APPG on Global TB Inquiry:

THE FUTURE OF TB AND GLOBAL HEALTH RESEARCH

DYING FOR A CURE II

appg THE ALL-PARTY PARLIAMENTARY GROUP Tuberculosis

CONTENTS

ACKNOWLEDGEMENTS

The author of this report is Janika Hauser, Policy Adviser to the APPG on Global TB.

The APPG would like to thank Dr Nick Chapman, Tabitha Ha, Professor Bertie Squire, Sharonann Lynch, Dereck Tait, Hester Kuipers, Mike Frick and Dr Ben Bleasdale for their participation in oral evidence sessions.

We would also like to thank Birmingham and Solihull TB Service, Deutsche Stiftung Weltbevölkerung, Dot2Dot, FIND, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Global Health Technologies Coalition, GSK, Médecins sans Frontières, MoxAfrica, Ostuka Novel Products GMBH, PolicyCures Research, Royal Manchester Children's Hospital Virtual TB Clinic, STOPAIDS, TB Alert, TB Alliance, Treatment Action Group, UK Academics and Professionals to End TB and the Union for submitting written evidence to this inquiry.

FOREWORD

COVID-19 has heightened awareness of the importance of science and innovation amongst the public and politicians. In response to the pandemic, unprecedented levels of funding have been mobilised to develop and deploy at pace new preventive, diagnostic and treatment tools. Regular reports of major scientific breakthroughs have offered new hope to millions of people around the world.

In this context, it is important to remember that health threats beyond COVID-19 have long undermined the well-being of individuals, communities and economies globally. In the aftermath of COVID-19, infectious diseases like Tuberculosis (TB) will remain and indeed spread with renewed menace. As health systems struggle to recover, the most dangerous forms of drug-resistant TB will continue to emerge. Just as an effective global response on COVID-19 is relying on the development of new tools, so too will global efforts to tackle older enemies such as TB.

The UK is home to world-class institutions at the cutting edge of global health, and TB research in particular. The UK's historical leadership in global health research, including through initiatives like the Ross Fund and support for Product Development Partnerships, have delivered significant improvements in the diagnosis and treatment offered to people affected by TB, and laid the foundations for much of the COVID-19 research being conducted today. Nonetheless, with a persistent funding gap of over US $1 billion a year for TB research alone, the world will not be able to deliver on commitments made through the Sustainable Development Goals or the UN High-Level Meeting on TB.

To help deliver these pledges, the UK can leverage its unique expertise and historical leadership on global health innovation. With millions of deaths a year still caused by infectious diseases like TB, and new emerging health threats around the corner, an ambitious and sustainable strategy global health research is urgently needed.

In the context of the spending review, the establishment of a new Foreign, Commonwealth and Development Office, the UK's R&D Roadmap, and a new WHO Global Strategy for TB Research and Innovation, the time is right for the UK to make its mark. Five years on from the APPG's first inquiry on the subject, this report reflects on lessons learned, considers progress to date, and makes a series of concrete recommendations on how the UK can foster innovation, deliver impact and achieve a greater return on investment through its global health research budget.

Virendra Sharma MP

Chair of the APPG on Global TB

Nick Herbert (Lord Herbert of South Downs CBE PC)

Co-Chair of the APPG on Global TB

EXECUTIVE SUMMARY

Our lives have long depended on the products of research and development (R&D). They have transformed the way we fight disease, saved countless lives through human ingenuity and continue to offer hope as new foes cause death and suffering.

Science has always relied on public investment. From funds provided to higher education institutions, investment in research infrastructures, funding for product development through to prize funds, tax incentives and publicly funded procurement of the eventual products of innovation. Research has also always been risky, with research projects and clinical trials wrongly described as a 'failure' when they make a substantial contribution to the scientific field but fail to deliver the desired golden bullet. In its 2014 report on global health R&D, the APPG highlighted how innovative funding mechanisms built on smart public investment were critical in areas where the traditional market-based model of innovation had failed but the societal benefit of this innovation would be truly transformational.[1]

The global tuberculosis (TB) epidemic is a case in point. It is estimated that for every year that critical investments in R&D are delayed there will be an additional 4.8 million people falling ill, 670,000 additional deaths and US $5.1 billion in TB treatment costs alone.[2] As TB continues to kill more people each year than any other infectious disease, damaging the life chances of millions and undermining the economic development of countries around the world, the need for research is critically apparent. The rapid emergence and spread of drug-resistant strains of the disease makes this all the more urgent. As does the COVID-19 pandemic's disproportionate impact on TB programmes, with national lockdowns leading to huge drops in case notification and the Stop TB Partnership estimating an additional 6.3 million cases and 1.4 million deaths by 2025.[3]

At a time when the general public is more aware than ever of the need for and power of public investment in R&D, it is encouraging to see the UK government's ambition on this agenda. A recent commitment to increase investment in R&D to 2.4 per cent of GDP by 2027 and the newly published R&D roadmap set the foundation for a transformational decade in which the UK can establish itself as a research superpower, globally connected and leading on efforts to tackle the world's greatest challenges.[4]

Crucially, at a time when the public finances will be squeezed by the fallout of the COVID-19 pandemic and taxpayers are set to feel the impact of a dramatic economic downturn, it is more important than ever to deliver real value for money. The public will rightly expect that such funds are stewarded shrewdly, and that they are able to see and experience the impact of these investments for years to come. This is particularly the case for research funded using the UK's Official Development Assistance (ODA) budget.

Drawing on evidence from a wide variety of stakeholders, this report makes the case for greater public investment in global health R&D, and TB R&D in particular, as an area of research able to deliver on these objectives. Considering lessons learned over the past decade of global health R&D, and particularly since the APPG's last report on the subject, it considers emerging bottlenecks and how funding could be effectively directed, coordinated and leveraged to deliver urgently needed scientific advancements to the people that need them.

As the report shows, UK investments in TB research have contributed to major scientific breakthroughs. By providing funding to UK researchers at the cutting edge of TB science, supporting critical partnerships and investing in innovative models to advance product development, UK Aid has saved countless lives and continues to do so. The need

1 APPG on Global TB (2017), *Dying for a cure: research and development for global health*.
Available online: https://51072cd5-c1a2-4ecf-9296-955a4a6c5720.filesusr.com/ugd/309c93_7911893821b24d4783234f7998b9497d.pdf (Accessed 1 September 2020)
2 Stop TB Partnership (2020) *Global plan to end TB 2018-22.* Available online: http://www.stoptb.org/assets/documents/global/plan/GPR_2018-2022_Digital.pdf
(Accessed 1 September 2020)
3 Stop TB Partnership (2020) *The potential impact of the COVID-19 response on tuberculosis in high-burden countries: a modelling analysis.*
Available online: http://stoptb.org/assets/documents/covid/TB%20and%20COVID19_Modelling%20Study_5%20May%202020.pdf (Accessed 1 September 2020)
4 HM Government (2020), *UK research and development roadmap*.
Available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/896799/UK_Research_and_Development_Roadmap.pdf
(Accessed 1 September 2020)

for investment remains great, however, and while gradual increases in funding and the market entry of new tools are hugely positive achievements, they take place in the context of new challenges. The report goes on to demonstrate how relatively small policy and funding decisions could maximise the impact of every pound spent by driving greater collaboration, leveraging additional funding and ensuring scientific innovation changes the course of the TB epidemic.

This is the perfect time to reflect and institute new systems and strategies for the UK's investment into global health R&D. At the global level, the appetite for international research collaboration is greater than ever before, and emerging donors are looking to invest substantially for the first time. The World Health Assembly formally adopted the new Global TB Research and Innovation Strategy recently, which provides a vital blueprint for where and how this investment can be best channelled.[5] In the UK, the government's R&D roadmap and the formation of the new Foreign, Commonwealth and Development Office has given an impetus to reconsider how best to spend the ODA R&D budget.

In the following four chapters, we make the case for 10 steps the UK government should take to strengthen the role of UK-funded global health R&D in the delivery of the Sustainable Development Goals:

10 Point Plan for UK Leadership on TB & Global Health Research

01 *Increase and stabilise long-term funding for research to ensure maximum return on investment, by committing to spend at least 5 per cent of ODA on research, and ensure spending for TB research does not fall below 0.1 per cent GERD between 2020 and 2025.*

02 *Improve the strategic direction, coordination and balance of global health R&D spending across government departments, through the creation of a global health research strategy with strategic oversight from the Foreign, Commonwealth and Development Office.*

03 *Strengthen international partnerships, including through continued association with the successor programme of the European and Developing Countries Clinical Trial Partnership and by evolving grant requirements to foster equitable international collaboration.*

04 *Sustain support for the Product Development Partnership model by providing long-term, flexible funding, while setting aside additional funds to trial innovative and enabling mechanisms that support the innovation landscape.*

05 *Retain a laser-like focus on delivering needs-based and high-impact innovation for challenges faced in low- and middle-income countries, by strengthening collaboration with affected communities and reinforcing critical civil service expertise in development research.*

06 *Align investments in global health R&D with support for global health multilaterals, providing additional funding flexibilities and top-ups for actors to undertake critical catalytic initiatives that support the roll-out and scale-up of health innovations.*

07 *Maximise the impact of UK-funded research by providing additional and targeted funding for operational research, evidence to policy and policy uptake initiatives.*

08 *Ensure equitable access to the products of UK-funded innovation, by strengthening access provisions and shaping the global health R&D landscape to deliver maximum impact on the epidemic.*

09 *Leverage UK investments and diplomatic networks to bring new donors to the table, forge partnerships and close the financing gap for TB research.*

10 *Improve global coordination of TB research investments through the creation of a global TB research forum hosted by the World Health Organisation.*

5 WHO (2020) -– *Draft global strategy for tuberculosis research and innovation.*
Available online: https://www.who.int/docs/default-source/documents/tuberculosis/may8-edited-globtbresstrat-v2-dox.pdf?sfvrsn=cb116dfa_2 (Accessed 1 Spetember 2020)

01 Research matters

At one point in time, TB was estimated to have been responsible for one quarter of all deaths in Europe. Known as the "white plague", it represented a slow and painful death sentence for the majority of people. The discovery of antibiotics was transformational. So transformational, in fact, that the UK's own Medical Research Council was first established to run clinical trials of the antibiotic therapy still used to treat TB today. Sir John Crofton, the scientist who led much of this work, was based at the University of Edinburgh, which continues to conduct ground-breaking TB research to this day. As treatments and improvements in public health throughout the 20th century drove down TB incidence in high-income countries, governments began to deprioritise TB in their public research spending. As a disease that predominantly affects the most vulnerable, few pharmaceutical companies were interested in maintaining a portfolio of TB R&D. For decades, this market failure led to an absolute dearth of innovation. The world entered the 21st century with fatally outdated tools for the fight against TB.

