APPG ON GLOBAL TB: INQUIRY INTO TB RESEARCH & DEVELOPMENT

Submission by Policy Cures Research, 30 June 2020

About Policy Cures Research

1. Policy Cures Research is an independent, non-profit think tank whose goal is to improve global health by using evidence to advance medical research for historically neglected and underfunded health issues. Through our flagship G-FINDER project, we collect data about global investment in research and development (R&D) for health issues that disproportionately affect people in low- and middle-income countries (LMICs). From this, we provide governments, funders and civil society organisations with the information they need to make optimal R&D policy and funding decisions, and help to improve accountability, transparency and performance in the global health R&D landscape. As part of this work, we have collected and analysed data on the global funding landscape of biomedical R&D for tuberculosis (TB) annually for over a decade.

2. Amidst the WHO's forthcoming Global Strategy for TB Research and Innovation, the evolution of the UK's post-EU global health investment portfolio, and the COVID-19 global pandemic, TB R&D is at a turning point. At this time of unprecedented attention to global health R&D, we fully endorse the All-Party Parliamentary Group on Global TB's decision to review the current TB R&D landscape, and welcome the opportunity to share findings and analysis from our G-FINDER project on TB biomedical R&D trends, gaps and patterns from the last decade.

Recommendations

3.

Recommendation 1: Global funding for TB R&D must be maintained in the face of other pressing global health challenges such as COVID-19, and should in fact be increased – particularly for vaccines and diagnostics – if global targets for tackling TB are to be met.

Recommendation 2: Greater funder diversity in TB R&D is critically needed to both expand the overall portfolio and reduce reliance on a few large historical donors. The UK public sector is well placed to play a leading role by building on the momentum of recent funding increases from DFID and expanding its overall public sector investment.

Recommendation 3: The public sector must play a greater role in incentivising critically needed industry investment in TB R&D. The UK is well positioned to lead on boosting industry support for TB biomedical R&D, including through innovative financing mechanisms or new strategic partnerships.

Recommendation 4: Coordination across all facets of TB R&D must be prioritised. Amongst numerous priority actions, the UK should consider further strengthening support and stewardship of PDPs, and continuing investment in effective north-south partnerships, such as the European & Developing Countries Clinical Trials Partnership (EDCTP).

Recommendation 5: Addressing the nexus between R&D and access will be critical to ensure equitable and sustainable uptake of products. Greater attention should be given to coordinating R&D support from global partnerships such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, Unitaid, and Gavi.

Recommendation 6: Accountability mechanisms must be in place to ensure commitments, indicators and targets to end TB are measurable at all levels. As per the WHO accountability

framework on TB, this should include granular data on annual, global TB R&D investment, such as that provided by the G-FINDER project.

TB R&D OVERVIEW: gaps amidst progress

5. Despite promising recent progress, gaps persist for improved tools and technologies to better meet the needs of people with TB globally, particularly those in low-income and low-resource settings. TB therefore remains a serious and ongoing public health issue, and as such, support for TB R&D must remain a global priority. Concurrently, global health is facing an unprecedented crisis due to COVID-19. It will be critical that support, funding and momentum for TB R&D is strengthened and accelerated in tandem with efforts to address COVID-19.

6. Current TB drug regimens are complex and can require up to two years of daily treatment, leading to poor compliance, drug resistance and treatment failure. New drugs are needed that have shorter treatment duration; are effective against multidrug-resistant (MDR-TB); suitable across age groups; and safe to use with HIV treatments. Some promising progress has been made, including paediatric formulations[i,ii]; once daily oral regimens with shortened treatment durations[iii]; and several ongoing Phase III trials for treatment of drug resistant TB.

7. The existing TB vaccine (BCG) provides limited protection for adults. A vaccine which provides protection against all forms of TB in all age groups is needed.[iv] Progress to date has been mixed, with recent positive developments but major disappointments.[v,vi] More effective and appropriate point-of-care diagnostic tests, including for drug-resistant and paediatric TB are needed.[vii] Progress on LMIC-appropriate diagnostics has been slow.

FUNDING FOR TB R&D: uneven attention

8. The G-FINDER report provides the most comprehensive and accurate picture available of global funding for TB R&D; the most recent report captures data to FY2018.

9. Funding for TB R&D reached an all-time high in 2018, peaking at US$685 million. This was the sixth consecutive year of increased funding for TB R&D and the largest annual increase since 2009, making TB the second-highest funded neglected disease after HIV/AIDS, narrowly ahead of malaria for the first time since 2015.[viii] However, this positive picture masks uneven investment between TB products and an overreliance on a limited number of key donors, several with stagnating or declining levels of funding.

