



DYING FOR A CURE: RESEARCH AND DEVELOPMENT FOR GLOBAL HEALTH



All-Party Parliamentary Group on
Global  **tuberculosis**

FOREWORD

We live in an age of unparalleled technological innovation. Reports of new scientific breakthroughs punctuate the daily media. Yet, despite the availability of tools to treat and cure diseases that would have been unimaginable just a few decades ago, diseases of the past continue to thrive in the 21st century.

Every year, 13.7 million people die from a group of diseases collectively known as 'poverty-related and neglected diseases.' These are diseases that are familiar to many: HIV, TB and malaria, but also diseases that are unfamiliar to many include Kala Azar, Buruli Ulcer and River Blindness. These diseases share one common theme: the traditional, commercial model for developing drugs, diagnostics and vaccines has failed to bring through the tools and treatments that are needed to eliminate them as threats to global public health.

The failure of commercially driven R&D for these diseases is a problem that affects us all. This is not only because infectious diseases have the power to threaten public health across borders and because people in the UK live with HIV and battle TB, but because poverty-related and neglected diseases are not the only conditions that commercially driven R&D has neglected.

Anti-microbial resistance (AMR) is a grave and pressing problem, not least due to a critical shortage of new antibiotics as a result of a lack of commercial incentives. Infections that were once simple and easy to treat can now require powerful antibiotics. As we work to tackle AMR, much can be learned from the approaches adopted to develop product pipelines for diseases like TB, approaches detailed in this report. We also believe that some of our proposed recommendations to enhance R&D for PRNDs could support the development of new antibiotics.

The recommendations of this report, then, are based on two principles. Firstly, that the UK is one of the few true global leaders in R&D for global health. From government departments to academic institutions, we support, fund and conduct outstanding research. Every penny of public funding should be spent as effectively and efficiently as possible. As a nation we excel at research and development, we should do more of it and we should share our expertise with our colleagues and neighbours.

Secondly, in the 21st century, international aid should not be focused on fixing the world's problems but on helping find solutions to them. We will never eliminate TB until we have an effective vaccine nor will we ever conquer HIV until we find a cure. These are solutions that can and must be found. With the right policies, and the right sustained, committed investments, the UK is uniquely placed to help discover those solutions for the health and safety of our own citizens and others all around the world.

This report was written by the APPG on Global Tuberculosis' Policy Adviser, Matt Oliver, in close consultation with the APPG co-chairmen and other officers.

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GLOSSARY

ABPI	The Association of the British Pharmaceutical Industry
AMR	Anti-Microbial Resistance
BCG	Bacille-Calmette-Guerin: the TB vaccine
BIO	Biotechnology Industry Organization
BIS	Department of Business, Innovation and Skills
BVGH	Bio-Ventures for Global Health
CEWG	Consultative Expert Working Group
CMO	Chief Medical Officer
CSOs	Civil Society Organisations
DNDi	Drugs for Neglected Diseases Initiative
DFID	Department for International Development
DR-TB	Drug-resistant TB
EDCTP	European and Developing Countries Clinical Trial Programme
EU	European Union
FIND	Foundation for Innovative New Diagnostics
GACD	Global Alliance for Chronic Diseases
HIC	High-Income Country
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IPM	International Partnership for Microbicides
LIC	Low-Income Countries
LMIC	Low and Middle-Income Countries
LSHTM	London School of Hygiene and Tropical Medicine
MDR-TB	Multi-drug resistant TB
MIC	Middle-Income Country
MMV	Medicines For Malaria Venture
MRC	Medical Research Council
MSF	Medecins Sans Frontieres
NGO	Non-Governmental Organisation
NICE	National Institutes for Clinical Excellence
PDP	Product Development Partnership
PHE	Public Health England
PhrMA	Pharmaceutical Research and Manufacturers of America
POC	Point-of-Care
QALY	Quality-Adjusted Life Years
R&D	Research and Development
SME	Small and Medium Sized Enterprises
SRL	Socially Responsible Licensing
TB	Tuberculosis
TRIPS	Trade Related Aspects of Intellectual Property
UKRC	UK Research Councils
WHO	World Health Organisation
WIPO	World Intellectual Property Organisation
WTO	World Trade Organisation
XDR-TB	Extensively Drug-Resistant TB

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INTRODUCTION

“Having considered the development and results of the global program on smallpox eradication initiated by WHO in 1958 and intensified since 1967 ... Declares solemnly that the world and its peoples have won freedom from smallpox, which was a most devastating disease sweeping in epidemic form through many countries since earliest time, leaving death, blindness and disfigurement in its wake and which only a decade ago was rampant in Africa, Asia and South America.”

WORLD HEALTH ORGANIZATION, RESOLUTION WHA33.3¹

On 8 May 1980 mankind took another huge leap forward in global public health – smallpox, one of history’s deadliest diseases, had been eradicated.² With this unprecedented achievement, and with polio in decline around the world, surely soon, all infectious diseases would follow smallpox into the pages of history.

Unfortunately, the eradication of smallpox did not mark the beginning of the end for infectious diseases. Thirty-four years later, it remains the only human infectious disease to have been eradicated: progress against polio has ground to a halt and the disease threatens resurgence in war-torn Syria and its neighbouring states; no vaccine or cure has yet been found for HIV; rates of incidence of TB in some parts of the world are higher than rates of flu in the UK; over two hundred million cases of malaria still occur every year.^{3,4,5}

In total, an estimated 13.7 million people die every year from ‘poverty-related and neglected diseases’ (PRNDs).⁶ These are diseases that are unfamiliar to many – in the Western world at least. In addition to HIV, TB, and malaria, PRNDs include Buruli ulcer, Chagas, dengue, guinea-worm, leprosy, river blindness, sleeping sickness and nearly a dozen others.

Although these diseases are defined by the World Health Organisation (WHO) as ‘neglected’, in truth it is the patients who have been largely forgotten by the global community. Some of the conditions that cause these deaths are preventable, treatable, or even curable. However, for a number of PRNDs there are no treatments or vaccines – research efforts have stagnated or been abandoned.⁷

This report will seek to explain why diseases that kill so many are neglected in research efforts. Through a comprehensive literature review, formal and informal interviews with expert witnesses and both oral and written evidence sessions we have drawn together a wide range of views and ideas, from an equally wide range of stakeholders in global health. We will attempt not only to define the problem but to propose solutions.

1.A. Framing the Answer

We are not the first group to seek to address these issues. The question of how to encourage or incentivise research into PRNDs has been asked for the better part of three decades. Most experts define two major challenges for patients with PRNDs:⁸

- Access
- Availability

Access relates to a situation such as with anti-retroviral drugs for HIV/AIDS. These drugs exist but have been developed with high-income markets in mind. Accordingly, these drugs may be too expensive for patients who need them in lower- or middle-income countries (LMICs).

Cost is not the only barrier to access. Patients may be unable to access drugs due to inconsistent provision, poor procurement, inadequate health services and/or a range of infrastructural problems. The drugs themselves can be of poor quality, either because they have limited efficacy, or because poor quality copies have been made of high quality drugs. Health commodities may also be inappropriate, such as with the TB diagnostic, Gene Xpert, which requires consistent electricity supply and air conditioning – neither of which are always available in areas with highest rates of TB.

Availability, on the other hand, relates to situations where no suitable commodities (drugs, diagnostics or vaccines) exist anywhere. For example, patients cannot access effective vaccines for TB, HIV, and malaria,⁹ or rapid point-of-care diagnostics for TB for the simple fact that they have not been developed.

In this report we focus on issues surrounding the availability of key commodities for PRNDs. Although access and availability are inextricably linked, for TB and many other PRNDs we consider that

the major obstacle is this lack of appropriate treatments or diagnostics. We will endeavour to ensure that any recommendations given for increasing availability of health commodities will bear in mind the need for patients to be able to access any commodities that are subsequently developed.

For those who are interested in learning more about access issues, our colleagues in the All-party Parliamentary Group (APPG) on HIV are publishing a companion report focusing on access to medicines issues. We encourage you to read it.

1.B. Building on Previous Work

As mentioned above, we are not the first group to examine R&D for PRNDs. A lengthy process through the WHO has led, most recently, to the Consultative Expert Working Group (CEWG) report in April 2012.¹⁰ This comprehensive analysis, entitled: 'Research and Development to Meet Health Needs in Developing Countries' included a global call for evidence and years of research and preparation. The CEWG has given rise to a number of demonstration projects which we shall briefly discuss later.

A number of civil society organisations (CSOs) are also heavily involved in this area. We are indebted to the work of organisations such as Médecins Sans Frontières (MSF), StopAIDS, DSW, Policy Cures and Universities Allied for Essential Medicines for the work they have done in this field. We would like to thank them, and indeed every other organisation and individual who submitted to the inquiry, for their thoughts and observations.

The aim of this report is not to replace the process being undertaken by the CEWG, or the campaigns of the organisations mentioned above. The APPG has neither the resources nor the capacity to push forward a campaign on its own. We must partner with others to inspire change, just as organisations across the sector must unite to make their voices heard.

In this report we will examine the current landscape of global health R&D, and seek to explain why access and availability are often seemingly pitted against one another. We will discuss a number of reform proposals both inside, and parallel to, the current system of pharmaceutical development. We will explore the unique role of the UK government in the global health R&D arena and ask what more can be done. Finally, we will produce a clear set of recommendations for the UK government and others that we believe will lead towards long overdue reforms to the global health R&D system.



AN EXAMINATION OF PATENTS

2.A The Creation of the Modern Patent

The windows of Eton College are a world away from the modern-day centres of the global TB epidemic. Nonetheless, they represent the starting point of our research. This is not due to some great discovery born under Eton's spires. Rather, a single sheet of paper which has gone on to define the world in which we live.

In 1449 a Flemish-born glassmaker called John of Utynam was given a letter. Whether John of Utynam could read or not is no longer known, but he would have recognised a substantial piece of wax attached to the bottom of the letter. It was the King's Great Seal.¹

In the middle of the fifteenth century, England was at risk of becoming a technological backwater. The great powers of the continent had advanced in a number of fields, leaving the English behind. Glassmaking was one of these fields. New technologies had spread from the Venetian Republic, and local manufacturers could not hope to match the quality of glass produced with these new methods.

John of Utynam's letter with the King's Great Seal was intended to bring England back up to speed. It granted him a twenty-year monopoly on making glass through this new manufacturing process,

making John a wealthy man. He would go on to manufacture stained glass for a number of buildings, including Eton College.

One might wonder what role a monopoly could play in helping England modernise. The monopoly, indeed the letter, came with a condition – in return John was required to train his English colleagues in his glassmaking techniques.

It is now 565 years since John of Utynam received the first English 'Letters Patent'. Across the intervening centuries, it is notable that many of the major features of that first English patent remain embedded in our modern-day patent system.²

Legalisation of a System

By the fifteenth century, patents were not a new idea. Some experts have traced them back as far as 500BC, though the practice around them evolved over time.³ By 1474 the idea had taken root to such an extent that the authorities in Venice decided to create a patent law.

The Venetian law granted the patent-holder monopoly rights, much as John of Utynam's Letters Patent had. Unlike the Letters Patent, however, it included formal penalties for patent infringers. Then, as now, the principal deterrent was a steep fine. The Venetian law also included a clause that is at the heart of a number of modern-day patent controversies in the form of the compulsory license:

*But our government will be free, at its complete discretion, to take and use for its needs any of the said contrivances and instruments ...*⁴

A compulsory license is a mechanism by which a government can break a patent. They have been used consistently for hundreds of years, right up to the present day. In 1965 Pfizer unsuccessfully challenged the UK government's use of compulsory licenses to secure cheap drugs for the NHS.⁵ Between 1969 and 1992 the Canadian government issued 613 compulsory licenses to keep the cost of medicines down.⁶ In 2001 the US government even threatened to issue a compulsory license against Bayer in order to assist in stockpiles of anti-Anthrax medication. In 1474, however, such events could not have been imagined; the challenge of the day was maintaining the Venetian Republic's technological dominance and patents were to help achieve that goal.

Patent Specifications

Following the introduction of the Venetian law, patents spread rapidly through the courts of Europe and varied in their use. John of Utynam's Letters Patent had been given on the condition that he teach his techniques to others, but who had the authority to decide which 'others' received instruction?

King Henry II of France overcame this issue with a relatively simple addition to the standard patent law.⁷ In 1555 the King introduced the practice of requiring applicants to publish a description of the invention. This description was kept secret until the expiry of the patent term when it then became available for anyone to read, and subsequently copy, if they so wished.

It may seem like a relatively small amendment, but this was actually a significant step forward. Innovation rarely happens in one great bound meaning that technological development tends to be an accumulative process with each invention built by refining and improving upon previous discoveries.

If the nature of previous innovations is kept secret, this process is greatly hampered. By ensuring that the details of each patent were public, discoveries became part of common knowledge. Nowadays, details of patents are available when they're filed (though they can be rather vague) rather than when the patent term expires in order to speed-up this cumulative development process.

The Statute of Monopolies

The awarding of patents was somewhat open to abuse. Queen Elizabeth I and King James I gained reputations for using the patent system to reward loyal subjects, Elizabeth even granted patents on things as common as soap. By 1624 the patent system had become unmanageable and the English Parliament decided that enough was enough. They wiped the slate clean and started again with the Statute of Monopolies. New provisions were adopted, including the granting of monopoly rights for a period of fourteen years:

... [providing] they be not contrary to the law nor mischievous to the state by raising prices of commodities at home, or hurt of trade, or generally inconvenient⁸

Quite how a modern court would define 'generally inconvenient' is hard to say.

Over the following centuries, patent law in England was further refined through court proceedings. Specifications were brought in as a requirement of gaining a patent – similar to King Henry II's provisions in France. The quality of this description was of sufficient importance that the court struck down the patent on the spinning machines of Sir Richard Arkwright due to a weak specification.⁹

By the end of the eighteenth century patents were being granted for incremental improvements on previous designs. Up until this point people could make innovations on previously patented products or ideas, but couldn't patent them. This system was, and still is, open to a wide range of interpretations. India, for example, does not allow new patents for 'non-significant' innovations on existing patents. In practice, this means that a company which makes a small tweak to an existing product cannot get a new patent. Defining what 'new innovations' merit patenting and which do not is obviously open to debate.¹⁰

At the start of the twentieth century, the process for being awarded a patent had developed somewhat, but the law was broadly the same. In 1902 it was decided that patent examiners should carry out a limited investigation into the novelty of an invention before approving the granting of a patent.¹¹ This still remains the case today.

The final step in the development of modern patent law came through the European Patent Convention. Approved in 1973, it established the framework for a unified patent system across Europe. For the first time, an individual could patent an invention across several countries with one single application, although individual States reserved the right to enforce or deny this patent if they saw fit. The law was passed in the UK in 1977, essentially repealing the venerable Statute of Monopolies, and, creating the legal framework in which the modern patent system operates.

2.B Patents in Practice

A patent is not a goal in itself, rather it is a right created ... as a means to achieving a larger social goal.¹²

TROTTER

Describing the history of patents has two broad purposes. The first is to highlight how, and why, some of the key components of patent law have come together. The second is to demonstrate just how firmly embedded patents are into the fabric of Western society. The vast majority of the technological innovations of the last five hundred years have come through under patent. That's not to say that they wouldn't have been developed in a system without patents, simply that we can't prove otherwise.

Mankind is incessantly inventive. We have an innate ability (or even instinct) to refine, develop and adapt the world around us. Since the first use of fire, and the invention of the first axes, society has been confronted with the question of how to encourage people to come up with the most useful innovations? Patents are a tool to incentivise that innovation. For every product there is a market, big or small. With goods, be it food or furniture, we define their utility by how much we're prepared to pay for them, and under that measure we can determine the size of the market. With a conceptual invention, we can't say how much its market is worth because we don't know how much utility would be gained from it.

Patents put the onus on the inventor. Come up with a product that a lot of people want to pay for (and therefore, we can assume, has significant utility) and you will be awarded the monopoly rights to make the most of that market. However, if you come up with something that no one wants to pay for, too bad. If inventing a useless product costs a lot, and inventor is the one who has to pick up the bill, there's a strong incentive not to invent a useless product.

Originally patents may have been developed out of a sense of 'fair play' – that an inventor should be able to profit from something they have created. Whilst the spirit of that continues, modern patents are primarily a tool to incentivise useful innovation, and it is the markets which decide what is useful and what is not.

In an ideal world, the market would offer the greatest returns for those innovations which are of the greatest benefit to society. Patents incentivise inventors to develop products to capture the largest markets, meaning that in this ideal world, the most profitable products would be those that create the most benefit for society. However, in our societies, certain individuals in the global market have greater wealth than others and shift the overall market demand to products that they want. As the patent is designed to capture a market monopoly, inventors focus on those products that return the greatest financial reward rather than do the greatest public good.

2.c Patents in Practice – Pharmaceutical Innovation

It is an expensive, time-consuming and financially risky endeavour to produce new and safe drugs... without patent rights... as soon as an inventor firm introduces a new innovation in the market, other companies will copy the innovation and given that these companies have had no costs in terms of R&D, they will be able to charge a lower price... eventually innovators will be driven out of the market.¹³

SONDERHOLM

Pharmaceutical companies, like any other private sector organisation, operate within the patent framework. Their innovations are in the form of medical commodities, which they then sell to individuals, organisations and national health systems. Income from those sales helps to pay for the previous round of innovation, provide capital to support future innovations and, of course, generates profit.

There are many critics of the patent system and particularly pharmaceutical patents but pharmaceutical innovation (however it has been incentivised) has brought benefits, particularly to the developed world, in length and quality of life. Taylor et al, in a paper for the UCL School of Pharmacy, identify that ‘New medicines and vaccines, along with developments in areas ranging from surgery to nursing, have been responsible for about half the global health progress since the end of World War II.’¹⁴

The Wellcome Trust, a huge philanthropic donor and one of relatively few such donors that mandate open-publication of research it has supported, has highlighted the positive role played by IPRs in encouraging such innovation, stating: ‘the protection of intellectual property is considered an essential factor to promote innovation and stimulate research and development of new products.’¹⁵

So we can see the link: patents encourage (some) research and development, research and development generates new products which increase quality of life. However, key questions remain: which diseases are being conquered? And who benefits?

As we have previously explored, in a system which grants patents, innovators will focus on the markets that can offer the greatest returns. This becomes even more the case as the innovation process itself becomes more expensive.

In the pharmaceutical industry, the result is an imbalance in the focus of research. In 2000 the Global Forum for Health Research released a landmark report estimating that less than 10 per cent of global spending on health research is devoted to diseases of conditions that account for 90 per cent of the global disease burden.¹⁶ Though the figures may have altered slightly since publication, the underlying principle is the same.

What has changed is our understanding of the degree of crossover between the health burdens of high-income countries (HICs) and lower- and middle-income countries (LMICs). Anti-microbial resistance (AMR) is a challenge across the world due to a failure to develop new classes of antibiotics. Non-communicable diseases like cancer and diabetes represent huge problems in LMICs as well as in HICs. Cancer drugs that are developed with the intention of capturing HIC markets are also available

in LMICs, and some experts would argue that patent-incentivised development of drugs, diagnostics and vaccines for HICs leads to long-term benefits for LMICs.

Whilst they may be available the real question is: are they accessible? Or, otherwise put, are they affordable? Drugs that are designed for HIC markets may not be appropriate for LMICs which often have less developed health systems, and may lack, for example, a cold chain to maintain drugs and vaccines at optimum efficacy. These drugs may also be priced at HIC levels as inventors use their monopoly powers to maximise their income and, therefore, be far too expensive for the majority of patients in LMICs.

This is where patents can create access problems. Companies are private enterprises, they have demanding shareholders and directors who are remunerated on quarterly performance. In a traditional model they set prices at such a level as to maximise profit, i.e. the highest price the market will support, not the price that will help the drug reach the greatest number of patients.

For diseases like PRNDs which often do not have major markets in HICs, the situation is worse because there are insufficient market incentives for companies to invest in research at all. As we’ve shown, if patents are designed to capture a market, they do not incentivise development where market value barely exists, and thus, there are no products.

This, then, is the heart of the problem with the commercial model of development (applying particularly for drugs and vaccines, less so for diagnostics). A patent-based incentive system appears to create a choice between access and availability. A commodity may be developed, but is inaccessible to LMIC patients because it is too expensive, or it will not be developed at all.

Pharmaceutical patents, however, do not last forever. Although patents are granted for a period of twenty years, in practice, once regulatory approval and the relevant clinical trials have been carried out, a product will be on the market and under patent for between eleven and thirteen years. During that period, if a suitable market exists, a patent-owner can make a significant profit.