Today, TB kills more people each year than any other infectious disease. Despite being curable, a human life is lost to TB every 18 seconds. Decades of persistent underinvestment in TB programmes have no doubt played their part in getting us to this point. But the outdated tools available to prevent, diagnose and treat TB have hampered efforts to curb the epidemic – they take too long, are too unreliable, and are too expensive or cumbersome for resource poor countries to roll out as widely as they are needed, particularly in the low and middle-income countries where 90 per cent of all deaths are occurring. Over these years of neglect, drug-resistance emerged and spread, now causing one third of all antimicrobial resistance (AMR) associated deaths. While AMR gained notoriety as a top public health enemy, we have long been playing catch up in the fight against TB. Even before COVID-19 pandemic, we were not on track to deliver on the Sustainable Development Goal of ending TB by 2030. In a previous report, the APPG estimated the economic impact of drug-resistant TB alone would exceed US $16.7 trillion between 2015 and 2050.[6]

The research gaps which hamper the global TB response are tangible in every health system, including the NHS. It is estimated that each year these research gaps persist, an additional 4.8 million people will fall ill with TB, with 670,000 additional deaths and US $5.1 billion in TB treatment costs alone.[7] As the COVID-19 pandemic has seen laboratory infrastructures and healthcare staff redeployed to the response, only the most agile and decentralised interventions have been sustained under lockdown conditions. During the course of this inquiry, the APPG received evidence on both impactful research successes and areas requiring additional investment, ranging from basic science, through to product development and implementation. In this chapter, we consider where additional targeted investments could help transform the global TB response, learn lessons from past successes and begin to consider the way forward.

6 APPG TB (2015) *Price of a pandemic: counting the cost of MDR-TB.*
Available online: https://51072cd5-c1a2-4ecf-9296-955a4a6c5720.filesusr.com/ugd/309c93_f0731d24f4754cd4a0ac0d6f6e67a526.pdf (Accessed 1 September 2020)

7 Stop TB Partnership (2020) *Global plan to end TB 2018-22.*
Available online: http://www.stoptb.org/assets/documents/global/plan/GPR_2018-2022_Digital.pdf (Accessed 1 September 2020)

FIVE BIG GAPS

01. Basic Science

Despite TB having been discovered over 100 years ago, our knowledge of how TB works is still far too limited. Without understanding exactly how and why latent TB infection reactivates into active TB disease, it is difficult to develop diagnostic tests that can accurately identify who among the 3 billion people estimated to have latent TB infection would most benefit from preventive therapy. Without the identification of correlates of protection, every TB vaccine candidate needs to be tested more intensively, expanding timelines and costs. The continued pursuit of basic science is also critical to maintaining a healthy pipeline of innovative products, as basic science lays the foundations for future gamechangers in TB prevention, diagnosis and treatment.

IN 2018 GLOBAL INVESTMENT IN BASIC SCIENCE REACHED NEARLY

US$ **178** million

According to the Treatment Action Group's (TAG) comprehensive mapping of TB research funding, global investment in basic science reached nearly US $178 million in 2018. The vast majority of available funding came from the United States government and Gates Foundation. While the Wellcome Trust reportedly invested over US $8 million, UK public investment remained much more modest, with the only substantial funding in 2018 coming through the Medical Research Council (US $3,414,523) and the UK Biotechnology and Biological Sciences Council (US $3,019,239).

THE UK GOVERNMENT REPORTEDLY INVESTED OVER

US$ **6.5** million

The Stop TB Partnership's updated Global Plan to End TB describes an estimated annual funding need for basic science of US $400 million per year between 2018 and 2022. The wealth of unanswered research questions certainly indicate that further investment would make a tangible difference. In the UK, the majority of public funding for basic science is distributed through research councils as opposed to government departments, where TB-specific funding calls are rare. As a result, the comparative lack of investment in TB basic science is perhaps understandable. Nonetheless, the UK is home to researchers at the cutting edge of TB science, who reported having to rely heavily on non-UK funding sources to finance their research endeavours. Furthermore, with upstream stages of R&D relying heavily on insights garnered in basic science, a more 'mission focused' approach to research might enable the UK government to leverage UK expertise and achieve greater coherence in its investment throughout the development pipeline.

TO REACH THE UNHLM TARGETS, THE GLOBAL PLAN TO END TB ESTIMATES THE TOTAL FUNDING NEED FOR TB BASIC SCIENCE 2018-22 AT

US$ **2** billion

02. Diagnosis

Current sputum-based TB testing relies on specialised staff and on a steady supply of electricity. Commercially available tests continue to be prohibitively expensive for some countries. Tests are disease-specific and so rely on healthcare providers to correctly identify signs and symptoms of TB. Complex drug-resistance testing can only be done at advanced laboratories. While there has been major progress in the field in recent years, the persistent 30 per cent 'diagnostic gap' demonstrates the urgency of developing more appropriate point-of-care diagnostics. As the Foundation for Innovative Diagnostics (FIND) pointed out in their submission, the diversion of laboratory infrastructures for COVID-19 testing has highlighted the urgency of strengthening diagnostic systems in high TB burden countries and developing tests that are less time intensive and vulnerable to disruption.

IN 2018 GLOBAL INVESTMENT IN DIAGNOSTICS RESEARCH TOTALLED ALMOST

US$ **80** million

According to TAG, global investment in diagnostics research totalled almost US $80 million in 2018, down US $1 million from the previous year. The largest UK investment came from the Department for International Development, which reported spending US $3,357,144 on diagnostics research in 2018, primarily through the Product Development Partnership (PDP) FIND. The Medical Research Council spent a further US $1,844,511 and additional investments were reported by Innovate UK, the UK National Institute for Health Research and the UK Engineering and Physical Sciences Research Council. It should also be noted that major funders of TB diagnostics research, the European and Developing Countries Clinical Trials Partnership and Unitaid, receive UK funding.

However, the research funding gap for diagnostics research remains the most substantial of any area of research when compared to funding targets set in the Global Plan to End TB. While this makes recent innovations on TB diagnostics all the more impressive, the lacklustre roll-out of new diagnostic tools and the impact of COVID-19 on TB case-finding efforts globally clearly demonstrate the urgent need for greater investment, from both a patient and a health systems perspective. Notably, both the government of Korea and the government of Japan (through the Global Health Innovative Technology Fund) have reported investments in TB diagnostics in recent years, and an Indian manufacturer released the first competitor product to the GeneXpert test, highlighting the potentially substantial role of emerging donors in helping to close this funding gap.

IN 2018, THE UK GOVERNMENT REPORTEDLY INVESTED OVER

US$ **7.3** million

TO REACH THE UNHLM TARGETS, THE GLOBAL PLAN TO END TB ESTIMATES THE TOTAL FUNDING NEED FOR TB DIAGNOSTICS 2018-22 AT

US$ **916** million

03. Treatment

The TB bacterium is uniquely adapted to develop resistance to antibiotics. People with TB therefore need to be given a cocktail of medicines over an extended period of time. Interruptions in treatment and the provision of incorrect or sub-standard treatments have allowed drug-resistant strains of TB (DR-TB) to emerge and spread, causing close to 500,000 cases every year.[8] The market failure for antibiotics has been widely discussed, but is particularly acute in TB, which is most common in low- and middle-income country contexts. Three novel TB medicines have come to market in the last 15 years, a considerable achievement given the funding constraints. Nonetheless, multiple witnesses emphasised that while representing a lifeline for people with DR-TB, they were still complex to administer, part of side-effect prone regimens and prohibitively expensive. Witnesses emphasised that without a shorter treatment, effective against multidrug-resistant TB, suitable for children, safe to use with HIV treatments and priced at less than US $500 per course, it would be difficult to effectively tackle the DR-TB crisis. Newer approaches and accompanying therapies could also be of considerable value. The promise of a pan-TB regimen described in the 2018 Lancet Commission sets an important goal, but any improvements achieved along the way would significantly improve the lives affected by DRTB.

