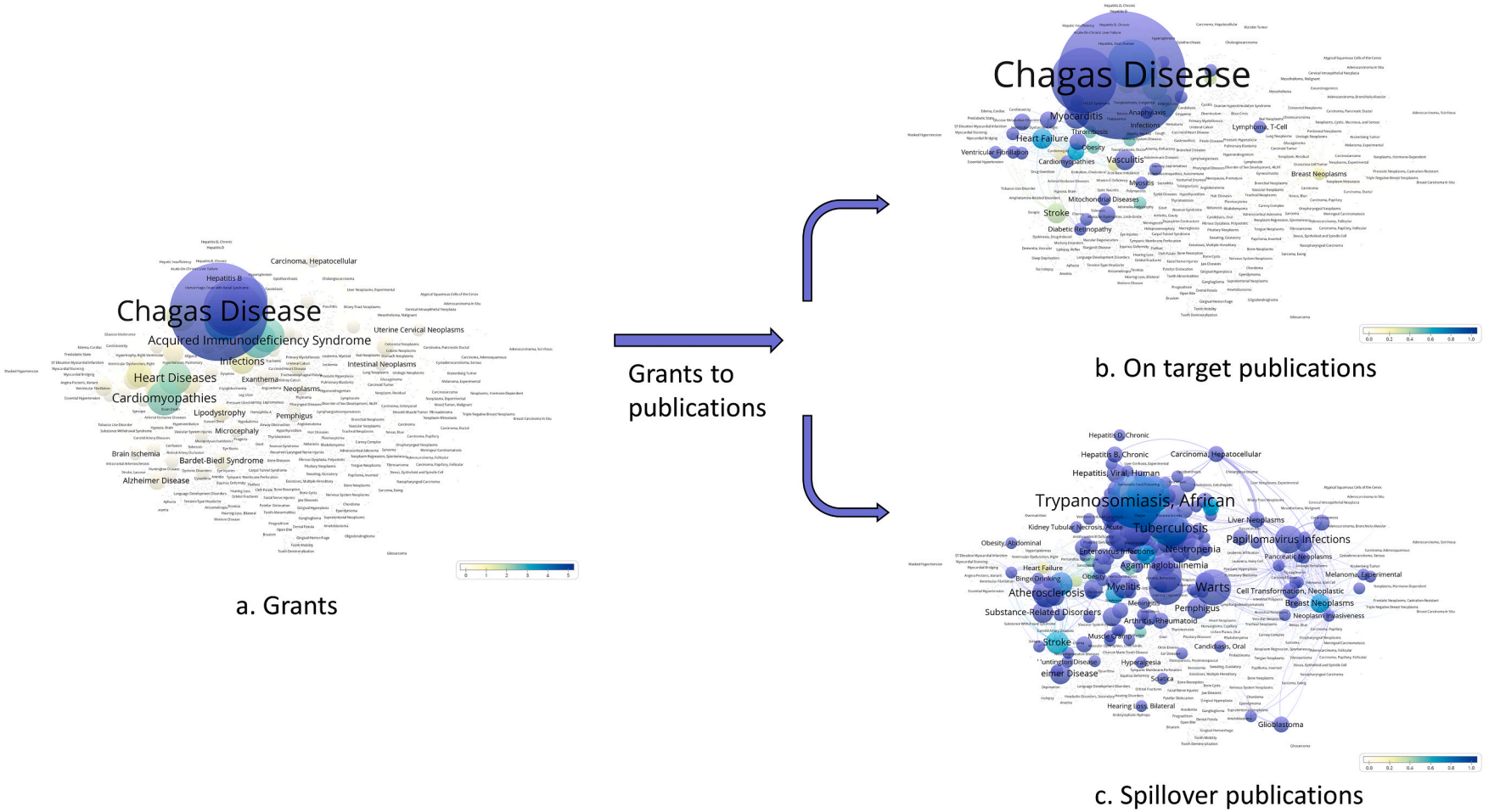


Fig. 4. Chagas disease mapping. Overlay maps based on the frequency of MeSH terms assigned to (a) grants, (b) on-target publications, and (c) spillover publications.