This could be a good thing, according to Aidan Hollis, one of the architects of the Health Impact Fund, a reform proposal which we will examine later: ‘Paying high prices today for rare disease drugs enables future low prices on the same drugs, following patent expiry. Those expensive drugs will become less expensive in the future – but only if they are developed.’¹⁷

Due to a number of factors that we will explore shortly, at the end of that patent period, the price of the commodity can fall dramatically. There will, of course, be a time delay between the drug being available to HIC markets, and it becoming cheap enough for the majority of LMIC patients, but this, according to Hollis, is the price you pay for innovation: patients in LMICs are only able to access high quality drugs at all because of the market pull created in HICs. They may not access the drugs immediately, but without that disparity (and the resulting window for profit), there would be no drugs at all and we would all suffer.

It is open to dispute whether there is generally an ‘access vs innovation’ issue with a patent-driven system, whether patents are necessary to encourage medical innovation. It is not the focus of this report to have that dispute. Nonetheless, few would argue against the claim that the patent-based system incentivises technological developments that benefit the wealthiest countries first and foremost. This is just as true for pharmaceutical companies as it is for mobile phone companies.

2.D Patents and Diagnostic Development

Although it can be tempting to draw drugs, vaccines and diagnostics under one roof to discuss issues relating to their respective development, in reality there are huge differences between the market, and innovation process, for each. Most of the comments above relate specifically to drug development, though they can apply broadly to vaccines in regards to the lack of a comparative financial return for vaccines, i.e. there is a financial market for many vaccines, but commercial entities have limited resources and thus tend to focus their resources elsewhere.

For diagnostics, most development is not conducted by large commercial entities: big pharma. Rather, they are designed, developed and produced by small and medium-sized entities (SMEs) like GBD-Bio, often in partnership with other organisations such as Product Development Partnerships (PDPs). Unlike the huge initial R&D costs of developing a drug or vaccine, diagnostics have lower up-front development costs, but greater long-term production costs, they have different markets, vastly different development cycles, and each individual unit generally has a greater array of technical components (not to mention software) than a standard drug or vaccine.

Nonetheless, diagnostic patents can represent both an incentive for innovation and an obstacle in terms of pricing and competition, just as with any other product.

2.E The Power of Patents

HIV and TB are two of the world's biggest killers. The majority of cases of both diseases are found in LMICs, and patients are often poor. Both also have a certain number of cases, albeit far fewer, that occur in HICs.

For TB, the HIC market is small. Drugs are old and off-patent, so even though London has higher rates of TB than any other capital city in Western Europe, the UK only spends seven million pounds a year on TB drugs. The global market for multi-drug resistant TB (which is much more expensive to treat than drug-sensitive TB) has been estimated at just three hundred million dollars a year.^{18 19}

By comparison there are roughly a hundred thousand people living with HIV in the UK. An estimated 50 per cent of people with the virus don't know they have it, but it's calculated that the UK spends 820 million pounds a year treating HIV and drugs for the lifetime of an average patient cost 360 thousand pounds. HIV, therefore, represents a significant HIC market, TB represents a small HIC market, and other PRNDs like Buruli ulcer do not exist in HICs and have no market at all.

In the last fifty years there has been one US Food and Drug Agency approved drug for TB, bedaquiline; Janssen, the pharmaceutical company that developed the drug, deserve credit for their investments in bringing it to market because, as demonstrated by the size of the overall market, at least some of their investment is unlikely to ever be recouped. In comparison, in the last twenty years there have been over twenty FDA approved compounds for treating HIV. In regards to diagnostics, there are cheap, point-of-care tests available for HIV, but no equivalent for TB.

Public and philanthropic funding for HIV has certainly been higher than funding for TB, but this alone seems unlikely to account for the disparity between drug development for the two diseases.

Even within one single disease there can be huge differences in the availability of medicines. Turn to

paediatric formulation of HIV treatments and the picture is different. The financial market for paediatric HIV is much smaller in HICs and, as a consequence, there is a lack of paediatric HIV formulations – they haven't been developed on nearly the same scale as adult ARVs. Such figures often lead to criticism of pharmaceutical companies, but in many ways they serve to demonstrate the remarkable capacity of the pharmaceutical industry to develop new treatments when the incentives are correctly aligned. The question that we must all answer is how do we align those incentives?

2.F The Price of the First Pill

In order to incentivise development of treatments for particular conditions, we must first try to understand how much it costs to develop those treatments. Then, although there will always be challenges with using public sector money to essentially 'give' a profit to a pharmaceutical company that invents a new product, we can at least devise systems that reduce financial risk/cost for the commercial sector whilst still engaging their considerable resources and expertise. Unfortunately, divining the cost of drug development is far from straightforward.²⁰

An article from *Forbes*²¹ took the straightforward approach of dividing the amount spent on R&D by pharmaceutical companies by the number of new drugs that they brought to market and found that each compound could cost up to ten billion dollars to bring through. This figure has been widely criticised not least because it is remarkable high.²² O'Hagan and Farkas estimated that each new drug cost just 20% of that figure at an average of 2.2 billion dollars when marketing and all clinical trials are included. This figure was generated in 2007 using an internal organisational model.²³

A more widely quoted estimate comes from a paper by DiMasi et al.²⁴ The researchers asked pharmaceutical companies to volunteer information regarding drug costs. Ten companies responded and the researchers chose sixty-eight drugs. The headline figure from the report was that each drug cost 802 million dollars to produce back in 2000. DiMasi included the opportunity cost of developing the drugs, which made up half of the total figure, suggesting an average cost today of around six hundred million dollars.

These figures all focus on the US pharmaceutical industry, European estimates were recently provided by the European Federation of Pharmaceutical Industries and Associations, which estimated the cost of a New Chemical Entity at 1,059 million euros.²⁵

The Chief Executive of GlaxoSmithKline (GSK), meanwhile, has been quoted saying that the one billion dollar price tag for a new drug was 'one of the greatest myths in the industry.'²⁶ He went on to say that the real figure could be much lower if companies addressed their R&D models as GSK had done. Meanwhile a report by Deloitte and Thomson Reuters found that the most effective company in the pharmaceutical industry spent an average of just 315 million dollars developing a new drug.²⁷

At this juncture, finding an accurate number seems impossible, not least because it may actually be impossible. Modern pharmaceutical companies are enormous institutions, with huge overheads, marketing costs, and regulatory requirements, not to mention that the chances of finding a molecule with therapeutic impact varies from 1 in 5,000 to 1 in 10,000 according to the EFPIA.²⁸ How would you decide what should be included in the calculated costs?

Of course, even if we could get an accurate and consistent average figure for developing drugs, that's not to say that a specific drug would cost that much to develop. We cannot assume that just because the average cost of developing a drug might be 315 million dollars that is how much it will cost to develop a TB drug. It could cost much more – or much less. Pharmaceutical R&D is an extremely complex process, it requires sustained investment, and R&D processes can take decades without a company experiencing success, by which point, the Chief Executive who started the process may have moved on, and the financial and political conditions in the company may have changed.

Nonetheless, estimates do exist of the size of market that is required to encourage private sector investment. Ridley estimates that you would need a pull of sales figures of roughly two hundred million dollars a year to inspire the development of a product. Assuming 'multiple products are already on the market, creating an element of competition, plus the fact that several of those are, or will become in the future, generic, thus putting pressure on prices, then one probably needs a total market size approaching one billion dollars.'²⁹

This is a significant market, one that probably doesn't exist for any PRND aside from HIV. So it is unreasonable to expect the pharmaceutical industry do more for PRNDs?

As a whole the industry has consistently been one of the most profitable in the world, it is probably fair to say that the industry could invest more in neglected disease research if it chose to. Researchers in 2002 suggested that the pharmaceutical industry was the most profitable industry of any other, returning 16 per cent profit.³⁰ Despite a widely reported 'crisis' in the pharmaceutical industry, this figure had actually risen to 19.3 per cent by 2010 when the industry ranked as the third most profitable of all.³¹ ³² In 2005 just 18 per cent of pharmaceutical sales went into R&D.³³

Further, we should not make the mistake of assuming that the cost of developing a drug is directly connected to the prices that companies charge for the final product, nor that these R&D costs make up anything close to the majority of costs incurred by pharmaceutical companies. Equally, we should recognise that some pharmaceutical companies do engage in a wide range of activities from which they do not generate profit, many of which we will explore later.

Nonetheless, we do believe that there is scope for pharmaceutical companies to do more in regards to R&D for global health. However, it is difficult to see how policymakers could incentivise full-scale private sector engagement in PRNDs due to the problems outlined above, and so it is clear that other mechanisms must be found.

2.6 After the Patent

The cost of a commodity to the patient has little association with the cost of manufacturing each individual pill. In addition to the manufacturing costs, the cost of clinical trials, research, licensing, marketing, regulatory responsibilities and a host of other things are included in the final price.³⁴ In addition to everything associated with the drug itself, the costs associated with unsuccessful development efforts are included. Given the EFPIA's assessment that between five and ten thousand compounds can be researched to a greater or less extent before finding one successful compound, those unsuccessful drug costs can be high.³⁵

Companies, therefore, have a lot of costs that they have to earn back with each drug before profits

can be generated. Nonetheless, representatives from the pharmaceutical industry have asserted that there is no link between the cost of R&D and the cost of the final product which takes a range of other things into account: competitors, product efficacy, medical need, or, in short, how much the market is willing to pay.³⁶

As a result of all of these factors, Professor Thomas Pogge estimates that 'the average drug has a mark-up of between sixty and one hundred times.'³⁷ Recouping the original R&D costs, and generating profit, rests on the monopoly rights afforded by a patent. Even discounting for profits, there are overheads, and a company without these overheads could manufacture the commodity and sell it at close to cost price. Such a company is known as a 'generic manufacturer' or simply a 'generic'.

When patents 'run out' generics can enter the market. Generic manufacturers, like most other businesses in an open market, compete over price. That doesn't necessarily mean that as soon as a treatment's patent-protection ends that the treatment immediately falls to rock-bottom price. What it means is that, having been part of a monopoly, the market for that treatment is open to those who can capture it.

Over a period of months and years, therefore, generic producers will compete to produce a better price and capture more of the market. This competition produces cheaper prices, so eventually, generic production is capable of producing treatments at prices which are almost always cheaper than Western pharmaceutical companies.

This creates a so-called 'patent cliff'. As soon as the treatment is no longer protected under patent-law, pharmaceutical companies can be undercut by generic manufacturers. Accordingly, there are huge incentives for companies to maintain monopoly control of the market for as long as possible, and, therefore, attempt to elongate the lifespan of their patents, usually by securing new patents, in order to maintain the IP and monopoly rights. This process is called 'evergreening'.

The success of such patent protection strategies depends on a country's legislation around patents, and how easily a company can produce credible secondary patents. As a result, a more common strategy is for the company to invest heavily in marketing and attempt to maintain some profit margins through brand recognition. A common example of this is the ibuprofen that you can purchase in your local supermarket. A pack of the cheapest generic version will cost you roughly 40p, a pack of Nurofen,³⁸ a branded equivalent with the same amount of the active pharmaceutical ingredient, will cost you more than two pounds.

Nevertheless, eventually, all treatments must come 'off-patent' and at this point anyone may manufacture them. Generic competition drives prices down, greatly expanding the potential for countries with limited resources to purchase these critical drugs.

So how long does this take? Due to evergreening, delays to generic provision, or issues relating to technology transfer, it can take much longer than the eleven to thirteen years estimated above before a treatment becomes generically available.

Firstly, it is not certain that generic manufactures will always enter a market at the earliest possible opportunity. Research by Danzon and Furukawa found that 26 per cent of molecules with no known patent obstacles had no generic competition.³⁹ Generic manufacturers sell on volume, so if the volume of sales for a potential commodity is low, there may be no incentive to enter the market at all. Additionally, some commodities, particularly vaccines and some diagnostics, can be very difficult to produce and

require considerable technology that generic companies may not be able to access.

Nonetheless, generally speaking, when they do enter a market, generic companies can produce off-patent or open-license commodities for the cheapest prices, thus avoiding price-based access problems. Unfortunately, for policymakers searching for a solution to a lack of overall R&D for PRNDs, generic companies rarely engage in R&D of their own accord, so are not a solution to availability problems.



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WHO HAS RESPONSIBILITY?

3.A Certain Unalienable Rights?

Having examined the role of patents in technological innovation and the challenge of identifying the costs of developing drugs and vaccines, we will now turn to the question of who should be responsible for developing new health commodities?

An estimated 13.7 million people die every year from ‘poverty-related and neglected diseases’ (PRNDs).¹ In twenty-two countries, all in Africa, 70 per cent or more of the life years lost are caused by infectious diseases.² These diseases impose significant social and economic burdens on individuals, communities and even entire countries.

Few would disagree that avoidable human suffering on this scale is morally wrong. We cannot prevent all pain and suffering, but the ‘wrongness’ of avoidable or preventable human suffering is so clear that it has been enshrined in documents articulating our most fundamental requirements and expectations: our human rights.

The ‘human right to health’ is found in Article 25 of the UN Declaration of Human Rights.³ It is found in greater detail in Article 12 of the International Covenant on Economic, Social and Cultural Rights which acknowledges the right of everyone ‘to the enjoyment of the highest attainable standard of physical and mental health’.⁴

The article in question goes on to list four ‘steps’ that each of the ‘States Parties to the present Covenant’ should take, including in steps three and four:

- 3) **The prevention, treatment and control of epidemic, endemic, occupational and other diseases.**
- 4) **The creation of conditions which would assure to all medical service and medical attention in the event of sickness.**⁵

Much of the suffering caused by these PRNDs is unnecessary. In some cases we have commodities available to treat, prevent, and cure some of these illnesses. With those diseases for which we do not have treatments it is not, on the whole, because of some significant scientific barrier, but because disease research in this area is chronically underfunded.

The distinction between poor health that is avoidable and that which is not is recognised in the application of these human rights. Individuals do not have a right to be healthy – we cannot always control what makes us healthy and what does not. However, as individuals we can expect our State to protect us from obvious risks to our health and maintain the ‘obligations which apply to every state regardless of how impoverished it may be’.⁶

These obligations are outlined, at length, in General Comment 14 of the UN Committee on Economic, Social and Cultural Rights. UN Committees produce General Comments to explain what is understood by documents such as the International Covenant. General Comment 14 explains:

*Functioning public health and health-care facilities, goods and services, as well as programmes, have to be available in sufficient quantity within the State party ... They will include, however... essential drugs, as defined by the WHO Action Programme on Essential Drugs.*⁷

The WHO Action Programme on Essential Drugs no longer exists and has been incorporated into the WHO list of Essential Medicines which is updated every two years and includes a wide range of drugs, some vaccines but very few references to diagnostics.⁸ As reported by Taylor et al, ‘Virtually all of the pharmaceuticals classified as essential by the WHO are already available as generic, or at least as off-patent but branded, products.’⁹ Individuals have a legal right to expect an ability to access these drugs. If a State blocks people from accessing these medicines it is violating people’s right to health. That is not to say that a State that is impoverished has to provide drugs that it cannot afford, but that once a standard has been set, it cannot, or should not be repealed. Fortunately, few States would seek to lower standards of healthcare amongst their population. Unfortunately, other forces may compel them to do so.

3.B The Right to Health vs the Right to Intellectual Property

*[The right] To benefit from the protection of moral or material interests resulting from any scientific, literary or artistic production of which he is the author.*¹⁰

INTERNATIONAL COVENANT ON ECONOMIC, SOCIAL AND CULTURAL RIGHTS

According to Article 15 of the International Covenant we have the right to profit from our inventions, or, otherwise put, Article 15 gives the right to Intellectual Property (IP). IP is often recognised through the allocation of a patent. As we have seen, a patent is a device that allows an inventor to exclude anyone else from using their invention for a period of time conferring to them the market monopoly. During the period of the monopoly anyone wishing to buy the product has to pay the price set by the inventor. If you can't afford the price or strike a bargain, you can't buy the product.

What, then, if the product is a medicine? Medecins sans Frontieres cite the example of HIV drugs in the late 1990s: "Competition among generic producers was instrumental in bringing down the price of the first generation of ARVs, and is one of the key reasons treatment could be scaled up to millions of people. Today, first-line ART is available for just under US\$100 per person per year (ppy), which is a 99% decrease from 2000, when treatments still under patent were priced at more than \$10,000 ppy."¹¹

Quite clearly, then, IP can raise barriers to accessing essential medicines which can have an impact on a State fulfilling its obligations to the rights of its citizens. However, the State's obligations apply particularly to the WHO list of Essential Medicines, what impact could IP have here? However, a glance at the WHO criteria for selecting essential medicines suggests the impact could be significant: "[Essential Medicines] are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness."¹² If IP can raise the cost of essential medicines, and high cost can be a factor in what is considered for the WHO Essential Medicines list, it seems that patents and pricing may be a factor in preventing certain medicines from making it onto the list, and thus from States having an obligation to provide them for their citizens. This may explain Taylor's assertion that the majority of medicines on the WHO list are off-patent.

Regarding IP raising barriers to access to medicines, General Comment 14 rules that:

States parties should therefore ensure that their legal or other regimes for the protection of the moral and material interests ... constitute no impediment to their ability to comply with their core obligations in relation to the rights to food, health and education ... States parties thus have a duty to prevent unreasonably high costs for access to essential medicines ... from undermining the rights of large segments of the population to health, food and education. Moreover, States parties should prevent the use of scientific and technical progress for purposes contrary to human rights and dignity,

*including the rights to life, health and privacy, e.g. by excluding inventions from patentability whenever their commercialization would jeopardize the full realization of these rights.*¹³

It is thus quite clear that States' obligations to public health, and the well-being of their populations, take precedence over their obligations to ensure moral and material interests resulting from scientific innovation. Nonetheless, with the nature of the WHO Essential Medicines list, and a tangled web of international agreements, the true picture is somewhat more complex.

3.C Internal and External Influences

In 1995 the newly formed World Trade Organisation (WTO), following up from a series of previous discussions at the Uruguay Round of the General Agreement on Tariffs and Trade (GATT), formally adopted an agreement known as the Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS requires all signatories to ensure minimum standards of IPR protection, standards that are much more stringent than those that previously existed in poorer countries.

Prior to the TRIPS agreement, the Indian government did not award product patents for pharmaceutical inventions.¹⁴ This meant that Indian pharmaceutical manufacturers could freely produce medicines created by foreign companies at a fraction of the cost. They did, however, award process patents. A process patent is a patent that protects how a product is created, not the product itself. This was designed to give Indian manufacturers an incentive to find cheaper ways to manufacture expensive products.

These IP laws made India the 'pharmacy of the developing world' and are responsible for the fact that it remains the 'second leading provider of medicines distributed by UNICEF in the developing world'.¹⁵ On January 1 2005, India became compliant with the TRIPS agreement which meant India had to abide by the 'WTO's minimum standards for intellectual property protection'.¹⁶ These minimum standards mandated, among other things, the awarding of pharmaceutical product patents for a period of twenty years.

Treatments that were developed before 2004 can still be manufactured generically, but from 2005 treatments could be patented for 20 years. Countries which previously bought relatively new drugs from generic Indian manufacturers now have no other option than to buy the branded drug, often at significantly greater cost, or not to purchase them at all.

Anand Grover, the UN Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, enters the story here. Grover, admittedly, is not entirely impartial, but has stated:

*TRIPS and FTAs [Free Trade Agreements] have had an adverse impact on prices and availability of medicines, making it difficult for countries to comply with their obligations to respect, protect, and fulfil the right to health.*¹⁷

According to Grover, there is a conflict between adhering to TRIPS and making medicines available at low costs to all patients. Further, General Comment 14 states:

In relation to the conclusion of other international agreements, States parties should take steps to ensure that these instruments do not adversely impact upon the right to health.

This seems pretty clear: international agreements, of which TRIPS is one, should not adversely impact upon the right to health. Moreover, the UN Special Rapporteur believes TRIPS makes it more difficult for countries to fulfil the right to health. This poses two questions in need of answers:

1. Why did countries sign up to TRIPS if it would have a negative impact on their ability to ‘respect, protect, and fulfil the right to health’?