In 2018, TAG reported a total of over US $336 million investment in TB drug development, compared to an estimated US $830 million annual funding need. The UK has provided sizeable investments in the field, including grants for the TB Alliance, a PDP that has played a critical role in a number of recent innovations, including the new 6-month BPaL regimen recently recommended by WHO and approved for use in Europe and the UK. The inquiry received evidence from civil society organisations, TB Alliance and the small number of pharmaceutical companies still involved in TB drug research, GlaxoSmithKline, Otsuka and Johnson & Johnson. Despite the broad range of stakeholder views among this group, there was universal

IN 2018, GLOBAL INVESTMENT IN TB TREATMENTS REACHED OVER

US$ **336** million

IN 2018, THE UK GOVERNMENT REPORTEDLY INVESTED OVER

US$ **28,768,971**

TO REACH THE UNHLM TARGETS, THE GLOBAL PLAN TO END TB ESTIMATES THE TOTAL FUNDING NEED FOR TB TREATMENTS 2018-22 AT

US$ **6.8** billion

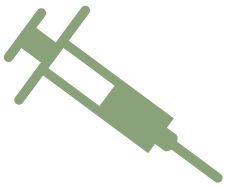
8 WHO (2020) *Global TB report 2020*. Available online: https://www.who.int/tb/publications/global_report/en/ (Accessed 1 September 2020)

agreement that given the market failure, both greater public investment in and coordination of the product development pipeline were essential to speeding up progress, maintaining partnerships and bringing essential new treatments to people affected by TB.

Historical investment in TB drug research has built a far more dynamic and healthy pipeline, with 12 new clinical entities currently in phase 1 or 2a trials. However, as GSK points out in their written evidence, "the proliferation of drug resistance means that we expect the regimens being researched and developed now will most likely develop resistance over time", making consistent and sustainable investment in this pipeline absolutely critical. Similarly, multiple witnesses emphasised the importance of learning lessons from recent innovations and roll-out delays caused by critical research gaps and a lack of preparation. Decisions made now – both about the volume and mode of funding for TB drug development – will be critical to the success of global efforts to end TB.

04. Vaccines[9]

The only way to eliminate TB would be through an effective TB vaccine that was widely available. Once developed and deployed, a TB vaccine could prove to be one of the most cost effective public health interventions in that it prevents disease, and therefore the need to diagnose, to treat and to manage the emergence of drug-resistance. While PolicyCures describes progress in TB vaccine research as "mixed", recent positive developments have created new hope. The M72 vaccine, initially developed by GSK and AERAS (a PDP) and now acquired by the Gates Foundation's Medical Research Institute, is perhaps the most promising candidate to date. However, with 15 candidates under active clinical development, the potential reward of investing in this exciting pipeline has never been greater.



IN 2018 FUNDING FOR TB VACCINE RESEARCH REACHED JUST

US$ **109** million

Funding for TB vaccine research has seen no substantial increases since 2005, reaching just US $109 million in 2018. This pales in comparison to annual spending on HIV vaccine research, which has exceeded US $800 million every year since 2006, and falls significantly short of the US $250 million annual target for TB vaccine research spending. Between 2013 and 2018, the Department for International Development (DFID) provided some funding to AERAS, but failed to renew its investment on the basis of insufficient results. In 2018, some UK funding for TB vaccine research was still provided by Public Health England and the Biotechnology and Biological Sciences Research Council. Even before the cessation of DFID funding, however, the vast majority of financing in this area relied on the US government, Gates Foundation and EU which, between them, provided almost three quarters of all funding.

IN 2018, THE UK GOVERNMENT REPORTEDLY INVESTED

US$ **4.75** million

Over the last six months, the government has shown immense ambition in vaccine research, championing the work of UK research institutions and investing staggering amounts in COVID-19 vaccine trials. It is fair to say, however, that this ambition has been lacking in the UK's approach to TB vaccine research. A few months after DFID funding came to an end, the breakthrough results of the M72/AS01E trial were published. All this came too late for AERAS, which was forced to wind down operations in 2018, with key components of their work taken on by IAVI, another PDP. Withdrawing funding at one of the most critical times in

TO REACH THE UNHLM TARGETS, THE GLOBAL PLAN TO END TB ESTIMATES THE TOTAL FUNDING NEED FOR TB VACCINES 2018-22 AT

US$ **3.06** billion

9 *It should be noted that TB prevention research, outside of TB vaccines, is a critical area of research that is also of considerable relevance to the UK context. Given the lack of data on both existing funding and funding need in this area, it has not been discussed at length in this report. This should not be interpreted as an intentional deprioritisation.*

TB vaccine research fails to deliver the 'patient finance' described as so critical to this inquiry, and misses out on opportunities to leverage the new vibrancy of vaccine research. Given the UK's established research capacity, and emerging donors like the Indian government scaling up investment, there is also a unique opportunity to strengthen the international research partnerships described as a core tenet of the UK's new R&D roadmap.

05. Implementation

IN 2018 TOTAL INVESTMENTS IN OPERATIONAL RESEARCH REACHED

US$ **122** million

N 2018, THE UK GOVERNMENT REPORTEDLY INVESTED

US$ **10.1** million

THE TB REACH PROGRAMME, WHICH SUPPORTS OPERATIONAL AND IMPLEMENTATION RESEARCH, HAS A 2021-25 ANNUAL FUNDING NEED OF

US$ **25-30** million

Multiple witnesses emphasised that operational, implementation and health systems research were essential to improving programmes and ensuring new tools could reach people affected by TB. For example, understanding more about the social determinants of disease or complementary therapies that would support treatment could prove to be transformational for the TB response. As the Union writes in their submission, "operational research can make use of national and programme data to influence actions and policies to promote better health". Indeed, this kind of research continues to be critical even in the UK, with highly impactful research presented to this inquiry by Birmingham and Solihull TB Service, the North West TB service, and Dot2Dot. Implementation research has also been critical to enabling the roll-out of new diagnostics and treatment, with several witnesses reporting major bottlenecks when this research was not prioritised.

According to TAG's research funding trends report, total investments in operational research reached US $122 million in 2018. Unitaid, a multilateral in which the UK invests, was the largest funder, spending US $13 million. Both the Canadian government and the Gates Foundation invested US $12 million respectively, with a substantial proportion of this through the Stop TB Partnership's flagship TB REACH programme that focuses on delivering TB services to last-mile communities. According to TAG, the UK's investment totalled almost US $10 million, channelled through a wide variety of funding streams including the Medical Research Council, Department for International Development and the National Institutes for Health Research among others. While a substantial proportion of the MRC and DFID funding is coordinated through the joint clinical trials initiative, much of the UK's spending on operational research was allocated through traditional research funding calls, which are rarely TB specific.

According to multiple witnesses to this inquiry, opportunities for and potential benefits of greater investment and coordination of operational research are considerable. Building research capacity and transferable skills of healthcare workers and civil society organisations in low- and middle-income countries enables them to better respond to a wide variety of health challenges. For example, TB REACH has indicated that it is in a position to disburse up to US $35 million to organisations with an established track record of working with hard-to-reach populations to find innovative new models for sustaining critical TB programmes during COVID-19 lockdowns. By increasing its investment in operational research, including through mechanisms like TB REACH, the UK government could strengthen the impact of investments in health programmes around the world, including in fragile and conflict settings. With TB high-burden countries having also committed to increasing TB research funding and understandably prioritising operational research, this is also an opportunity to strengthen bilateral relationships by leveraging UK expertise.

FROM INVESTMENT TO IMPACT

The TB research field has proven itself to be an exceptional steward of public investment. With gradual increases in public funding for TB R&D, our understanding of the disease and the tools at our disposal to prevent, diagnose and treat TB have grown considerably.

Here, the APPG profiles some notable successes.

RAPID TB DIAGNOSIS

For over 100 years, TB diagnosis remained relatively unchanged, relying on microscopes and culture in laboratories. On top of being labour intensive, these tests were unreliable and often took days or weeks to produce a result.

The GeneXpert test analyses the genetic material of a sample to assess if TB bacteria are present, and if it they are resistant to one of the most commonly used TB medicines. Producing results in a matter of hours, the test was a game-changer.

The Foundation for Innovative New Diagnostics (FIND), a Product Development Partnership, was critical to the development and roll-out of this new diagnostic tool. FIND has been a long-term recipient of UK Aid funding. The test is now widely used, not only in the developing world but also in the NHS, where, among other uses, it is deployed as part of the Find-and-Treat outreach service that offers TB diagnosis to under-served populations at highest risk of TB.

A LIFELINE FOR CHILDREN WITH TB

Every year, approximately 1 million children fall ill with TB. Because of a lack of access to adequate treatment, more than 550 children die from TB every single day. For decades, the only TB medicines available were produced in adult dosages, leaving many parents and doctors with no other choice but to break down adult pills into powders, estimate approximate dosages and mix horrible tasting medicine into a child's food or drink.

The Product Development Partnership TB Alliance worked with a coalition of partners to produce paediatric dispersible medicines. These medicines are appropriately dosed, can be easily diluted and have an appealing taste, transforming the treatment of children with TB. The paediatric formulations are now being used in over 116 countries.

The development of this product was co-funded by UK Aid, alongside the US, Irish, Australian and Dutch governments, demonstrating the power of leveraging partnerships for innovation. Through this investment in the paediatric TB medicines market, a number of additional paediatric formulations for DR-TB have since been developed.

