Research for Health: What has been achieved and what more needs to be done to deliver on the Sustainable Development Goals?

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Introduction

The Wellcome Trust asked for a scoping report analysing historic reports and initiatives on research for health and mapping the current global research-for-health ecosystem. The report is intended to provide background for the development of the SDG Action Plan, currently being developed by the World Health Organization (WHO) with partners.[1]

The motivation for commissioning this report was a recognition of the massive changes that have occurred in the last 30 years in the way research for health is conducted, in the economic and political context, and in the changing epidemiology of disease. The Commission on Health Research for Development's 1990 report "Health Research: Essential Link to Equity in Development" was the first serious analysis of how the global system of research for health should develop in order to contribute to improving the health of people in developing countries.[2] Since then, there have been many reports addressing issues concerning research for health, directly or indirectly. Moreover, the institutional actors that conduct, fund or influence research for health have proliferated in ways that could not have been anticipated in 1990. Therefore, the time has come to look again at whether the global system of research for health is optimally structured - in terms of its financing, architecture and outputs - to address today's global health priorities in countries at all income levels.

The Changing Context

Income, population and poverty

There have been many changes in the world since 1990. The rapid growth in incomes in many, but not all, low- and middle-income countries (LMICs) could not have been expected by the 1990 Commission which worked in the wake of the debt crisis and structural adjustment programmes of the 1980s. In 1990, 3.1 billion people, or 62% of the world's population, lived in countries classified by the World Bank as low income. By 2017 only 0.7 million, or 10% of the world population, did. In the same period, the number living in lower-middle and upper-middle income countries expanded from nearly 1.1 billion to 5.6 billion, so that over 73% of the world's population now live in middle-income countries (Figure 1).

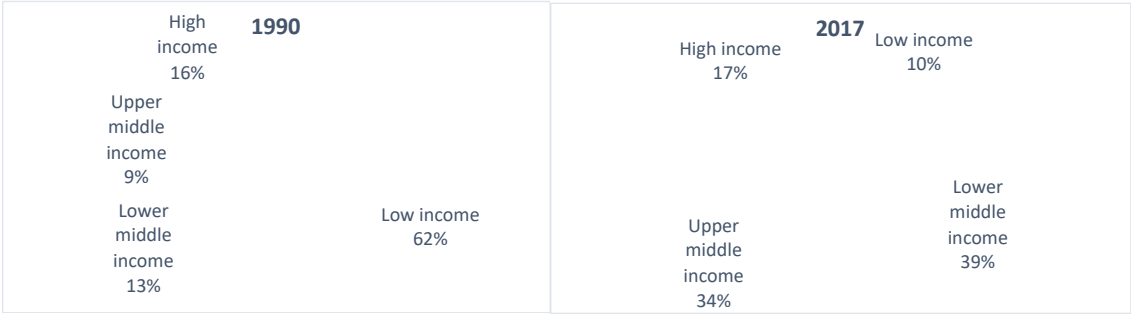
The change in the country classification is reflected also in a dramatic fall in poverty rates. Overall the World Bank estimates that the number of people earning less than $1.90 a day declined from 1.9 billion in 1990 to about 780 million in 2015, or from 45% of the population of LMICs to 12%. The most dramatic decline was in today's upper-middle-income countries where the poverty headcount declined from 42% of the population to under 2%. In lower-middle-income countries, poverty numbers more than halved but this still left over 400 million living in poverty in 2015. Low-income countries saw a smaller decline in poverty rates, but an increase in absolute numbers to 320 million as their populations have more than

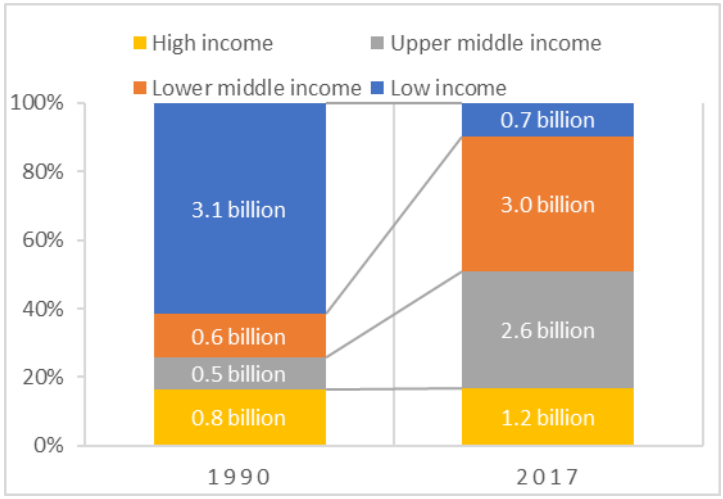
[1] World Health Organization. Global Action Plan for healthy lives and well-being for all. 2018. Available from: http://www.who.int/sdg/global-action-plan

[2] Commission on Health Research for Development. *Health Research: Essential Link to Equity in Development.* New York: Oxford University Press,1990. Available from: http://www.cohred.org/downloads/open_archive/ComReports_0.pdf

doubled since 1990 (Figure 2). As a result, most poor people now live in lower-middle-income countries (410 million) and most of the remainder in low-income countries (320 million).

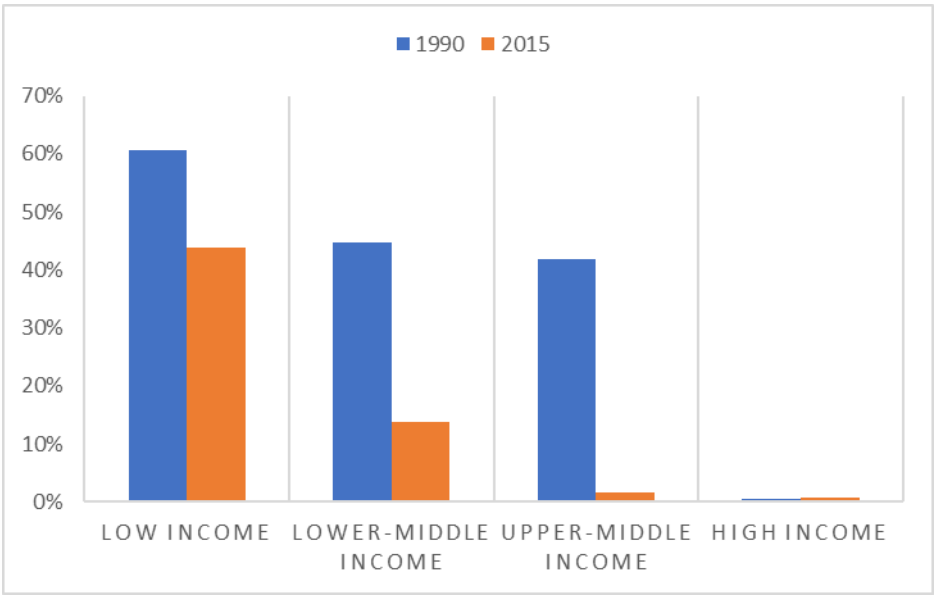
Figure 1. Share of world population by World Bank income category 1990-2017





Sources: (1990) Basic indicators. World Development Report 1992. Page 219. Available from: http://documents.worldbank.org/curated/en/995041468323374213/pdf/105170REPLACEMENT0WDR01992.pdf (2017) World Development Indicators: Size of the economy. Available from: http://wdi.worldbank.org/table/wv.1

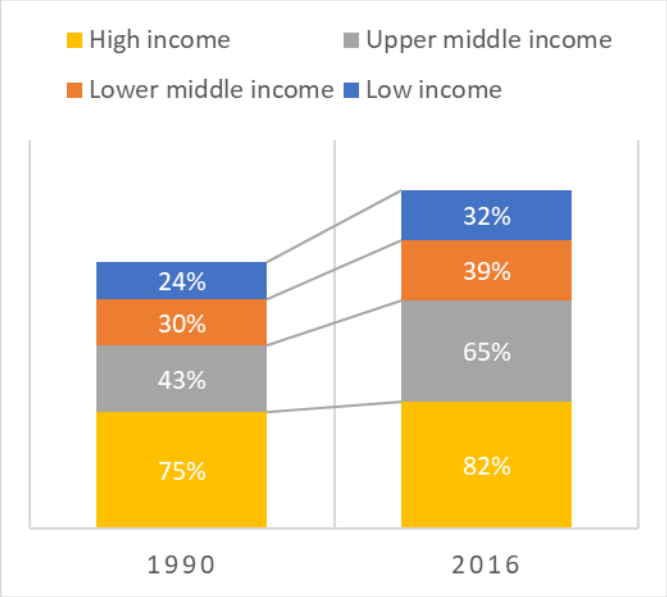
Figure 2. Proportion of population living on less than $1.90 a day (1990-2015)



Source: The World Bank. Poverty headcount ratio at $1.90 a day (2011 PPP) (% of population). Available from: https://data.worldbank.org/indicator/SI.POV.DDAY?locations=XM-XD-XN-XT

Of particular relevance for health is the proportion of the population living in urban areas. Since 1990 urban dwellers have increased by nearly 2 billion, or from 43% of the world population in 1990 to 54% in 2016. Urbanization has occurred particularly rapidly in upper-middle-income countries, rising from 43% to 65% of the total population.

Figure 3. Proportion of population living in urban areas (1990-2016)



Source: The World Bank. Urban population (% of total). Available from: http://wdi.worldbank.org/table/3.12

The Environment

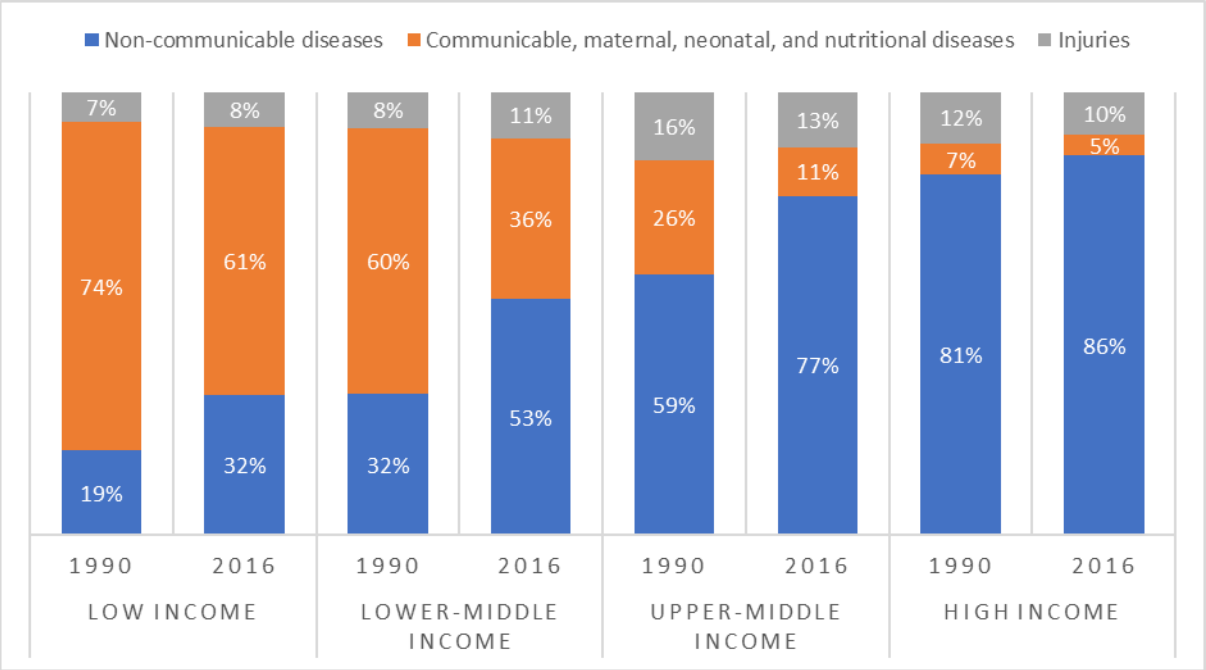
While these fundamental transformations in incomes and demography have occurred since 1990 new health threats have emerged that were not recognised then. The 1990 report dealt rather cursorily with environmental threats to health, while noting that the health risks associated with economic development were often overlooked. Most notably, it ignored climate change as a health issue although the Intergovernmental Panel on Climate Change (IPCC) also published its first report in 1990 with a section on health impacts as well as an agenda for future research on health impacts.[3] Since 1990, average global temperatures have risen by more than 0.5°C.[4] Nowadays, much more attention would need to be given, alongside the health impacts of climate change, to the impacts arising from air and water pollution, plastics, the other pollutants fuelled by economic growth and modern consumption patterns.[5]