10. More than half of all global investment in TB R&D in 2018 was for drug development. Drug R&D has received the lion's share of TB R&D investment since 2010, with this proportion increasing steadily over the last five years, and in 2018 surpassed the 50% mark for the first time (US$359 million, 53%). This has been largely driven by continued support for and growing portfolios in TB drug R&D by a handful of donors, particularly the US NIH, whose 2018 investment represented over a quarter (US$94 million, 26%) of TB drug funding.[ix]

11. Funding for TB basic research is the second largest investment after drugs, and at US$184 million currently receives more than all other TB R&D (minus drugs) combined.[x] Given the need to better understand basic TB pathophysiology to drive product innovation, this funding level is both appropriate, and moving (increasing) in the right direction.

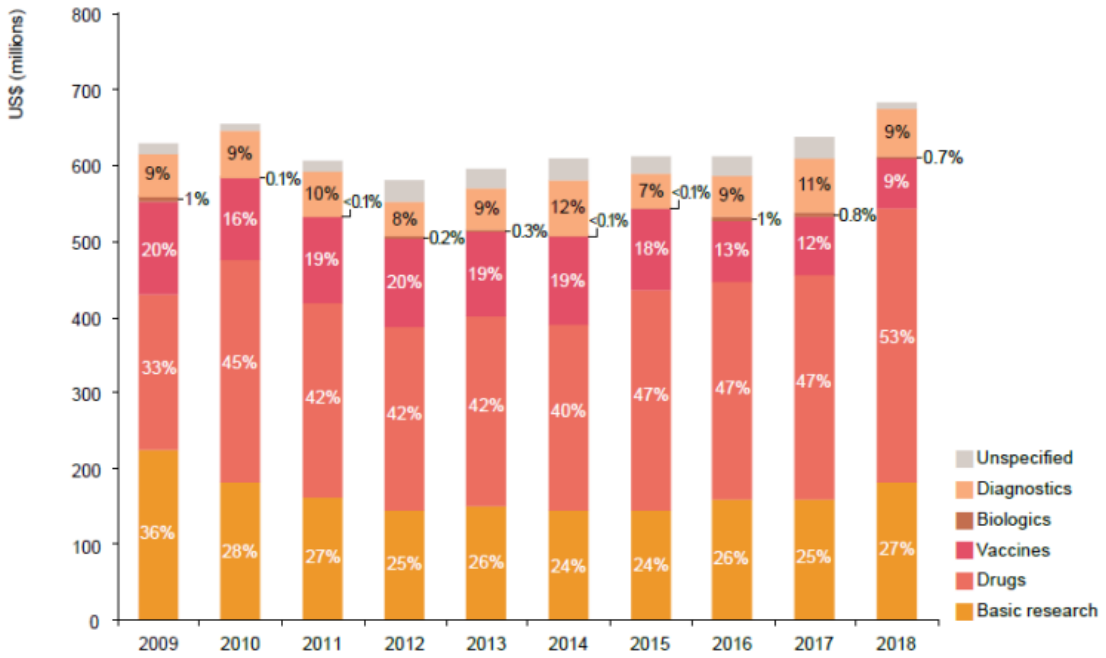
12. Unfortunately, outside of drugs and basic research funding for TB R&D is either declining or static. Funding for vaccine development currently makes up under a tenth (US$65 million, 9.5%) of all annual TB R&D investment. Investment in diagnostic R&D is just US$63 million (9.2%) and has remained at a similarly low level (averaging around 9% of annual funding) for the last decade.

Meanwhile funding to biologics (including therapeutic vaccines) represents a miniscule portion of current TB R&D (US$4.6 million, 0.7%).

13. Despite the growth in overall funding for TB R&D, investment in vaccines fell to an all-time low in 2018, declining for the fourth consecutive year. The winding down of Aeras' activities in 2018 was a factor behind this drop, but funding for vaccine development has been falling sharply in recent years, and funding from the Gates Foundation – far and away the largest funder of TB vaccine R&D over the last 12 years – has been trending downwards for most of the last decade.[xi] It is hugely concerning that there is as much funding for TB diagnostic R&D as there is for vaccine R&D, given the overwhelmingly different costs associated with the development of these two technologies.