INTERNATIONAL PARTNERSHIPS DRIVE NEEDS-BASED INNOVATION

TB remains the single biggest cause of death for people living with HIV, who are more vulnerable to contracting TB disease and for whom treatment is more challenging. The diagnosis of TB among people living with HIV is notoriously difficult, and many of the tools used to diagnose TB are not suited for those who have advanced HIV disease and/or are critically ill. As rapid diagnosis is critical to increasing chances of survival and cure, this is a problem that healthcare providers have grappled with on a daily basis, particularly in countries with high rates of TB/HIV.

The Malawi-Liverpool-Wellcome Trust Clinical Research Programme is an international health institution led by Malawian and international scientists, founded in 1997. With funding from the UK Medical Research Council, the Department for International Development, the Wellcome Trust and the National Institute for Health Research, the STAMP trial investigated rapid urine-based screening for TB in HIV-positive hospital patients. The breakthrough trial increased diagnosis of TB in HIV-positive people by 50 per cent through a simple, point-of-care test called TB-LAM.

As efforts to increase global access to this important technology continue, the UK funded Product Development Partnership FIND is working to further improve TB-LAM technology to ensure this innovation has the greatest possible programmatic impact.

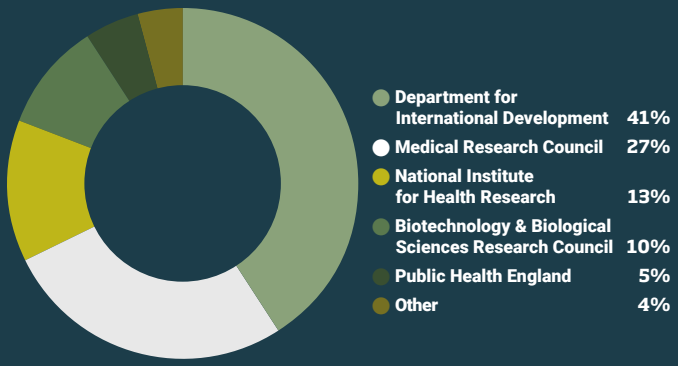
TRANSFERABLE RESEARCH IN ACTION

As COVID-19 spread around the globe, attention turned to understanding the virus and developing tools to prevent, diagnose and treat. The rapid response of the research community was based on decades of research findings which could be rapidly deployed, including many from the field of TB research.

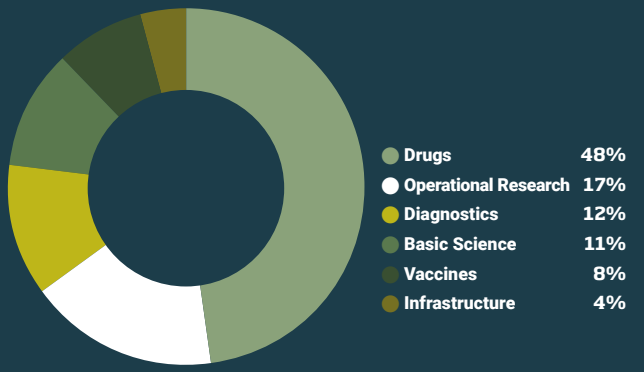
This has included transmission modelling, artificial intelligence used to evaluate chest Xrays, diagnostic tools like GeneXpert, vaccine platforms, as well as the 'off target' effects of the BCG vaccine. FIND, the product development partnership behind major TB diagnostic innovations, is a founding partner of the Access to COVID-19 Tools Accelerator. Future clinical trials will rely heavily on infrastructure built through decades of investment in global health research, including capacity and community engagement in low- and middle-income countries.

UK INVESTMENTS IN TB RESEARCH

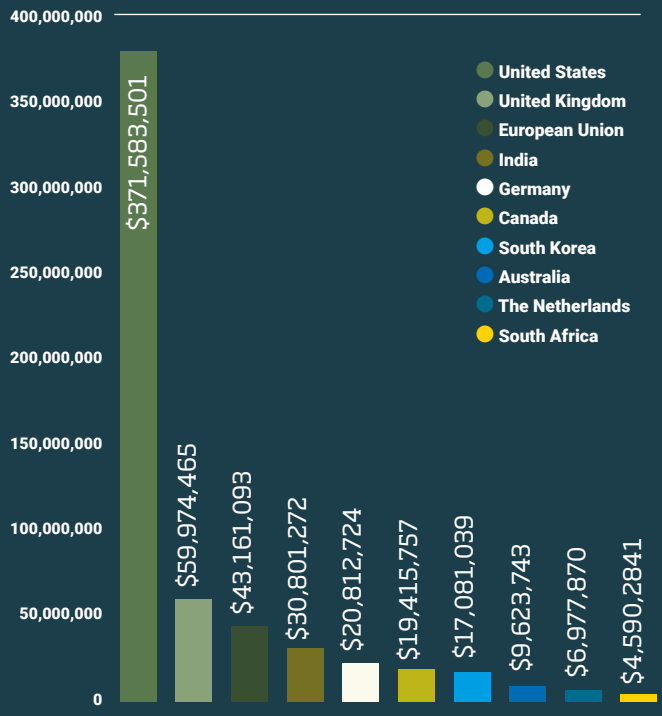
UK TB RESEARCH SPENDING BY FUNDER (2018)



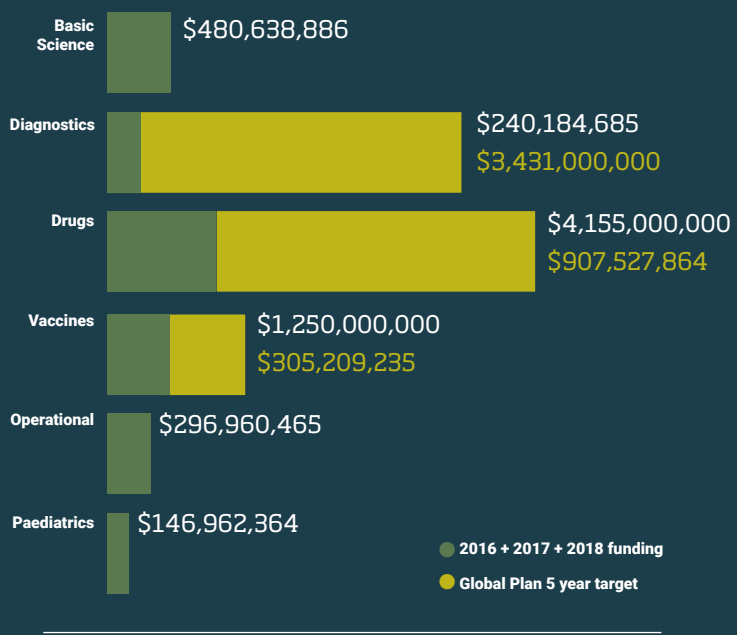
UK TB RESEARCH INVESTMENT BY RESEARCH AREA (2018)



GOVERNMENT FUNDERS FOR TB RESEARCH - TOP 10 (2018)



PROGRESS TOWARD GLOBAL PLAN 5-YEAR TB RESEARCH FUNDING TARGETS (2016 - 2020)



NOTE: *Data based on Treatment Action Group TB R&D funding trends report 2019. Revised totals based on corrected figures received from Treatment Action Group (TAG). Totals reported as BEIS investments in the 2019 report (US $3,820,815) are removed since its awards are included within reported totals for UKRI institutions. This correction will be reflected in the forthcoming TAG TB R&D funding trends report 2020. In email correspondence, FCDO confirmed updated calculations of historical DFID/FCDO investments in TB research, amounting to GBP 19.65 million in 2019, and GBP 18.68 million in 2018 (calendar years). These revisions will also be reflected in the forthcoming TAG TB R&D funding trends report 2020.*

There are many reasons for TB's continued high impact worldwide, including complex medical, epidemiological and demographic factors. But one of the most important factors is that the current tools available to combat TB – including drugs, diagnostics and vaccines – are insufficient because the development of new alternatives has not been prioritised

IAVI

TB research funding reached US $906 million in 2018, a US $134 million increase on 2017. Of this total, the UK government funding amounted to US $59,974,465[10]

Despite gradual funding increases in recent years, the financing gap for TB R&D has long been substantial. As Mike Frick of TAG pointed out in his oral evidence, the targets initially set out in the Global Plan to End TB were not annual but cumulative over five years. With every year that expenditure on TB research fell short of this US $2 billion annual target, the total funding gap to deliver on the Sustainable Development Goal target grows, becoming increasingly insurmountable. In 2018, world leaders committed finally to catch up, addressing the long-standing shortage of global health R&D funding and ensuring TB R&D spending reached the US $2 billion a year target by 2022. Such funding levels would open up the possibility of dramatic research breakthroughs that could transform the TB response. Historical investments in TB research have led to healthier product pipelines that now need to be tested in far more expensive late-stage clinical trials. A failure to mobilise this funding now would not only be a failure to deliver on a critical international commitment, but also allow decades of carefully targeted spending to go down the drain. The question for this inquiry, and for the UK government, is how we close this gap over the coming years.

While greater private and philanthropic investment may well be mobilised, the market failure for TB products means that the bulk of funding will need to come from the public purse. In addition to the volume of funding required to advance TB research, the challenge also lies in that the vast majority of funding is currently provided by a small number of donors. This makes the funding base for global health R&D vulnerable to political changes in individual countries and undermines the power of international cooperation and innovation. It would also be inherently unfair to ask any government already providing the lion's share of international funding to increase their investment further without other governments sharing in the risk that comes as part of investing public funds in R&D.