2. Should TRIPS be considered illegal under international law?

In answering the first question, Professor Thomas Pogge explains that adhering to ‘the TRIPS Agreement is a condition for membership to the WTO, basically saying if you want most-favoured nation status and access to our markets, you have to sign up to TRIPS.’¹⁸ States perceive it to be in their economic interest to be a member of the WTO and as membership requires signing up to TRIPS, countries signed up to TRIPS. It is also worth noting that, given the imbalance of resources available to HICs vs LMICs in the negotiations that led to TRIPS and the WTO, it’s altogether possible that LMICs agreed to TRIPS with a relatively poor understanding of the consequence.

It should be noted that there is provision within TRIPS for countries to issue ‘compulsory licenses’ for serious health emergencies. A compulsory license allows a country to break a patent and produce a commodity itself. The US threatened to do exactly that to Bayer in 2001 in order to strengthen its stockpile of drugs against anthrax.¹⁹ However, given the severity of the AIDS epidemic, a surprisingly small proportion of countries have issued compulsory licenses, with only 12 such licenses being issued between 1995 and 2011 and a further 12 were threatened. Of those 24, 13 were in upper middle-income countries.²⁰ Critics have cited a number of reasons to suggest why countries may not have used compulsory licenses as much as they could but political pressure from the developed world may be a factor, despite the World Health Organisation making it clear that they should not:²¹

*The TRIPS Agreement does not and should not prevent members from taking measures to promote public health and in particular to promote access to medicines for all.*²²

In the spirit of this declaration then, HICs, including the UK, should support LMICs who utilise TRIPS flexibilities such as compulsory licenses in order to safeguard public health and promote access to medicines for all.

Unfortunately States do not have to be a member of TRIPS to be affected by it – even though many are. Many of the poorest countries don’t have generic manufacturing capability. If a country that does have generic manufacturing capability signs up to TRIPS (as India, Brazil and South Africa have done) the consequences for cheap supply of drugs across a region are significant.

Regarding the second question, TRIPS is argued to have benefits for health. Prior to the TRIPS agreement, countries adopted their own patentability standards to suit their own needs. In practice this meant that large countries like South Africa, Brazil and India offered a relative lack of patent protection. Pharmaceutical companies could not be certain that a local manufacturer – who didn’t have to recoup the original R&D costs – wouldn’t undercut them. When deciding research priorities, pharmaceutical companies, therefore, would not take into account conditions that affected these countries specifically or disproportionately, yet, in each of those countries there is a large middle class who could pay market prices, or an approximation, for certain commodities. Due to the lack of patent protection, there was limited incentive to create those commodities. TRIPS, therefore, with its strengthened patent protection is intended to secure the market of that large and growing middle-class and thus incentivise the development of products directed at them. This does not, however, help the poorest in society access those products will be priced for that middle class and its spending power.

There are two main arguments that are currently used in support of TRIPS in regards to the pharmaceutical sector. Firstly, pharmaceutical companies might become interested in diseases that were not previously considered profitable because they would have the guarantee of securing the middle-class market. Secondly, when the patent on those new commodities ran out, as they eventually would, the poorest people in those countries would have access to diagnostics and treatments that otherwise would never have been invented.²³

In the short-term, TRIPS presents an accessibility problem as individuals are no longer able to access cheap, generic alternatives to branded medicines. In the long term, they may be able to access these drugs when all the patents have run out and in the interim they may benefit from programmes run by aid agencies to make those drugs affordable.

Edward Gresser is one of the academics who has made a particularly spirited defence of TRIPS. He argues that TRIPS have overseen an increase in research spending, an increase in patent awards, and highlights the benefits to society at large when commodity patents expire as articulated above. He also argues that the developed country share of the global pharmaceutical market is declining from 89 per cent in 1990 to a projected 69 per cent in 2016.^{24 25}

In the context of availability of medicines, Gresser’s defence of TRIPS doesn’t seem to apply. A greater number of patents awarded do not, by themselves, translate into effective drugs, vaccines or diagnostics. Likewise, greater research spending is not beneficial if it isn’t focused on the areas that really matter. Finally, a change in the balance of the global pharmaceutical market may be welcome news, but further investigation would be required.

In any case, at the time of writing, 159 countries have adopted TRIPS, and so far, there aren’t many new products targeting PRNDs coming through the pipeline. That does not mean to say they won’t eventually arrive, just that so far, they haven’t – and do not appear to be on the horizon.

The TRIPS agreement, and in fact much written so far about IP and human rights, are fundamental elements of both access and availability issues. Arguments for TRIPS (and for tighter IP rights in general) are ostensibly based on extending the benefits of the system which has successfully encouraged pharmaceutical investment in HICs to LMICS. Particular arguments in favour of TRIPS are that:

- pharmaceutical companies will target PRNDs as leading health issues in LMICs because of more stable market returns
- strong IP protection stimulates foreign direct investment
- strong IP protection will stimulate the domestic pharmaceutical industry

Addressing each of these issues in turn, the first ‘benefit’ of TRIPS is yet to materialise and evidence does not appear to support the second point either. Between 1994 and 2007, thirty-five pharmaceutical manufacturing plants in South Africa – belonging mainly to R&D multi-national corporations – were shut down.²⁶ Looking more broadly than just the pharmaceutical industry, recent evidence seems to suggest that strong IP protection can have a negative impact on growth associated with foreign investment.²⁷

On the third point, South Africa grants a remarkably high number of patents, roughly ten times as many in one year as Brazil granted in five years.²⁸ These patents may actually hinder local pharmaceutical companies rather than help them develop according to TAC:

Pharmaceutical companies that are locally manufacturing medicines produce almost exclusively generic, not patented, medicines. By granting an excessive number of patents, South Africa is actually protecting the interests of foreign MNCs at the expense of local producers who are unable to enter the market for extended periods of time – in fact, of the 2,442 pharmaceutical patents granted in South Africa in 2008, only 16 were held by local companies.²⁹

The apparent failure of TRIPS agreement to support investment in diseases that predominantly affect LMICs, or to support local economic development or the local pharmaceutical industry, serves to highlight that strong IP laws are not the solution to a lack of R&D for PRNDs. This is not, then, a criticism of pharmaceutical companies, rather it should lead to criticism of the overarching system in which pharmaceutical companies operate. In many sectors, patent driven innovation appears to work well, but it is not the case in all aspects of health.

As IP rights have been spread across the world through TRIPS and other Free Trade Agreements, these rules have prevented patients in LMICs from accessing generic versions of drugs that would otherwise have been available via India or another country with generic capacity, whilst continuing to fail to incentivise the development of commodities for PRNDs.

So, if the traditional private sector, patent model is not helping resolve availability of medicines issues, does anyone have an obligation to produce these commodities? And if so, who?

3.D Commitments, Obligations, Directives and Treaties

International Covenants, Treaties and Agreements Enshrining the Right to Health and the Requirement to Assist

Government Obligation Towards Own Citizens	Government Obligation for International Assistance
Universal Declaration of Human Rights	Declaration of Alma Ata
International Covenant on Economic, Cultural and Social Rights	UN committee on Economic, Cultural and Social Rights, General Comment No.14
Convention on Elimination of All Forms of Discrimination Against Women	Millennium Development Goals 4, 5, 6
Convention on the Rights of the Child	Convention on the Rights of the Child

Of the seven documents in the table above (the Convention on the Rights of the Child is listed twice), the UK has ratified, signed, or supported all of them. Moreover, it has committed significant resources to programmes that aim to achieve the Millennium Development Goals.

Perhaps unsurprisingly, details as to what governments have to do in order to meet these obligations are rather thin on the ground. The Convention on the Rights of the Child, for example, reads:

States Parties undertake to promote and encourage international co-operation with a view to achieving progressively the full realization of the right recognized in the present article. In this regard, particular account shall be taken of the needs of developing countries.³⁰

General Comment No. 14 articulates that States should provide assistance wherever possible:

*Depending on the availability of resources, States should facilitate access to essential health facilities, goods and services in other countries, wherever possible, and provide the necessary aid when required.*³¹

And then expands:

*For the avoidance of any doubt, the Committee wishes to emphasize that it is particularly incumbent on States parties and other actors in a position to assist, to provide “international assistance and cooperation, especially economic and technical” which enable developing countries to fulfil their core and other obligations ...*³²

These requirements seem pretty clear; States should do everything in their power to facilitate access to medicines and certainly not to create barriers to them. Whilst it may be incumbent on a State to facilitate access to medicines, however, General Comment 14 specifies that States should facilitate access to medicines that are on the WHO Essential Medicines list and the same requirements do not apply for other medicines. Further, a State may fulfil its duties to ‘facilitate access’ through a wide range of international aid mechanisms, and given that no State has been prosecuted for being inactive on facilitating access to medicines it is unclear in international law what exactly is expected of a State. Nonetheless, it is clear that an obligation exists in theory. What is less clear is whether any State has an obligation of any variety to facilitate in the creation of a health commodity.

General Comment 14 makes clear that everyone, not only States as parties to the Covenant, have an obligation to support the rights of individuals, particularly those in a position to assist. These obligations are extended to private organisations, and supported by the UN Global Compact which states: ‘Businesses should support and respect the protection of internationally proclaimed human rights’.³³

3.E Conclusion

The fundamental human rights that underpin issues relating to R&D are critical to understanding some of the key challenges and obstacles in the development of medical commodities. Obligations are built around a ‘do no harm’ principle, and there are few solid requirements to act in a certain way.

Additionally, there are significant failings with the overarching system which need to be addressed. It is all very well to make a justification for patent protection on the basis that there will be a short-term access problem for long-term provision of drugs, but we must remember that in the ‘short-term’ millions of people are dying every year from diseases, notably HIV, where the drugs already exist.

The global spread of the TRIPS agreement, and stronger IP protection, has not lead to an increase

in private research efforts for PRNDs as was hoped and may have actually decreased access to medicines.³⁴ If anything, it seems plausible that TRIPS may have strengthened the pull of conditions and diseases that primarily affect HICs because such products can be sold into more secure markets in LMICs.

Most importantly of all, when it comes to availability of medicines, it is clear that the international frameworks do not place a responsibility on any individual, organisation or State when it comes to R&D. An effective TB vaccine would save millions of lives around the world, but no one has an obligation to develop one, point-of-care diagnostics are critical for quickly and effectively treating any condition, but their importance is barely recognised in the WHO Essential Medicines list which provides the foundation of States’ obligations.

It is a classic problem related to public goods. Everyone would want to use it, but no individual actor with the capacity to develop such a vaccine is prepared to do so under the traditional, IP-driven paradigm of technological innovation.

Taking this into account, there are two options for policy-makers wishing to incentivise R&D for global health:

- to make amendments to the application of existing patent laws to pharmaceutical innovation and thus encourage commercial development, or
- to support or create a paradigm for development that does not rely on IP.



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CURRENT STRUCTURES

4.A Academic Research – Monetising IP Rights

We have so far explored R&D for PRNDs solely through looking specifically at the conventional, commercial, paradigm of technological development. In reality, there are a great number of different types of organisations involved in research, both on their own and in partnership.

One of the major sectors is academia, where, generally speaking, the product process begins with the most fundamental research. Academic research is often ‘upstream’ – early in the development process – and tends to pursue the accumulation of fundamental knowledge of molecules, organisms and structures.¹ This research is often thought of as being more theoretical and is funded through a variety of routes, most commonly for health in the UK through the Medical Research Council.

The world of academic research is changing. Traditionally, the fruits of an academics labours were open-source and available to the world.² In the complete inverse of the incentive structure for private sector enterprises, academics are encouraged to publish papers, demonstrating the knowledge that they have discovered.

Until relatively recently, university intellectual property offices did not exist, or if they did, they didn’t hold a significant amount of IP. This is changing; between 1982 and 1998, the number of patents held by universities in the United States rose from five hundred to more than 3,100.³

One manifestation of this is the successful ‘spinning off’ of research in the United States, a trend has developed for universities to claim the intellectual property discovered in their institutions and monetise them as far as possible – usually through the form of patents.⁴

The incentive for an academic institution to monetise its intellectual property is clear. Universities thrive on the quality of their research and of their facilities. Financing from central governments and students could always be augmented to improve the depth and breadth of research or install the best facilities. Correctly monetised IP can secure the income required for these improvements.

Just because such a process is good for the University, however, does not mean that it is good for the wider research agenda. Upstream patenting can lead to a problem known as ‘the tragedy of the anti-commons’ proposed by Heller and Eisenberg.⁵ This is when so many different actors have patents over certain parts of a process that no one can actually bring a product to market. Although this could occur anywhere in the development process it is particularly troublesome upstream because there are so many potential applications for fundamental knowledge that only become apparent when researched. However, if there are too many patent barriers that research might never happen because an organisation or individual who wants to do further research has to negotiate so many patents that progress seems impossible.

Secondly, the cost of doing research is increased as researchers have to license patents or use patent-protected innovations. This has a multiplying effect, with each stage of the development process costing more than the last and leading to highly expensive end products.

Thirdly, excessive IP at a fundamental level can create ‘patent thickets’. A patent thicket is when a group of patents operate together to protect a certain idea, innovation, or product. Different patents in the thicket may serve different purposes, including blocking competitors from advancing their own research and producing an alternative, but similar, treatment.⁶

On the one hand we might argue that it is a good thing if academic institutions can monetise their IP rights, it will make them less dependent on public financing. In practice, however, organisations within universities are ‘spun-off’ if they can produce a marketable product because academic institutions are rarely geared to maximise the success of an SME. Accordingly, there is little likelihood of benefit to the institution in the long-run, but in the short-term they may benefit from selling or licensing their IP.

However, it is not necessarily an either/or situation as seen in the case of the pharmaceutical company, Bristol Myers Squibb, and Yale University at the start of this century. Yale University held a license on the drug, d4T which Bristol Myers Squibb had taken to market. Yale students pushed for a license which allowed generic production for exclusive distribution in LMICs and immediately triggered a price drop of 96 per cent in South Africa at no cost to the University.⁷

Universities Allied for Essential Medicines (which grew out of the Yale University initiative above) propose that universities implement “Socially Responsible Licensing.” This would see universities mandate that any product developed from their IP was made available to the developing world at cost-price or as cheaply as otherwise possible. SRL does not imply that universities shouldn’t own IP, rather that they should leverage their IP to help:

... remove barriers to generic production of such medicines, institute tiered pricing mechanisms of mandate at cost pricing in low and middle income countries, thereby greatly improving access to new drugs from publicly funded research.⁸

There are a number of arguments for and against the proposal. Firstly, there is the moral responsibility. If an academic institution can lower the price of a product through applying conditions on its IP, and thus make such a product accessible to people who otherwise would not be able to access it, then they should do so. Secondly, much of the research carried out in academic institutions is publicly funded, accordingly, if a discovery is made and then patented, the costs to the taxpayer will be higher, either through paying for it through the NHS, or through paying for it as part of international development initiatives. Thirdly, depending on the type of licensing, patent thickets could be avoided, helping facilitate the progress of much-needed products to market.

On the other hand, there are arguments against such licenses. Firstly, most products require some degree of industry collaboration to make it to market, and SRLs may be a disincentive to such collaborations or partnerships as commercial partners will seek remuneration. However, such returns are relatively limited from LMICs anyway in the case of PRNDs, however, for NCDs and other conditions with significant HIC markets, such licenses may indeed prove a disincentive. Additionally, for diagnostics companies, which are more likely to be spun-out of universities, open-licensing would have a severely negative impact on the business model which is, on the whole, already based on low-cost, high sales.

Broadly speaking, we believe that SRL should be adopted by academic institutions in the right circumstances. However, who should implement it? One option is for the Medical Research Council (MRC) and other UK public funders to mandate inclusion of SRL for all publicly funded research. This blanket approach, however, the point of fundamental research is that it is difficult to be certain as to its final application so mandating SRLs on all publicly funded research in the PRND arena may have more negative consequences than intended, notably the potential disincentive to commercial partnerships.

An alternative approach would be for universities to apply such provisions themselves. The MRC offers a medium for academic institutions to make binding agreements with commercial partners in regards to IP and other variables. Universities could take the initiative themselves, presumably under pressure from their students.

The concern here would be that such an approach might lead to no significant changes at all and it is our opinion that publicly funded research should be as open as possible, and, should it result in the development of a new medical product, that product should be made accessible to the poorest patients as cheaply as possible.

Therefore, we feel that whilst the immediate onus falls on the university, funders should also be prepared to act. The UK government should take a lead and conduct a study into how SRL could be implemented across its publicly funded research, not only UK Research Councils, but also research funded by DFID, DH and other UK government departments. The findings from such a study would lay the foundations for the widespread use of SRLs to ensure access to new products for LMICs at cheap prices, and, set a new standard of open innovation for the rest of the world to follow.

4.B Focusing Research in the Right Places

In a world with limited financial resources – even among the great academic institutions of the highest income countries – it is clearly vital that research is as effectively targeted as possible. Sever-

al submissions to our inquiry revealed that this was, unfortunately, not currently the case and that a proportion of research carried out in academic institutions focuses on what is considered academically interesting, rather than what will lead as quickly as possible to new treatments and diagnostics for TB and other diseases.⁹

In the absence of a clear idea of what these priorities should be, a lack of focus might be acceptable, however, lists have been drawn up by the World Health Organisation for a range of conditions, of which the following represent a flavour for TB:

- Clearer insights into the nature of TB latency (for drugs, diagnostics and vaccines)
- An understanding of how to activate TB latency
- Validated animal models (for drugs and vaccines)
- Correlates of immunity
- Recognised bio-markers or surrogate outcomes¹⁰

It is not the role of this inquiry to identify a complete and comprehensive list of exactly what is required. However, that such a list could be relatively easily created is not in doubt. Again, there are questions as to who would be primarily responsible for ensuring that the research agenda pursues the ‘right’ path. Research councils are required to fund the best science, and whilst this should also be the science with the greatest applications, it is not always the case. Academic institutions, therefore, could be self-policing and direct their research along the WHO roadmap, but we believe that no researcher in this field would deliberately target research with no practical outcomes.

We are also cognisant of the fact that fundamental research (by its nature) is difficult to direct, one does not know which projects will be successful or yield advances. The MRC, therefore, is content if there is a degree of overlap between the projects that it funds.

Nonetheless, the MRC can launch specific funding calls if a particular need is identified, as the Technologies Strategy Board has done for a joint bovine and human TB rapid-diagnostic test. We believe that the MRC should carefully examine its current portfolio of PRND research, along with academic experts, and launch specific funding proposals to fill key gaps if necessary. At the same time, universities should critically assess their own research priorities and applications against WHO specifications of global requirements and act accordingly.

4.C Academic Engagement with Policymakers

Another common theme that emerged from submissions to the inquiry was that UK academic institutions are, more than ever, globally focused and globally connected. There is a great reservoir of knowledge being accumulated from all corners of the world that is not then being translated into more targeted government interventions.

In such a situation, it is easy to lay the blame at the door of the government, but it must be acknowledged that there is also a responsibility on the part of the academics concerned to make the findings of their research known to policymakers – or at least to make all reasonable attempts to do so. Furthermore, the challenge for any government department when searching for insight is that they will inevitably be criticised by those who weren't consulted and lauded by those who were.

Putting such issues aside, it seems clear to this Group that mechanisms should be enhanced for the sharing of information and ideas between government and its leading academic institutions. Finding the resources to achieve this may not be straightforward, but establishing such a mechanism is within the realms of possibility.

Operational Research

One sector of research that perhaps falls slightly beyond the remit of this inquiry, but is absolutely essential to ensuring that drugs, diagnostics, and treatments get to the patients who need them most is operational research.

Submissions to this inquiry highlighted the importance of investing in operational research and the relative facility with which the discovery of potential improvements to one drug-delivery mechanism in one country could be translated to another. Submissions also articulated that, broadly speaking, potential existed for findings to be translated from one disease area to another, and that operational research was critical to the strengthening of health systems.

DFID was recognised for the operational research that it does fund, although these levels remain relatively low.

4.D Introduction to Partnership Models

The idea that there is a relative lack of investment in R&D for global health from the private sector can hardly be considered as original. These challenges have been recognised by policymakers, and the MSF Access Campaign – perhaps the most high profile campaign to drive change in the way drugs, diagnostics and vaccines are developed – will this year celebrate its fifteenth birthday.

For nearly thirty years, but certainly over the last fifteen, the global health world has seen the steady emergence of new players, partnerships, and organisations seeking to overcome the challenges posed by the traditional paradigm of medical innovation.

The most prominent of these organisations are Product Development Partnerships (PDPs), but they have been joined by the likes of WIPO Re:Search, and a range of 'bilateral' industry partnerships.