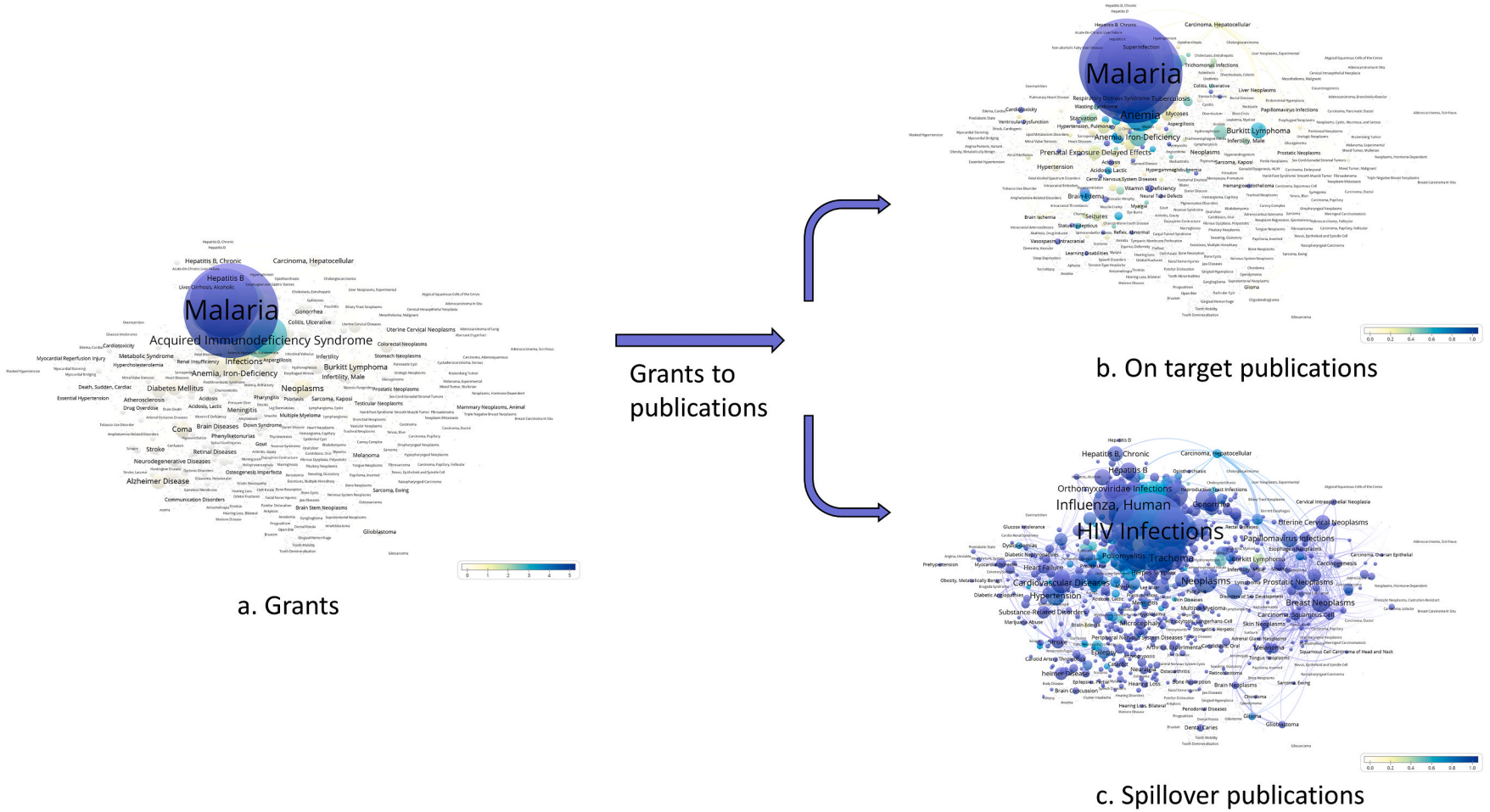


Fig. 5. Malaria mapping. Overlay maps based on the frequency of MeSH terms assigned to (a) grants, (b) on-target publications, and (c) spillover publications.