Alongside increased investments, efforts to align and coordinate funding more effectively are also needed to smooth and align the "hybrid effort from various sources and partners contributing to different phases of the R&D process" described by MSF. This can result in wasteful duplication, critical gaps and challenges in "accelerating the transition from innovation and impact" described by Johnson & Johnson. In order to close the funding gap for TB R&D specifically, and global health R&D more broadly, and ensure greatest return on investment for the UK taxpayer, the government must therefore not only find ways of mobilising increased resources in its own right, but also leverage those resources to secure a broader funding base and coordinate its investment with others.

The current national and international policy environments are particularly fruitful to advancing progress on global health R&D in general, and TB R&D in particular. The government's new UK R&D roadmap, and its commitments to increase the UK's investment in and support of the research and innovation landscape, offer a unique opportunity to evaluate the UK's global health research offering. The Global Action Plan for Healthy Lives and Wellbeing's accelerator on research continues to drive forward a conversation on the global R&D landscape, including efforts to develop a new 'Global Forum' to identify and address key bottlenecks from bench to bedside. Meanwhile, the WHO TB Research and Innovation Strategy, passed by the World Health Assembly earlier this year, provides an indepth framework for translating big-picture commitments of the UN High-Level Meeting into concrete policy and investment priorities to advance TB research.

As PolicyCures writes in their written submission, "TB R&D is at a turning point". Throughout the subsequent chapters, this report considers the evidence received from a wide variety of stakeholders to make a series of specific recommendations, ranging from the big picture to the small, to consider how the UK can better leverage its commitments to increase spending on research, its world-class expertise and its one-of-a-kind diplomatic network to drive the delivery of the SDGs through cutting-edge science.

10 *This is based on corrected data received from Treatment Action Group (TAG), which removed 2018 BEIS funding from the total (US $4,820,815) since its awards are included within totals for UKRI institutions. This correction will be reflected in the forthcoming TAG TB Research Funding Trends report 2020.*

02 Funding innovation

INCREASE FUNDING FOR TB AND GLOBAL HEALTH R&D

ODA-funded research has played a vital role in developing and rolling out technologies that have made major contributions to the delivery of the Sustainable Development Goals. The economic returns of these investments can be enormous, like the development of M-PESA mobile finance in Kenya, which was funded by a £1 million grant from the UK government but has contributed to mobile transactions being worth 50 per cent of the country's GDP.[11] The total economic cost of the COVID-19 pandemic will dwarf all investments in COVID-19 research. The same can be said of TB, which only receives 0.25 per cent of the total global spend on medical research despite accounting for 2 per cent of all deaths and 2 per cent of disability adjusted life years globally each year. As GSK writes, "funding at this level may be enough to achieve some near-term successes, but at least two times the current investment will be needed to achieve breakthroughs in innovation".

Insufficient funding is the central problem facing TB R&D.

Treatment Action Group

The UK Academics and Professionals to End TB network (UKAPTB) noted in their written evidence that despite recent increases in public funding for TB research, all of their members faced significant challenges in securing research grants. In their submission, IAVI raised the concern that "UK funding for TB R&D will fall at exactly the time it needs to rise", given the impact of COVID-19 on the economy and aid budget, and the uncertainty of both Brexit and the dissolution of the Department for International Development. The Global Health Technologies Coalition (GHTC) emphasised that the UK must "retain its leadership position as a renowned and longstanding funder of global health R&D" by increasing or at the very least maintaining its investment in global health research in real terms.

The UK has an established track record of providing significant funding to support global health R&D, as shown by the annual G-Finder report. As is apparent from the previous discussion, however, there is a clear need for greater investment in the field. As the Union points out, the large investments made in COVID-19 research in recent months show that large funding gaps can be filled with sufficient political will. Indeed, the UK government has itself committed to mobilising increased investment in TB R&D. Through its participation in the UN High-Level Meeting, the government committed "to mobilise sufficient and sustainable financing, with the aim of increasing overall global investments to US $2 billion… ensuring all countries contribute appropriately to research and development".

The question of what it means to contribute "appropriately" is an obviously challenging one. The UK has recently reached the 0.01 per cent of GNI spending on global health research advised by the WHO consultative group on R&D, which the APPG welcomes. With regard to TB specific spending, the APPG finds the 0.1 per cent of Gross Expenditure on Research and Development (GERD) on TB R&D threshold proposed by TAG and included in the WHO TB research and innovation strategy to be an appropriate measure, in that it considers a country's economic strength and research infrastructure and would see the US $2 billion a year target met across donor and high burden countries. In the most recent review of TB research funding trends, the UK reached this threshold for the first time, though it is important to emphasise that this represents a floor and not a ceiling, and governments with the capacity and ambition to invest greater sums must play a role in driving global efforts to close the funding gap. While the APPG recognises the challenges with specific funding targets, there is clearly a value in establishing a means of assessing the 'appropriateness' of investment both to ensure the UK is meeting its own international obligations and to establish norms that drive other countries to increase their spending.

11 Centre for Global Development (2020). *Reforming UK research and development ODA for maximum development impact.* Available online: https://www.cgdev.org/sites/default/files/Kenny-ODA-RD-brief.pdf (Accessed 1 September 2020)

It is encouraging to see the UK's research roadmap demonstrate this ambition, promising a "step change", and committing to its own specific target for the entirety of the UK's public research investment. Importantly, the roadmap also recognises that "short-term spending settlements can limit people's ability to develop long term plans". Historically, DFID spent around 3 per cent of its total budget on research. Additional funding mechanisms established in recent years, including the £1 billion Ross Fund, £1.5 billion Global Challenges Research Fund and £735 million Newton Fund, have increased the total ODA spend on global health research across government considerably. As PolicyCures points out, however, the recent increases in DFID investment in TB research followed years of limited investment and took place alongside flat-lining investment across other UK public bodies. Given the prevailing research needs around the world, it is critical that new COVID-19 funding commitments do not "cannibalise" funding for poverty-related and neglected diseases.

While the APPG's last report on global health research called on the government to commit to allocating 5 per cent of the ODA budget on health research, this was difficult to achieve given the fragmentation of investments across government departments. The Ross Fund, Global Challenges Research Fund and Newton Fund all reach the end of their funding cycles in the coming year. Much of the funding increase seen over recent years was driven by these mechanisms, meaning that to sustain UK funding these Funds must either be renewed or their budgets integrated into other research funding streams. The dramatic return on investment of research spending, and the costs of failing to provide adequate funding, have been highlighted once again by the COVID-19 pandemic. With the dissolution of DFID, which housed much of the policy expertise on global health research spending and provided the vast majority of product development funding, there are also still unanswered questions about the size and nature of the new Foreign, Commonwealth and Development Office's (FCDO) research spending. Given the importance of long-term funding security for innovation, however, and the opportunity to reassess the government's ODA research strategy, there is an urgent need to secure the UK's future global health research offer.

RECOMMENDATION

Increase and stabilise long-term funding for research to ensure maximum return on investment, by committing to spend at least 5 per cent of ODA on research, and ensure spending for TB research does not fall below 0.1 per cent GERD between 2020 and 2025.

SUPPORT INTERNATIONAL COOPERATION

European Union funding mechanisms have played a major role in advancing global health research, particularly through the European and Developing Countries Clinical Trials Partnership (EDCTP) and the Innovative Medicines Initiative (IMI). The APPG heard of a long list of research projects receiving substantial funding through these schemes, including ERA4TB, AnTBiotic, ClickTB, RESPIRI-TB, and EU-PEARL, as well as the ongoing work of numerous PDPs. TB vaccine research has relied particularly on these mechanisms, with DSW reporting that the majority of vaccine candidates had been developed in and supported by the EU. UKAPTB reported that 75 per cent of their responding members received some EU funding for their work, with one university relying on EU funds for 90 per cent of their TB research. It is also notable that of the research consortia described to this inquiry with pharmaceutical industry involvement, many received substantial EU funding. It is understandable, therefore, that the Wellcome Trust and others noted considerable uncertainty and concern among UK researchers and partners following the UK's decision to leave the EU.

As DSW writes, these mechanisms have a "unique capacity to pool funding but also to manage collaboration between EU donor countries, ensuring coherence, complementarity and avoiding overlaps or duplication", particularly critical given the ODA-funded nature of this research. Indeed, many of the innovations described in the previous chapter have received funding from EDCTP alongside UK investments. The UK has historically recognised the value of these mechanisms, with Policy Cures reporting an increased UK investment of US $57 million in 2018 – 40 per cent of the scheme's total funding that year. It is also worth noting that the UK has been the second biggest beneficiary of EU research funding, receiving about €1 billion a year to support research and innovation across a range of disciplines. As DSW highlights, continued UK support is essential both to making the initiative a success and ensuring the continued participation of UK researchers. Following extensive negotiations over Horizon Europe, the EU's future research funding programme, there has now been agreement that non-EU member states will be able to 'associate' with the successor programme of EDCTP. Formal association would enable the UK to continue contributing to these critical mechanisms, while also allowing UK-based researchers to apply for funding. As negotiations over the future relationship continue, it is critical that the UK builds on decades of positive partnership to pave the way forward for effective research collaboration with the EU.