[3] IPCC. Climate Change: The IPCC Impacts Assessment. Chapter 5. Australian Government Publishing Service Canberra, 1990. Available from: http://www.ipcc.ch/ipccreports/far/wg_II/ipcc_far_wg_II_chapter_05.pdf
[4] NASA. Global temperature. Available from: https://climate.nasa.gov/.
[5] World Health Organization. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. Geneva, 2016. Available from: https://www.who.int/quantifying_ehimpacts/publications/preventing-disease/en/

Epidemiology

The 1990 report highlighted the ongoing "health transition" in developing countries from infectious to non-communicable disease. This transition has continued (Figure 4).

Figure 4. Cause of DALYs lost by country income group (1990-2016)



Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from: http://vizhub.healthdata.org/gbd-compare

The 1990 report also recognized that ageing would become a growing source of health problems along with substance abuse, but it failed to anticipate the extent to which obesity, closely connected with urbanization, as well as continued malnutrition, would become a major contributor to chronic health problems.[6] Other areas that were ignored in 1990 but are now prominent included addressing antimicrobial resistance[7] and also research to address emerging diseases and disease outbreaks.[8]

Achievements in health

One of the remarkable changes since 1990 is that we now have much better data on what is going on in health and health research, albeit with many outstanding gaps. One important

[6] International Food Policy Research Institute. Global Nutrition Report 2018: Shining a light to spur action on nutrition. Bristol, UK: Development Initiatives, 2018. Available from: https://globalnutritionreport.org/reports/global-nutrition-report-2018/

[7] Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. London, 2016. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

[8] World Health Organization. A research and development blueprint for action to prevent epidemics. Available from: https://www.who.int/blueprint/en/

example is the ongoing work on mapping the global burden of disease, first initiated as an input to the World Bank's 1993 World Development Report *Investing in Health* which was then transferred via the WHO to the Institute for Health Metrics and Evaluation (IHME). In itself, this constitutes a large investment in research for health, involving more than 1000 researchers world-wide.[9] There are now several organizations compiling data on health research including the Organization for Economic Cooperation and Development (OECD), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the WHO, G-FINDER for neglected diseases and reproductive health, as well as many national organizations such as the Treatment Action Group (TAG), the US National Science Board and many others. The Millennium Development Goals (MDGs) also increased the efforts put into monitoring progress at international and national levels and the Sustainable Development Goals (SDGs) are having a similar effect on the much wider range of indicators included in the SDGs (including SDG3 on health).[10]

Analysis of the results of the MDGs provide a record of progress in some important areas of health between 2000 and 2015. The health goals of the MDGs focused on three areas: child mortality (goal 4), maternal health (goal 5) and major infectious diseases, HIV/AIDS, malaria and tuberculosis (goal 6). Much was achieved, but most of the goals were not met. Child and maternal mortality fell by about half against the respective targets of two thirds and three quarters. The target for the number of new HIV infections annually was largely met, falling by 40%, but the hugely ambitious target of universal access to treatment by 2010 was not. Nevertheless, the increase from very few people on treatment in 2000 to over 15 million in 2015 was impressive. The incidence of malaria decreased by nearly 40% and mortality by nearly 60%. The incidence and mortality of tuberculosis also decreased but more slowly in the absence of new treatments and vaccines and in the face of growing multi-drug resistance.[11]

Two key indicators of overall improvements in health are life expectancy and the under-five mortality rate. Between 1990 and 2016 life expectancy at birth increased globally from 65 to 72. The biggest proportionate increase was in low-income countries (Figure 5). Improvements in under-five mortality have been even more dramatic, falling by nearly 60% between 1990 and 2017 (Figure 6). However, the recent stagnation or even decline in life expectancy in high income countries, and its implications, needs to be noted.[12]

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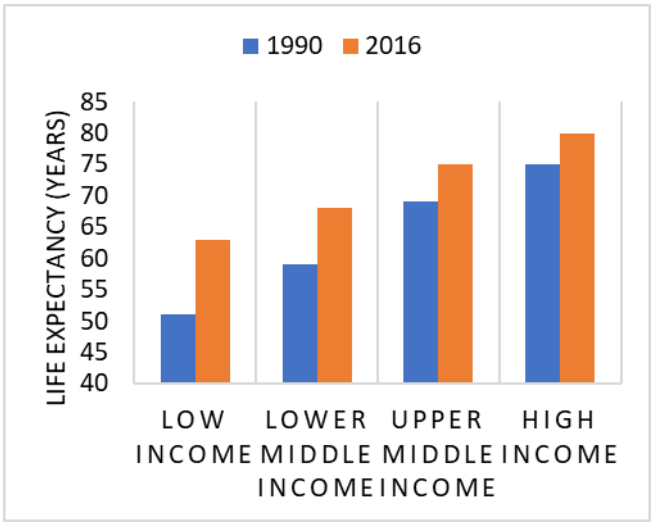
[9] Institute for Health Metrics and Evaluation. GBD History. Available from: http://www.healthdata.org/gbd/about/history

[10] Sustainable Development Solutions Network. Indicators and a Monitoring Framework for the Sustainable Development Goals. New York, 2015. Available from: https://sustainabledevelopment.un.org/content/documents/2013150612-FINAL-SDSN-Indicator-Report1.pdf

[11] United Nations. The Millennium Development Goals report 2015. New York, 2015. Available from: http://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20rev%20(July%201).pdf

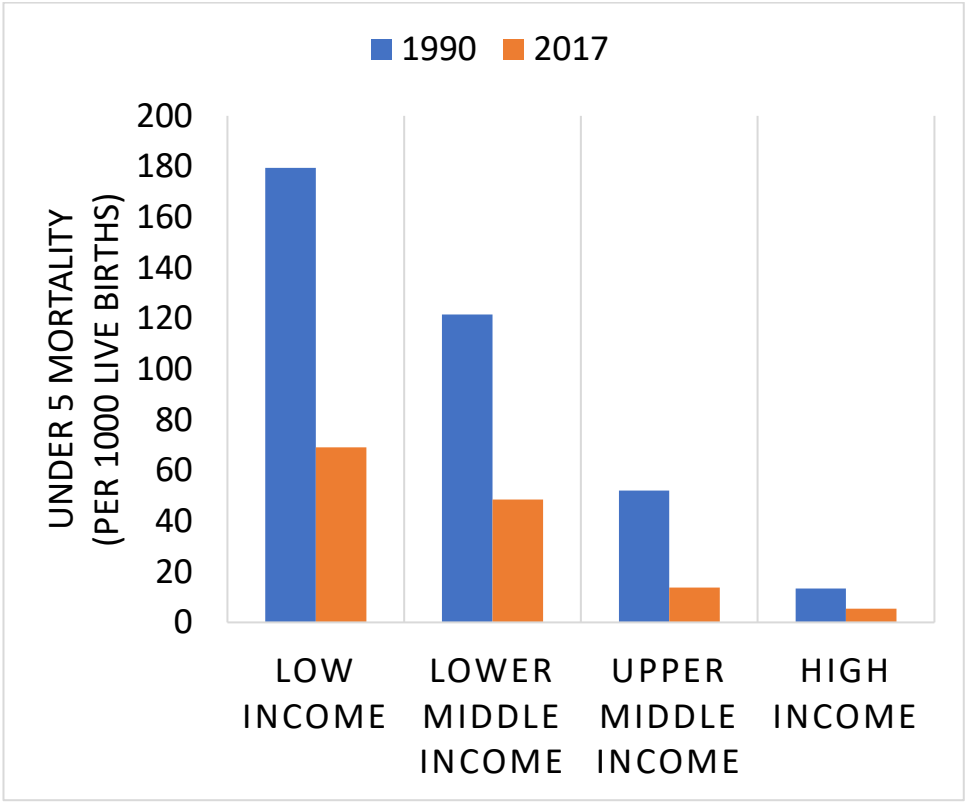
[12] Jasilionis D. Reversals in life expectancy in high income countries? Warning signs must not be ignored. *BMJ* 2018;362:k3399. Available from: http://press.psprings.co.uk/bmj/august/lifeexpectancyedit.pdf

Figure 5. Life expectancy at birth, by country income category



Source: The World Bank. Life expectancy at birth, total (years). Available from: http://wdi.worldbank.org/table/2.18

Figure 6. Under-five mortality, by country income category



Source: The World Bank. Life expectancy at birth, total (years). Available from: http://wdi.worldbank.org/table/2.18

Respondents to our survey highlighted a number of specific health gains attributable to research for health. These include:

- The development of treatments for HIV/AIDS coupled with implementation research which enabled, along with the availability of new sources of finance and dramatic reductions in prices, widespread access to treatment. From zero in 1990, 21.7 million people were estimated to be on treatment in 2017 and deaths from AIDS-related illnesses have halved since 2004, but there remains much to do to meet the SDG target of eliminating the epidemic by 2030. In particular, while new infections have also nearly halved to 1.8 million annually since 2004, particularly in Africa, many regions have actually seen increases and the target of 500000 new infections by 2020 seems unattainable.[13]
- Research to develop insecticide-treated bed nets to protect from malaria, including behavioural research related to increasing acceptability and utilisation. Over 1 billion bed nets have been distributed since 2000 in Africa, a major contributor to the reduction in malaria prevalence.[14] Research continues to be necessary to increase uptake of bed nets, and also to overcome the problem of resistance that has developed to commonly used insecticides, decreasing their effectiveness. In recent years, the progress in reducing malaria incidence has stalled.
- In other infectious diseases, the new antivirals for curing hepatitis C have been transformational and WHO has committed to a plan for eliminating viral hepatitis by 2030.[15]
- Research has produced new vaccines. These include pneumococcal conjugate vaccines (PCVs), first introduced in 2000, and human papilloma virus (HPV) vaccines, introduced in 2006, which offer the possibility with universal coverage of virtually eliminating cervical cancer.[16] A conjugate vaccine against meningococcus A, prevalent in parts of sub-Saharan Africa, was introduced in 2010. Gavi, the Vaccine Alliance, estimates that its support for vaccination has helped prevent more than ten million deaths.[17] A partially effective malaria vaccine has been developed, and the feasibility of its large-scale introduction is currently being tested (it requires four doses to be given to children).[18]
- In non-communicable disease, research has contributed to generations of new antihypertensives as well as statins which have contributed to reductions in cardiovascular events such as strokes and heart attacks. A major part in this reduction has also been played by the rapid reductions in smoking in many countries – medical

[13] UNAIDS. Global AIDS Update 2018. Available from: http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf
[14] UNICEF. Malaria. Available from: https://www.unicef.org/health/index_malaria.html
[15] World Health Organization. Global health sector strategy on viral hepatitis 2016-2021: Towards ending viral hepatitis. Geneva, 2016. Available from: https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/
[16] World Health Organization. Accelerating cervical cancer elimination. EB144/28. 30 November 2018. Available from: http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_28-en.pdf
[17] Gavi. Facts and figures. Available from: https://www.gavi.org/about/mission/facts-and-figures/
[18] World Health Organization. Q&A on the malaria vaccine implementation programme (MVIP). Available from: https://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/

research has played a key role in first identifying the health risks associated with smoking[19] and then behavioural research has played a large part in subsequent efforts and policies to reduce smoking.[20]

- There have been many technical advances in surgery including the use of new imaging technologies to improve accuracy and minimally invasive surgery.

Aside from specific examples such as the above, there is a recognition that the use of the internet, and the increase in computing power has transformed the ability of researchers to disseminate and share outputs and data across countries and different disciplines. The move towards open access for scientific journals has also increased the ability to access the latest research, including in LMICs. Digitalisation and eScience could transform the way research is done. Moreover, there is widespread optimism that the application of information and communications technologies, as well as artificial intelligence, could play a significant role in improving prevention, diagnosis and treatment at low cost. Digital health technologies may offer solutions for resource- and infrastructure- poor countries to remotely access healthcare and modernise their health provision in the way that mobile phones leapfrogged landlines.[21]

The other technological advance is genomics – whose promise is beginning to bear fruit. The new CRISPR-Cas9 technology has the possibility of application to a wide range of diseases as well as revolutionising diagnostics, while also raising a number of ethical issues that need to be addressed from a public policy perspective.[22]

Box 1 A Case of Multiple Sclerosis

'You've done well. Quite a bit better than I expected, in fact," says Khaled Abdel-Aziz, consultant neurologist at St George's Hospital in south London. Khaled has overseen my care for three years: he prescribed me Tecfidera, a new drug approved for NHS use in 2014, which trials indicate reduces MS relapses by 50%.

Khaled has an arsenal of drugs to call on. "The progress in the past 10 years has been enormous. We have a range of new disease-modifying therapies" — he trots out a list of names I struggle to keep track of, car crashes of seemingly random syllables: ocrelizumab, cladribine, fingolimod, alemtuzumab. "We don't know what will happen with these 10 years down the line, but we do know the short-term responses are excellent.

"It's more than the drugs. We're now able to treat patients if we see lesions appearing in their MRI scans rather than just wait for a relapse when the damage is already being done. And the expansion of specialist MS nursing has meant patients feel better cared for and are monitored for relapses and side effects."

[19] US Department of Health, Education and Welfare. Report of the Advisory Committee: Smoking and Health. Washington, 1964. Available from: https://profiles.nlm.nih.gov/ps/access/NNBBMQ.pdf

[20] Fichtenberg C and Glantz S. Effect of smoke-free workplaces on smoking behaviour: systematic review. *BMJ* 2002;325:188. Available from: https://www.bmj.com/content/325/7357/188.short

[21] World Health Assembly. Digital Health. WHA 71.7. Geneva, 2018. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_R7-en.pdf

[22] Adli, M. The CRISPR tool kit for genome editing and beyond. *Nature Communications 9:*1911 (2018). Available from: https://www.nature.com/articles/s41467-018-04252-2

"When your father was diagnosed, there were no treatments, so that was it," says Dr David Schley, research communications manager at the charity the MS Society. "The drugs didn't start coming through until the late 1990s, but we've gained so much pace since then.

"We're driving research into more and better treatments, and there's been real international co-operation. We've got to be very efficient to make this kind of progress." He talks of T-cells and lymph nodes, of phase one, two and three double-blind trials, the intricate language of scientific inquiry. I can't follow it. But I realise that, if I owe my continuing ability to walk and think to any one thing, it's not me: it's the Enlightenment.

The infrastructure of learning and curing is invisible to most of us, until it works a miracle for ourselves or our loved ones. A cancer cured, a hip replaced, a baby saved: science swoops in, a modern deus ex machina, sets us on our feet, and then retires back to its distant lab.

We must not forget the wonder of this, or the effort it takes to sustain it. Without men and women in white coats, the cancer goes uncured, the hip seizes up, the baby dies. And I would miss the chance to see the voluptuous folds of my own brain, captured by that MRI scanner and now flickering on Khaled's computer screen, looking — for the moment, at least — unblemished by lesions.

Source: Stephen Bleach, Letters editor of The Sunday Times. 28 October 2018. Sufferer from multiple sclerosis after his father. Available from: https://www.thetimes.co.uk/article/multiple-sclerosis-killed-my-dad-but-selma-blair-and-i-have-a-mighty-ally-gwfzwd8xg?shareToken=d8e7edeaa20fb96e675cbfaa6b351bf9

Institutional Innovations

The period after 1990 has also been marked by the proliferation of new organizations in global health, and in research for health. The Bill & Melinda Gates Foundation (BMGF), founded in 2000, has had a profound influence on global health generally, and in technology development in particular. By 2017, it was providing $3.3 billion annually as development assistance for health, about 50% more than the WHO's annual budget.[23] The 1990s saw the first of many of the new product development partnerships (PDPs), in which initially the Rockefeller Foundation was a catalytic influence beginning with the establishment of the Sabin Vaccine Institute in 1993, the International AIDS Vaccine Initiative (IAVI) in 1996 and the Medicines for Malaria Venture (MMV) in 1999. Now the G-FINDER report tracks the funding of 18 PDPs, which received $508 million in 2017, of which under 40% was provided by the BMGF, down from total PDP funding of $688 million in 2008. BMGF funding for PDPs has declined from a peak of $408 million in 2008, nearly 60% of total PDP funding, to $197 million in 2017.[24] In 2017 the BMGF announced the establishment the Bill & Melinda Gates

[23] Institute for Health Metrics and Evaluation. Financing Global Health 2017. Seattle, 2018. Available from: http://www.healthdata.org/sites/default/files/files/policy_report/2018/IHME_FGH_2017_fullreport.pdf

[24] Policy Cures Research. Neglected disease research and development: Reaching new heights. Sydney, 2019. Available from: https://www.policycuresresearch.org/g-finder-2018/

Medical Research Institute as a non-profit to tackle tuberculosis, malaria and diarrhoeal diseases.[25]

The upsurge of global concern about antimicrobial resistance has resulted in the formation of two new PDPs in the past two years: CARB-X[26] (Combatting Antibiotic Resistant Bacteria Biopharmaceutical Accelerator) and the Global Antibiotic Research & Development Partnership[27] (GARDP). Similarly, response to the 2014 Ebola outbreak in West Africa, gave rise to the birth of the Coalition for Epidemic Preparedness Innovations (CEPI).[28] Other important new international institutions involved in funding and conducting research include the European & Developing Countries Clinical Trials Partnership (EDCTP)[29], founded in 2003, which funds clinical research to accelerate the development of new health products against poverty-related infectious diseases in sub-Saharan Africa, and the Global Health Innovative Technology Fund[30], which facilitates global research and development (R&D) partnerships for the discovery and development of new health technologies for the developing world.

Box 2 A selection of research institutions in LMICs

Fundação Oswaldo Cruz (FIOCRUZ), Brazil, (established 1900)
As well as being a research institute covering a wide range of infectious and public health areas, and housing a hospital, FIOCRUZ also includes the Drug Technology Institute (Farmanguinhos), a public pharmaceutical manufacturer that supplies 40% of medicines purchased by the Brazilian Ministry of Health, and the Immunobiological Technology Institute (Biomanguinhos), a manufacturer of biological products and the world's largest manufacturer of the yellow fever vaccine.[31]

Alliance for Accelerating Excellence in Science in Africa (AESA) (established 2015)
AESA focuses on people, places, and programmes in Africa to accelerate world-class research, foster innovation and promote scientific leadership. AESA also functions as a think tank, setting, aligning and ensuring an Africa-led, Africa-centred, and Africa-relevant science and technology agenda on the continent. AESA is a partnership between the African Academy of Sciences (AAS) and the New Partnership for Africa's Development (NEPAD) Agency with the support of the Wellcome Trust, the Bill & Melinda Gates Foundation and the UK's Department for International Development (DFID).[32]

The Noguchi Memorial Institute for Medical Research (NMIMR), Ghana (established 1979)

[25] Bill & Melinda Gates Medical Research Institute. Available from: https://www.gatesmri.org/
[26] CARB-X. Available from: https://carb-x.org/
[27] Global Antibiotic Research & Development Partnership. Available from: https://www.gardp.org/
[28] Coalition for Epidemic Preparedness Innovations. Available from: http://cepi.net/
[29] European & Developing Countries Clinical Trials Partnership. Available from: http://www.edctp.org/
[30] Global Health Innovative Technology Fund. Available from: https://www.ghitfund.org/en
[31] Fiocruz. Available from: https://portal.fiocruz.br/en
[32] Alliance for Accelerating Excellence in Science in Africa. Available from: https://aesa.ac.ke/

The NMIMR, part of the University of Ghana, was built by the Government of Japan as a donation to Ghana. The main areas of focus at the NMIMR are regionally prevalent infectious diseases, such as malaria, schistosomiasis, lymphatic filariasis, and HIV/AIDS.[33]

The Africa Health Research Institute (AHRI), South Africa (established 2016)
The AHRI was formed through the joining of the KwaZulu-Natal Research Institute for TB-HIV (founded 2009) and the Africa Centre for Population Health (founded 1997) and is funded primarily by the Wellcome Trust and Howard Hughes Medical Institute. University College London and the University of KwaZulu-Natal are academic partners of the AHRI. The research focusses of AHRI are HIV, TB, and related diseases.[34]

Public Health Foundation of India (PHFI) (established in 2006)

The PHFI is a public private initiative that has collaboratively evolved through consultations with multiple constituencies including Indian and international academia, state and central governments, multi & bi-lateral agencies and civil society groups. PHFI is a response to redress the limited institutional capacity in India for strengthening training, research and policy development in the area of Public Health. [35]

Tsinghua University, China (established 1911)
Tsinghua University is a major research university in Beijing, which regularly figures in among the top universities in the world in various rankings. The university undertakes research in a wide range of health areas, including on diagnostic technology and traditional Chinese medicine.[36] In 2016, the University and the BMGF jointly established the Global Health Drug Discovery Institute within the Tsinghua University School of Pharmaceutical Sciences. Areas of focus will include TB, malaria, and broad-spectrum antivirals.[37]

The Mahidol Oxford Tropical Medicine Research Unit (MORU), Thailand (established 1979)
The MORU is a collaboration between Thailand's Mahidol University, Oxford University in the UK, and the Wellcome Trust. MORU develops diagnostics and treatments for malaria, TB, and other neglected diseases.[38] Mahidol University houses other large health research centres, including the Center for Emerging Bacterial Infections and the Excellent Center for Drug Discovery.