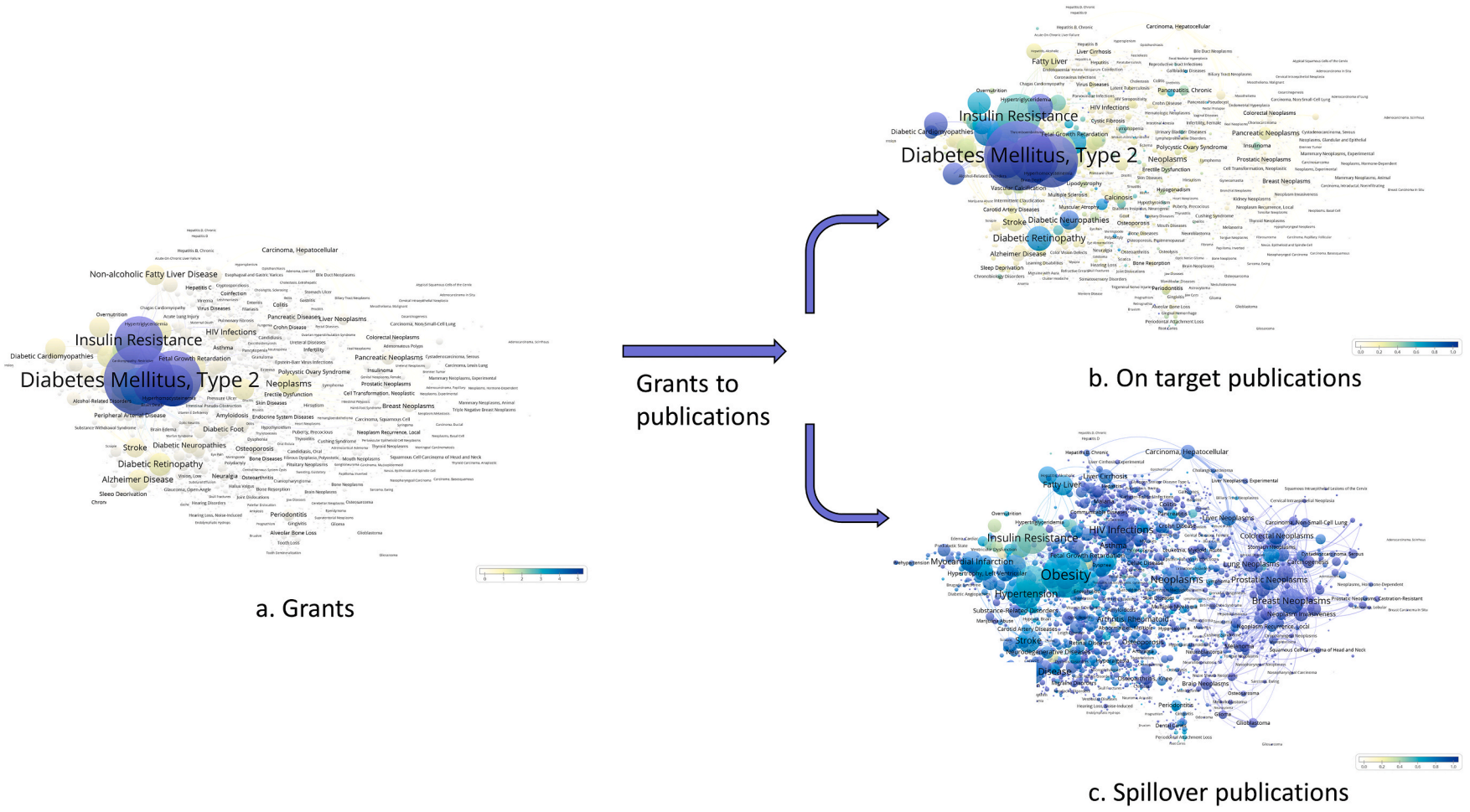


Fig. 6. Diabetes mapping. Overlay maps based on the frequency of MeSH terms assigned to (a) grants, (b) on-target publications, and (c) spillover publications.