The UK also provides funding for international research partnerships directly, particularly through the research councils. As the UK further evolves its international research offering, it is important also to evaluate the equity of partnerships. A recent briefing produced by the Center for Global Development noted that the vast majority of research conducted in Southern Africa involved partnering with external institutions, resulting in research priorities often being set by scientists outside of the continent.[12] UKAPTB noted that burdensome conditionalities placed on funding for institutions in low- and middle-income countries had created barriers to collaboration, limited access to populations with which TB researchers need to work and undermined effective partnerships to develop locally-driven solutions. We also heard from TB Alert and the Union, who described challenges in securing longer term funding for international research programmes that were highly impactful but not financeable for high-burden countries themselves. A review of the Independent Commission for Aid Impact has also concluded that many UK research funding programmes continue to favour British researchers to the detriment of the usefulness of research.[13] With increases in its overall investment in research, an interest in strengthening bilateral relationships, and an opportunity to reshape major funding mechanisms, it is imperative that the UK prioritises science-led, needs-driven and equitable partnerships.

RECOMMENDATION

Strengthen international partnerships, including through continued association with the successor programme of the European and Developing Countries Clinical Trial Partnership and by evolving grant requirements to foster equitable international collaboration.

12 Centre for Global Development (2020). *Reforming UK research and development ODA for maximum development impact.* Available online: https://www.cgdev.org/sites/default/files/Kenny-ODA-RD-brief.pdf (Accessed 1 September 2020)

13 Independent Commission for Aid Impact (2020) *ICAI follow-up review of 2018-19 reports*. Available online: https://icai.independent.gov.uk/wp-content/uploads/ICAI-follow-up-review-of-2018-19-reports.pdf (Accessed 1 September 2020)

SUPPORT PDPS & INNOVATIVE MODELS

> ***Collaboration between private and public entities is particularly important in R&D for TB. There are several reasons for this, including the fact that the disease cannot be treated with a single drug, but requires a combination of several drugs. Therefore, it is beneficial when a range of partners bring their assets to a collaboration. A second reason is efficiency - resources are finite, and collaboration in R&D enables a pooling of knowledge.***
>
> **GSK**

The APPG's first inquiry report into global health R&D focussed specifically on the market failure that had led to the withdrawal of the vast majority of pharmaceutical companies from the field of antibiotics and poverty-related, neglected tropical diseases. The report concluded that PDPs were one of the most effective means of channelling public investment to drive forward global health innovation. As GHTC describes, PDPs target defined public health goals by harnessing "expertise, resources and investments from the public, philanthropic, and private sectors". By maintaining a portfolio of products, de-risking the development process for pharmaceutical companies in exchange for licencing and improved access conditions, PDPs have been critical to a huge number of research breakthroughs. By investing in PDPs, governments can also ensure that the findings garnered through public investment in earlier stage research can be built upon and transformed into innovative tools with tangible impact on an epidemic. In doing so, PDPs perhaps come closer than any other research financing model to the principles for publicly funded health innovation outlined by the economist Mariana Mazzucato in the 'People's Prescription' report, namely being mission driven, collaborative and transparent, sustaining a long-term and patient investment portfolio and ensuring the products of innovation are accessible.[14]

The PDP model has proven its worth in recent years. FIND has been involved in the development of 24 new tools used in 150 low- and middle-income countries since 2003. TB Alliance became the first not-for-profit organisation ever to develop and register an anti-TB drug and new regimen for people with the most severe forms of drug-resistance. Despite the challenges it faced in securing funding, the PDP AERAS was critical to the breakthrough M72 vaccine trial. IAVI, which acquired many of AERAS assets and clinical programmes, has established a world-leading capacity for clinical trials and is leveraging these resources for a portfolio of products ranging from TB vaccines through to antibodies for HIV and antivenoms for snakebite. In their written submission, GHTC described how PDPs are adapted to tackle bottlenecks as they emerge, with many now producing additional evidence for regulators and conducting translational research. As noted previously, PDPs have also stepped up in relation to COVID-19, by using existing platforms and assets to develop new tools. FIND is building on decades of experience in managing complex partnerships to take on a core role within the Access to COVID-19 Tools Accelerator.

The UK should be applauded for the leadership it has demonstrated in supporting and strengthening the PDP model to deliver these outcomes. According to PolicyCures, DFID is the second largest funder of PDPs internationally, with STOPAIDS reporting that in 2015 almost half of the UK's spending on health research and innovation went via PDPs. This is of particular importance because, as GHTC explained to the inquiry, PDPs can often struggle to secure funding

14 UCL Institute for Innovation and Public Purpose (2018) The people's prescription: re-imagining health innovation to deliver public value. Available online: https://stopaids.org.uk/wp/wp-content/uploads/2018/10/report.pdf (Accessed 1 September 2020)-

from donors whose mandates are limited to specific projects or geographies. In oral evidence, we were repeatedly told about the value of DFID's flexible, long-term and non-earmarked funding, which enabled PDPs to advance product portfolios on the basis of scientific evaluations alone and gave the flexibility required for effective product development. As TB Alliance concludes in their written submission, the long product development timeline means investments in R&D "must adopt a focus that has a longer term horizon", and that "it is a waste of public money when funding for R&D gets abruptly cut or decreased".

As the development of the anti-TB drug bedaquiline and the vaccine candidate M72 show, the pharmaceutical sector often relies on PDPs to advance products in their own portfolios. As both MSF and GSK noted in their submission, collaboration between various actors is especially critical in drug development, since monopoly-based systems are ill-suited to develop efficiently the full drug regimens required to treat TB effectively. As part of the inquiry, the APPG heard of multiple collaborations between public, private, and philanthropic actors, often involving PDPs in some capacity or another, including the TB Drug Accelerator, the PAN-TB initiative and various EU-funding networks. Many witnesses, however, noted that current funding mechanisms were often insufficient to enable effective partnerships across the full development pipeline. There was widespread agreement about the need for what Johnson & Johnson described as "a basket of thought through measures". This could include pull incentives like prize funds, public-interest focused milestone payments, advance market commitments or targeted market entry rewards.

The APPG's 2014 report on the subject explored a wide range of innovative funding mechanisms to incentivise and enable effective collaboration. As TB Alliance writes, however, the field of innovative and alternative R&D models has become "somewhat static", with no major innovations since the foundation of the Coalition for Epidemic Preparedness Innovation (CEPI) and CARB-X, both of which exclude TB and other poverty-related diseases. Part of the challenge here lies in that newer models of R&D incentivisation are rightly viewed as 'high risk' until proven otherwise. No individual government is likely to be able to leverage the kind of funding levels required to make such mechanisms work effectively for global health products, particularly when relying on its inherently limited ODA budget. This report will go on to discuss how to forge international partnerships to overcome these challenges. Nonetheless, it is clear that alongside sustaining its support for the PDP model, there would be some value in the UK establishing a financing mechanism to fund innovative push and pull mechanisms, including pilots, trials, buy-outs and prizes when opportunities emerge.

RECOMMENDATION

Sustain support for the Product Development Partnership model by providing long-term, flexible funding, while setting aside additional funds to trial innovative and enabling mechanisms that support the innovation landscape.

03 Securing value for money

Ensuring that everyone with TB or at risk of TB can benefit from advances in TB research requires new models of innovation and delivery that are needs driven and evidence based, and which are guided by the core principles of affordability, efficiency, equity and collaboration

WHO Global Strategy for Tuberculosis Research and Innovation

MAINTAIN FOCUS ON NEEDS-DRIVEN INNOVATION

The British public rightly expect the aid budget to be spent effectively and efficiently, targeting the world's greatest challenges in the national interest. The specific poverty focused nature of ODA-financed research is therefore essential. In their written evidence, IAVI emphasised the importance of new health tools being suitable for the communities which need them most, a core principle of the UN High-Level Meeting and WHO TB research and innovation strategy. Delivering this kind of innovation requires not only focusing on diseases that predominantly affect people living in low- and middle-income countries, but also prioritising technologies applicable in low resource contexts. Ultimately, this requires research priorities to be informed by affected communities, clinicians and policy makers living and working in these contexts. As Professor Bertie Squire explained in his oral evidence, the research needs of the world's poorest are least likely to be met, and therefore the most important to prioritise. The principles for aid effectiveness agreed by world leaders through the Accra Agenda for Action and the Busan Partnership Agreement should therefore continue to be at the heart of the UK's approach to ODA-funded research.[15] WHO's leadership on the production of 'Target Product Profiles' is particularly useful in this regard, in that they define a series of innovations that would be transformative in the TB response. The newly published WHO TB research and innovation strategy provides further guidance on where and how governments can direct TB research investments to have the greatest impact on the epidemic.

The effective engagement of civil society and affected communities throughout the research process, especially when conducted in low- and middle-income countries, is also critical in ensuring that research is not only conducted in an ethical way, but that the outcomes of research are applicable and acceptable to communities where they will eventually be used. The APPG notes the important role of Community Advisory Boards in this regard, and encourages all UK research funders to ensure that effective community engagement is integrated into their investments in TB research. Civil society and affected community groups with disease-specific expertise should not only be involved with research, but also empowered to conduct it in their own right. As TB Alert writes in their submission, these groups can play a leading role in TB research. By identifying programmatic challenges, informing research priorities and trialling and implementing programmes, these groups can demonstrate the applicability and replicability of certain tools and approaches in practice, and additional funding is urgently required to support their work.

Over decades of managing projects directed at health challenges in low- and middle-income countries, DFID has built up vital expertise and experience in this field. In written submissions, a number of witnesses raised the concern that this expertise may be lost or diluted through the integration of the department with the new FCDO. This expertise is not only critical in ensuring value-for-money, but also enabling the UK government to quickly and expertly respond to urgent global research needs. As the FCDO is established, it is essential that this expertise is not lost but strengthened and empowered to continue leading on this important global agenda.