14. Some of the imbalance in TB R&D funding reflects the state of the pipeline in each product area. Overall, more than half (US$371 million, 54%) of all TB R&D funding is currently for basic & early-stage research, just under a third (US$214 million, 31%) is for clinical development & post-registration studies; this balance has been largely unchanged for over a decade, with funding to pre-clinical research averaging about double investment in clinical R&D since 2007. However, the distribution of funding varies a great deal between products. Around two-thirds (63%) of all funding for vaccine R&D goes to discovery & pre-clinical research, whereas nearly half (49%) of all drug R&D funding is invested in clinical development & post-registration studies.[xii]

Figure 1: TB R&D funding by product type 2009-2018 (G-FINDER 2019)



15. Investment in TB R&D has been highly concentrated – and reliant on – the US NIH, Gates Foundation and industry for the last decade. In 2018, these funders collectively provided nearly three-quarters (US$485 million, 71%) of all TB R&D funding. While this is less than the share of total funding these organisations provided in many of the early years of G-FINDER (when the proportion was closer to 80%), the recent increases in TB R&D funding were mostly due to large additional investments from the US NIH and the Gates Foundation. Funding from the US NIH has increased every year since 2013, while funding from the Gates Foundation has largely flatlined over the last decade.[xiii]

16. At the same time there is declining interest in TB R&D by industry, with current investment dropping to an all-time low. As of 2018, just 14% (US$97 million) of all TB R&D funding came from the private

sector, trailing behind the philanthropic (US138 million, 20%) and public sectors ($448 million, 65%), and reflecting closure of many large industry-led TB programmes. Industry investment in TB R&D has fallen by nearly half (down 45%) between 2010 and 2018.[xiv]

17. Some funders have promisingly begun to expand interest and support to TB R&D. In 2018, DFID invested US$24 million in TB R&D, an increase of US$9.5 million (up 67%) from 2017, returning funding to near its historic high in 2010. While this has made DFID the fourth highest funder of TB R&D overall – and second highest high-income country (HIC) public funder after the US NIH – these funding levels are orders of magnitudes lower than those at the top, and follow several years of minimal investment from the department.[xv]

18. At the same time, investment across other UK public bodies has been very limited, either flatlining at low levels (the UK MRC has averaged around US$10 million for the last decade, recently declining to less than US$8 million; while Innovate UK has invested less than US$1 million for only a handful of years); or declining to nothing (the British Council, UK NHS and some UK academic institutions have all recently bottomed out to zero). Funding through the EC has also been flat for several years, and has recently declined following conclusion of several projects, including TBVAC2020.[xvi] There is need for greater funder diversity in TB R&D, and room for the UK to both expand its public sector support to TB R&D, and diversify its portfolio.

19. Unquestionably, public sector finance will continue to play a strong role in driving progress towards eliminating TB through direct investment in R&D, both at early stage where industry investment will likely continue to be limited, and at late stage by making available public funding to facilitate promising products through the pipeline. However, it also has a critical role to play in incentivising and creating an enabling environment for industry to invest, including through both direct financial support and through innovative financing mechanisms.

Figure 2. Top TB R&D funders 2018 (G-FINDER 2019)

Funder / US$ (millions)	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2018 % of total
US NIH	202	193	187	195	181	204	212	222	244	274	40
Gates Foundation	119	125	105	111	137	144	138	105	92	113	16
Aggregate industry	141	176	169	146	120	111	109	100	105	97	14
UK DFID	16	20	11	1.5	13	14	12	7.9	14	24	3.5
Indian ICMR	2.3	3.7	3.8	7.4	8.9	8.8	8.5	13	19	19	2.8
USAID	10	10	10	11	9.3	14	14	17	12	16	2.4
German BMBF	5.1	4.4	4.1	5.2	5.2	6.3	7.1	10	17	16	2.3
US CDC	18	11	10	0.0	0.0	16	9.5	8.9	15	15	2.1
Unitaid	0.0	0.0	0.0	0.4	2.1	0.5	6.4	34	12	13	1.8
EC	31	24	20	12	20	16	27	22	18	12	1.7
Wellcome Trust	7.6	12	11	12	13	12	10	9.1	9.3	10	1.5
Gates Ventures									5.5	9.0	1.3
Subtotal of top 12^	578	606	554	526	531	559	561	557	565	618	90
Disease total	629	654	606	579	592	607	610	611	635	685	100

^ Subtotals for 2009-2017 top 12 reflect the top funders for those respective years, not the top 12 for 2018.
- No reported funding
Funding organisation did not participate in the survey for this year. Any contributions listed are based on data reported by funding recipients and so may be incomplete.

COORDINATION WITHIN TB R&D: Critical for success

20. Coordination at multiple levels is vital in order to accelerate impact of global TB R&D efforts, and this is reflected in the draft Global Strategy on TB Research and Innovation[xvii]. However, with only five years left until the 2025 deadline for the introduction of major technological breakthroughs envisioned by the End TB Strategy, there is already a pressing need to translate strategy into coordinated global, regional and national-level actions.

21. Product development partnerships (PDPs) offer an important avenue for coordinating financial support for TB R&D. TB Alliance has been the largest recipient of PDP funding for TB R&D since 2012, peaking at US$68 million in 2018, more than twice all other PDP funding combined. This position has been assisted by increased support from DFID – which nearly doubled its funding between 2017 and 2018 – and recent funding via DHSC. There has been a much more limited interest in other PDPs for TB R&D – including zero investment from the UK outside of Aeras either leading up to or at the time of its wind down in 2018. The UK could leverage its position as strong funder of PDPs overall (with DFID currently the second largest funder of PDPs globally)[xviii], and help steward the direction of new and existing PDPs to coordinate impact towards new TB products.