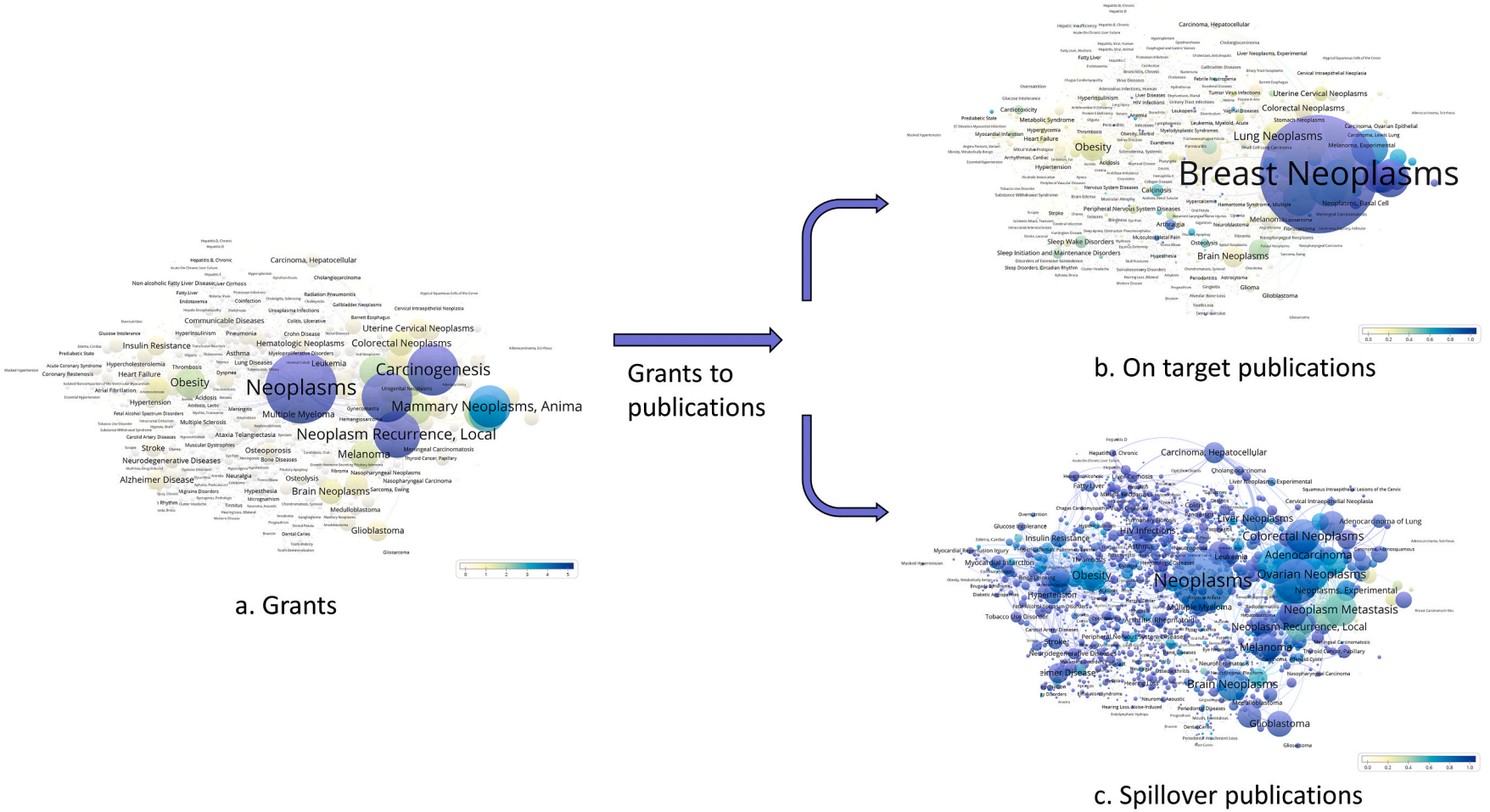


Fig. 7. Breast cancer mapping. Overlay maps based on the frequency of MeSH terms assigned to (a) grants, (b) on-target publications, and (c) spillover publications.

Table 5
Frequency and proportion of the top 10 MeSH terms for spillover grant–publication pairs for Chagas disease.

	MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillover publications as a proportion of total publications
1	Warts	0	110	110	1
2	Primary Immunodeficiency Diseases	0	106	106	1
3	Immunologic Deficiency Syndromes	0	101	101	1
4	Zika Virus Infection	0	54	54	1
5	Malaria, Cerebral	0	53	53	1
6	Dengue	0	46	46	1
7	Papillomavirus Infections	0	46	46	1
8	Lyme Disease	0	45	45	1
9	Chikungunya Fever	0	41	41	1
10	Atherosclerosis	0	36	36	1

Table 6
Frequency and proportion of the top 10 MeSH terms for spillover grant–publication pairs for malaria.

	MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillover publications as a proportion of total publications
1	Tuberculosis, Multidrug-Resistant	0	112	112	1
2	Cardiovascular Diseases	0	60	60	1
3	Orthomyxoviridae Infections	0	60	60	1
4	Trachoma	1	92	93	0.99
5	Sexually Transmitted Diseases	1	69	70	0.99
6	Hepatitis C	1	62	63	0.98
7	Influenza, Human	6	359	365	0.98
8	Pneumococcal Infections	2	74	76	0.97
9	Zika Virus Infection	2	74	76	0.97
10	HIV Seropositivity	2	66	68	0.97

Table 7
Frequency and proportion of the top 10 MeSH terms for spillover grant–publication pairs for diabetes.

	MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillover publications as a proportion of total publications
1	Breast Neoplasms	90	1,805	1,895	0.95
2	HIV Infections	143	2,805	2,948	0.95
3	Lung Neoplasms	43	675	718	0.94
4	Colorectal Neoplasms	56	811	867	0.94
5	Asthma	70	969	1,039	0.93
6	Prostatic Neoplasms	76	990	1,066	0.93
7	Alzheimer Disease	245	2,571	2,816	0.91
8	Osteoporosis	123	689	812	0.85
9	Neoplasms	596	2,721	3,317	0.82
10	Vitamin D Deficiency	152	609	761	0.80

Table 8
Frequency and proportion of the top 10 MeSH terms for spillover grant–publication pairs for breast cancer.

	MeSH term	Number of on-target publications	Number of spillover publications	Total number of publications	Spillover publications as a proportion of total publications
1	Carcinoma, Renal Cell	5	498	503	0.99
2	Kidney Neoplasms	13	606	619	0.98
3	HIV Infections	9	311	320	0.97
4	Glioblastoma	24	747	771	0.97
5	Urinary Bladder Neoplasms	13	361	374	0.97
6	Alzheimer Disease	17	353	370	0.95
7	Glioma	27	550	577	0.95
8	Carcinoma, Hepatocellular	23	423	446	0.95
9	Skin Neoplasms	39	667	706	0.94
10	Carcinoma, Pancreatic Ductal	23	374	397	0.94

grant, either related in the MeSH tree hierarchy or not related; a different non-disease topic in the publication compared to the grant; or the broad scope of the grant leading to diverse publications. Spillovers may be influenced by basic science being shared between the grant and the publication; shared capabilities, for example if the grant is a capacity-building grant that includes training; shared infrastructure, for instance if the grant is for a programme or unit that includes funding some aspect of scientific infrastructure such as laboratory space; shared instrumentation, such as a mass spectrometer paid for by the grant; or shared methods, for example algorithm development paid for by the grant. The results from the manual review give an insight into what kinds of issues might be overlooked when taking a strong disease-based focus in biomedical research.

It is important to note that these types of spillover are based on our own reading of grant and publication texts and other readers may interpret them differently. For this reason, in forthcoming work, we talk to researchers about how they perceive changes in their research directions to better characterise these changes and to better understand what influences them.

5. Discussion and conclusions

This study provides two main findings. First, cross-disease spillover publications are common. Secondly, there is variation across diseases in the frequency and direction of spillover publications. Some of this variation seems to be associated with the poverty-relatedness and neglected-ness of the funded disease.

The four diseases we examined—Chagas disease, malaria, diabetes, and breast cancer—are near the extremes of multiple policy-relevant dimensions: their research funding levels, their mortality and morbidity burdens, and their geographical distributions across rich and poor countries. Yet, despite these differences, the presence of cross-disease spillover publications for all four diseases suggests that spillover is a consistent feature of medical research. For the diseases we examined, the spillover frequency ranged between 60% and 77%.

Our study shows that research funding directed to a particular disease does partly lead to "on-target" publications on the same focal disease. This suggests that disease-focused analyses prior to funding allocation decisions provide policymakers with at least some information on scientific and technical opportunities, which when funded are then exploited by researchers and lead to publications in the same disease area. However, this is true only up to a point. Our data also show that funding for a particular disease frequently results in publications related to other, non-focal, diseases. This lends some support to calls for research to be shaped by a broad and wide-ranging set of influences. An important contribution of this study is demonstrating that, empirically, these are not mutually exclusive perspectives.

Moreover, concerns about possible rivalry between competing research funding interests may have been overstated. Our evidence of cross-disease spillover corroborates a sentiment expressed by Senator Kennedy, in response to a heart-disease advocate concerned about being shortchanged by cancer funding: "There are those who say if you can't get a raise yourself, the best thing that can happen is for the fellow next to you to get a raise" (quoted in Best, 2019, p. 127). This suggests that markets and alliances among specific disease organisations could be more dynamic than previously recognised, as cross-disease spillover introduces complementarities and opportunities to collaborate.