Other new institutions in research for health included the Council on Health Research for Development[39] (COHRED), which was founded in 1993 and whose origins lie in the 1990

[33] Noguchi Memorial Institute for Medical Research. Available from: https://www.noguchimedres.org/
[34] Africa Health Research Institute. Available from: https://www.ahri.org/about/
[35] Public Health Foundation of India. Available from: https://phfi.org/
[36] Tsinghua University. Available from: http://www.tsinghua.edu.cn/
[37] Translational Medicine | Global Health Drug Discovery Institute (Beijing). Available from: http://www.sps.tsinghua.edu.cn/en/medical/core.html
[38] Mahidol Oxford Tropical Medicine Research Unit. Available from: http://www.tropmedres.ac/home
[39] Council on Health Research for Development. Available from: http://www.cohred.org/

Commission; the Global Forum for Health Research in 1997, which merged with COHRED in 2010, and the Alliance for Health Policy and Systems Research[40] (AHPSR) in 1999. The Alliance later contributed to the formation of Health Systems Global in 2012, a membership organization which convenes researchers, policy-makers and implementers from around the world to develop the field of health systems research.[41] The IHME, founded in 2007, is the centre of international collaboration on the global burden of disease as well as tracking funding flows for global health generally, and is supported by the BMGF as is G-FINDER, founded also in 2007, which reports annually on funding flows for neglected diseases. Another ongoing project is Disease Control Priorities (DCP) which evaluates the cost-effectiveness of interventions to address the disease burden in LMICs, the first edition of which informed the World Bank's 1993 World Development Report. A second DCP was published in 2006 and the latest volume of DCP3 was published last year.[42]

Other institutions that influence research

Beyond new institutions that focus specifically on research for health, the first decade of this century saw new health financing institutions that have helped create a market for new products, and thus an incentive for research. These include Gavi[43], launched in 2000, the Global Drug Facility[44] (for tuberculosis, founded in 2002), the Global Fund to Fight AIDS, Tuberculosis and Malaria[45] (GFATM) founded in 2002 and Unitaid[46], initially called the international drug purchase facility, started in 2006. Bilaterally, the US President's Emergency Plan for AIDS Relief[47] (PEPFAR) has played a very important part in funding treatments for HIV/AIDS. Nationally, Brazil's provision of universal access to antiretrovirals beginning in 1996 was instrumental not only in addressing Brazil's HIV/AIDS epidemic but also in demonstrating to many sceptics that a developing country could manage effectively such a large programme of drug administration as well as creating the first significant market in developing countries for suppliers of antiretrovirals.[48]

There are a number of other institutions and policy initiatives established in the last 30 years that condition the environment for research. The Agreement on Trade-Related Aspects of Intellectual Property Rights[49] (TRIPS) in 1994 set minimum standards for countries to follow

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[40] World Health Organization. Alliance for Health Policy and Systems Research. Available from: https://www.who.int/alliance-hpsr/en/

[41] Health Systems Global. Available from: https://www.healthsystemsglobal.org/

[42] Universal health coverage and intersectoral action for health: key messages from Disease Control Priorities, 3rd edition. *Lancet* 2018; 391: 1108–20. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32906-9/fulltext

[43] Gavi. The Vaccine Alliance. Available from: https://www.gavi.org/

[44] Global Drug Facility. Available from: http://www.stoptb.org/gdf/

[45] Global Fund to Fight AIDS, Tuberculosis and Malaria. Available from: https://www.theglobalfund.org/en/

[46] Unitaid. Available from: https://unitaid.org/#en

[47] U.S. President's Emergency Plan for AIDS Relief. Available from: https://www.pepfar.gov/

[48] Greco D and Simao M. Brazilian policy of universal access to AIDS treatment: sustainability challenges and perspectives. *AIDS* 2007, 21 (suppl 4): S37–S45. Available from: http://www.who.int/hiv/events/artprevention/greco.pdf

[49] World Trade Organization. Trade-Related Aspects of Intellectual Property Rights. Available from: https://www.wto.org/english/tratop_e/trips_e/trips_e.htm

in respect of intellectual property rights with implications for incentives to invest in health R&D, and for the accessibility and affordability of patented drugs. In addition, bilateral and multilateral trade agreements often include provisions relating to patent terms or data exclusivity that go beyond TRIPS and may diminish access to generic medicines.[50]

The regulatory framework is important for conducting R&D, for determining quality and efficacy and also in influencing the scope and cost of clinical trials necessary to gain marketing approval. The European Medicines Agency[51] (EMA) was founded in 1995. More recently the establishment of the African Medicines Agency has been announced.[52] Regulators have also introduced measures to incentivize the development of certain kinds of drugs. These include incentives for "orphan drugs" with small patient numbers, including a period of marketing exclusivity, which were introduced in the USA in 1983 but in Japan and the European Union only in 1993 and 1999 respectively. In the US, priority review vouchers were introduced in 2007 which allow developers of drugs for a list of neglected diseases and, more recently, rare paediatric diseases to receive a transferrable voucher which they can either sell or use to receive accelerated review of another product they have developed.[53] A similar scheme, but involving an additional five years of market exclusivity, was introduced in the US in 2012 to stimulate the development of new antibiotics with limited success.[54] A scheme to speed the development and delivery of pneumococcal vaccines was introduced by Gavi in 2009 (the pneumococcal Advance Market Commitment or AMC) which provides guaranteed prices to manufacturers in return for a commitment to supply the vaccine at an affordable price in the longer term.[55] Others have introduced a variety of prize schemes to incentivize development of medical technologies e.g. the Longitude[56] and Horizon[57] prizes for diagnostics.

Beyond that, there have been a number of innovations in health technology assessment (HTA) which are relevant to research for health. The Cochrane Collaboration was founded in 1993 to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence. It is now a global network with Cochrane groups in 43 countries.[58] Also in 1993 the International Network of Agencies for Health Technology Assessment (INAHTA) was created, now a network of 50 HTA

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[50] Clift C. Data Protection and Data Exclusivity in Pharmaceuticals and Agrochemicals**.** Oxford, 2007. Available from : http://www.iphandbook.org/handbook/ch04/p09/

[51] European Medicines Agency. Available from: https://www.ema.europa.eu/en

[52] African Union. African Union leaders adopt the Treaty for the establishment of the African Medicine Agency (AMA). Available from: https://au.int/en/pressreleases/20190211/african-union-leaders-adopt-treaty-establishment-african-medicine-agency-ama

[53] Priority Review Vouchers. Available from: https://priorityreviewvoucher.org/

[54] Regulatory Affairs Professionals Society. Updated: FDA to Congress: Consider Changes to GAIN Act. 7 February 2018. Available from: https://www.raps.org/news-and-articles/news-articles/2018/2/fda-to-congress-consider-changes-to-gain-act

[55] Gavi. About the pneumococcal AMC. Available from: https://www.gavi.org/investing/innovative-financing/pneumococcal-amc/about/

[56] Longitude Prize. Available from: https://longitudeprize.org/

[57] European Commission. Horizon prizes. Available from: https://ec.europa.eu/research/horizonprize/index.cfm

[58] Cochrane. Available from: https://www.cochrane.org/about-us

organizations.[59] Health Technology Assessment International (HTAi) was founded in 2003 and there are several other regional organizations for national HTA bodies.[60] Prominent national HTA organizations include the National Institute for Health and Care Excellence[61] (NICE) in England established in 1999, and the Health Intervention and Technology Assessment Program (HITAP) in Thailand, established in 2007.[62]

How the Report was Compiled

Terms of reference

The terms of reference asked us to undertake a review of previous reports and initiatives which have taken a macro perspective on research for health and conduct an analysis of the current architecture and investment in research for health. The review should identify where progress has been made against previous recommendations; where there is still more to do, and why; and gaps and issues which may not have been previously systematically identified. The scoping report should:

1. Extract major points of the 1990 *Health Research* report's 'Agenda for Action', including key elements, recommendations and subsequent initiatives.
2. Define criteria and data sources to measure the implementation of these recommendations, disaggregated to different levels (global, regional, national).
3. Measure implementation and progress against these criteria.
4. Identify other major macro-level reports and initiatives on research for health since 1990, and similarly track their implementation. Identification and prioritisation of reports and initiatives to analyse should be part of the work for this report.
5. Analyse why historic reports and initiatives may not have been fully or successfully implemented.
6. Map existing organisations and initiatives in the current research for health ecosystem. This should include funders, coordinators, and research organisations, from public and private sectors, operating at national, regional, and international levels.
7. Map unmet targets, challenges and areas for further investment and innovation.

The report is expected to provide a comprehensive literature review and in-depth interviews with key stakeholders involved in past reports and initiatives, and in the current research for health ecosystem.

Work on the study began on 27 August 2018.

[59] International Network of Agencies for Health Technology Assessment. Available from: http://www.inahta.org/
[60] Health Technology Assessment international. Available from: https://htai.org/
[61] National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/
[62] Health Intervention and Technology Assessment Program. Available from: http://www.hitap.net/en/

Method of work

The first step was to seek to widen our preliminary list of stakeholders by asking prominent people in the field to nominate others who should be contacted, particularly to increase representation from LMICs. This resulted in a list of nearly one hundred stakeholders.

It was also agreed with the Wellcome Trust that we would seek responses from the full list by means of a survey based on a short list of questions to elicit their views (see Annex 1). Recognizing the importance of maximizing responses we offered the choice of a written response or a telephone call. In the end we received nine written responses and 20 telephone interviews, giving a total of 29 respondents (see Annex 2).

Given the short time frame, and the fact that the questions were open-ended, the overall response rate seems satisfactory for a survey of this nature. Most of the respondents were researchers (academic or biomedical), in global health organizations, NGOs, governments, PDPs or a combination of these roles over the years. However, there are several notable deficiencies. Only six of the respondents were from LMICs. Major funders were also underrepresented – we had two respondents from the National Institutes of Health (NIH), one from the World Bank, and one from a development agency but none from the two major foundations, Gates or Wellcome. There was no industry respondent.