4.E Product Development Partnerships – Introduction

Product Development Partnerships (PDPs) harness the strengths of the private, public, and academic sectors in order to efficiently drive innovation for otherwise neglected diseases. PDPs broker and leverage partnerships across these different sectors which – due either to lack of resources, incentive, scope, or capacity – have independently been unable to catalyze research and development for neglected diseases such as tuberculosis. Combining the private sector's expertise with the goals of global public health, they prioritize health-related return on investment rather than financial returns alone, aligning the needs of governments and global health with available resources.

TB ALLIANCE

With the majority of research expertise – chemical compounds and regulatory experience based in private pharmaceutical companies – it is hard to imagine how a public organisation could bring a product to market by itself. Pharmaceutical companies have been reluctant to engage substantial resources for most PRNDs, so some sort of partnership was necessary.

Product Development Partnerships (PDPs) is the overall term for the wide range of partnerships that have come into agreement. They share a common goal: to bring together the best thinking and thinkers from across the world to produce better treatments and tools for global health. Almost without fail they focus on conditions and diseases that are not compatible with market-driven development processes.

Indicative of the strength of the PDP sector is the number of different organisations which responded to our inquiry. In the TB arena there are three notable organisations: Aeras, TB Alliance, and FIND who work on TB vaccines, drugs, and diagnostics respectively. Yet we were glad to receive submissions and input from half a dozen other groups, all of which demonstrated their specific approaches to combatting their focus-diseases.

PDPs operate with a range of different models, some have their own laboratories and research space. Others act as virtual laboratories, coordinating research efforts across a range of different jurisdictions.

As articulated in the quote above, PDPs operate as intermediaries in the development space, targeting and focusing their own income to leverage other research already taking place, and, in some cases, to commission new research. Aeras, for example, have implemented a rational selection approach to vaccine candidates with a view to maximising their resources. This approach is underlined by several key principles:

- Each vaccine carried forward into efficacy studies must address a new hypothesis, rather than pursuing a vaccine approach that has already failed.

- Among those candidates that are likely to induce similar immune responses, only the best vaccine candidate must be chosen, utilizing head-to-head comparisons of candidates in animal and early human studies.
- There must be a diverse and robust pipeline of candidates utilising novel approaches that test different immunologic hypotheses.

These principles are under-pinned by the fundamental research that the organisation supports, some of which is attempting to address the broad list of ‘fundamental research targets’ outlined in the academia section.

Of course, PDPs are, and should, be judged on their achievements, and for any organisation or group of organisations working in this field, the primary yardstick is the number of products they’ve brought through.

On the whole, PDPs have been successful at bringing through new products, particularly new drugs, although not yet to the extent required to finally and conclusively combat neglected diseases. Of the 850 new therapeutic products registered in 2000–11, thirty-seven (4 per cent) were indicated for neglected diseases, comprising twenty-five products with a new indication or formulation and eight vaccines or biological products. Only four new chemical entities were approved for neglected diseases (three for malaria, one for diarrhoeal disease), accounting for 1 per cent of the 336 new chemical entities approved during the study period. Of 148,445 clinical trials registered by Dec 31 2011, only 2,016 (1.4 per cent) were for neglected diseases.

These overarching figures may seem relatively negative, only 4 per cent of new therapeutic products indicated were for neglected diseases? Yet this represents a fairly marked increase in development, and whilst pipelines are thin, the fact that pipelines even exist for some of the diseases in question is quite an achievement. Of the nearly 1,400 new medicines which were developed between 1975 and 2001, only sixteen were targeted at diseases specific to developing countries.

PDPs have also been successful at bringing new resources into the global health R&D space by providing clear and visible avenues for governments and other donors to invest in global health. As Medicines for Malaria Venture highlighted in their submission over the last two decades, there has been a five-fold increase in annual funding for malaria R&D (from 131 million dollars in 1993 to 610 million dollars in 2011).

4.F Product Development Partnerships – Strengths and Weaknesses

The major challenge for PDPs is financing. As we have previously discussed, research and development can take decades before a final product is approved, yet most of the funding that PDPs receive is short-term in the form of three to five year grants. This is challenging for drugs, but particularly difficult for vaccines. IAVI, the International AIDS Vaccine Initiative, highlighted that it took forty-seven years to bring the polio vaccine to market and the recently-developed rotavirus vaccine took thirty-three years.¹¹ IAVI itself is approaching twenty years of effort in developing an effective AIDS vaccine.

These sorts of lead-times do not encourage sustained pharmaceutical investment – only governments can provide the long-term financing necessary and even then, governments’ priorities change and aid agencies can become impatient. Consequently, PDPs are almost constantly fundraising and have to devote significant resources to maintaining visibility and bringing in additional resources. The lack of financial security may have a knock-on effect in slowing down progress towards developing new commodities.

Even as we appear to be emerging from the financial crisis, securing funding is not getting easier. 2012 saw the largest cut in PDPs’ funding so far with a reduction of 20 per cent although this does partially reflect the uneven nature of grant funding.¹² As such, the WHO 2013 Update Priority Medicines for European and the World, proposed a mechanism for research partnerships, including PDPs, need to be put in place to secure the production of new and improved technologies to reduce the burden of neglected diseases including TB.¹³

Despite these challenges, PDPs have had considerable successes, especially in successfully engaging with the private sector. As previously identified, the overarching structures that incentivise pharmaceutical development do not facilitate significant engagement from pharmaceutical companies. PDPs offer a different approach, one that doesn’t require hundreds of millions of up-front investment.

Whilst this report was being written, one PDP, the International Partnership for Microbicides, announced a global partnership with Janssen Pharmaceuticals to develop, manufacture and commercialise dapiravine-based products.¹⁴ Another excellent example of this is PATH’s partnership work with GSK to develop RTS,S, probably the world’s most advanced malaria vaccine candidate. RTS,S is currently in phase three trials across eleven sites in seven African countries and early results are promising. Simply put, without the input of both sides of the GSK/PATH partnership, it seems unlikely that RTS,S would ever have made it this far, let alone all the way to market.

These partnerships are not always with big pharmaceutical companies. To reduce the risk of vaccine wastage due to heat damage, PATH partnered with a small start-up company, Temptime, to adapt their heat exposure indicator technology for use with vaccines. After working with WHO to test the vaccine vial monitor (VVM), today, all vaccines procured by UNICEF must include VVMs to ensure that only potent vaccines are administered in routine immunisation programmes. The VVM saves the global health community millions of dollars each year by markedly reducing vaccine wastage.

Perhaps the most important success of PDPs is that they have proved that it is possible to bring tools and treatments to market without the traditional, patent-driven, approach to development. Some submissions went so far as to argue that PDPs are at the centre of a new paradigm for R&D for global health, much as pharmaceutical companies are at the centre of the existing paradigm for medical innovation.

PDPs have not, however, been a completely unqualified success. As articulated above, a greater number of products have been developed in the last ten years than in the previous decade, but there is a long way to go. Despite many PDPs having the capacity to direct fundamental research, there are still significant gaps in our scientific understanding and many academics do not feel that these gaps are being filled.

Private sector partners have highlighted the dependence of PDPs upon the private sector, for expertise, for partnerships, and even for highly-qualified staff. This weakens PDPs and leaves an already imbalanced relationship with pharmaceutical companies almost entirely dependent on the good will of those companies.

One of the strengths of the model is that there is limited competition between PDPs, so public funding is directed to one organisation working on one problem. For a pharmaceutical company this concentration would be an unacceptably high level of risk, but for a PDP it allows maximum oversight and the ability to compare different products in house and advance those that are most promising.

This, however, is also a weakness because they can become closed to external ideas. There are many different ways to go about developing anything: a drug, diagnostic or a vaccine, and the best approach might not be the first attempted, or even the second. This can be especially problematic for diagnostics, where the relationship with the private sector is the inverse of that described above. SMEs, who often develop diagnostics, can be dependent on PDPs for support in developing, trialling and ultimately bringing a product to market. If a PDP is operating down a single route, promising products might be lost.

Nonetheless, if a PDP maintains its flexibility, and adopts, for example, an approach like Aeras' which mandates that candidates must be different, then there's a greater chance of eventually becoming successful. If that PDP becomes single-minded in its approach, there is a very real possibility that investment will be wasted and progress stunted.

Furthermore, there should be some accountability arrangements so that funders and other external experts can take a critical view of the way an organisation is operating. If not, how is a funder to determine between slow progress due to the huge challenges of developing a product and slow progress because an organisation is being inefficient? Payment on results is not an option given slow R&D timescales, so superior mechanisms should be developed to allow accountability and oversight, and to facilitate alignment of research – particularly fundamental research – with other institutions and organisations to ensure that research funding and focus is not duplicated.

Perhaps the most significant issue is that whilst the variety of different models across PDPs permits flexibilities that allow them to adapt for their specific issue areas, some variations are less welcome. DNDi is particularly well-known for its strict adherence to open-access principles – all products which the organisation has a role in developing are immediately made available for generic manufacturing. This guarantees that these drugs are accessible as cheaply and quickly as possible.

Not all PDPs have these same access provisions built into everything that they do. Some would argue, quite reasonably, that implementing such access requirements would limit the number of partners who might be willing to work with them and thus slow the development of these much needed products. This would be a fair argument, but in our opinion, as PDPs are almost universally publicly or philanthropically funded – and are producing public goods – so the products they develop should be made available to everyone as rapidly and cheaply as possible.

Further, we are sceptical that a pharmaceutical company would choose not to engage or support a project such as those proposed by PDPs given that most of the costs of R&D are borne elsewhere and there do not appear to have been a lack of willing partners for DNDi. This opinion is articulated by one of the submissions to the inquiry:

“Virtually all neglected disease products from this public/philanthropic pipeline are made available to the poor at low-or-no-profit prices...¹⁵ Low pricing is possible because most pharmaceutical companies now use the ‘no-

profit-no-loss’ model when conducting neglected disease R&D. This means that they seek public or philanthropic funding to cover some or most of their R&D costs and in return agree not to charge profits in poor countries (they normally retain IP rights to OECD markets). The ‘no-profit-no-loss’ model is now routine for most large pharmaceutical companies, particularly in Europe. However, this model depends entirely on the presence of public and philanthropic partners willing to provide funding to company neglected disease programmes, in particular PDPs.”¹⁶

DSW AND POLICY CURES

4.G European and Developing Countries Clinical Trial Partnership (EDCTP)

EDCTP was established in June 2003 to overcome some of the major challenges around R&D for global health. In recognition of the fact that European public sector funding of R&D is fragmented and unlikely to support costly and complex clinical trials, the partnership focuses on pooling funding and expertise, coordinating activity focusing on developing and evaluating new and improved medical interventions for HIV, TB and malaria.¹⁷

It promotes a more integrated approach to research on neglected diseases by allowing the European Commission to fund research programmes jointly undertaken by several participating States, while also facilitating partnerships with sub-Saharan counterparts. EDCTP was designed to pool resources from the European Commission, EDCTP's Participating States and third parties, including industry and non-governmental funding agencies.

EDCTP is a ‘downstream’ intervention, it does not fund discovery and pre-clinical development and projects only become eligible once approval for in-human testing has been granted. Accordingly, it focuses its efforts on supporting phase II and III clinical trials, building sustainable clinical research capacity in Africa, and supporting the integration of the national research programmes of participating states.

Initially EDCTP was funded via a two hundred million euro contribution from the EU, and matching funds from European participating states who could either give in cash or in kind via the research that they were already carrying out through national research programmes. In May 2014, EDCTP2 was launched with a much bigger endowment (683 million euros from the EU and the same matched by participating states) but with the aim to operate for ten years.

One of the strengths of the EDCTP model is that it requires research teams from European and African countries to collaborate. As well as being especially cost-effective, this helps develop the skills and capacities of partner countries, as well as guaranteeing that any product developed is more likely to be appropriate for the environment of the majority of patients.

The numbers behind EDCTP are significant, as one would imagine for such a significant investment. As of 31 December 2013, one hundred clinical trials have been supported by EDCTP: thir-

ty-four trials on malaria, thirty trials on HIV/AIDS, twenty-seven trials on tuberculosis, and nine trials on HIV/TB co-infections. These trials are testing new and improved treatments (including preventive therapy), vaccines, diagnostics, microbicides and one trial is investigating methods to enhance retention rates in trials. TB research receives one-third of all grant-funding and 86 per cent of that has been dedicated to clinical trials.

EDCTP does, however, suffer from two particular challenges which the UK government can play a role in addressing. Firstly, some participating States have chosen to provide in-kind contributions which weakens EDCTP's ability to coordinate research across a number of states. EDCTP can only truly reach its full potential as a co-ordinating platform for R&D into neglected diseases if it has enough in-cash contributions to manage to launch integrated and joint activities. From in-cash contributions indicated by participating States in the EDCTP 2 Strategic Business plan (2013: 48), the UK will be the leading in-cash contributor. It should therefore use its leadership role to encourage other participating States to invest in EDCTP's potential through increased in-cash contribution rather than simply in-kind.

Secondly, monitoring and transparency of participating States' in-cash and in-kind contribution are not always optimum. Improved tracking and planning would enable EDCTP to better identify gaps in investment in R&D for neglected diseases, and to increase EDCTP's impact in advancing R&D in this field. The UK could be a leading example given its vast experience in fund tracking and could work towards encouraging the ten Member States which entered the EU after 2004 to join EDCTP so as to further increase the European expertise in health R&D to ultimately reduce the burden of neglected diseases.¹⁸

Despite these challenges, though, EDCTP has been a success and could become even more effective after the launch of EDCTP2. It has proved that there are alternative models for conducting expensive clinical trials and bring a product to market. In fact, a large body of experts have long argued for clinical trials to be publicly funded for all products.^{19 20}

It is beyond the remit of this inquiry to look at the mechanics of publicly funding all trials, but public funding for clinical trials is vital for bringing commodities for PRNDs to market as they represent a major proportion of the overall cost. Through EDCTP's trials programme, it would be theoretically possible (along with the other partnerships detailed in this section) for a product to be taken from the lab right through to final approval largely with public financing and almost entirely open-access.

That is not to say that a collection of PDPs, plus EDCTP and WIPO Re:Search have made pharmaceutical companies obsolete – far from it – each of these organisations depends on the positive engagement of the pharmaceutical sector in order to operate, let alone flourish. What they do allow is for the skills, knowledge and expertise of the pharmaceutical sector to be engaged in the R&D process without some of the unfortunate consequences of the traditional development model which pits innovation against access.

4.H WIPO Re:Search

The World Intellectual Property Organization (WIPO) is not the most well-known of UN institutions. Nonetheless, in the context of R&D for neglected diseases, it clearly has an important role

to play. In partnership with Bio Ventures for Global Health (BVGH) (a non-profit) and a number of pharmaceutical companies, WIPO has created WIPO Re:Search.

WIPO Re:Search is a consortium that aims to create partnerships and facilitate the sharing of IP assets. These assets can range from expertise and knowledge, to libraries and technologies, to advance the discovery and subsequent development of new tools and treatments for global health.²¹

Membership of the Consortium is voluntary, although as one would imagine for the World Intellectual Property Organization, there are certain conditions regarding IP rights that individual members must adhere to. These include:

- The IP Providers agree to grant IP Users royalty-free licenses to IP assets for research and development that addresses NTDs, malaria, or tuberculosis.
- The IP Providers agree to grant IP Users royalty-free licenses to the IP assets for the sole purpose of selling these products in the Least Developed Countries.²² Members are also encouraged to consider product access for other disadvantaged populations.
- The IP Users retain ownership of and may apply for registration of any new IP generated through Consortium-mediated research. Users are encouraged to license the new IP to third parties under terms consistent with these Guiding Principles.

These principles are guiding rather than binding, but as the IP Providers (usually drawn from the private sector) know this when they join up, in practice there would be little point in joining the Consortium if you weren't willing to abide by the Guiding Principles, particularly given the Consortium is entirely funded by its private sector, IP-providing members.

Consortium Provider Members contribute a wide variety of IP assets to the online database. The database can be searched by any member of the public and, at the time of writing, contains more than 180 different entries detailing Member contributions including compounds, screening data, marketed products, vaccine technologies, and clinical and field samples for use by User Members – usually PDPs or academic institutions.

BVGH's role is to encourage new membership and facilitate partnership working between the various Provider and User Members, and has so far fostered collaborations where Providers have shared their expertise in a wide range of product development issues. So far, BVGH has facilitated over fifty agreements between WIPO Re:Search Members. These agreements span thirteen diseases and range from the sharing of expertise during phone conversations or transfer of compounds upon completion of a Material Transfer Agreement, to more involved, longer-term collaborative research arrangements.

An illustration of how it works in practice: one could imagine a situation where a UK academic institution as a User Member was given access to a compound and found an application for that compound as a global health treatment which was different to the initial application of the compound (for example, the compound was originally intended as a diabetes drug, but had efficacy on TB). In this instance, the academic institution would retain the IP for that discovery under the third Guiding Principle above.

WIPO Re:search provides an example of the kind of partnership work that the private sector is clearly willing to engage in with the non-profit sector for the express aim of enhancing product development for neglected diseases. The Consortium is only in its third year, having been founded in October 2011, but already boasts some eighty members. If its work is to continue, and if it is to expand to enhance the partnership activities it offers, clearly additional financing will be required.

4.1 Further Industry Engagement

The engagement of the pharmaceutical industry goes above and beyond that described above. Given the concentration of expertise, resources, and scientific ability in the pharmaceutical industry sustaining and deepening existing partnerships, as well as forging new ones, is of critical importance.

It should be noted, of course, that at the time of writing, there are two prominent examples of private sector development of TB drugs. Otsuka and Janssen have respectively brought delamanid and bedaquiline through the final stages of clinical trials, with bedaquiline becoming the first US FDA-approved TB drug in fifty years.

Both drugs have required significant and sustained financial investment from the respective companies concerned, and neither is likely to recoup that investment. In fact, there are questions as to whether bedaquiline would ever have made it through the first phases of development had its synthesis not been kept a secret by the scientists concerned. A story which further highlights the challenges of getting treatments developed, it is impossible to know how many other compounds which could have a positive impact on global health have currently been shelved.

Janssen has chosen to partner with TB Alliance regarding the further development of bedaquiline. TB Alliance has been granted a global, royalty-free license to use the drug for drug-sensitive TB regimens, and is including bedaquiline in one of its trial regimens. Janssen has retained the rights to market and sell the drug for multi-drug resistant TB.²³

These two cases, unfortunately, are the exceptions that prove the rule. No other privately developed TB drugs have come through the pipeline for close to fifty years.

That does not, however, mean that the rest of the industry is inactive. GSK is one company that has taken a leading role in R&D for global health, particularly at present through its work on the RTS,S malaria vaccine with PATH, but also its investments regarding pneumococcal and rotavirus vaccines. GSK has invested hundreds of millions of dollars in dedicated factories for these compounds, reflecting the huge sunk costs that can play a factor in commercial sector engagement.

Another initiative led by GSK is the research centre at Tres Cantos which allows independent researchers to access GSK facilities, resources and expertise.

Of the twelve projects currently running at Tres Cantos, nine are working on TB. Any successful projects will have the opportunity to partner with GSK to take any products forward through the development process. In addition to the lab at Tres Cantos, GSK has recently but 177 compounds that may prove the starting point for new TB medicines into the public domain. These are made available to researchers on the condition that any findings that those researchers generate must also be open access.

Finally, GSK are partners of TB Alliance and support with the development of TB drugs through a dedicated TB Discovery Performance Unit. As they reported to us:

The TB DPU strategy is to place collaborations at the core of the delivery model, to enable access to external expertise whilst maintaining core GSK drug discovery expertise. The funding made available by various institutions (BMGF, Wellcome Trust, EU-FP7, IMI, NIH, TCOLF) has made it possible to build a network of private and public academic institutions working in TB.²⁴

Another leading organisation in the field is Eli Lilly, whose long history includes the breakthroughs that led to the polio vaccine. Eli Lilly created the Lilly MDR-TB Partnership in 2003 and embarked on protracted efforts to transfer technology and know-how from manufacturing two MDR-TB medicines, capreomycin and cycloserine, to manufacturers in high burden countries at an overall cost in the region of 140 million dollars. The organisation also founded the Lilly TB Drug Discovery Initiative, a not-for-profit public-private partnership targeting the discovery of new TB drugs.²⁵

These are just a handful of a wide range of treatment discovery partnerships in which the private sector is engaged, and, most importantly, demonstrate a commitment from the sector to support the discovery of new treatments. Nonetheless, the test for these partnerships will be their longevity, medical innovation, as previously seen, can take decades.