RECOMMENDATION

Retain a laser-like focus on delivering needs-based and high-impact innovation for challenges faced in low- and middle-income countries, by strengthening collaboration with affected communities and reinforcing critical civil service expertise in development research.

15 OECD (2011) *Busan partnership for effective development cooperation.*
Available online: - https://www.oecd.org/dac/effectiveness/49650173.pdf (Accessed 1 September 2020)
OECD (2005) *Paris declaration on aid effectiveness and Accra agenda for action.*
Available online: - https://www.oecd.org/dac/effectiveness/parisdeclarationandaccraagendaforaction.htm (Accessed 1 September 2020)

FROM BENCH TO BEDSIDE – MAKING THE LINK WITH IMPLEMENTATION

In many low- and middle-income countries, donor funding remains pivotal to the national TB response. The Global Fund to Fight AIDS, TB and Malaria (the Global Fund) provides the lion's share of international donor funding for TB programmes, alongside an annual investment of US $1 billion in broader health systems strengthening. According to their 2020 results report, the Global Fund has helped save 38 million lives since its foundation in 2002, with 6 million lives saved in 2019 alone. In their submission to this inquiry, the Global Fund describes the UK as "one of our strongest partners". It goes on to describe how many of its core objectives "fundamentally rely on sustained investment in R&D to identify the most effective approaches to ensure maximum impact and continued progress towards the Sustainable Development Goals". IAVI emphasised the importance of striking a balance between programmatic investments and in R&D. This point was also echoed by numerous witnesses from the pharmaceutical industry, who emphasised that building a sustainable market for TB products was critical to their ability to maintain an R&D portfolio.

The value of closer alignment between research efforts and TB programmes has become especially clear over recent years, as bottlenecks have hampered the roll-out of new tools. In their written evidence, the pharmaceutical company Otsuka describes the historical uptake of new drugs as "abysmal", but notes significant improvements since the UN High- Level Meeting in 2018. Bottlenecks have ranged from delays in securing regulatory approval, in countries' willingness to update guidelines on the basis of limited programmatic data, in capacity to implement newer treatments which require more intense clinical management, in high prices meeting tough funding constraints, and in a reticence to scale-up new tools before previously purchased commodities are used up. There was agreement among witnesses that further work was needed to overcome these, with implementation delays costing lives and undermining the effectiveness of investments in both programmes and R&D.

Recent initiatives, such as collaborative registration procedures and the WHO-convened task force composed of the Global Drug Facility, the Global Fund, USAID and other technical partners to encourage and support countries in transitioning towards newer treatment regimens are to be welcomed. Similarly, it is encouraging to see ongoing efforts in tackling "failure to launch" bottlenecks, with PDPs and pharmaceutical companies integrating drug registration and support for operational research efforts within their programme design, and donors like the Global Fund establishing grant flexibilities that enable countries to switch to new tools more quickly. As a number of witnesses pointed out, greater investments and coordination on country preparedness, market shaping, health worker and community training, and investment in long-term stewardship of new tools are critical to ensuring countries can quickly move beyond donation programmes or pilot projects to sustainably and responsibly scale critical innovations. Greater engagement from bodies like Unitaid would be especially helpful here, as would additional funding flexibilities and strategic top-ups for actors like the Global Fund and PDPs to undertake critical catalytic initiatives. The role of operational and implementation research is essential in this regard. In order to inform programmatic decision-making and enable the effective roll-out of new tools and approaches, investments in this kind of research must be sustained and also aligned with both needs-driven international agendas and advancements in the product development pipeline.

The majority of the UK's operational and implementation research is funded through research councils rather than through central government. In their submission, UKAPTB noted that many academics conducting this type of research still face barriers to engaging with decision makers, which limited their ability to feed research findings into both national and international policy. Throughout its history, the APPG has benefitted from the engagement of the UK academic and professional community. While this has been possible thanks to the enthusiasm

of these stakeholders, it is unsurprising that particularly researchers based in low- and middle-income countries struggle to engage in policy translation efforts without targeted funding support. Initiatives like the Global Challenges Research Fund's 'networking grants' go some way to tackle these barriers, and should be expanded and targeted on the basis of solid evaluations.

RECOMMENDATIONS

Align investments in global health R&D with support for global health multilaterals,providing additional funding flexibilities and top-ups for actors to undertake critical catalytic initiatives.

Maximise the impact of UK-funded research impact by providing additional and targeted funding for operational research and policy transfer initiatives.

ACCESS TO HEALTHCARE INNOVATIONS

The APPG's first report on global health R&D focused its attention on models to support and incentivise research on poverty-associated and neglected diseases such as TB. Two of the report's core conclusions were that "it is practically impossible to effectively and efficiently incentivise global health R&D through a commercial development model", and that "no solution to the availability problem is complete without also addressing access issues". It is absolutely critical that, as Policy Cures writes, R&D and access are not perceived as separate siloes, but integral to delivering a return on public investment by producing accessible tools with an impact on a particular global health challenge. The report made a number of important recommendations, many of which continue to be reflected in this report, including on de-linking the cost of development from the price and volume of sales, and ensuring pro-access conditions are at the heart of publicly funded and/or supported research.

The management of intellectual property is no doubt challenging in an environment where partnerships between public, private and philanthropic actors are essential to success. Yet striking a careful balance between incentivising collaborative product development and ensuring access to the resultant tools is critical. The costs of not getting it right are enormous, particularly in global health research. A number of witnesses noted that the comparatively high price points of new tools like bedaquiline and GeneXpert had hampered roll-out considerably, multiplying the cost of diagnosis or treatment, and leading to many countries over-relying on donation programmes or scaling products at a snail's pace. Public funding supported the development of both tools, as well as a number of operational and implementation studies. The implication of these delays on the individuals affected by TB and the overall course of the epidemic are considerable, and undermine the cost-effectiveness of the initial public investment.

Similar emphasis also needs to be placed on data transparency, the principles of which should be instituted from the earliest stages of research. In its research roadmap, the government recognises the importance of transparency, noting publishing publicly funded research behind paywalls and not publishing underlying data "slows down research and puts its validity at risk, reducing trust and impact". In one case study recounted to this inquiry, a PDP was forced to replicate clinical trials after the company licencing the product did not grant access to key clinical data. It is therefore that this principle of transparency is also applied to health research and product development, including that funded with the

ODA budget. Institutions like the Medicines Patent Pool (MPP) have been successful in facilitating more transparent data sharing, licencing and patent pooling for critical public health tools. While the UK government contributes to the work of the MPP through its support to Unitaid, its benefits have not been fully leveraged. Building on its successes and learnings, more could be done to integrate use of the MPP and its norms into UK funding conditionalities, for example, and expanding the model's application to other disease and product profiles.

In their submission to this inquiry, TB Alliance highlighted efforts to achieve long-term affordability and market sustainability. In the development of their most recent product, the BPaL regimen, this included launching at a reduced price through their partnership with the global pharmaceutical company Mylan, but, perhaps most importantly, announcing a partnership with Macleod's Pharmaceuticals only four months after the drugs initial launch. The rapid introduction of a generic competitor creates hope for a more accessible product that low- and middle-income countries are willing and financially able to scale-up more widely.

As one of the most important funders of global health product development, STOPAIDS describes the UK as having a "critical stewarding role" in shaping and enabling effective collaboration between public, private, philanthropic and not-for-profit actors to deliver accessible health tools. As TB Alliance explains, "countries investing a significant amount in product development can negotiate, upfront, much better agreements on access and prices for products... this means that investing in product development can pay back at the health systems stage". By placing stringent pro-access and transparency conditions on investments at every stage of R&D, including support to PDPs, the UK government can ensure that every pound of British taxpayers' money works towards delivering on the Sustainable Development Goals. Moreover, by clearly articulating these principles, the UK government is able strategically to shape the global health product development landscape to be more effective as a whole.

RECOMMENDATION

Ensure equitable access to the products of UK-funded innovation, by strengthening access provisions and shaping the global health R&D landscape to deliver maximum impact on the epidemic.

SOFT POWER IN ACTION: BRINGING OTHER DONORS TO THE TABLE

The UK's departure from the EU presents new opportunities to define and strengthen Britain's place in the world at a time when the global landscape is changing dramatically

UK government[16]

Policy Cures describes TB R&D investments as "highly concentrated", with donors like the US National Institutes of Health, the Gates Foundation and the European Commission providing the majority of funding for TB research internationally. While recent increases in investment have been driven by these donors, it will be impossible to close the substantial funding gap for TB research without dramatically increasing the investments of other donors. This is particularly the case given the number of later stage clinical trials that will need to be funded in the coming years following advancements in the product development pipelines. As Professor Squire noted, conversations about funding distribution and gaps are inherently limited when everything is neglected to varying degrees. The urgency of mobilising additional resources is clear.

At the UN High-Level Meeting on TB, world leaders committed to contributing "appropriately" to TB R&D. As has been previously stated, the APPG supports the methodology devised by TAG to assess the "appropriateness" of national investments, based on 0.1 per cent of GERD being spent on TB research each year. According to TAG's 2019 research funding trends report, very few countries come close to meeting this target. In fact, the UK is the only donor country to have met the target in 2018, with the US, Canada, Taiwan, Ireland, and New Zealand being the only countries to reach upwards of 70 per cent of their target. Encouragingly, a number of high-burden countries have clearly recognised the value of research spending, with the Philippines, South Africa and India all investing substantial sums. More funding from the BRICS countries (Brazil, Russia, India, China and South Africa) is especially needed, given their status as emerging economies with burgeoning research and pharmaceutical development infrastructures, while also being home to the greatest burden of TB globally.