We also compiled a list of reports, mainly those produced by official organizations which we considered to be influential or important or both. In Annex 3 we provide a list of what we consider the most significant, but there are many others and many journal articles which have made significant contributions in relation to thinking about research for health.

We also compiled a list of initiatives (Annex 4). Again, this is rather selective, but it does illustrate the very wide diversity of organizations that are involved in, or influence, research for health.

In respect of the terms of reference it should be noted that tasks 2 and 3 were challenging. Partly this a matter of the time available – there are in total hundreds of recommendations in the reports reviewed. Moreover, the great majority of recommendations are unquantified or unspecific – more usually recommendations ask governments, funders or other stakeholders to strengthen/expand/provide/promote some desired end. To take one example, the 1990 Commission asked developing countries, inter alia, “to develop reliable and continuing links between researchers and research users”. In principle, it would be possible to assess whether this had happened and in which countries, but it is way beyond the scope of this rapid study to undertake such a task, let alone disaggregate the results to national, regional and global levels.

We have therefore been pragmatic about this. Where it is possible to establish whether a specific recommendation has been implemented we have provided the evidence where it is available from the existing data or literature. More generally we can also assess the extent to which the broader thrust of recommendations has borne fruit. For example, the central point of the 1990 Commission was the advocacy of Essential National Health Research (ENHR) and

it is possible from subsequent reports and other literature to say something meaningful about the extent to which countries have developed capacity in this area.

Key reports and their implementation

The reports

The **1990 Commission report**, as noted above, made one seminal recommendation on Essential National Health Research (ENHR). While most countries might not have the capacity to develop new health technologies needed by developing countries, every country should have the research capacity to determine its particular health problems, to analyse different ways of dealing with them and to choose the most appropriate course of action to achieve the greatest health improvement with limited resources. Strengthening research capacity in developing countries was a high priority. This would require primary commitment by developing countries themselves but should be strongly supported by the international community including strengthening networks and partnerships at the regional and international levels. One outcome of these recommendations was the establishment of COHRED in 1993, whose central priority was the promotion of ENHR.

The Commission also recommended that at least 2% of national health expenditures should be devoted to EHNR, and at least 5% of aid for health should be earmarked for research and development – recommendation that has been echoed in various ways in subsequent reports and documents. Figures on health research expenditures are not available for LMICs, but our calculations suggest that less than 2% of development assistance for health is devoted to R&D (as defined by G-FINDER which essentially covers biomedical research).

The other main contribution of the report was to highlight what has become known as the 10/90 gap. In fact, the report calculated, based on data for 1986, that $1.6 billion, or less than 5% of global health research spending of $30 billion, was devoted to the health problems of developing countries which accounted for 93% "of the years of potential life lost in the world". Intriguingly it estimated that governments of developing countries spent $650 million on research, a sum far in excess of current G-FINDER estimates which is just $105 million in 2017.[63] This seems to derive from an assumption that all health research funded by developing country governments was on diseases mainly affecting developing countries which was unlikely to have been the case (see Box 5).

The **1993 World Development Report Investing in Health**[64] was influential in a number of ways not least in giving birth to the Global Burden of Disease and Disease Control Projects mentioned above. It popularised the use of disability-adjusted life years (DALYs) as a means of prioritising health care priorities as well as those for research and development. The report echoed many of the recommendations of the 1990 report, including on the need for EHNR and health policy research on financing and healthcare delivery. Total investment in health

[63] Policy Cures Research. Neglected disease research and development: Reaching new heights. Sydney, 2019. Available from: https://www.policycuresresearch.org/g-finder-2018/

[64] World Bank. World Development Report: Investing in Health. Washington, 1993. Available from: https://openknowledge.worldbank.org/bitstream/handle/10986/5976/9780195208900_fm.pdf

technology research relevant to developing countries was woefully inadequate. Moreover, an international mechanism was required for the better coordination and more stable funding of technology research and the research needed for its application.

The **1996 Ad Hoc Committee on Health Research: Investing in Health Research and Development**[65] identified four key challenges:

- The traditional threats to maternal and child health from infection, malnutrition and perinatal conditions, which still accounted for more than one third of the disease burden globally, and nearly half in LMICs.
- The continually changing threat from microbial evolution and spreading antimicrobial resistance amidst greater human mobility – posing threats, for example, in relation to tuberculosis, malaria, HIV and pneumococcus.
- Emerging epidemics of noncommunicable diseases and injuries which required cost-effective interventions for prevention, diagnosis and treatment.
- The efficiency and equity of health service provision. Governments struggled to meet the rising demand for, and cost of, health service provision without adequate information or knowledge on how best to provide an equitable and efficient service, or of the impact on health of other sectors such as education or employment.

Research, ranging from the biomedical to health policy, was vital to develop new tools and to put existing tools and interventions into effective use. The Committee's recommendations included:

- More resources for developing and evaluating packages of interventions to address maternal and child mortality as well as for developing new tools including vaccines and new contraceptive methods.
- A Health Product Development Facility or Alliance should be created to "focus and synergise" the research needed to address microbial threats, including antimicrobial resistance.
- Establishing three new Special Programmes for Research and Training related to Noncommunicable diseases and Healthy Aging, Injuries and Health Systems and Policy. The last resulted, as noted above, in the formation of the Alliance for Health Policy and Systems Research (AHPSR) in 1999.
- Incentives beyond the current patents system should be explored to incentivize R&D in the private sector.
- A Forum for Investors in International Health should be formed to undertake dialogue and analytic work to allow better decisions on resource allocation. This recommendation appears to be the origin of the Global Forum for Health Research.

[65] World Health Organization. Investing in Health Research and Development. Geneva, 1996. Available from: http://apps.who.int/iris/handle/10665/63024

The **2001 Commission on Macroeconomics and Health**[66] was commissioned by the WHO with the objective of demonstrating the contribution that investing in health could make to economic development. The larger part of the report was about the actions and resources needed to scale up a package of essential health interventions for poor people. To that end it made quantified and ambitious recommendations for the resources countries and the donor community should devote to health.

It recognized the importance of new knowledge in scaling up health interventions - a critical area was operational research where much was not known about what did or did not work, and even when it was known there was a need to adapt interventions to local conditions and context. It thought 5%, rather than 2%, of health programmes should be devoted to operational research. There was also an urgent need for better information and surveillance on the disease burden which was essential for disease control. Beyond that greater investment was required in biomedical research to develop new tools to fight killer diseases.

It advocated a Global Health Research Fund amounting to $1.5 billion annually by 2007 and $2.5 billion annually by 2015. A further $1.5 billion annually should be channelled through existing research institutions such as the Special Programme for Research and Training in Tropical Diseases (TDR) or the PDPs. Further it called for more investments in global public goods including, for example, disease surveillance, data collection and analysis of global health trends (such as burden of disease), analysis and dissemination of international best practices in disease control and health systems, and technical assistance and training. These would require an additional $1 billion annually by 2007 rising to $2 billion by 2015. Apart from these quantified targets, it strongly supported moving to open access for all journal articles.

It also made a number of proposals for incentivizing private sector R&D (e.g. by modifying orphan drug laws to cover neglected diseases) while encouraging pharmaceutical companies to adopt differential pricing and to supply low-income countries at the "lowest viable commercial price". It encouraged the voluntary licensing of patents on essential medicines to generic producers to supply low-income countries, an idea that later came to fruition in the establishment of the Medicines Patent Pool.[67] It also supported the right of countries to use compulsory licensing in order to import products from generic suppliers, including the option for countries without manufacturing capacity to import from third countries under a compulsory licence (as recently enshrined in the 2001 Doha Declaration on TRIPS and Public Health).[68]

In reality, none of its specific recommendations on R&D have come to pass, notably a global fund for research which, as noted below, has encountered significant opposition from

[66] Commission on Macroeconomics and Health. Macroeconomics and health: Investing in health for economic development. Geneva, 2001. Available from: http://www1.worldbank.org/publicsector/pe/PEAMMarch2005/CMHReport.pdf

[67] Medicines Patent Pool. Available from: https://medicinespatentpool.org/

[68] World Trade Organization. Declaration on the TRIPS agreement and public health. 14 November 2001. Available from: https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

potential funders. Where it broke new ground was its emphasis on facilitating access to medicines through differential pricing, or ultimately through the use of compulsory licensing. The previous reports had largely ignored this important issue, which could no longer be ignored in the wake of controversies about patents and access to antiretrovirals. Its more general recommendations for scaling up aid for health on a massive scale were partially realised in the following decade when aid for health tripled in real terms before stagnating in recent years.[69]

The **2004 World report on knowledge for better health: strengthening health systems**[70] argued that much more investment was needed for a new, innovative approach to research on health systems, which needed to be managed more effectively and a stronger emphasis should be placed on translating knowledge into action to improve public health by bridging the gap between what is known and what is actually being implemented.

The report noted that:

- Science must help to improve health systems. It should not focus solely on advancing academic knowledge or confine itself to producing drugs, diagnostics, vaccines and medical devices.
- Biomedical discoveries could not improve people's health without research to find out how to apply them specifically within different health systems, population groups, and diverse political and social contexts.
- Health systems must interact closely with health research systems to generate and use relevant knowledge for their own improvement.
- Every country should have a national health research system that focuses its energies on health problems of national interest, especially those which will strengthen health systems. Each health research system should have strong leadership and effective management.
- Equitable access to both published and unpublished research information is a priority. In particular, an environment should be created where the users of research can access and find relevant knowledge to inform their decisions.
- New research should build on existing knowledge and health decisionmakers should use research syntheses to inform policy and practice. Failure to do so may result in serious consequences for patients and to the inefficient use of limited resources for health-care provision and research.

The report recommended 1) Increasing investments in health research both in health systems and new tools; 2) Strengthening management of health research systems including through better access to information and an international clinical trials' register and 3) Bridging the

[69] Institute for Health Metrics and Evaluation. Financing Global Health 2017. Seattle, 2018. Available from: http://www.healthdata.org/sites/default/files/files/policy_report/FGH/2018/IHME_FGH_2017_fullreport_online.pdf

[70] World Health Organization. World report on knowledge for better health: strengthening health systems. Geneva, 2004. Available from: http://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf

gap between knowledge and action by evidence-informed policy and practice and use of evidence by policy and decision makers.

The **2004 Mexico Statement on Health Research**[71] issued by the Ministerial Summit noted that research, both biomedical and social science, had a critical but under-recognized part to play in strengthening health systems and the prevention, diagnosis, and treatment of a wide range of diseases. But it said that crucial research aimed at strengthening public health and health systems has been neglected and under-funded. It called for governments, funders, researchers, and other stakeholders to take a number of actions to strengthen health research and its utilisation including establishing "sustainable programmes to support evidence-based public health and health-care delivery systems, and evidence-based health related policies."