4.J The Bill and Melinda Gates Foundation

No discussion of research and development for global health can be considered complete without reference to the Bill and Melinda Gates Foundation (BMGF) which has played a critical role financing and supporting a huge range of research, particularly through PDPs.

BMGF are by far the biggest philanthropic donors to global health R&D, having committed close to three billion dollars over the last six years. The Wellcome Trust is second, committing close to five hundred million dollars across the same period. BMGF contributed over 80% of total philanthropic funding for R&D from 2007-2010, 78% in 2011 and 70% in 2012. Total contributions to R&D are of such a scale that BMGF's contributions in 2012 were equivalent to all the top 12 funding nations, minus the United States, combined. In many years during the same period, BMGF also contributed more to global health R&D than the aggregated commitments of private industry. The vast majority of that philanthropic funding went to Malaria (24%), HIV (23%) and TB (17%).

In addition to devoting significant sums to R&D, BMGF's leadership has been critical in encouraging other donors and in championing the PDP model. The Foundation also sponsors a number of initiatives looking at innovative ways of financing or incentivising R&D, and was a forefront of the campaign that led to the establishment of the Advanced Market Commitment (AMC) which we will explore later in the report.

Without BMGF, much of the architecture in place for non-commercial development of R&D for global health would not be in place, and the PRND pipelines of products would certainly be much weaker, if not completely inexistent. BMGF can be more agile than some public funders and thus can be more flexible in the research and the projects it supports, particularly in regards to supporting

portfolios, which some public funders are unable to do. BMGF also plays an important role finding additional resources for drugs, diagnostics or vaccines that need investment to advance to the next round of clinical trials or testing. These can represent significant, one-off costs that can fall outside of set funding cycles and therefore represent a challenge for governments or other public institutions to fund.

There are, however, potential challenges associated with so much funding coming from one donor, though it should be noted that BMGF invests heavily in organisations that advocate for greater public resources to be developed to R&D for global health and thus bring additional donors to the table. One of the major challenges is, as we have seen with PDPs, major powers in one space can be problematic should they happen to focus all their resources down one particular line, or style of research. The other side of the coin, however, is that coordination across a large research portfolio in a single organisation is easier than across smaller portfolios in a number of different organisations.

Nonetheless, much of the progress made over the last decade in R&D for global health, even if it has been slower than required, can be fully or partially attributed to the considerable efforts of BMGF.



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THE UK'S COMMITMENTS TO GLOBAL HEALTH R&D

5.A The UK's Historical Role

At the turn of the century the UK was the indisputable global leader in the impact of patents and IP rights on global health. The UK established a commission to explore issues around R&D for global health, in addition to being the principle sponsor and secretariat to the World Health Organisation's Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, a direct predecessor of the CEWG.¹

The UK government's Commission on Intellectual Property Rights report in 2002 on the integration of IP and development policy came to some clear conclusions.² It opened by saying:

Our starting point in this analysis is that healthcare considerations must be the main objective in determining what IP regime should apply to healthcare products. IP rights are not conferred to deliver profits to industry except so that these can be used to deliver better healthcare in the long-term. Such rights must therefore be closely monitored to ensure that they do actually promote healthcare objectives and, above all, are not responsible for preventing poor people in developing countries from obtaining healthcare.

The same report concluded:

So what role does IP protection play in stimulating R&D on diseases prevalent in developing countries? All the evidence we have examined suggests that it hardly plays any role at all.

In the intervening years since the Commission on Intellectual Property Rights and the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property reports were published nothing significant has changed in the fundamental architecture of R&D for global health – the findings of those commissions are as valid now as they were then. Unfortunately, however, the UK's global leadership on these issues has receded. We remain one of the principle funders of R&D for global health, but the leadership in thinking has gone, and should be reclaimed.

5.B UK Government Spending

The UK government, primarily through DFID and BIS, is the world's second largest funder of global health R&D, investing 740,976,744 pounds from 2007-2012 or an estimated 6.3 per cent of total global funding. Only the United States funds more research as shown in the table below:

Figure 1: From G-Finder 2012 Report³

Country	US\$ (millions) [^]						Percentage of total (%)					
	2007	2008	2009	2010	2011	2012	2007	2008	2009	2010	2011	2012
United States of America	1,253	1,258	1,461	1,387	1,355	1,445	70.6	67.2	69.2	69.7	69.5	72.2
United Kingdom	104.7	103.3	142.6	163.8	133.2	93.4	5.9	5.5	6.8	8.2	6.8	4.7
European Commission	121.4	129.9	118.3	92.5	105.2	93.1	6.8	6.9	5.6	5.6	5.4	4.7
Germany	12.1	3.7	34.1	37.8	31.8	54.6	0.7	0.2	1.6	1.6	1.6	2.7
France	15.7	29.3	48.2	40.5	59.9	53.3	0.9	1.6	2.3	2.3	3.1	2.7
Australia	18.2	25.1	22.8	25.0	31.3	39.5	1.0	1.3	1.1	1.1	1.6	2.0
India		32.5	24.6	31.1	33.8	34.4	0.0	1.7	1.2	1.2	1.7	1.7
Brazil	22.1	26.8	31.8	10.9	11.3	19.7	1.2	2.0	1.5	1.5	0.6	1.0
Sweden	21.6	25.6	33.1	18.9	19.4	18.2	1.2	1.4	1.6	1.6	1.0	0.9
Canada	19.1	23.1	16.9	9.5	9.3	17.1	1.1	1.2	0.8	0.8	0.5	0.9
Netherlands	34.1	27.0	28.7	18.1	24.2	15.3	1.9	1.4	1.4	1.4	1.2	0.8
Switzerland	6.6	3.9	7.0	11.9	11.9	13.4	0.4	0.2	0.3	0.3	0.6	0.7
Subtotal top 12 public funders*	1,666	1,734	1,982	1,854	1,829	1,897	93.9	92.6	93.9	93.9	93.8	94.8
Total public funding	1,775	1,873	2,112	1,990	1,949	2,001	100.0	100.0	100.0	100.0	100.0	100.0

[^] Figures are adjusted for inflation and reported in 2007 US dollars

* Subtotals for 2007 – 2011 top 12 reflect the top funders for those respective years, not the top 12 for 2012

■ Funding organisation did not participate in the survey for this year. Any contribution listed are based on data reported by funding recipients so may be incomplete

A remarkable piece of research by Head et al offers a complementary set of figures for the spending from the UK government and from other major sources in the UK.⁴ Head and his colleagues break down the differing spending priorities of different funders in the UK. The Wellcome Trust, for example, is more likely to focus on preclinical research, whereas UK government departments spend more on operational and implementational research. Between them, the MRC and the Wellcome Trust account for over half of all spending on research in the UK.

5.c DFID Spending

DFID's commitments to R&D for global health were widely praised throughout our inquiry process. DFID's flexible approach to funding – a willingness to support portfolios rather than targeting individual products – was viewed as of particular importance to the group of PDPs which it currently supports.

The International Development Act of 2001 'untied' DFID's spending – untied aid is development assistance given to countries which can be used to purchase goods and services in any country rather than specifically from the donor country. DFID's research funding is similarly untied; it cannot directly fund UK institutions, or fund any other organisation that commits tied funding.

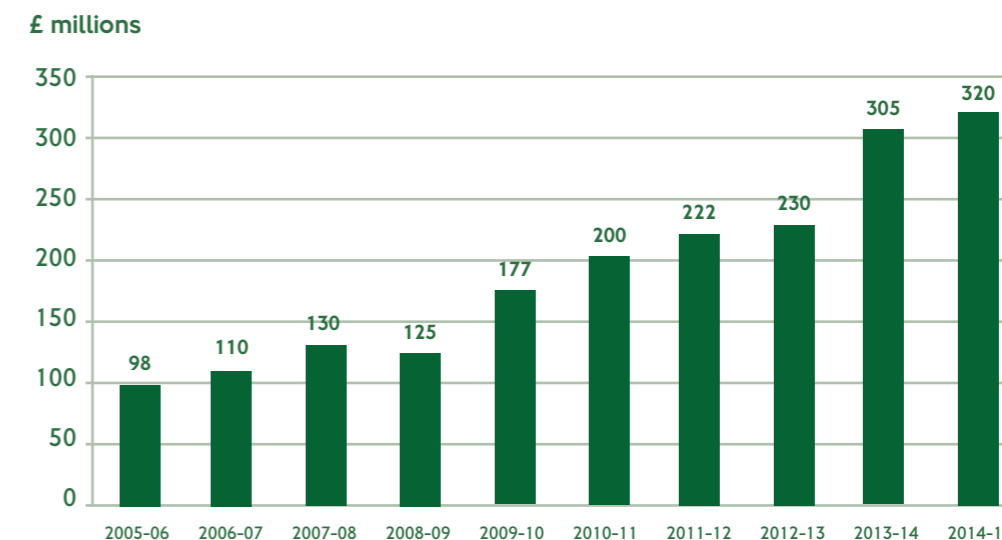
An example of this would be its funding of PDPs. DFID's commitment to Aeras of ten million pounds over five years is with the condition that Aeras only funds the best research centres for its purposes. DFID cannot say to Aeras that it must make a certain sum of that money available to UK research institutions. This sets DFID apart from many other aid agencies which mandate that research funding must then be spent in their own country.

In Autumn 2013, DFID announced a new round of funding to nine PDPs: Aeras, DNDi, FIND, Innovative Vector Control Consortium, IAVI, IPM, MMV, PATH and TB Alliance. Of these DNDi and MMV received the greatest sums, with over 40 per cent of the funding. Commitments of 138 million pounds were made to cover the period 2013–2018. This represents a small drop from the previous funding period, but was seen as an indication from DFID that it felt the PDP model was delivering.

DFID has committed to spending 3 per cent of its total budget on R&D, although this covers all issue areas and a combination of product and operational research. As DFID's budget has risen rapidly over the last five years, so too has the R&D budget.

DFID reports that close to 40 per cent of its total health R&D budget is spent on PDPs. Using these figures, and assuming annual spend on PDPs of around twenty-eight million pounds, DFID's health spend is in region of seventy million pounds per year. Based on figures from the National Audit Office (below) we can calculate that health as a whole represents just short of one third of R&D spending in 2012–13, 25 per cent for 2013–14, and will be 23.4 per cent in 2014–15.

Figure 2: Research and Evidence Devision's expenditure on research, 2008–9 and 2011–12 actuals and 2012–13 to 2014–15 planned:



NOTES

All values in cash terms

Values for 2013–14 and 2014–15 are based on provisional budgets which, like those of the Department's other business units, were being revisited in December 2012

Values include core funding provided by Research and Evidence Division to multilateral organisations such as the Consulative Group on International Agriculture Research.

Source: NAO presentation of departmental data

Although DFID's aid is untied, some research money is channelled to UK institutions through a forty-five million pound concordat with the MRC. The concordat runs over five years and is unique in the coordination it allows between DFID and the MRC's research priorities for global health. Submissions to this inquiry stated that Science and Technology Departments often do not coordinate closely with Development Departments and thus fund a significant proportion of research which may be of academic interest but does not support development needs. The DFID/MRC concordat is designed to address this very issue.

The stated objectives of the DFID/MRC concordat are as follows:

- High quality biomedical and health research (including clinical trials) with a focus on translational and implementation research in developing countries, which can include public health research; health services research and health systems research.
- High quality treatment and prevention research (including clinical trials) into HIV and AIDS, TB, malaria and other neglected tropical diseases conducted in low income countries with match funding through EDCTP.
- Capacity development activities to strengthen the scientific research base for both individuals and institutions, particularly in sub-Saharan Africa.

DFID also jointly funds programmes with the MRC and the Wellcome Trust focusing on global health trials. Costs are split evenly between the three funders, and the most recent call for proposals promised funding of up to fifteen million pounds.

5.D Medical Research Council

The vast majority of the UK government's spending on UK-based research is funded through Research Councils UK either directly, or through partnerships with government departments. Over the period from 2010–2015, the government estimated that these groups between them would disburse in the region of eighteen billion pounds for research of all types. The largest of the research councils is the Medical Research Council. The MRC awards over five hundred million pounds a year for a wide range of health research.

Table 2: Showing MRC research spend for assorted PRNDs 2007–2011⁵

Disease	2007	2008	2009	2010	2011	2012	Total
Bacterial Pneumonia & Meningitis	£1,776,770	£1,985,766	£2,034,450	£1,065,294	£706,005	£330,930	£7,899,422
Dengue	£228,096	£306,612	£199,792	£96,722	£840,728	£491,968	£2,163,918
Diarrhoeal diseases	£365,085	£928,370	£762,993	£674,710	£374,564	£1,110,318	£4,216,040
Helminths (Worms & Flukes)	£1,096,017	£1,396,827	£1,093,338	£1,158,367	£3,515,932	£2,438,203	£10,698,682
HIV / AIDS	£13,101,548	£11,635,919	£11,737,927	£11,940,880	£6,767,982	£5,275,945	£60,460,202
Kinetoplastids	£2,868,065	£3,464,747	£2,405,299	£2,799,630	£2,382,418	£1,673,145	£15,593,303
Malaria	£18,594,597	£18,985,044	£20,012,611	£22,432,699	£20,550,640	£25,425,280	£126,000,871
Salmonella infections	£976,150	£1,229,604	£868,676	£746,135	£1,730,847	£1,380,592	£6,932,005
Tuberculosis	£12,710,433	£12,832,477	£12,595,664	£15,108,715	£15,701,044	£16,029,377	£84,977,711
Total	£51,716,968	£52,765,367	£51,710,748	£56,023,153	£52,570,160	£54,155,760	£318,942,155

Broadly speaking, MRC funding has stayed consistent across the period. MRC research priorities in global health are established by the MRC Global Health Group, Strategy Board and Council. These bodies are constituted of independent scientific experts. The MRC's current strategic plan, 'Research Changes Lives', has a specific strategic aim targeting research challenges in global health.

The MRC also considers emerging opportunities and seeks advice to develop a view on any action that should be taken. This includes members of the Global Health Group (which includes experts from developing countries), the research community, and wider stakeholders.

While the MRC's strategic priorities are not usually directed towards specific diseases, it is evident from previous funding that HIV/AIDS, TB and malaria have been seen as key focus areas within R&D for global health.

The MRC's research strategy is coordinated with other major funders in the UK including DFID, the Wellcome Trust, Department of Health (DH) and the Economic and Social Research Council (ESRC) through a funders' forum for health research in developing countries which meets every six months.

The MRC is also a member of the UK Collaborative on Development Sciences (UKCDS) which is a group of fourteen UK government departments and research funders working in international development. The forum brings together stakeholders from funding, research and policy arena, to share knowledge and identify opportunities for collaboration. Members include the Wellcome Trust, DFID, BIS, DH and the Scottish Government.

UK CDS has been remarkably successful at steadily increasing the proportion of research that is jointly funded by at least two of its members, and thus steadily increasing the degree of cooperation and coordination between such funders. As we have seen, coordination between funders is critical to making the most of limited resources and UK CDS plays a critical, if often unrecognised, role in UK-based coordination.

The MRC also has a number of major partnerships in global health with other international funding agencies and stakeholders where there are areas of common or complementary interest. Specific initiatives arising from such partnerships include:

- EDCTP
- The Joint Global Health Trials Scheme with DFID and the Wellcome Trust.

In addition, the MRC has two overseas units, both of which are in Africa:

- MRC The Gambia Unit – Established in The Gambia in 1947, it is the UK's single largest investment in medical research in a developing country. The Unit's research focuses on infectious diseases (including TB) of immediate concern to The Gambia and the continent of Africa, with the aim of reducing the burden of illness and death in the country and the developing world as a whole.
- MRC/UVRI Uganda Research Unit on AIDS – Since 1989, the Unit has conducted multi-disciplinary research on HIV infection and AIDS in Uganda. The Unit is a key facilitator in building research capacity in East Africa. The Unit works in partnership with the Ugandan Government and the private sector, and with international organisations and academic institutions across Africa.

It is important to note that although the MRC receives a significant majority of its money from the Department of Business, Innovation and Skills (BIS), it is independent from BIS in accordance with the Haldane Principle.

The Haldane Principle states that:

decisions on individual research proposals are best taken by researchers themselves through peer review. This involves evaluating the quality, excellence and likely impact of science and research programmes. Prioritisation of an individual research council's spending within its allocation is not a decision for Ministers.⁶

Nonetheless, the government does have certain areas of priority as outlined:

Every Government will have some key national strategic priorities such as addressing the challenges of an ageing population, energy supply or climate change. The research base has an important role to play in addressing such priorities and the research councils, with the support of independent advice, have proposed research programmes to tackle them. It is also appropriate for Ministers to ask research councils to consider how best they can contribute to these priorities, without crowding out other areas of their missions. But it is for the research councils to decide on the specific projects and people to fund within these priorities, free from Ministerial interference.⁷

5.E Department of Health and Public Health England

Given the relatively high rates of TB in the UK, it is probably not surprising that the Department of Health also carries out a significant quantity of research, focussed on addressing Public Health England, Department of Health and international priorities.

Much of the research and development is in collaboration with leading academic groups in the UK and overseas. Research on TB is also embedded in several of the newly created health protection research units, which will combine research groups from academia and PHE.

Current areas of ongoing research in PHE include (there are others that do not apply solely to TB):⁸

- Development of an evidence-base to control TB in underserved groups
- Assessment of whole genome sequencing to more rapidly detect TB in clinical samples, and apply this approach to outbreak recognition and national surveillance

- Trial and development of improved diagnostic tests for latent TB
- Evaluation of new anti-TB drugs to shorten treatment times and target MDR strains.
- Development and evaluation of more effective vaccines for TB through several EU-funded consortia.

In addition to the work outlined above, the Department of Health has also collaborated with the Department for Environment, Food and Rural Affairs and the Technology Strategy Board to develop new rapid diagnostic tests for bovine and human TB.

The Department of Health was at the forefront of the updated UK Government health strategy through 'Health Is Global: an outcomes framework for Global Health 2011-2015.'⁹ The update, completed shortly after the current government was elected, identified ten guiding principles. Principles 8, 9 and 10 are:

- 8. Work in partnership with other governments, multilateral agencies, civil society and business in pursuit of our objectives.**
- 9. Ensure that the effects of foreign and domestic policies on global health are much more explicit and that we are transparent about where the objectives of different policies may conflict.**
- 10. Use health as an agent for good in foreign policy...**

The document goes on to identify 12 outcomes, notably 9 and 12:

- better coordination of UK and EU global health research,
- and investment and operational partnerships to address critical challenges in scaling up innovation and evidence-based interventions to achieve universal coverage, especially for the poor and in hard to reach areas.

It is clear that the UK has achieved some of these targets, notably improved coordination with the EU through the UK's commitments to EDCTP. In other areas there is more work to be done.

5.F The Technology Strategy Board

The Technology Strategy Board (TSB) has the stated aim of accelerating economic growth by stimulating and supporting business-led innovation.¹⁰ It works across a remarkably wide range of subjects and issues to help bring innovative ideas through to a final, marketable product.

TSB works specifically to create partnerships and promote collaborations between different sectors of the economy, support knowledge exchange, and reduce the risk of bringing through new products.

TSB has identified the ‘detection and identification of infectious agents’ as one of its priority areas, reflecting the role of SMEs (a key target for the TSB) in the development of diagnostics. Submissions to this inquiry identified the absolutely critical role that targeted financial support plays in taking an idea for a diagnostic from the laboratory bench to the market. As noted above, one example of TSB’s work in this area has been their recent project to support the development of a rapid diagnostic test that will identify bovine and human TB. Operating broadly like a specific funding proposal from the MRC, TSB identified a gap in the market and provided grant funding to projects that it deemed were best suited to closing that gap.

This approach could, and arguably should, be replicated for other PRNDs. However, as noted, the market is small for such diagnostics, and given the focus of TSB in accelerating economic development, it seems that supporting such research might fall outside of the TSB’s mandate. Nonetheless, the support it offers for TB diagnostic platforms, which does offer a market, should be continued and scaled-up where possible.