22. There is a real risk of interrupted support for effective bilateral and multilateral north-south partnerships. The EDCTP has been an important collaborative effort to advance clinical development of public health medicines and products – including for TB – by effectively bridging the gap between researchers and innovators is HICs and LMICs. EDCTP has received recent boosts of funding, catapulting it to funding levels upwards of US$142m in 2018. After the EC, the UK has been a major driver of the increases in funding to EDCTP, with the UK DHSC almost doubling their funding to the EDCTP in 2018 (up US$25 million, 95%). The UK also represents the second largest funder overall to EDCTP, with combined funding from the UK DHSC, MRC and DFID totalling US$57 million in 2018, or 40% of the scheme's total funding.[xix] However, with the UK departure from the EU, divested funding could undermine the success of the initiative. With the partnership now entering its third stage, post-Brexit UK support will be critical to keep up momentum, help further expand the collaboration, and drive success across EDCTP's portfolio – including TB R&D.

MARKET SHAPING & ACCESS: Strengthening the R&D:access nexus

23. Investing in – and fostering an enabling environment for – the research & development of new health technologies is meaningless unless these innovations are made accessible to the people who need them, both equitably and for the long term. Taking concrete steps to address this nexus between R&D and access is especially critical in a disease such as TB, where the majority of people affected live in LMICs. 'R&D' and 'access' are not separate silos, but operate on a continuum, with feedback – often via late stage and operational research, and support to help shape regulation – helping to drive progress. Organisations working at this nexus are therefore critical to the success of all efforts to accelerate TB R&D and fast-track progress towards global targets.

24. Implementing partners such as Unitaid and the Global Fund to Fight AIDS, TB and Malaria are central players in ensuring access to new and existing TB products in LMICs, and Gavi's involvement will be vital to ensure scalable, affordable roll-out of any successful TB vaccine when it becomes available. But in addition, these organisations are also (to varying degrees) becoming more aware of the important role they can play in funding R&D to develop and support the approval and introduction of new tools. In the case of TB this is largely only true for Unitaid, which was the ninth largest funder of TB R&D globally in 2018 (at US$13m), following sharp growth since 2014 related to funding to Partners For Health for the development of a paediatric fixed-dose combination[xx]. In general, these organisations and mechanisms could and should play a larger role in supporting TB R&D, and the UK could help to coordinate and incentivise this activity, including through paired funding mechanisms or similar.

ACCOUNTABILITY IN TB R&D: Granularity is key

25. The global health community must maintain a focus on transparency and accountability in TB R&D to ensure effort is allocated to areas of pressing need, is not unduly duplicative, and is making an impact. This is echoed squarely in the WHO Multisectoral Accountability Framework to Accelerate Progress to End TB by 2030 released in 2019. Within this, monitoring and reporting of commitments made at the global and regional level include the need to track granular data on investment in TB R&D, with the annual G-FINDER report cited as a key reference.[xxi]

[i] https://www.tballiance.org/child-friendly-medicines
[ii] https://www.ema.europa.eu/en/documents/pip-decision/p/0058/2019-ema-decision-26-february-2019-agreement-paediatric-investigation-plan-granting-deferral_en.pdf
[iii] https://www.tballiance.org/access/pretomanid-and-bpal-regimen
[iv] http://www.who.int/biologicals/areas/vaccines/bcg/en
[v] http://www.nejm.org/doi/10.1056/NEJMoa1803484
[vi] http://www.who.int/tb/publications/global_report/en/
[vii] http://www.who.int/tb/publications/global_report/en/
[viii] https://www.policycuresresearch.org/analysis
[ix] https://www.policycuresresearch.org/analysis
[x] https://www.policycuresresearch.org/analysis
[xi] https://www.policycuresresearch.org/analysis
[xii] https://www.policycuresresearch.org/analysis
[xiii] https://www.policycuresresearch.org/analysis
[xiv] https://www.policycuresresearch.org/analysis
[xv] https://www.policycuresresearch.org/analysis
[xvi] https://www.policycuresresearch.org/analysis
[xvii] https://www.who.int/tb/features_archive/Revised_draft_Researchstrategy_based_on_public_comments.pdf
[xviii] https://www.policycuresresearch.org/analysis
[xix] https://www.policycuresresearch.org/analysis
[xx] https://www.policycuresresearch.org/analysis
[xxi] https://www.who.int/tb/WHO_Multisectoral_Framework_web.pdf?ua=1