A follow-up ministerial summit took place in Bamako in 2008 producing the **Bamako call to action on research for health: Strengthening research for health, development, and equity.**[72] It called for greater equity in research for health: only a small proportion of global spending on research addressed the health challenges that disproportionately affect the poor. Research and innovation for health improvement, especially in the context of the MDGs, was not sufficiently inter-disciplinary and inter-sectoral. There was a need to mobilize all relevant sectors (public, private, civil society) to work together in effective and equitable partnerships to find needed solutions. Funding for research for health, especially in LMICs, was difficult to secure, but there were considerable societal returns available as a result of that investment. Unlike at the Mexico summit it explicitly recommended that governments should invest 2% of their health budgets in research and funders should allocate 5% of their development assistance for health to research. Ministers also called for the better alignment, coordination, and harmonization of the global health research architecture and its governance through the rationalization of existing organizations, to improve coherence and impact, and to increase efficiencies and equity.

The **2006 Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH)**[73] focussed on the interaction between intellectual property rights, innovation and public health in the context of biomedical research – the development of new tools to address diseases disproportionately affecting developing countries, and the ways in which access to the products of R&D could be facilitated. It observed that whereas there was an innovation cycle operating in developed countries that broadly worked to sustain innovation and deliver the health care needed by their inhabitants, this was not the case in developing countries where the lack of effective demand – but not the need – meant that there was little incentive to

[71] Ministerial Summit on Health Research. The Mexico Statement on Health Research: Knowledge for better health: strengthening health systems. 2004. Available from: http://www.who.int/rpc/summit/agenda/en/mexico_statement_on_health_research.pdf

[72] Ministerial Summit on Health Research. Bamako Call to Action on Research for Health: Strengthening research for health, development, and equity. 2008. Available from: http://www.who.int/rpc/news/BAMAKOCALLTOACTIONFinalNov24.pdf

[73] World Health Organization. Commission on Intellectual Property Rights, Innovation and Public Health. Geneva, 2006. Available from: http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf?ua=1

develop new or modified interventions appropriate to the disease burden and conditions of those countries.

It made a total of 60 detailed recommendations – for governments, funders, the pharmaceutical industry and the WHO. It summarised a list of key issues that need to be addressed going forward:

- Identification of gaps in the current coverage of research for diseases that disproportionately affect developing countries.
- Providing a sustainable source of funding for public–private partnerships and other R&D institutions in the field.
- Seeking ways to channel greater funding to research organizations in developing countries in both the public and private sectors.
- Whether common interests of product developers and producers in various areas might be better addressed collectively in areas such as facilitating clinical trials and product delivery.
- Supporting product introduction in developing countries through improved regulation, at national, regional and international level.
- Monitoring the impact of TRIPS and the Doha Declaration on innovation and access for medicines and other health-care products.
- Measuring performance and progress towards objectives, and monitoring and evaluation of programmes.

It said that there was an urgent need for action to generate more and sustainable funding for R&D to address the health needs of developing countries, and to engage governments in this endeavour. To that end it called for the WHO to develop a Global Plan of Action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that disproportionately affect developing countries.

Box 3 Follow-up to the CIPIH report

In response to the CIPIH, WHO member states established an intergovernmental working group (IGWG) to draw up a **global strategy and plan of action (GSPA)** in order to provide a medium-term framework aimed at securing an enhanced and sustainable basis for needs-driven, essential health R&D relevant to diseases that disproportionately affect developing countries. The IGWG, after tortuous negotiations, agreed a GSPA consisting of eight elements, 25 sub-elements and 108 specific actions.[74]

An independent review of the GSPA in 2017 concluded that implementation of the strategy was extremely problematic, not least because most stakeholders in the research community were unaware of it. By covering multiple elements in the pathway from research to practice to policy, the GSPA was too unwieldy for effective implementation. In

[74] World Health Organization. Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. Geneva, 2011. Available from: http://www.who.int/phi/pubslications/Global_Strategy_Plan_Action.pdf

order to be effective, it would have to impact the work of research funders, researchers, regulators of medicines and health products, funders of medicines and health products and health care regulators and providers at many levels in each jurisdiction nationally and locally. It concluded this was not realistic.[75]

One specific recommendation of the GSPA was to establish an expert working group to examine the financing and coordination of research and development (R&D) and proposals for "new and innovative" sources of funding for R&D. The reason for this recommendation was that it represented a compromise between the many member states in the IGWG negotiations pressing for a global fund for research and an opposing group of potential major contributors who vigorously resisted it. After the first expert working group produced a report that failed to satisfy many member states, a Consultative Expert Working Group (CEWG) was established which reported in 2012.

The **2012 Consultative Expert Working Group on Research and Development: Financing and Coordination**[76] proposed a series of measures to incentivize R&D including open approaches, prizes and patent pools. After considering various ways in which sustainable funding for R&D could be generated – including 'sin' taxes on food products and tobacco as well as a financial transactions tax – it made a series of specific recommendations:

- All countries should commit themselves to dedicate at least 0.01% of their GDP to government-funded R&D on mandated diseases. (This was the proportion of GDP spent by the USA at that time on R&D for such diseases.) This would deliver an approximate doubling of funding for research from $3 billion to $6 billion, as originally recommended by the Commission on Macroeconomics and Health in 2001.
- Developing countries with potential research capacity should aim to commit 0.05–0.1% of their GDP to government-funded health research of all kinds.
- Developed countries should aim to commit 0.15–0.2% of their GDP to government-funded health research of all kinds.

In respect of coordination, the CEWG considered that the WHO should play a stronger central role in improving coordination of R&D on the health needs of developing countries. The main elements of such coordination by WHO should be:

- a global health R&D observatory to collect and analyse data, including financial flows to R&D and the R&D pipeline, and to learn lessons; and
- advisory mechanisms, comprising a network of research institutions and funders, that might provide input to an advisory committee that could be based on the current Advisory Committee on Health Research.

[75] World Health Organization. Overall programme review of the global strategy and plan of action on public health, innovation and intellectual property. Geneva, 2017. Available from: http://www.who.int/medicines/areas/policy/GSPA-PHI3011rev.pdf?ua=1

[76] World Health Organization. Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination. Geneva, 2012. Available from: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

In conclusion, the CEWG considered it time to consider new ways to achieve the objectives with which WHO Member States had been grappling for so long. A coherent global framework was required that combined the different elements and recommendations into a concerted mechanism. It therefore proposed that discussions on negotiation of a R&D convention be initiated.

Box 4 CEWG and Follow up

The CEWG focussed on an important point that development assistance was the source of a small proportion of research funding for neglected diseases. According to G-FINDER, the NIH was responsible in 2016 for over 40% of all research it covers. The top five funders (NIH, BMGF, industry, Wellcome Trust and the US Department of Defense) together provided nearly 80% of all funding. In that light the emphasis on the importance of development assistance in earlier reports, beginning with the 1990 Commission, seems misplaced. Hence its focus on targets as a percentage of GDP – in particular the target of 0.01% of GDP for all countries. In reality, the figures for developed countries mainly show a marked movement in the opposite direction between 2010 (on which CEWG figures were based) and 2017. The US proportion has declined from 0.01% to 0.008% although the UK has increased from 0.006% to 0.007%.[77] No other country exceeds 0.004%. In respect of overall developed country health research, the average for the OECD is 0.11% of GDP in 2016, ranging from 0.22% in Sweden to under 0.01% in Switzerland.[78]

The follow up to the report in the WHO was protracted. Governments of high-income countries strongly resisted the idea of an R&D convention. There was also no support for even a relatively modest pooled fund for R&D (disbursing $100 million annually) as proposed by the WHO.[79] An initiative to select and fund "demonstration projects" illustrating new ways of doing research also proved problematic and attracted insufficient funding. The only verifiable concrete outcome was the establishment in the WHO of a Health Research and Development Observatory, but according to all reports this is seriously underfunded and not in a position to do much beyond bringing together existing data bases on health R&D.[80] In line with the CEWG recommendation for an advisory committee the WHO also committed in 2016 to establish an expert committee on health research and development "to provide technical advice to the Director-General on the prioritization of health research and development" but this initiative has not yet been implemented.[81]

[77] Reworking by authors of figures in Table 4.3 of CEWG report using same sources.
[78] Data from OECD. Joint OECD-Eurostat international data collection on resources devoted to R&D.
[79] World Health Organization. Health Product Research and Development Fund: Proposal for Financing and Operation. Geneva, 2016. Available from: http://www.who.int/tdr/publications/r_d_report/en/
[80] World Health Organization. Global Observatory on Health R&D. Available from: http://www.who.int/research-observatory/en/
[81] World Health Organization. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Terms of reference of the expert committee on health research and development. EB140/22. 21 November 2016. Available from: http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_22-en.pdf?ua=1

The **2013 World Health Report: Research for Universal Health Coverage**[82] has three key messages:

- Universal health coverage cannot be achieved without evidence from research. Research has the power to address a wide range of questions about how we can reach universal coverage, providing answers to improve human health, well-being and development.
- All nations should be producers of research as well as consumers. Research should be used to strengthen investigations not only in academic centres but also in public health programmes, close to the supply of and demand for health services.
- Research for universal health coverage requires national and international backing. To make the best use of limited resources, systems are needed to develop national research agendas, to raise funds, to strengthen research capacity, and to make appropriate and effective use of research findings.

Research has been fundamental to the improvement of human health. Research is vital in developing the technology, systems and services needed to achieve universal health coverage. The report identifies two kinds of research questions. Most important are questions about improving health and well-being – that will help us to define the interventions and services that are needed, including financial risk protection, discover how to expand the coverage of these services, including the reduction of inequities in coverage, and investigate the effects of improved coverage on health. The second set of questions is about measurement – of the indicators and data needed to monitor service coverage, financial risk protection, and health impact.

The results of some research studies are widely applicable, but many questions about universal health coverage need local answers. All nations therefore need to be producers of research as well as consumers of it (an echo of the 1990 Commission). In LMICs, the principal challenges are to strengthen research systems, identify key research questions, and generate the capacity to turn research into practical applications.

Achieving universal health coverage depends on research ranging from studies of causation to the functioning of health systems. Most health research is devoted to developing new interventions - far too little is devoted to turning evidence from research into actions that improve health. A large number of cheap, efficacious and cost-effective existing interventions remain inaccessible to many who could benefit from them. Some are hardly used at all; for others, widespread implementation takes years or decades.

Because of this, there is a particular need to close the gap between existing knowledge and action. Many of the determinants of health and disease lie outside the health system so research needs to investigate the impact of policies for “health in all sectors”. Research will

[82] World Health Organization. Research for Universal Health Coverage. Geneva, 2013. Available from: http://apps.who.int/iris/bitstream/handle/10665/85761/9789240690837_eng.pdf;jsessionid=A7FA83BD7AF5D3A8AF003FFF854ECA8E?sequence=2

add to the evidence on how human activities affect health, for example through agricultural practices and changes to the natural environment.

The **2013 Lancet Commission on Investing in Health: Global health 2035 – a world converging within a generation**[83] was prompted by the 20th anniversary of the 1993 World Development Report. It argues that, with rising incomes in the developing world and continued improvements in health and delivery technologies, an achievable goal for nearly all countries in 2035 is to reduce the rates of infection and maternal and child mortality to the current levels of the four best-performing middle-income developing countries (Chile, China, Costa Rica and Cuba).* It endorsed a move towards universal health coverage by what it called "progressive universalism". It recommended public financing of a defined set of interventions for all, particularly for the health needs of the poor, at no cost to the patient.