5.6 Anti-Microbial Resistance

One of the major priority issues for the current UK government, and the research that it carries out, is anti-microbial resistance (AMR). The Chief Medical Officer has made AMR her top priority and is driving forward a cross-government strategy to slow the development and spread of AMR. Of the three aims of the strategy, the third is most relevant to this inquiry: “stimulate the development of new antibiotics, diagnostics and novel therapies.”¹¹

Commercial development of antibiotics faces many obstacles. The market for antibiotics is fragmented and uncertain, there are no set financial rewards, and treatments are prescribed for the briefest periods possible. Each time a treatment is prescribed, it slightly increases the overall pool of antibiotic resistance to that treatment, thus the treatment operates in such a fashion as to make itself obsolete.¹²

Improving prescribing practices, diagnosis, and fundamental understanding of AMR is critical to slowing its spread, however, developing new antibiotics is equally important. The models seen in the previous section and the reforms seen in the next two sections can be adapted and applied to the challenge of developing new drugs and diagnostics for AMR. As one of the leading priorities of this government, the UK has a strong incentive to put itself at the front-line of these reform efforts.

5.F Conclusion

The UK government, and UK institutions, was repeatedly praised throughout the process of formulating this report. From policies, to levels of funding, to coordination and cooperation, the UK is at the forefront of R&D for global health. Organisations such as TSB and the Wellcome Trust with their ability to support SMEs in developing diagnostics are critical to ensuring that the product gets brought to market and remains reasonably priced. The thought leadership demonstrated at the turn of the century has receded somewhat, but the UK still has every right to be proud of the role that it plays.

Nonetheless, improvements can be made. DFID’s current balance between operations and R&D is weighted heavily towards operations. We believe that balance should be shifted slightly to enhance

R&D capacity and capitalise on DFID’s excellence in supporting research. Whilst not specific to health, we believe that the need to develop new tools (and that it is unlikely such tools will be developed commercially) is as such that DFID’s spending on health R&D should return to the levels of 2012/2013: 33% of total R&D budget.

Such an uplift, accompanied by an appropriate increase in staff capacity, could have huge implications for global health. Additional resources could be made available to support existing PRND product pipelines and the DFID/MRC Concordat could be expanded. Additionally, DFID would have capacity to drive the greater international cooperation and coordination so desperately needed to maximise the resources currently available for R&D for PRNDs.

Finally, the UK government has made AMR one of its chief priorities. Given that the challenges around the development of new drugs, diagnostics and vaccines for AMR are similar to those for PRNDs (the failure of a purely commercial model), the UK has a strong incentive to support some of the reform proposals which we will examine in the next section, both financially and in terms of critically needed global leadership.



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INCENTIVISING RESEARCH AND DEVELOPMENT – PATENT PARADIGM

6.A An Introduction to Incentives

Policymakers have been grappling for years with the challenge of encouraging investment in conditions which don't offer financial returns for commercial investors. These efforts have resulted in a myriad of reform attempts – some successful, others less successful – all aimed at addressing this common problem.

In the next section we will take a look at the fundamental components of reform proposals and discuss some of those which have been raised that work within the current patent system. First, however, it is important to remember that the challenge for policymakers is two-fold:

1. **The traditional development paradigm does not incentivise R&D for conditions which do not offer significant financial returns such as PRNDs.**
2. **We do not know the size of the incentive necessary to encourage a pharmaceutical company to invest their time and resources in developing a treatment for a certain condition.**

6.B Push and Pull

Generally speaking all of the tools available to policymakers for incentivising research fall into one of two families: push or pull. Michael Kremer argues that the distinction between push and pull programmes is that one 'is paying for research inputs, the other for outputs'.¹

Push

The majority of government interventions in technological R&D can be categorised as push mechanisms. A push mechanism is something that essentially pays an individual or an organisation to look into a specific area. By providing funding for a researcher to work on a specific issue, funders hope that knowledge will be advanced in that area.

A common example is a research grant. Grant funding is available from a variety of sources and, after a successful application, the researcher is given the money to carry out the project as applied for. Depending on the scientific need, a funder can make very broad grants available or tailor specific grants for certain issues with a narrower set of characteristics. In either case, these remain push funding because the resource is given to the researcher at the start of the process – although it may be disbursed in instalments, being dependant on certain milestones.

One of the major problems with push mechanisms is that you do not know who is going to be successful at the start of the process. Accordingly, significant resources can go to waste if you fund a wide range of researchers with a common goal as some will, inevitably, fail.

A second challenge is that push funding is usually short-term. The money is provided by an investor up-front, so when that money has been spent, you need to ask for more and political priorities, or financial capacities, may have changed by the time you come to applying a second time. As a consequence, projects can be frozen or fall by the wayside because there is not sufficient sustained support; a critical requirement for long-term R&D projects.

Nonetheless, governments tend to prefer push mechanisms. The most obvious reasons are that they're relatively easy to set up, require a relatively limited amount of oversight, and make life easier for the company accountants because you know how much grant money you have available to disburse, and you do so early in the process.

There's nothing to stop push funding being extremely proscriptive. In the context of this inquiry, such an approach may well prove beneficial if it helps focus research efforts in important areas.

Pull

The opposite of push funding is pull funding. The incentive here is situated at the end of a process, most commonly in the form of a large financial reward – the organisation or individual who puts up the reward dictate the conditions for receiving it.

Perhaps the best known example of pull funding is the Google Lunar XPRIZE. This fund aims to incentivise lunar exploration by offering thirty million dollars in incentive-based prizes. To win the money, a private organisation must land a craft on the moon, travel five hundred metres and send back to 'Mooncasts' to Earth. The XPRIZE has additional prize funds available for completing certain other

challenges. The aim is to encourage individuals and organisations who might otherwise not have participated in research to engage their own capital to win the prize. Instead of giving thirty million dollars in grant funding to one organisation to try to achieve the objective, an unlimited number of private companies could each invest twenty million dollars to achieve the objective, giving a greater chance of finding the solution because there are more approaches being attempted.

There are several advantages to pull funding. Firstly, you only have to pay if someone wins, so if no one manages to achieve the objective, there's no payment. Secondly, the market is incredibly efficient at incentivising researchers to only target successful approaches, one of the arguments commonly cited for the success of the private sector (patents are a pull mechanism).

Despite these positive aspects, governments do not invest too heavily in pull funds. The first, and most obvious, reason is that no one might win the prize, in which case, whilst you haven't lost anything, you are open to the criticism of not having achieved anything at all. Of course, this would be troublesome for a government, even though significant new knowledge may have been generated in the process of failing.

Secondly, in certain sectors, you might struggle to encourage competitors. If the UK government created a prize of five million pounds to generate a certain set of bio-markers for TB, the likelihood is only academics would take part. Aside from the odd academic institution it's likely the UK government would already be funding the research taking place, thus creating a situation where not only does it fund the failed attempts, it also then gives additional recompense to the winner.

Accordingly, pull mechanisms have to be carefully calibrated. On the one hand, if your pull is too large you run the risk of over-incentivising, thus rewarding someone far too generously for their achievement. On the other, if your pull is too small no one is going to take it up apart from experts in the field, and if things really go awry you could end up pushing and pulling at the same time – paying twice and still not achieve anything.

6.c Legislative Approaches

As the country with both the largest healthcare bill in the world and the largest public investor in R&D for health, the US has led the way on legislation designed at stimulating the private sector to invest in R&D. This has led to five major pieces of legislation, three of them passed in just four years in the 1980s.

The first was the Bayh-Dole Act of 1980, the second the Orphan Drug Act of 1983, the third the Hatch-Waxman Act of 1984, the fourth was certain provisions included in the FDA Modernization Act of 1997, and the fifth was the Priority Review Voucher included in FDA Amendments Act of 2007. Some aspects of these pieces of legislation can help in understanding some of the levers which have already been pulled by governments, and also in illuminating those which still remain to be pulled.

Bayh-Dole

Bayh-Dole was conceived with a simple intention: to transfer IP from the public sector to the private sector. Prior to 1980 the US Government owned the IP generated through the research it funded, after 1980, as remains the case in the US and the UK, the institution that carried out the research had

the right to own the IP.

After the Bayh-Dole Act was brought into law, unsurprisingly, licensing and patenting increased across US academic institutions. However, such a trend had been taking place for several years and therefore it is hard to pinpoint the exact impact of the Act. In any case, increased patenting and licensing is not by and of itself a sufficient endpoint for determining the success or otherwise of any Act. Many would argue quite the contrary; that an increase in patenting is bad for innovation, not least because of the tragedy of the anti-commons which we have previously discussed.

Finally, Bayh-Dole may have inadvertently led to the establishment of Universities Allied for Essential Medicines. It is interesting to note that whereas previously Universities and academic institutions had pushed to be allowed to increase patents and licensing, their students are now increasingly asking them to decrease those same practices.

Orphan Drug Act

An 'orphan' drug is one where the market in the US is fewer than twenty thousand people a year. The Orphan Drug Act, therefore, was designed to help incentivise treatments of these drugs and had little to do with diseases of the developing world directly, although there obviously would be cross-over with diseases like TB.

The Orphan Drug Act took a completely different approach to incentivising innovation – in fact, it took three:

- grants (push funding) for clinical trials of 'orphan' products
- a 50 per cent tax credit of clinical testing costs
- an exclusive right to market the drug for seven years from marketing approval

This last point is particularly interesting because it is essentially a patent, but one that applies from the date of marketing approval by the FDA rather than any other patent conditions.

Analysis of the Orphan Drug Act suggests that it did encourage investment in those conditions, but that 'the cost-effectiveness of those incentives remains unknown'.² Similar provisions to the Orphan Drug Act were introduced in the EU in 2000 with a ten year exclusivity period but only fourteen new drugs were approved in the first five years, and none which appears to be of relevance to this particular inquiry.

Hatch-Waxman

Hatch-Waxman came about in response to a decline in the amount of time left available after FDA approval, which by some estimates had dropped as low as 8.1 years by 1980. Hatch-Waxman included two principal measures, an extension of the patent period through a relatively complex calculation, although it couldn't exceed fourteen years after FDA approval. To give generic manufacturers a boost, the Act also permitted generic manufacturers to prove bio-equivalence to the brand name equivalent (and thus avoid the cost of clinical trials) and new rights to challenge patents.

The long-term consequences of the Act are hard to define because the FDA subsequently greatly improved its response times, thus restoring patent lengths. Kesselheim argues:

no evidence has linked market exclusivity extensions arising from patent term restoration to enhanced innovation ... it has been said that patent expiration is a greater driver of innovation and development than are extended monopolies.³

Paediatric Exclusivity

Children are a neglected population in nearly every class of drug development. They represent a smaller market and have differing responses to adults when it comes to drugs. As a consequence, relatively few treatments are trialled for children. As a consequence, the FDA offered a six-month market exclusivity extension to any company that conducted paediatric trials. The idea being that the greater exclusivity would offset the cost of the trials.

The Paediatric Exclusivity did result in a greater number of trials for children being carried out. However, as with most clinical trials there were questions about the utility of the information generated and some drugs were trialled in children that had no conceivable paediatric use but did give the producer another six months of exclusivity.

Priority Review Voucher

The FDA Amendments Act in 2007 included the possibility of granting a 'priority review voucher' (PRV) which any company who developed a new treatment for a neglected disease could use for any other treatment. The idea was that by achieving expedited review from the FDA (usually a year) for a different product, the company would be able to add another year onto its patent term, thus, potentially, generating significantly greater income. In return for producing an drug to treat dengue, the inventor gets an extra year of monopoly prices for a drug that treats Alzheimers.

Thus far, only one priority review voucher has actually been used. Novartis were awarded the voucher for the development of an anti-malarial (which was actually already in development when the FDA Amendments Act was created) and attempted to use the PRV for an arthritis treatment. That FDA approval was later denied, thus wasting the PRV altogether.

The principle that one drugs proceeds should pay for the development of another is controversial for a number of reasons.⁴ In terms of providing a sufficient incentive, however, the key issue is that it's very difficult to judge how big that incentive will be. Gilead has just posted record turnover figures for one drug from its first three months with sales of 2.3 billion dollars. If Gilead had been granted a PRV in advance of bringing this drug to market, it could have generated as much as eight billion dollars of additional income. That's a significant recompense for developing a drug. On the other hand, if the PRV was unsuccessful then, as was the case for Novartis, there would be no additional incentive.

Another criticism of the PRV scheme is that it doesn't address issues relating to access. There is no requirement that the PRND treatment will be affordably priced. This could be a condition for receiving a PRV, but it isn't at present.

Finally, PRV schemes are speculative. Why invest in developing a treatment with no certainty of how much it will cost to develop? Without knowing the cost of development, means that investors

also have no certainty of the scale of recompense due to it being dependent on another treatment with uncertain costs and rewards. A PRV might work to encourage companies to push through treatments already at late stages of development, but it does little to resolve the problems of R&D not happening in the first place.

Legislative Approaches – Conclusion

To date, legislation has been broadly unsuccessful at stimulating investment in neglected disease. It is very difficult to legislate around something which doesn't exist. In the case of neglected diseases, there is no market, but legislation generally involves a transaction, i.e we'll give you more of this, if you do that. This results in two problems for neglected disease:

1. It is impossible to work out an appropriate incentive, there are far too many uncertainties in the costs and returns on both sides of the transaction.
2. If investment does go ahead, the government, and therefore the taxpayer, ends up paying on multiple occasions because it's on both sides of the equation.

This second problem can work out well for the government with PRVs. If in the Novartis case the company had decided to invest in its anti-malarial drug because of the incentive given by the PRV, private money would have gone into developing the development (in theory) and as the application with the PRV failed, there would have been no extra cost. However, all of this is all undone by problem one, which would most likely keep a company well away from engaging in the first place.

6.D Non-Legislative Approaches

Advance Market Commitments

The concepts behind Advance Market Commitments (AMC) were laid out by Michael Kremer in a series of papers and developed further in partnership with an expert committee funded by the Gates Foundation.⁵ As defined in a paper by the GAVI Alliance (GAVI) and the World Bank: 'An AMC for vaccines is a financial commitment [by donors] to subsidize the future purchase of a vaccine not yet available, if an appropriate vaccine is developed and if it is demanded by developing countries.'⁶

The agreement was supposedly legally binding, and was designed to incentivise private sector development of a public good. Governments promised to purchase a certain quantity of the vaccine at a set price, as and when all conditions were met, and after a pre-agreed number of vaccines had been purchased, the originator companies would have to provide the vaccines at a pre-agreed price.⁷

Vaccines were particularly well suited for AMCs because market failure is experienced even in wealthy countries. The incentive for developing a vaccine according to Donald Light of Health Action International, 'saves millions of people from suffering, disability and medical costs; but they are invisible so they cannot be captured in the price.'

The AMC was intended to create a big enough market to incentivise private sector interest in

LMIC markets. This model puts all of the cost onto the developers who have to design a treatment that meets a specification (no easy task) whilst the donor only has to pay for results. As previously discussed, it is extremely challenging to estimate the correct size of an incentive, so the risks are high for any company seeking to develop a treatment from scratch to benefit from an AMC.

Unfortunately, when it was put into practice some of the principle features disappeared. Backed by a number of donors, including the UK, the GAVI offered 1.5 billion dollars as an incentive for the development of a pneumococcal vaccine. Fairly quickly, however, the AMC switched from its intended target of incentivising the development of a product that had not yet been invented, to purchasing two vaccines that were already in development; one produced by Wyeth and one by GSK. As a mechanism to incentivise new development to meet a specific need, then, the AMC had already failed. However, it is possible that the two vaccines would never have made it through to the final stages of development without the AMC on offer.

Because the two vaccines purchased were already substantially advanced, the AMC didn't have to match the costs of early stage development meaning it was grossly over-priced. At one point, MSF estimated that the total sum put forward for the AMC would result in about one billion dollars in profits for Wyeth and GSK – of which at least six hundred million dollars constituted excess profits over and above what the companies would have usually generated.

The AMC is not universally criticised. Some submissions to this inquiry praised the role of the UK in the AMC, and quite rightly highlighted that millions of lives have been saved and other sources estimated that the AMC will help save seven million lives by 2030.⁸

The AMC may not have worked perfectly, or have achieved everything that it could have done, but it has saved many lives and proved that, although imperfectly, donors can create markets. The challenge is to prove that an AMC, or similar mechanism, can encourage R&D from scratch, rather than just bringing through products that were already in advanced stages of development.⁹

Tax Credits

The UK currently offers one of the most generous R&D tax credit systems in the world and a broadly supporting tax framework. Anyone doubting the appeal of that framework need merely look at some of the arguments cited for Pfizer's attempted takeover of AstraZeneca.

Under current UK law, 175 per cent of qualifying expenditure on R&D activities is deducted for small and medium size enterprises when calculating profit for tax purposes, and 130 per cent for large companies. This is compared to just 13.5 per cent in Belgium. The criteria for qualifying for tax credits is relatively loose, companies are simply required to be attempting to 'advance science and technology' according to the law.

As a consequence, the cost of the scheme to the UK government has spiralled from just eighty-nine million pounds in 2000-1 to 1.1 billion pounds in 2010-11 with the majority going to large companies. But in spite of all this extra resource, the number of innovative medicines coming to the market has been falling despite tax credits effectively having already reduced the actual cost of developing a drug to remarkably low levels.¹⁰

This is not to say that tax credits cannot work, but certainly there are problems to be overcome. First

of all, tax credits largely constitute a transfer of cash from the government back to the company, and amount to a public subsidy of private R&D. That same money could, perhaps, be spent more effectively to encourage the kind of R&D that is required.

Ultimately, tax credits at their current levels have not been successful in stimulating greater pharmaceutical engagement in PRND markets, and in all likelihood a credit system would have to reduce the cost of investing in R&D to practically zero in order to encourage investment in TB or other neglected diseases, which might be unsustainable.

An alternative might be to target tax credits to support the kind of partnership working models laid out in previous sections. This would reward companies who engage with PDPs rather than providing a blanket subsidy for any form of development. A few small tweaks of tax credits to reward membership of WIPO Re:Search, work with PDPs, donations of medicines, and the sharing of resources and IP could present a significant incentive to pharmaceutical companies to increase their (in some cases) already significant investments in PRNDs.

There could be an additional benefit in encouraging transparency of R&D costs (essential to developing appropriate incentive mechanisms). Taking a company like Janssen as an example, if significant or enhanced tax credits were available on the costs incurred developing Bedaquiline as a PRND product, companies would have an incentive to present those costs. They would also, however, have an incentive to exaggerate such costs, so appropriate safeguards would need to be put in place to ensure that the costs presented for PRND R&D were accurate.

Tiered Pricing

Tiered pricing is the practice of offering different prices for drugs to countries with differing income levels. Generally, these prices are determined by the country income classifications as defined by the World Bank: high income countries, middle-income countries, and low-income countries.

Tiered or differential pricing has been proposed as a solution to problems relating to access to medicines.¹¹ By charging different prices to countries with different abilities to pay you ensure that a greater proportion of people are able to afford the medicine.

This approach is not without some problems. Firstly, from the side of the producer there is the potential of third parties buying the treatments in low-income countries and selling them in high-income countries, thus undermining the market and pocketing the difference. This 'parallel trade' has been cited as a serious obstacle to effective differential pricing and proponents of these systems have also proposed stronger measures to prevent parallel trading from occurring.¹²

Secondly, the prices that companies will set will be miniaturised versions of those found in high-income countries today – the price will be set at the level that will maximise profit. Given that the majority of the world's poorest people live in middle-income countries, such a pricing strategy would still create huge problems in access to medicines. It is for this reason that MSF defines tiered pricing as a commercial strategy rather than an access strategy.

Thirdly, even if the price for LMICs is 'at cost', the price at which a western pharmaceutical company can manufacture drugs can be quite different to those offered by a generic manufacturer. Accordingly, tiered pricing does not go far enough in reducing costs to LMICs.

Most importantly for this inquiry, even proponents of tiered pricing accept that it does not encourage or incentivise the development of drugs or other treatments for PRNDs. It is in the developing world that drug development costs are recouped – and the price paid can be hundreds if not thousands of times the price of those in LMICs. Without a market in HICs, there is little to no chance of private sector investment producing a new treatment for a PRND.¹³

Tiered pricing is designed to increase access to medicines, but it does little to incentivise the development of new medicines and therefore is not a solution to availability of treatments.

Medicines Patent Pool

Another reform proposal that is primarily focused on addressing access issues is the Medicines Patent Pool (MPP) which is operated by UNITAID. Like some of the other initiatives described in this section, it does not encourage or incentivise the development of new treatments. The MPP is successful at overcoming some access problems, and therefore represents a partial solution to some problems of availability, notably paediatric and fixed dose combinations for HIV drugs.

The MPP operates by companies voluntarily choosing to license their patents to the Pool. Generic manufacturers can then apply for sub-licenses to produce drugs cheaply under certain circumstances (i.e. for the least developed countries) and to create new formulations. The original patent holder receives royalties for their licenses, thus securing some return on their intellectual property.