In addition to estimating the overall frequency of cross-disease spillover, our results show that there is some variation by focal disease. Breast cancer and diabetes had a higher frequency of cross-disease spillover than malaria or Chagas disease. Taken together, the frequency and variation in cross-disease spillover publications makes evaluating claims of misalignment in research funding less straightforward. Apart from where the misalignments are shown to be very large, this brings into question the validity of simple and direct comparisons of funding into different diseases.

Amongst the four diseases in our study, our evidence on the direction of cross-disease spillover for diabetes illustrate well the importance of the nature of the disease category and its boundaries. The notion of "diabetes" does not necessarily capture a single, narrowly defined, pathology in the same way that malaria or Chagas disease does. Rather than a singular disease, diabetes could also be described as a constellation of closely related, less vast diseases, each of which is subject to mutable definitions in different contexts (e.g., type 1 juvenile, type 2 adult onset, gestational, pre-diabetes). Moreover, clinical discussion of diabetes often draws on a host of lifestyle and nutritional factors that may not feature as strongly in research discussions. It seems plausible that such differences are likely to drive some of the variation in cross-disease spillover, both in terms of its frequency and direction.

The four diseases vary in terms of the broader institutional pathways by which research might be translated into effective treatments and taken up by healthcare delivery systems in different parts of the world. Both malaria and Chagas disease fall into the category of neglected diseases, and both had less cross-disease spillover than diabetes and breast cancer. Fewer cross-disease spillover publications may be a reflection of fewer connections to clinical practice settings and to the broader innovation system within which research on the disease may be undertaken (Gittelman, 2016). Notably, diabetes and breast cancer not only benefited from higher research funding than Chagas disease and malaria in our data, but a greater number of the publications for these diseases carried a hospital affiliation. This suggests that diabetes and breast cancer may benefit additionally from institutionalized funding and from better connections to clinical settings for research translation efforts. Fruitful connections among researchers and clinicians may show up later as cross-disease spillover publications. The converse may also be true: diseases with less cross-disease spillover may be more isolated from broader innovation systems.

These considerations regarding the relationship between poverty relatedness and neglected-ness and the frequency and direction of spillovers across different diseases are difficult to parse into isolated factors. As Bowker and Star (2000) argue, categories are social: "There is no such thing as an unambiguous, uniform classification system" (Bowker and Star, 2000, p. 322). There is "slippage" between classifications and "the contingencies of practice", and people "organize and reorganise when the local circumstances of their activities do not match the prescribed categories" (Bowker and Star, 2000, p. 293).

An important policy implication of our study is that, although focusing on disease is one of way to think about how to improve health, there are other ways too. Cross-disease spillover is a reflection of myriad issues running through biomedical research—capabilities, personnel, infrastructure and equipment, instrumentation, methods, clinical practice, etc. For priority setting, diseases are a blunt unit of comparison because other ways to classify research funding make sense too. However, for at least the foreseeable future, it seems that disease category seems poised to retain its prominence in policy discussion. The World Health Organization (WHO) was recently moved to adopt the notion of Disease X, an abstract hypothetical disease, to help plan for future epidemics. Resorting to a non-existent disease to help raise funds for surveillance, prevention, and response (in essence, quite fundamental functions of the WHO), is an indication of how readily organisations feel the need to invoke a disease category.

Some caveats about these findings should be noted. Firstly, by choosing to use high quality, well-curated data, this study has neglected research funded outside the U.S., U.K., and E.U.; and publications outside PubMed or WoS. These exclusions may create biases towards HIC-centred science and away from LMIC-centred science. Nevertheless, these exclusions are a small proportion of global research funding, the vast majority of which continues to originate in HICs (Adam et al., 2019; Ralaidovy et al., 2020; Røttingen et al., 2013). As such, these biases are unlikely to have affected our results substantially. Further research in developing country contexts could shed further light on this assumption. Second, whilst successful at generating quantitative evidence, our

reliance on bibliometric analysis offers little in terms of establishing causality or researcher motivation. Further research drawing on survey, interview and narrative evidence, or econometric work exploiting sources of exogenous variation, would help to broaden the understanding of the processes at work.

Despite these limitations, the evidence in this paper raises important questions about priority-setting, how we evaluate research funding, and the extent to which organising it by disease can be better understood and improved upon.

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Not Applicable.

CRediT authorship contribution statement

Josie Coburn: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Data curation, Conceptualization. **Ohid Yaqub:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Ismael Ràfols:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Joanna Chataway:** Conceptualization, Supervision.

Data availability

Data will be made available on request.

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