It recommended, like the CEWG report, that funding for health R&D targeted at diseases that disproportionately affect LMICs should be doubled from current amounts of $3 billion annually to $6 billion per year by 2020, with half of this increment coming from middle-income countries themselves. Development of new tools to tackle the growing global crisis of antibiotic resistance should be high on the agenda.

It also emphasised the importance of what it called population, policy, and implementation research (PPIR). This had an important role, for example, in curbing NCDs and injuries - studying the population factors, policies, and delivery systems that work best for scaling up of interventions for NCDs and injuries. Progress in the arena of PPIR has been slower, although in recent years studies of implementation success factors and barriers had increased in number. Little empirical research evidence existed about how best LMICs could structure insurance reforms to move towards UHC. Much remained to be learned about the financial protection value of specific interventions and platforms. This knowledge would then need to be combined with evidence of the health benefits of these interventions and platforms to chart possible pathways to UHC that could inform national decision making. Another important aspect was to support implementation research—to ensure that today's efforts yield sound empirical guidance for tomorrow's decisions.

In an **update** published in October 2018,[84] while reiterating the call for doubling biomedical research, the Commission reemphasized the importance of PPIR. It argued that progress in global health is being hindered by a large delivery gap—the gap between our knowledge of evidence-based interventions and their actual delivery. Investments in PPIR are needed across many health areas. However, given the ongoing shifts in the global burden of disease,

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[83] Jamison D et al. Global health 2035: a world converging within a generation. *Lancet* 2013; 382: 1898–955. Available from: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(13)62105-4.pdf

* Interestingly, the 1990 Commission had singled out the same four countries and Sri Lanka as having health outcomes far better than their GNP per capita would predict.

[84] Watkins D. et al. Alma-Ata at 40 years: reflections from the Lancet Commission on Investing in Health. *Lancet* 2018; 392: 1434–60. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32389-4/fulltext

PPIR would be particularly important for NCDs. Financing PPIR related to health systems quality and resilience will also be crucial.

The **2016 United Nations Secretary-General's High-Level Panel on Access to Medicines**[85] focussed on the policy incoherence between international trade rules and international human rights law. As such, its recommendations mainly related to the use of the patent system and the flexibilities inherent in the TRIPs agreement to facilitate access to medicines. Beyond that it asked governments to increase their current levels of investment in R&D to meet unmet health needs and to test new models of financing R&D. It called, like the CEWG, for negotiations for a binding R&D convention which delinked the costs of R&D from end prices. The report contained commentaries by some panel members either arguing that it had not gone far enough to facilitate access to medicines, or that it had gone too far in ways that threatened the incentives for private sector innovation.

The **2016 Report of the High-level Panel on the Global Response to Health Crises**[86], which was established in the wake of the 2014 Ebola crisis, noted that the availability of effective medical countermeasures, including vaccines, therapeutics and diagnostics, was crucial in preventing and responding to communicable disease outbreaks, but that of the $214 billion invested in health R&D globally in 2010, less than 2 per cent was allocated to neglected diseases. Even where vaccines or therapeutics existed, they are often inaccessible or unaffordable to vulnerable populations.

Public policy intervention, including more public funding, was required to ensure greater resources are focused on R&D for NDs and other dangerous pathogens, particularly in developing countries. It therefore recommended that the WHO oversee the establishment of a fund of at least $1 billion annually to support R&D of vaccines, therapeutics and diagnostics for neglected communicable diseases. R&D efforts should be targeted according to a priority list of pathogens developed by the WHO. This recommendation led to the WHO R&D Blueprint and the establishment of CEPI. Similar recommendations were made by the **Harvard-LSHTM Independent Panel on the Global Response to Ebola** in 2015,[87] and the Commission **on a Global Health Risk Framework for the Future** in 2016.[88]

The **2016 report of the Review on Antimicrobial Resistance**[89], which was established by the UK government to analyse the global problem of rising drug resistance and propose concrete

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[85] United Nations. Secretary-General's High-Level Panel on Access to Medicines: Promoting Innovation and Access to Health Technologies. New York, 2016. Available from: http://www.unsgaccessmeds.org/final-report/

[86] United Nations. Report of the High-level Panel on the Global Response to Health Crises: Protecting humanity from future health crises. A/70/723. 9 February 2016. Available from: http://undocs.org/en/A/70/723

[87] Moon S et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. *Lancet* 2015; 386: 2204–21. Available from: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2815%2900946-0

[88] Commission on a Global Health Risk Framework for the Future. The neglected dimension of global security: A framework to counter infectious disease crises. Washington, 2016. Available from: http://nam.edu/GHRFreport

[89] Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. London, 2016. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

actions to tackle it, produced a list of recommendations designed to improve the stewardship of existing antibiotics and to incentivize the discovery of new antibiotics and other health technologies needed to address the problem. It emphasized the importance of investing in improved surveillance to better understand the dynamics of resistance and therefore the best ways to tackle it. It called for research to develop rapid diagnostics which were essential if the widespread unnecessary or inappropriate use of antibiotics was to be avoided and the life of existing antibiotics was to be extended. It advocated for the development and wider use of vaccines to reduce the prevalence of infections and the need for antibiotics, as well as searching for alternatives to antibiotics to treat infections. It proposed establishing a Global Innovation Fund of up to $2 billion over five years to encourage early stage and "blue sky" research into innovations necessary to tackle resistance. Finally, it called for the introduction of "market entry rewards" of about $1 billion to incentivize the development of specified new antibiotics and to delink the reward from R&D from sales revenues, which currently provides a perverse incentive for the inappropriate or excessive use of antibiotics.

The report was an important contributor in raising the political profile of the fight against antibiotic resistance being followed by a political declaration in September 2016[90] and a commitment by the G7 in 2017 to establish a Global AMR R&D Hub.[91] Jim O'Neill, the chair of the Review, considers that one of its successes has been to help stimulate greater investment by a number of actors in early stage research. However, the proposal for market entry rewards, which has also been supported in a number of academic studies, has made no headway.[92]

The **2017 World report on health policy and systems research**[93] notes that the HSPR field has demonstrated a remarkable maturation over the past 20 years - the level of funding, the number of publications and the numbers of researchers engaged in HPSR have all grown substantially.

In the mid-1990s there were three principal challenges to the growth of the field of HPSR: (i) the fragmentation and lack of a single agreed definition of the field; (ii) the ongoing dominance of biomedical and clinical research; and (iii) a lack of demand for HPSR. Cross-cutting all these challenges was the problem of relatively limited capacity to undertake high-quality HPSR. There was no common understanding of how various components of a health system – e.g., health financing, the private sector, community health systems – might fit together. There were few textbooks, readers or courses that described the array of methods that those engaged in HPSR might employ. There was confusion between the terms "health systems research" and "health services research". The latter formed a relatively well accepted

[90] United Nations. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. A/71/L.2. 22 September 2016. Available from: https://digitallibrary.un.org/record/842813/files/A_71_L-2-EN.pdf

[91] German Federal Ministry of Education and Research. A global effort to fight resistant pathogens. 22 May 2018. Available from: https://www.bmbf.de/files/PM%200522-041%20Global_AMR_Hub_engl.pdf

[92] Jim O'Neill. An Earnest Proposal for Tackling AMR. Project Syndicate. 2 November 2018. Available from: https://www.project-syndicate.org/commentary/market-entry-reward-antibiotics-by-jim-o-neill-2018-11

[93] World Health Organization. World report on health policy and systems research. Geneva, 2017. Available from: http://apps.who.int/iris/bitstream/10665/255051/1/9789241512268-eng.pdf?ua=1

and supported field of study in high-income countries but differed from health systems research which was primarily discussed with reference to LMICs. While health services research, at the time, focused primarily on micro- and meso-level questions about the interaction between patients, providers, and service-delivery organizations, health systems research typically focused on more macro-level questions concerned with the organization of health systems as a whole.

The 1990 Commission report was a landmark document that played a significant role in drawing the world's attention to the imbalance firstly between investment in health research relevant to the global south vis-à-vis the global north, but also in identifying particularly under-funded areas of research. While it did not use the term HSPR or even health systems research at any point, it did underline the neglect of "policy and social science, and management research" as well as "problems not classified as diseases, such as health information systems, costs and financing, and the wasteful misuse of drugs". The focus on biomedical and clinical research had broader ramifications, particularly with respect to the development of research capacity. While biomedical and clinical research may be best addressed in large centres of excellence sited in locations with relatively good infrastructure and support, with the anticipation that research findings are transferable to other similar contexts, HPSR requires very different types of capacities. Given the context-specific nature of much HPSR, it depends on the existence of capacity in every country and preferably at sub-national levels too. Thus, the dominance of a biomedical and clinical research paradigm also contributed to the severe imbalances in research capacity identified in the 1990 Commission report and in later reports by COHRED and the Global Forum.

A final critical challenge during the mid-1990s was a lack of demand for evidence to inform decision-making about health-systems strengthening. The field of knowledge translation was still nascent; indeed, it was not until the late 1990s and early 2000s that the term "knowledge translation" became widely used to describe the process of supporting the implementation of key research findings. Very little attention was paid to the need for countries to have their own capacity for generating evidence and no attention at all. was paid to the need for investing in the skills of policy-makers so that they could better understand and support research. There was no acknowledgement that HPSR capacity needed to exist widely, including outside of the research sphere.

Since then there has been a growing recognition of the importance of strong health systems, not least because of the experience of disease-focussed delivery organizations such as the Global Fund and that improvements in child health, for example, had been adversely affected by weaknesses in health systems. More recently, the push towards UHC has highlighted the direct links to HPSR, requiring an understanding of appropriate financing mechanisms not just for single diseases but for the health system as a whole, as well as knowledge on how best to organize and deliver health services so as to ensure that they are accessible, affordable and accountable.

There has recently been growing interest and advocacy in implementation science. The WHO launched the Implementation Research Platform in 2010, under the leadership of the Alliance. This global momentum was further driven by a strong focus on implementation

research within PEPFAR, as well as the appointment of Jim Kim as President of the World Bank in 2012, from where he championed "delivery science". Further, the field of improvement science, particularly as it relates to improving the quality of health care and patient safety, has also attracted growing attention, particularly in high-income countries.

Increased international funding for HPSR is slowly trickling down to researchers in LMICs and in some cases national funding is available. But more domestic funding is needed if institutional capacity for HPSR in LMICs is to be strengthened, and to ensure that research is more relevant to local challenges. Domestic funding for research at all levels of the health system must be sustainable. This is particularly true for funding used to support research that is embedded within health-systems decision-making processes, given the time that it takes to build appropriate institutional capacity.