6.E Making New Finances Available

A number of other solutions have been proposed that look specifically at the challenges behind financing R&D for global health. A series of roundtables by the Milken Institute in partnership with the Gates Foundation producing a report summing up five possible solutions that could be more closely explored, they were:¹⁴

1. More efficient donor mechanisms such as prize funds, AMCs and the International Finance Facility for Immunization (IFFIm).

The IFFIm is a mechanism created by GAVI to help leverage greater funding for GAVI projects. The mechanism is managed by the World Bank and pools donor funding to offer a bond. The four rounds of highly rate bonds have raised over 3.6 billion dollars since 2006. Unfortunately, in terms of long-term implementation, an IFFIm type model requires significant, up-front donations from governments and significant oversight and accountability.

2. Blended Capital Mechanisms. This included a PDP financing facility and a pay-for-performance model similar to Social Impact Bonds.

A PDP financing facility borrows up-front, against government backing, to finance R&D efforts and then investors are repaid through the returns generated by various treatments. This is predicated on the basis that meaningful returns can be generated

from whatever products the PDPs generate. This particular proposal seems to create access problems rather than resolving them. Social Impact Bonds, meanwhile, have been trialled successfully, but not for pharmaceutical products.

3. Capital Based Market Models, including the Global Health Investment Fund, Social Impact Investing and Debt Models.

The Global Health Investment Fund is a scheme co-sponsored by the Gates Foundation and JP Morgan. GHIF is designed to encourage investment in a ‘package’ of promising pipeline products, with returns paid for when the products reach market and generate returns in HICs. LMICs, meanwhile, get access to products that wouldn’t otherwise have been developed and (presumably) at cost price.

4. New Private Sector Models, including Fund-of-Fee models and Exchange-traded funds and GDP linked funds.

These models rely on a range of different activities in the financial markets, from a certain percentage of transaction fees being devoted to PDPs or other institutions, to GDP-based securities that pay out as country’s develop with the help of the new health technologies developed with the original investments.

5. New Partnerships, including variations on PDP models.

A number of alternative ways for generating income through the PDP model were proposed, including PDPs selling-on, or contracting out, the infrastructure generated to run clinical trials in developing countries.

Some of the initiatives proposed by the Financial Innovations Lab clearly could be successful in certain circumstances. The Global Health Investment Fund is perhaps the best known, and had ninety-four million dollars in commitments in September 2013.

Nonetheless, whether such initiatives will solve availability problems for truly neglected diseases is uncertain. A number of them, and particularly the GHIF, rely on making profits on products that have a market in HICs and LMICs. Whilst these may be present for HIV, TB and (through the tourism market) malaria and dengue, they will not prove a solution for the most neglected of PRNDs.

That doesn’t mean that such proposals should be ignored, simply that they represent a partial solution, if any such mechanisms can be found to be successful. With the GHIF very close to its capacity, the first of these new financing mechanisms could soon be put to the test.

6.F Conclusion

Few of the reforms already put into practice have been truly successful at encouraging R&D in PRND. Had they been, this report probably would never have been written. The AMC is perhaps the stand-out example of an initiative that could incentivise innovation, but the failure of its initial execution probably means that companies and donors are unlikely to engage with similar models in the future. Criticism of the AMC highlights one of the major challenges with trying to artificially create a market,

primarily, that determining an appropriate size for that market is extremely challenging.

Reforms focused at engaging the private sector are particularly important because the partnership, and broader engagement, of the private sector is critical to successfully developing new products. Legislative approaches have experienced numerous problems and have long-reaching consequences which can be unforeseen, therefore, we would not propose legislative solutions to incentivising global health R&D.

At the end of Section 3 we identified two challenges for policymakers:

- to make amendments to the application of existing patent laws to pharmaceutical innovation and thus encourage commercial development, or
- to support or create a paradigm for development that does not rely on IP.

In this context, we conclude that it is practically impossible to effectively and efficiently incentivise global health R&D through commercial development model, either through legislative models, or otherwise. We must, therefore, turn to measures that support or create a paradigm for development that does not rely on the rewards offered by a combination of IP and large financial markets.

In Section 4 we have seen that such a paradigm may well exist in the form of PDPs and other partnership models, so how can we augment that?

Of the proposals examined above there are two that stand out. Firstly, tax credits. The UK has a generous tax credit system which could be tweaked to reward exactly the kind of partnership and charitable investments that UK-based companies like GSK already make. Tax credits alone are unlikely to incentivise completely independent commercial investments from big pharma (though they could well support SMEs working on diagnostics) but could be used to encourage companies to invest more in partnership working.

Secondly, we are cautiously optimistic about some of the models proposed for securing additional finances, although we are concerned that many of them rely on securing some sort of financial return, which, though less than the returns required to engage big pharma, may still create undesirable barriers to access in LMICs.

In the next section we will examine some additional proposals to global health R&D that are based on parallel mechanisms for incentivising R&D that don't rely on the promise of achieving monopoly control of any particular market.



INCENTIVISING RESEARCH AND DEVELOPMENT – PARALLEL PROPOSALS

7.A Introduction to Delinking

Most of the reform proposals set out thus far are designed to enhance the commercial model for R&D (legislative approaches, tiered pricing) or raise extra finances for PDP development (financing solutions). The AMC and tax credits perhaps sit outside of either of these categories, but the AMC was still designed at using traditional market pull mechanisms to incentivise commercial sector development.

Commercial investors target their resources where returns can be generated. This is as true in bond markets as it is in pharmaceutical markets. In practice, this means that where there is no market for a product, there is no product for the market.

The solution to this problem is known as ‘delinking’. Delinking is the introduction of an intermediary between the development of a treatment and the sale of the treatment. It is often described as a way of separating the price of the final product from the cost of the development. This is based on the premise that treatments are expensive because companies need to recoup significant R&D costs, but we know that this is not always the case. A preferable way, therefore, of describing delinking is to look at the process in reverse. A successful delinking model would be one that separates the incentive to innovate from the scale of financial market for a product.

If it were devised and executed correctly a delinking strategy would address the lack of availability of treatments for neglected diseases because decisions on what products and diseases to research wouldn't be based on the ability of the patient to pay. Furthermore, as research wouldn't be recompensed by the need to generate financial return, there would be no need for products to have significant mark-ups.

Delinking therefore is designed to achieve two things:

- 1. To address a lack of availability of key treatments by incentivising research into areas which offer no financial markets.**
- 2. To address a lack of access by ensuring that treatments are marketed at low (or cost) prices.**

7.B The Consultative Expert Working Group

The Consultative Expert Working Group (CEWG) is the latest in a long line of WHO initiatives designed to achieve fundamental reforms in the financing of R&D global health. The group published a report which provides a clear a wealth of information on the various reform proposals and their background.

The CEWG examined a number of proposals and then took forward a small group of demonstration projects that were designed to prove different models were possible. At the most recent meeting, four were taken forwards for further examination, these are: ¹

- The Visceral Leishmaniasis (VL) Global R&D & Access Initiative – Drugs for Neglected Diseases initiative (DNDi), submitted via AFRO and EMRO.
- Exploiting the Pathogen Box: an international open source collaboration to accelerate drug development in addressing diseases of poverty – Medicines for Malaria Venture (MMV), submitted via EURO.
- Development of Class D Cpg Odn (D35) as an Adjunct to Chemotherapy for Cutaneous Leishmaniasis and Post Kala-Azar Dermal Leishmaniasis (Pkdl) – United States Food and Drug Administration (US FDA), et al., submitted via AMRO.
- Development for Easy to Use and Affordable Biomarkers as Diagnostics for Types II and III Diseases – African Network for Drugs and Diagnostics Innovation (ANDI), et al., submitted via AFRO.

These are mostly proposed by PDPs and on the whole involve an open-access approach to development (the final products will be made available to generic manufacturers or at cost price). The exception is the US FDA project which states in its summary that it would achieve delinking because it doesn't want its money back.

Whilst we hope these projects are successful, rather than representing significant reforms or innovative approaches, they are fine examples of a sector that already exists: the PDPs. As a result, some have been disappointed by the CEWG projects, not because the projects in themselves are in any way flawed, but because they do not represent the big, innovative, leap forward that many were hoping would be proposed by the CEWG.

A secondary strand of the CEWG process was the proposal 'that formal intergovernmental negotiations should begin for a binding global instrument for R&D and innovation for health'. The full details of exactly what this might entail can be found within the CEWG report.² However, shortly after the publishing of the CEWG report hopes for a Convention or Treaty quickly began to fade. Concerns were raised over the 'binding' nature of the agreement and the requirement that countries contribute a fixed amount of money to a centralised fund for R&D.³ It very quickly became apparent that there was no desire for such an international agreement, particularly on the part of the EU and US, and discussions regarding the Convention were delayed until 2016.

At the time of writing it seems unlikely that discussions will restart in earnest in 2016, despite widespread realisation that there is insufficient innovation for everything from antibiotics to AIDS. There is insufficient collaboration or coordination, let alone funding, to plug the gaps in global R&D and this is unlikely to change without a global R&D convention. There is, evidently, huge demand from LMICs and potentially enormous benefits, in 2012, IAVI estimated that an AIDS vaccine could save up to ninety-five billion dollars in ten years through averted costs of ARV provision alone.⁴

However, HICs, particularly those who host pharmaceutical companies are unwilling to commit to an R&D convention. In our opinion, this is short sighted but we believe the UK is ahead of the curve, through its global leadership on AMR. Structures created by an R&D convention focusing on PRNDs and AMR would not be in competition with pharmaceutical companies but could actually benefit them. HICs would also benefit through increased flows of resources to their top-class academic institutions.

Further, although there have been challenges with the demonstration projects, there are other reform proposals that offer promising alternatives for development of new products and could be considered for inclusion in a Convention.

Finally, at the most recent World Health Assembly, there was agreement on the creation of a pooled fund for global health R&D, one of the central components of the CEWG recommendations. At this stage it is unclear who would donate funds to the pool, and who would receive funds from the pool. There also does not appear to be widespread support from donor countries in regards to contributing to such a pool. Nonetheless, if a pool could be made operational and bring new money for R&D for global health, it would be another small step forwards.

Coordinating and Monitoring

In a resource limited setting it is critically important that every penny or cent is spent as effectively as possible. In an ideal world, no aid agencies, funders, or donors would fund the same research as any other. This way, resources are distributed as effectively as possible and progress can be made as quickly as possible.

The CEWG proposed a WHO Global Observatory that would provide much-needed coordination across issues relating to global health. The Observatory would collect and analyse data in the following areas:

- Financial flows to R&D.
- The R&D pipeline: Monitoring the current composition of R&D and the progress of R&D as well as identifying gaps and unnecessary duplication.
- Learning lessons: A capacity for analytical and advisory work on key issues in R&D responding to the needs of funders and researchers and monitoring and evaluation.

The CEWG also proposed an advisory mechanism, the precise details of which would need to be agreed by member states but would include:

- A network of research institutions and funders that may include specialized sections according to the subject of research (e.g. type of disease).
- An advisory committee; subcommittees could be established to tackle specific topics and facilitate regional inputs.

The first of these bullets is the key issue. The R&D Observatory would provide information, and advisory committee might suggest how this information should be actioned, but the network of research institutions and funders is critical because this is the point of real coordination and action.

Coordinating global R&D seems like an enormous, and impossible, task. However, in regards to PRNDs it is important to note that, as Policy Cures reported, from '2010–2011, just 12 funders (including aggregated private pharmaceutical investments) accounted for almost 90 per cent of all investments in R&D targeting technologies addressing the health needs of LMICs.'⁵

The first challenge, then, is to get representatives from these twelve funders around a table and start to explore a mechanism for coordinating work between them. One possible model could be the Global Alliance for Chronic Diseases (see box), which has proved that it is possible to have genuine international cooperation on shared priorities between major public funders. The GACD has so far focused on predominantly operational research, but there is no reason why similar principles couldn't apply to fundamental research.

Moving from operational research to fundamental research brings other organisations in this space into play, particularly PDPs and the pharmaceutical industry, but also research institutions, academics

and some CSOs. It is apparent that a mechanism would need to be established to coordinate these stakeholders, but also that participants in a mechanism must be self-selecting (on the basis of willingness to engage and act). We propose a meeting of heads of global health research from the leading public funding organisations in each of the 12 biggest donors to global health R&D, plus key additional stakeholders, with the intention of establishing a GACD or equivalent for PRNDs.

Global Alliance for Chronic Diseases

The Global Alliance for Chronic Diseases (GACD) is an international coordinating mechanism that pulls together the world's leading public funders of research into chronic conditions such as diabetes and hypertension.

It was created out of recognition that there were shared priorities across these funders which include:

- Australia's National Health and Medical Research Council
- Canadian Institutes of Health Research
- The Chinese Academy of Medical Sciences
- The U.K.'s Medical Research Council
- The U.S.'s National Institutes of Health*, specifically its National Heart, Lung, and Blood Institute (NHLBI), the Fogarty International Center (FIC), the National Cancer Institute, and the National Institute of Mental Health
- The Indian Council of Medical Research
- The Medical Research Council of South Africa
- The European Commission
- Mexican National Institute of Medical Sciences and Nutrition Salvador Zubiran

Members launch coordinated calls for proposals but fund work separately to seek out the best research in the world. Findings are open access and shared across the network. Current projects are broadly focused on operational research and innovative ways of maximising existing tools.

The GACD is hosted by University College London which was selected after an open application process, a small secretariat (currently of four staff) coordinate the activities of the coalition.

GACD has been described as a 'coalition of the working', and although a young organisation, shows immense promise as a model for coordination and collaboration between public funders. A Global Alliance for PRNDs, with a similar focus on operational research, would augment existing structures, increasing global coordination and collaboration and demonstrating that a genuine international partnership can be forged to tackle PRNDs. However, further collaboration and coordination would clearly be required to tackle issues at the fundamental and product research stages.

7.c The Health Impact Fund

The Health Impact Fund (HIF) proposed by Aidan Hollis and Thomas Pogge with the support and input of a number of other experts, is a global fund to incentivise pharmaceutical research. The key innovation proposed by the HIF is an improvement on the AMC model which attempted to artificially create a financial market for a public good. The HIF achieves this by offering a financial reward to any product that has a beneficial impact on the health of the population. If realised, it would shift the financial pull from the biggest financial market, to the greatest human need.

Governments, or other investors, would create a reward pool of around six billion dollars (though the figure could always be greater). Companies would then register their products with the HIF, and the total funding available would be divided between the companies depending on the positive health impact generated by their products.

A central department would measure the benefit of each product in Quality Adjusted Life Years (QALYs). If a treatment generated 8 per cent of the QALYs saved by all the products during that year, that company would receive 8 per cent of all the money available in the Fund for that year. Similar calculations would be made year on year.

Companies would be able to register products for a period of up to ten years and in registering would forgo financial rewards generated by patents. Companies would put the right to manufacture their drugs or vaccines out to tender. The cheapest reliable bid, that is the cheapest bidder who could give a guarantee of the quality of the final product, would manufacture the product which would then be sold at price around the world.

The HIF proposal has as many advocates as critics – and practically every aspect of its design has been debated and disputed. We do not have the time here to cover all of these arguments in full, but will address the primary ones.

One potentially interesting benefit of the HIF proposal is that companies would have a strong incentive to ensure that their treatment was as widely accessible as possible. Their financial return would be based on the overall quantity of QALYs generated by that specific product, so the more people who could access their product, the better. Pogge and Hollis argue that this would help overcome some of the 'last mile problems' associated with healthcare and give commercial companies an incentive to support procurement processes and health systems in developing countries.

Additionally, drugs that are only available in high-income countries would fall in price were they registered with the HIF and thus become available all over the world at cost. In their submission, Incentives for Global Health (the organisation behind the HIF) noted the below example:

Clopidogrel (trade name Plavix). The drug is an antiplatelet agent used to inhibit formation of blood clots in patients with vascular diseases (essentially, it is used to prevent heart attacks and strokes). The sales for Clopidogrel are currently concentrated in the world's wealthiest nations, but the need is present in all nations, not just those with affluent populations. Though Clopidogrel would be sold at a lower price if registered with the HIF, the associated drastic increase in sales may actually increase the drug's profitability.

Above all else, however, this increased access would give rise to tremendous health benefits, and these benefits would be realized globally in nations and populations of various socioeconomic statuses.⁷

Another major advantage of the HIF is that drugs would be available at cost price all over the world. High-income countries could see major benefits immediately in the form of significantly reduced drug costs, so Pogge and Hollis argue that the HIF would not need much new money, but could be funded by governments paying for their drugs in a different way.

There is, however, some disagreement over the definition of ‘cost price.’ Generic competition is generally considered the most effective way of getting to the cheapest price as quickly as possible, but the HIF proposal currently does not allow for generic competition, merely a competitive tender and then a single manufacturer. Pogge and Hollis argue that generic competition does not always secure the cheapest prices. Nonetheless, if the HIF were to introduce immediate generic competition, which should not undermine the effectiveness of the incentives, it may go some way to winning over the critics.

The HIF is designed to lie parallel to the existing commercial infrastructure for pharmaceutical innovation – not to be a replacement for that system. Innovators would always have the choice as to whether any of their products were licensed through the HIF, or continued to be marketed through the traditional system. Nonetheless, the HIF is not restricted to PRNDs but is an option available for any drug or vaccine, and has recently been proposed as a potential solution to the global dearth of development of antibiotics.

The HIF idea is elegant and simple in explanation, but complex to implement. This was the criticism levelled at it by the CEWG and the major reason why it was not taken forward as a demonstration project. The success of the HIF on a theoretical level depends on the ability to accurately measure the global QALY impact of a certain product. This is an enormous task, and one that Pogge and Hollis quite rightly identify as requiring significant resources; an estimated six hundred million dollars a year. It would be challenging for governments or donors to justify such expenditure – even were it to be recouped by savings through the procurement of drugs for their national health services.

Measuring QALYs has proved difficult enough in the UK with our world class resources, measuring QALYs saved for an individual component of a treatment which might include six or seven different compounds could well prove impossible.

One of the major challenges to advancing the HIF proposal is proving that this QALY measurement can work. The proposers of the HIF have received funding to trial the all-important measurement system of the HIF with Janssen, the company who produces bedaquiline, one of the two new TB drugs coming through to market. The trial will take place in India, and examine whether QALYs can be measured for a single drug in a multi-drug treatment, with all the added complications of making real-life assessments of health benefit in real-life settings rather than the perfect models that are generally used for clinical trials.

Incentives for Global Health noted with considerable understatement: ‘This pilot will allow the HIF scheme to be studied from every angle, challenged, and refined.’ And they are absolutely correct. The success of the HIF model rests on being able to provide evidence that the measurement process can actually work.

This, however, only represents the first step towards proving the model can work at a suitable price. Once success has been proved in one setting, the next major obstacle is to prove that measurement can work across a number of jurisdictions. As the final HIF is intended to cover the entire world, being able to measure QALYs saved in a range of different conditions, circumstances and with varying co-morbidities will be important.

The final step in proving that the measurement process is effective is proving it can be done quickly at scale. Multi-drug resistant TB, as an example, takes twenty-four months to treat; if a company is to receive a pay-out in the first year of their treatment being registered with HIF, it is hard to see how an accurate QALY calculation could be presented in that timeframe.

Another challenge is that, as we have seen, it is extremely difficult to accurately judge the size of the incentive required to encourage private sector investment in neglected diseases. Although the HIF is an improvement on the AMC, it faces the same challenges with providing the right scale of incentive.

With the HIF proposal, this incentive is determined by two things: the number of products already registered to the Fund and the size of the Fund itself. Both are susceptible to change over time. Pogge and Hollis argue that the market will essentially solve the problems for itself: if a company does not feel there is enough to be gained by registering through the HIF it could continue to use the commercial paradigm, this would mean that there was one less competitive product in the HIF, thus leaving a greater returns, and providing superior incentives, for future products.

A compounding problem is related to the way the Fund is supported. Pogge and Hollis estimate that the Fund could operate for six billion dollars a year. This would probably be too small initially to attract the blockbuster drugs, but, as we’ve already identified, neglected diseases do not have blockbuster drugs. Even with this relatively small Fund size, it would need to be guaranteed for at least ten years in order to provide an incentive for new drug development, a pool of sixty billion dollars that could be used, instead, to augment existing R&D structures. However, even if the HIF is fully funded, the inconsistency of the incentive, as we have seen, may not be sufficient to encourage full scale commercial-sector research and development. That said, taking Ridley’s estimate of a two hundred million dollar return representing the minimum requirement for investing in a new product into account, the six billion dollars offered by a fully operational HIF may be appropriate regardless of the fluctuations.