As the APPG was told on numerous occasions during written and oral evidence, the UK has a longstanding leadership position and is renowned for its expertise in global health R&D. A number of witnesses emphasised the potential impact of the UK leveraging both its diplomatic networks to bring donors to the table, and using its financing to leverage increased investments in joint research endeavours. This approach is not new, with the government recently announcing a new partnership with India on tackling AMR, with both governments investing £4 million. Had this initiative been TB-focused, it would have increased India's investment in TB research by over 10 per cent. The already well-established Science and Innovation Network could also play a critical role in fostering new and impactful research partnerships if global health is emphasised as a key priority in their new strategy. By leveraging its world-class diplomatic network to build links between UK research institutions and countries around the world, the UK government would strengthen its bilateral partnerships while increasing the effectiveness of its ODA investments.

RECOMMENDATION

Leverage UK investments and diplomatic networks to bring new donors to the table, forge partnerships and close the financing gap for TB research.

16 Gov.uk (2020) *PM outlines new review to define Britain's place in the world.* Available online: - https://www.gov.uk/government/news/pm-outlines-new-review-to-define-britains-place-in-the-world (Accessed 1 September 2020)

04 Strategic Directions

UK COORDINATION

The UK's TB research funding flows through a wide variety of funding mechanisms, ranging from numerous UKRI research councils, through to direct grants from various government departments as well as some spending by Public Health England. While overall funding for global health research increased following the 2015 spending review, the fragmentation of this funding grew alongside it, with government departments including the Department for Business, Energy and Industrial Strategy and the Department for Health and Social Care receiving substantial new ODA funding allocations. This was in large part driven by the foundation of the Global Challenges Research Fund, as well as the Ross and Newton Funds. While some research funding has been allocated jointly through initiatives like the DFID/MRC Concordat and Joint Global Health Trials, much of the UK's TB research funding flows through institutionally distinct funding mechanisms. As is perhaps inevitable with this fragmentation of funding and the absence of overarching ministerial oversight, the coherence of the UK's overall TB research funding is not as strong as it could or should be.

UK-based academics reported real challenges in securing investments for larger research projects, which are essential for TB research given the need for large sample sizes, long follow up times and staff in low- and middle-income countries, but which few research council calls are suited to provide. The UK's overall spend on TB research is heavily skewed towards drug development, with substantial but more limited investments in diagnostics and operational research. Other areas of research have been severely neglected, including basic science and vaccines research, where DFID has previously argued that the pipeline was not advanced enough to warrant DFID funding, but DHSC seeing investments in povertyassociated diseases such as TB as outside of their core mandate. The frequent exclusion of TB from AMR-specific funding mechanisms is also notable, given the significant contribution of MDR-TB towards global AMR rates and the level of priority rightly given to poverty associated diseases as part of the ODA budget. As IAVI points out, this approach also "overlooks the fact that R&D for one disease often benefits others". DFID has been able to identify these opportunities exceptionally well, with research insights garnered through HIV research being used to develop snakebite antivenom, for example. Whether this would be possible across government departments or research councils, however, is more questionable.

In terms of UK funding recipients, the picture is also heavily skewed towards London, creating space for greater investments in research hubs in Scotland, the North and Midlands as part of the government's 'levelling up' agenda. At a global scale, UKAPTB noted greater research spending in Africa, with high-burden contexts in Asia, Europe and South America being neglected. IAVI meanwhile noted that funding appeared to be moving increasingly towards high-value, long-term partnerships with a smaller group of recipients, at the detriment of more competitive open funding calls. UKAPTB also note that "TB research coordination in the UK is informal…and often fragmented", which, alongside the absence of any comprehensive funding or output monitoring hinders the ability of researchers to "avoid duplication, maximise our research outputs and strategically target the most critical questions in TB elimination".

While the fragmentation of TB research funding clearly represents a number of challenges, the APPG recognises that there is a value in different research funders, with different funding mechanisms and areas of expertise, and there would be little benefit from a centralised TB research budget. The creation of the UK Collaborative on Development Research (UKCDR) is a welcome step towards addressing some of these challenges by convening UK ODA research funders. However, the body is not empowered to monitor consistently the entirety of the UK's ODA research spend or to provide overarching strategic direction. The WHO TB research and innovation strategy's recommendation for countries to develop national TB research strategies is no doubt more relevant for high-burden than donor countries. Nonetheless, a more coherent approach to the UK's overall ODA research investments in global health would most certainly be welcome.

The development of a cross- government global health research strategy would help ensure greater alignment across bodies involved in allocating ODA research funding. UKCDR is an invaluable mechanism to support the implementation and monitoring of such a strategy. Nonetheless, with DFID having the most established track record of managing ODA-funded research programmes, it is right that its successor the FCDO provide oversight of the strategy.

RECOMMENDATION

Improve strategic direction, coordination and balance of global health R&D spend across government departments, through the creation of a global health research strategy with strategic oversight from the Foreign, Commonwealth and Development Office.

INTERNATIONAL COORDINATION

Ending the TB epidemic by 2030 and averting the looming crisis of antimicrobial resistance will require breaking out of business-as-usual approaches. States must work together and in partnership with other stakeholders to develop and deploy innovative mechanisms for financing research.

World Health Organisation

The imbalances, gaps and overlaps the UK faces within its own research spending are mirrored by the situation globally. Johnson & Johnson, for example, note that "there is still a lack of a unified higher-level strategy globally that ensures the relevance and value of R&D carried out". The size of the funding gap for TB research is enormous but imbalanced, with more than half of all global investments in TB R&D in 2018 going into drug development, with much less funding available for diagnostics and preventive tools. Funding for more expensive large-scale and late-stage clinical trials will require unprecedented international cooperation. As the product development pipeline enters a new era, this report has already highlighted the importance of newer, more comprehensive models of innovation. Investing in such innovative approaches and in new or neglected areas of research is often seen as too great a risk for any single research funder to be willing to bear. Fundamentally, a failure to overcome these challenges is a waste of time and money that the TB community cannot afford. To overcome them, however, greater international coordination and collaboration will be essential.

The WHO Strategy for TB Research and Innovation provides a series of helpful recommendations for how TB research can be more effectively managed at the national, regional and global scales. While the strategy states that "WHO will support Member States in implementing the global strategy and monitoring progress", it stops short of instituting a specific mechanism by which to do this effectively. The UK has already demonstrated leadership in its support for innovative and responsive R&D coordination mechanisms. This includes the formation of the PDP funders group, which facilitates information exchange, facilitates collaboration between donors and PDPs and enables operational efficiencies through closer coordination. Similarly, the UK was one of the first supporters of the groundbreaking Access to COVID-19 Tools Accelerator, which brings together a wide range of actors to advance product pipelines and prepare for

implementation as quickly as possible. It stands to reason that such initiatives will have long lasting effects on how the world manages global health R&D.

Given the critical importance of improving the coordination of international research spending on TB, the primary question is what arrangement would be sustainable and fit-forpurpose? It is important to note that by endorsing both the UNHLM and WHO TB research and innovation strategy, member states have already committed to the principle of improved global coordination. Their active participation in coordination efforts would need to be incentivised, however. Creating a focused and engaging forum in which critical information about product pipelines is consolidated and shared will be vital, as will the opportunity to align and influence the spending priorities of allies and partners.

Such a mechanism should work closely with those monitoring global TB research funding trends, including Policy-Cures, TAG and the Global R&D Observatory, to both inform decision making and enable effective accountability. In this context, the fair share targets proposed by TAG could function as an important tool. Through a regular co-ordination forum, where new research opportunities are presented and donors are able to discuss their priorities, greater coordination could be achieved and funders such as the UK could utilise their established R&D portfolios to leverage investments from other donors to build new partnerships.

While the forum should be convened and driven by member states with support from the WHO, the engagement of a wide range of stakeholders will be critical to its success. This includes civil society and affected community groups, as well as academia, PDPs and the pharmaceutical industry. The close involvement of institutions such as Unitaid and the Global Fund would meanwhile enable the management of the full range of product development bottlenecks identified in this report, and enable the kind of rapid and widespread roll-out of new tools that would, in itself, be an incentive to invest in TB R&D. Close alignment with initiatives such as the global health R&D forum proposed under the Global Action Plan would allow effective cross-learning between very broad and very focused efforts to tackle barriers and bottlenecks to efficient and effective global health research, development and the deployment of new innovations. Such efforts will be critical to enable governments effectively to steward public investment in TB R&D to deliver the biggest impact, with limited resources, as quickly as possible. Given the UK's established leadership in the field, its interest in improving the effectiveness of its own research spending, in mobilising greater investments and in building new partnerships, it is within the UK government's interest and gift proactively to support the formation of such a forum.

RECOMMENDATION

Improve global coordination of TB research investments through the creation of a global TB research forum hosted by the World Health Organisation

APPG ON GLOBAL TB

The All Party Parliamentary Group on Global TB's mission is to accelerate progress towards ending the TB epidemic. We work primarily through the UK parliament to push the UK government to improve its policies on TB and devote more resources to tackling the epidemic.

The APPG TB is hosted by RESULTS UK, with financial support for the Secretariat from the Foundation for Innovative Diagnostics. The APPG would like to thank them for their ongoing support.

Published November 2020

info@appg-tb.org.uk