The first, and most important step, towards implementation of the HIF is the proof that the QALY calculating procedure can operate to a reasonable degree of accuracy and across a large geographical area. Refining and improving this measurement system may take years, but would be an important step forward, not only for the HIF, but for measuring the impact of treatments on global health in general.

The second step is to put the HIF into practice. It will take at least a decade to prove that the HIF can successfully incentivise development of products for PRNDs from scratch. Once QALY measurement has been proved, the HIF could attempt to slowly scale-up, registering products targeted at PRNDs which are relatively new to the market, this would:

- Overcome any access problems.
- Provide additional funding for PDPs.
- Prove that the HIF could operate year on year without major fluctuations in market return.

In conclusion, we consider the HIF to be a strong proposal, and though requiring quite significant investment, it is investment that could be realised if there is evidence that it can be applied. The only way to convincingly answer that question is to trial it.

7.D Prize Funds

The use of Prize Funds to incentivise innovation has a long history. A research note from Knowledge Ecology International in 2008 identified dozens of historic uses of prizes with one going back as far as 1627 when William Douglas, a Scottish nobleman, offered prizes to develop new weaponry and was partially successful.⁸

The use of Prize Funds has since been updated and proposed as a solution to availability and access problems in relation to the R&D for global health. James Love and Tim Hubbard at Knowledge Ecology International have been the most vocal proponents of such a system, but it has received support from a wide range of academics and researchers, including Joseph Stieglitz.⁹

A Prize Fund is a classic ‘pull’ mechanism. A government, donor or agency would offer a significant sum of money to incentivise researchers and private organisations to develop a certain product that would meet a certain specification. Upon achieving that specification, the Prize would be awarded. Products developed through Prize Funds would be open-licensed, thus ensuring that all products could be made available to as many people as possible as cheaply as possible.

As with the Health Impact Fund, Prize Funds have been widely debated and criticised. A major question is how to judge the size of the Prize? With a second problem being to do with who competes? If a government is providing the funding for a prize, then it will want to attract competitors who are independently financed – probably not academia. Attracting new entrants into a field as technologically complex as pharmaceutical R&D could require huge up-front prizes.

Nonetheless, prize funds take a different approach to funding R&D that could be complimentary to the current system of public and philanthropic push funding and Love and Hubbard identify that:

*The prize mechanisms should be thought of as part of a larger ecosystem of financing of medical R&D, and should be implemented in combination with other instruments, such direct or indirect government funding of basic research, non-profit product development partnerships (PDPs), clinical trials, and other traditional and non-traditional types of funding R&D. What the prizes offer uniquely is an alternative to the marketing monopoly as an incentive for private investment.*¹⁰

The UK is currently running its own prize fund competition through the Longitude Prize. The Prize marks the 300th anniversary of a challenge made by the British government to solve the greatest scientific challenge of the century – how to pinpoint a ship’s location at sea by knowing its longitude.¹¹ The current incarnation offers the public a choice between six challenges, with the final selected challenge becoming the target for a prize fund which will then incentivise development of key products in

relation to that particular challenge. For example, should antibiotics be selected, the challenge will be to create a cost-effective, rapid, and easy-to-use test for bacterial infections.

In the context of this inquiry the Longitude Prize demonstrates that Prize funds are actively considered as a tool within the R&D ecosystem, and that they can generate significant PR and public interest around common challenges. The next proposal incorporates prizes into precisely the kind of ‘larger ecosystem’ envisaged by Love and Hubbard.

7.E The 3P Project

The launch of MSF’s Access Campaign in 1999 took campaigning on R&D for global health to a new level and the organisation has stayed at the forefront of the debate for the intervening years.

In consultation with a wide range of stakeholders, MSF has recently proposed the ‘3P project’ proposal to create an incentive for TB drug development.^{12 13} The three ‘P’s of the title represent:

- Push funding to finance R&D activities up front (i.e. through grants).
- Pull funding to finance R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes).
- Pooling of intellectual property to ensure open collaborative research and fair licensing for competitive production of the final products.

The 3P Project aims to rapidly deliver affordable, effective new regimens for TB through an open and collaborative approach, and, if successful, could provide a model for all PRNDs. In its submission to this inquiry MSF said: ‘researchers and clinicians will be incentivised to share scientific data and clinical trial results, and to conduct medically appropriate research on multiple compounds.’

The project would be overseen by a Technical/Scientific Advisory Committee, which could be hosted at the WHO. The project would incorporate key milestone prizes for the achievement of specified R&D objectives. Further prize funding would be used to reward the licensing of IP rights to a patent pool during early discovery and ensure that the upstream aspects of research were kept clear of patent problems. Further milestone prizes would be awarded at Phase I to incentivise advancement of existing compounds, and further prizes at the completion of Phase II of the clinical trial process. As a key twist to dealing with the specific problems associated with TB care and treatment, neither prizes nor grants would be available for single drugs.

In concluding, MSF state:

The proposal seeks to leverage as much existing capacity and expertise in TB as possible to foster greater collaboration between researchers and developers. There are several different organisations working on aspects of TB drug R&D, but without the necessary incentives and co-ordination they have

*not yet been able to produce the new regimen required. The 3P proposal does not seek to duplicate or replace the work of these organisations, but rather to create an overarching framework to further facilitate this work through the provision of additional incentives and an open collaborative framework to stimulate progress.*¹⁴

From the perspective of this group, there are three great strengths of the 3P Project:

- 1. Flexibility – the project has a number of tools at its disposal that can be used selectively to advance research.**
- 2. Coordination – the project recognises that there are a wide range of different organisations in this space and coordination between them would maximise return.**
- 3. Scale – although TB drug provision is a huge, global challenge, it remains just one small component of R&D for global health. By starting small, the 3P Project is, therefore, an appropriate pilot for a potential future model.**

There are also benefits in that countries could choose, or not, to invest resources as part of the project.

The 3P Project was originally proposed as one of the WHO demonstration projects through the CEWG and secured the backing of the UK government at that time although it wasn't included in the final selection. To be successfully launched, the 3P Project requires both financial and political backing from a wide range of countries. Given that the UK has already expressed support for the initiative, it should not only leverage its role a world-leader to encourage other countries to support, but it should work with France and other countries to put up the necessary funding to initiate the project. Nonetheless, like a Global Alliance for PRNDs built on the GACD model, the 3P Project could represent exactly the kind of small-scale, international coalition of the willing which could prove that an R&D Convention could be a success. Additionally, the 3P Project could create a model that could be implemented on other issue areas, like any individual PRND or group of PRNDs.

7.F WTO Agreement on the Provision of Public Goods

R&D for global health is beset by problems in relation to the public goods, i.e. everyone ends up using them but no one wants to pay for them.

To tackle this challenge, Love and Hubbard have come up with an innovative approach building on and adapting the WTO General Agreement on Trade in Services (GATS). With GATS, countries make voluntary commitments to provide a service, but once they volunteer their commitment is binding. The commitment is put on a schedule, and if they don't provide the service, they are eligible for the international arbitration and settlement system that is built into the World Trade Organisation.

Under this approach, a new schedule would be devised which would allow for the provision of public goods. States could choose to participate or not. If they did choose to participate they would make voluntary but binding commitments to provide a certain public good – whether that be IP around TB drugs or anything else.

Love and Hubbard identify three major benefits to the proposal:¹⁵

- 1. Such a schedule would allow countries to coordinate or aggregate their need or willingness to pay for certain public goods.**
- 2. Further options would be introduced in general WTO trade negotiations: there would be a new type of 'ask' or counter 'offer' that could be used to secure agreement on different aspects of WTO negotiation. For example, 'in cases where a WTO member is being asked to liberalize a sensitive sector of its economy, by lowering tariffs or subsidies or by removing barriers to market entry, it could then "offer," as an alternative, to participate in a global public goods project.'**
- 3. The voluntary nature of the schedule could lead to demands from some members for offer to address problems that are important for them. For example, a group of TB-affected countries could insist that they would not agree to a broader trade agenda unless there were a number of commitments to supply open-source research to a certain level on TB.**

They also identify a list of 'public goods' that could be included in such a schedule, including:

- The development of new drugs and vaccines, including but not limited to treatments for tropic neglected diseases, and new antibiotic drugs
- Funding innovation inducement prizes to stimulate the development of new low cost open source diagnostics for cancer and other diseases
- Funding clinical trials to have objective and unbiased evidence regarding efficacy of different drugs

There are, however, some concerns associated to such a system. Primarily in that addressing the provision of public goods as part of a transaction could put pressure on low-income countries to strike deals that are not advantageous to them, giving high-income countries further tools to influence low-income countries is not always a good thing.

In the opinion of this group, the advantages of this proposal outweigh the negatives, particularly because there is no obligation upon any country to do anything, but potentially significant benefits to countries if they do. There may be additional benefits through coordination of research and provision. For the UK, as a leader in global R&D, our existing commitments could become a more obvious soft power tool and a WTO Agreement on the Provision of Public Goods could help convince new partners to join initiatives such as the 3P Project.

RECOMMENDATIONS

Through this report we have outlined some of the major components of the commercial model that drives the majority of technological innovation including in health; explored the organisations and structures within that model; investigated the UK's role in global health; and looked at a number of proposals that could support the commercial model, or help the further development of alternative structures and models for product development.

In this last chapter we will make a number of recommendations for the UK government and a range of other stakeholders to implement. Through taking these steps, we believe that funding for R&D for global health will be better coordinated and more effective, and, in some instances, help create models that should be mirrored and implemented across the world.

1. Capitalise on Existing UK Excellence

The UK is a world leader in R&D for global health, from DFID's untied aid policy to world class academic institutions. With a limited pool of funders, the UK's leadership is critical to achieving the reforms necessary to bring through a new generation of drugs, diagnostics and vaccines.

- a.** DFID's Capacity to Support Excellence – DFID's R&D budget is set at around 3% of the total DFID budget, yet DFID's support for R&D is one of the Department's unsung success stories. DFID should commit to spending at least 5% of its budget on R&D, return funding for global health to previous levels of 1/3rd of total R&D funding, and invest in the necessary staffing and capacity building to maintain its record of funding excellence and excellence in funding. (DFID)
- b.** Champion EDCTP - EDCTP is a unique mechanism that could play a critical role in the development of new commodities for global health. As the leading cash-funder, and an exemplar of best-practice in transparent commitments, the UK should encourage other Participating States to increase in-cash contributions to EDCTP. The UK should also encourage the EU ten Member States which entered the EU after 2004 to join EDCTP so to further increase the European expertise in health R&D, and promote the work that EDCTP carries out. (UKRC)

- c.** Advance Existing Pipelines – The PDP model has been successful over the last decade but many promising products remain in development, hampered by a lack of resources. As a leading financier of PDPs, the UK government should champion the role of PDPs in global health R&D, encourage other donors to support portfolios rather than individual products, and provide the financing required to strengthen and accelerate product pipelines. (DFID)
- d.** Lead on Open-Access Provisions and Socially Responsible Licensing – No solution to the availability problem is complete without also addressing access issues. The UK Government should commission a report examining the implementation of open-access and/or socially responsible licensing (SRL) across UK publicly funded health R&D. DFID should work with PDPs to encourage the inclusion of open-access provisions in partnership with large commercial entities. Likewise, UK academic and research centres engaged in R&D for global health which generates patentable IP should implement their own policies on SRLs. (UKRC, DFID, BIS, UK Research Centres)
- e.** Explore a WTO Agreement on the Provision of Public Goods – A World Trade Organisation Agreement on the Provision of Public Goods could enhance incentives for countries to invest in R&D for global health and facilitate new collaborations and coordination. It would strengthen the UK's position in trading agreements and help capitalise on significant financial commitments already made to global health. (FCO, BIS)
- f.** Ensure Trade Agreements Safeguard Access – The UK should make sure that TRIPS flexibilities are not undermined in Free Trade Agreements agreed through the EU. As a major international power the UK should encourage and support countries utilisation of TRIPS flexibilities through investment to develop the technical capacity to do so and by championing their rights to do so in global forums. (FCO, BIS, DFID)
- g.** Sustain Commitment to R&D – R&D timelines are significantly longer than political ones. All political parties, recognising the importance of the continued development of new drugs, diagnostics and vaccines, should identify and champion the critical importance of non-commercially driven models for health products in their party policy platforms. (All Parties)

2. Changing the Global Landscape

Improvements have been made over the last decade in regards to the availability of critical medicines and tools for PRNDs, however, progress has been slow and much more needs to be done. Recommendations 2.a and 2.b follow-up from the CEWG recommendations, whilst the remaining recommendations in this section advocate for the creation and support of alternative mechanisms that could provide a framework, model, or foundation for reforms included in a global process but would not be reliant upon them in the event of a failure to make a global agreement.

- a. Lead towards a WHO Global R&D Convention –The scale up in funding, coordination and collaboration required to develop necessary health products will be extremely difficult to achieve without global agreement. A WHO Global R&D Convention would create structures that would delink the R&D process from the sale of the final product and incentivise innovation based on global health need. This agreement will be unlikely to succeed without the backing of a powerful HIC government such as the UK. The government should spearhead efforts to consolidate support for the change, working to ensure the 2016 WHA agree and act upon such a plan. To support this process, the UK should commission an economic paper to contrast the total costs of developing and purchasing medical tools using the current prevailing R&D model with the costs of a de-linked model, using the findings to steer UK global public health policy and provide the evidence base for reforms in the international arena. (UK Government)
- b. Establish the WHO Global R&D Observatory – A WHO Global R&D observatory would act as a central repository of information on global health R&D priorities, funding and research activities. It would allow funders to identify gaps and duplications, and allow developers to coordinate their R&D efforts. Globally-agreed neglected disease R&D funding targets to which countries should adhere, and be reported against, should be included. The UK Government should support its establishment and, once formalised, should encourage academic institutions and public funders to align their work with the Observatory as much as possible. (WHO, DFID, MRC)
- c. Drive forward with non-commercial models to tackle AMR – The Chief Medical Officer has made AMR a UK Government priority, with DH at the heart of efforts to implement the UK AMR strategy, including work on R&D. Governments and pharmaceutical companies have acknowledged that traditional incentives are not going to deliver the next generation of

antibiotics. Building on the recently launched ‘Longitude’ prize, the government should drive forward with establishing a non-commercial model of antibiotic development, and use progress in this area to build support for wider R&D reform and prove that alternative models can be successful. (DH, BIS)

- d. Champion the 3P Project – The 3P Project is one of the leading proposals that this inquiry saw for an alternative method of developing new commodities for global health. It is relatively small-scale, focussed and immediately implementable. Developing on previous support for the proposal, the UK should work with MSF and other governments to provide the funding, technical support, and coordination required for the 3P Proposal to operate successfully. New funds should be allocated from major donors to drive the creation of the first set of prizes and establish proof of concept. The UK Government should evaluate the outcomes to establish proof that a de-linked model can successfully develop products. (MSF, DFID, Stop TB)
- e. A Global Alliance for PRNDS – Coordination between public funders, PDPs, the private sector, research institutions, academics, and CSOs is critical to maximising scarce PRND funding. The UK and other major public funders of R&D for global health should organise a preliminary meeting with the directors of global health research in the major funding nations, with a view to establishing a mechanism following the model of the Global Alliance for Chronic Diseases. This would connect and coordinate the work of the world’s major R&D public funders, facilitating partnership working, and seek to incorporate a wider range of stakeholders including PDPs and the private sector than are currently included in the GACD. (MRC, DFID, DH)

3. Supporting and Strengthening Industry Engagement

The private sector is a critical partner in R&D for global health and many companies are positively engaged in a wide range of partnerships. Incentives for pharmaceutical and diagnostics companies should be examined to ensure that they reward the best partnership models, and encourage poor industry performers to engage with global health more heavily.

- a.** Bring poor industry performers on board. Companies can do a great deal for neglected diseases without harming commercial interests – many already do. Nevertheless, a handful of more recalcitrant big pharmaceutical firms remain. The WHO and industry host countries should negotiate improved performance by these firms, including through discussions with companies and industry peak bodies such as the ABPI, IFPMA, BIO and PhRMA, as well as sharing of information on best-practice company behaviours. (BIS, WHO)
- b.** Adjusting Tax Credits to Support Partnership Working - The UK has one of the most generous tax credit arrangements in the world but the system is not targeted to reward companies who engage in partnership working for R&D for global health, nor does it give the maximum possible support to SMEs working on diagnostics and other health technologies. The Treasury should adjust the existing tax credit system to incentivise cash donations and in-kind contributions to PDPs and other platforms such as WIPO Re:Search on condition that the products of such partnerships adhere to open-access principles, and thus support the inclusion of open-access provisions and SRLs in publicly funded research. This should not involve an increase in the percentage of overall tax credits available. (Treasury)
- c.** Transparency in R&D Costs - One of the fundamental challenges of devising appropriate reform proposals is lack of clarity over the costs of developing new products. All governments should work with pharmaceutical and diagnostics companies to breakdown costs of R&D, marketing and other overheads so as to develop a clearer picture of the true cost of commercial R&D for drugs and vaccines and how it can be incentivised most efficiently. Greater transparency in diagnostic development costs would help public funders provide an appropriate level of support in order to bring a product to market. This greater transparency could, and should, be linked to a reformed tax credit system in the UK. (BIS)

- d.** Support the Development of QALY Calculations – Effectively incentivising commercial sector R&D rests on defining a suitable level of reimbursement. Indeed, existing financial markets fail to correlate revenues with the public health benefit of a medical commodity. Therefore whilst a clearer idea of R&D costs will support this, accurately measuring the true impact of a commodity could play a central component to future incentive mechanisms. The UK, through NICE and academia, is an expert at calculating the QALY impact of various treatments, UK government should look at how this expertise can be transferred into a robust method for calculating the QALY impact of new treatments in an LMIC context, and explore ways to use this to incentivise commercial sector engagement in PRNDs. (DH, PHE, NICE)

TIMELINE OF KEY EVENTS RELATING TO THE DEVELOPMENT OF TB TREATMENTS

October 19 1943 – Albert Schatz discovers streptomycin which goes on to be the first TB drug. Drug-resistance is discovered in early trials.

1965 – Pfizer loses its challenge to the UK government on use of compulsory licensing for NHS.

1967 – Rifampicin introduced into TB treatment, marks the end of two decades of drug discovery and becomes the last drug to be added to the standard TB regimen.

1986 – Launch of the Uruguay Round of GATT (predecessor to WTO).

1993 – WHO declares TB a ‘global public health emergency’

1995 – The TRIPS agreement is formally adopted by the newly formed World Trade Organisation.

1997 – Work begins on Bedaquiline.

1999 – MSF launches its Access Campaign.

2000 – Stop TB Partnership formed.

2000 – TB Alliance, a Product Development Partnership working to develop new TB drugs, is founded.

2001 – 39 pharmaceutical companies drop their lawsuit against the South African government relating to intellectual property infringement on generic drugs.

2001 – The Doha Declaration on TRIPS and Public Health is adopted by the WTO, accepting that public health requirements can overrule IP protection.

2002 – The Global Fund to Fight AIDS, TB and Malaria is established.

2003 – Aeras, a Product Development Partnership that aims to develop a TB vaccine, is founded.

2003 – James Love, and later Tim Hubbard, start proposals regarding Prize Funds for pharmaceutical development.

2004 – First public data is shared around Bedaquiline, a new TB drug.

2005 – Thomas Pogge makes first proposal of the Health Impact Fund.

2006 – UNITAID, a market-shaping organisation, is established.

2006 – The World Health Assembly establishes the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property.

2007 – Five countries, including the UK, come together to launch the first Advance Market Commitment for a pneumococcal vaccine.

2008 – The World Health Assembly adopts the Global Strategy and Plan of Action on Public Health, Innovation and IP.

2008 – The Medicines Patent Pool is established by UNITAID.

2008 – The Expert Working Group is established to produce recommendations for improving global health R&D.

2010 – EWG recommendations are rejected by the World Health Assembly due to a divergence “between the expectations of Member States and the output of the group.”

2011 – The Consultative Expert Working Group holds its first meeting.

2012 – The Consultative Expert Working Group publishes its report including recommendations around an R&D convention for global health.

2012 (November) – Discussions regarding an R&D convention are postponed until 2016.

2012 (December) – Bedaquiline receives approval from the FDA, the first new TB drug in over 40 years.

2013 (November) – The European Medicine’s Agency recommends conditional approval to Delamanid, the second new drug in over 40 years.

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