Box 5 G-FINDER Reports

G-FINDER, funded by the BMGF, has been producing annual reports on investment in R&D for neglected diseases since 2008. The 2017 report[94] reviewed investment over the last decade. Total funding increased in real terms from $2.77 billion in 2007 to $3.20 billion in 2016, but most of this increase occurred up to 2009 when funding peaked at $3.39 billion. Funding for PDPs also peaked in 2008 at $667 million but has since declined by 2016 to a decadal low of $420 million. G-FINDER's assessment is that an "overreliance on US government funding is reflected in the heavy concentration of global funding on HIV/AIDS, malaria and TB, and the overwhelming focus of HIC government funding on basic and early stage research. The growth of non-traditional funders is promising, but their collective contribution is still just a fraction of overall global funding. And while Gates Foundation investment in product development has consistently been relied on to balance the public sector focus on basic research – it has provided 55% of all funding to PDPs and 47% of all funding for platform technologies over the last decade – this is again a reflection of overreliance on a single funder. The world can ill afford to keep relying on the US government and the Gates Foundation to provide two-thirds of all global funding for neglected disease R&D over the next ten years, as they have done for the last decade."

The 2018 report[95] found that funding for neglected diseases in 2017 was $3,566m, the highest level ever recorded by the G-FINDER survey. Large increases in funding from the UK government (up $87m, 89%) and the European Commission (EC, up $40m, 50%) narrowed the gap between the second and third-largest public funders and the US government, although US government funding also increased (up $23m, 1.5%) and it remained the largest public funder of neglected disease R&D. The increase from the EC was the result of a nearly seven-fold increase in its funding to the EDCTP. Other large increases came from

[94] Policy Cures Research. Neglected disease research and development: Reflecting on a decade of global investment. Sydney, 2017. Available from: http://policycuresresearch.org/downloads/Y10_G-FINDER_full_report.pdf

[95] Policy Cures Research. Neglected disease research and development: Reaching new heights. Sydney, 2019. Available from: https://www.policycuresresearch.org/g-finder-2018/

India and Germany. The increase in Indian government investment helped drive an overall increase in public funding from LMICs (up 19%), marking the third consecutive year of growth and the second-largest LMIC public investment on record (behind only 2013).

G-FINDER has been an invaluable source of information on R&D for product development for neglected infectious diseases in the last decade. However, the following issues in relation to its coverage and methodology need to be considered:

- The scope is confined to biomedical R&D for health products – other forms of research for health are excluded.
- The scope excludes non-communicable diseases which are growing rapidly in LMICs and where there is a great need to develop and adapt methods of diagnosis, prevention and treatment to the specific conditions of LMICs.
- The 2018 report only captures public funding amongst LMICs by Argentina, Brazil, Colombia, Cuba, Egypt, India, Mexico, Thailand and South Africa who collectively invested $105 million in 2017. This contrasts strikingly with the 1986 estimate of investment of $685 million by developing country governments (for the 1990 Commission) and the 1992 estimate of $1.2 billion (for the 1996 Ad Hoc Committee). While this difference may obviously result from G-FINDER's tight definition of neglected diseases, where LMICs may not focus either, it clearly suggests that there is far more research being done in LMICs, including on neglected diseases, than is captured by G-FINDER. Recent reports suggest that China may very soon overtake the US in total R&D funding, a significant proportion of which is likely to be biomedical or health-related.[96] [97]

The **2017 OECD report New Health Technologies: Managing Access, Value and Sustainability**[98] notes that the proliferation of high-cost medicines and rising drug prices are increasing pressures on public health spending and calling into question the pharmaceutical industry's pricing strategies. Governments needed to work with the industry and regulators to define a new approach to the development and use of new health technologies that encourages innovation while also delivering more affordable and value-for-money treatments.

Pharmaceutical spending is increasingly skewed towards high-cost products. The launch prices of drugs for cancer and rare diseases are rising, sometimes without a commensurate increase in health benefits for patients. In the United States, the launch price of oncology drugs per life-year gained has been multiplied by four in real terms and now exceeds $200000. Payers are increasingly struggling to pay for high-cost medicines targeting very small populations, which are expected to proliferate with the development of precision medicine.

[96] National Science Board. The rise of China in science and engineering. 2018. Available from: https://nsf.gov/nsb/sei/one-pagers/China-2018.pdf

[97] Wu Y et al. China's medical research revolution. *BMJ* 2018;360:k547. Available from: www.bmj.com/content/360/bmj.k547

[98] OECD. New Health Technologies: Managing Access, Value and Sustainability. Paris, 2017. Available from: http://www.oecd.org/health/managing-new-technologies-in-health-care-9789264266438-en.htm

While new treatments for hepatitis are very effective and cost-effective in the long-term, they are unaffordable to many who would benefit in almost all OECD countries because of their high cost.

A rebalancing of the negotiating powers of payers and manufacturers is needed. This could be through increased transparency and co-operation between payers and international joint procurement initiatives, as tested in Europe and Latin America. Pricing agreements, which link the final price paid to the actual performance of the drug, as used in Italy and England, may also be effective if management and administration costs are controlled and the clinical data and evidence collected made widely available to the scientific community.

The report also notes that investment in R&D to treat neglected diseases, such as HIV/AIDS or tuberculosis, fight antimicrobial resistance and address dementia has also become less attractive as their profitability is lower (although many have criticized the inclusion of dementia citing the difficulties of the science rather than the absence of profit potential). The incentives for private investment in these areas should be strengthened.

Many biomedical technologies are today approved and adopted based on limited evidence of their safety and effectiveness. Assessment of their performance in real world conditions is rare. This compromises safety, is wasteful and no longer sustainable.

More efforts are also needed to harness the potential of health data more effectively. Use of personal health data creates major opportunities for health system improvement, research and disease surveillance, but requires the right governance frameworks to realise these benefits while managing the privacy risks.

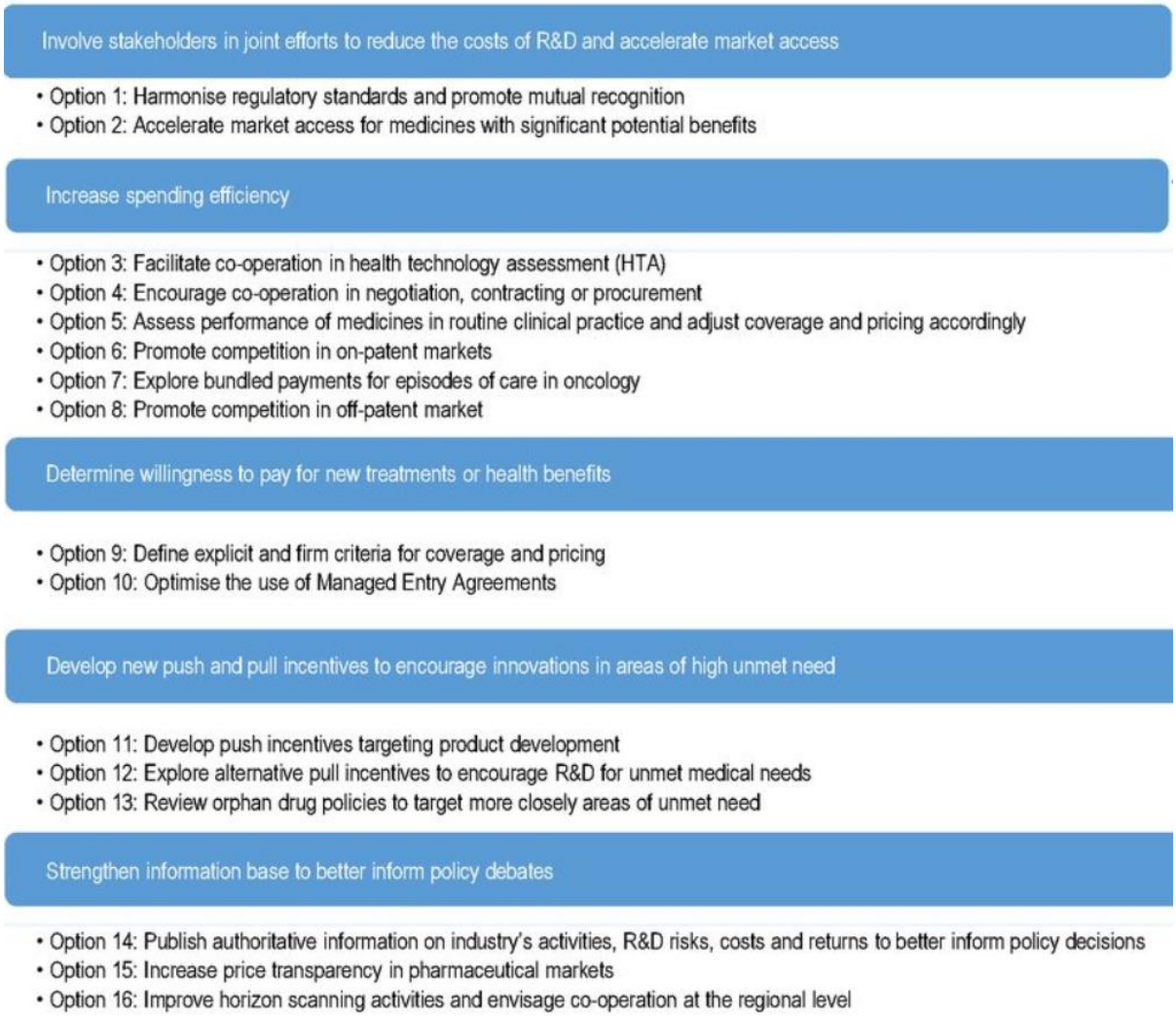
The **2018 OECD report Pharmaceutical Innovation and Access to Medicines**[99] builds on the earlier report by proposing a number of measures to address the current challenges in access to medicines confronting health systems: sharp price increases particularly in relation to oncology and some rare diseases; the cost shock from novel medicines (such as the new hepatitis C drugs) targeting large patient groups; sudden price increases for single-source off-patent medicines and lack of innovation in certain areas such as antimicrobials and some rare diseases. It identifies five broad principles:

- Increasing the value of spending on medicines
- Ensuring access at different levels of development
- Supporting a rules-based system
- Fostering competition in both on-patent and off-patent markets
- Promoting better communication and dialogue between payers, policymakers, pharmaceutical companies, and the general public.

It then identifies 16 policy options tabulated in the figure reproduced below.

[99] OECD. Pharmaceutical Innovation and Access to Medicines. Paris, 2018. Available from: http://www.oecd.org/health/pharmaceutical-innovation-and-access-to-medicines-9789264307391-en.htm

Figure 3.1. An overview of policy options



Commentary

It is interesting to consider the extent to which these reports have with significantly influenced the course of events. In general, it is not so much the specific recommendations, particularly quantified targets for spending, that are effective. Few, if any, of the quantified targets in all of these reports have actually been achieved or been actively supported by the collectivity of governments who are inherently reluctant to commit to such targets. Fifteen years on, the resolution passed at the World Health Assembly in 2005 following the Mexico summit of health ministers simply urged member states "to consider implementing" the recommendation of the 1990 Commission that developing countries should invest at least 2% of national health expenditures, and at least 5% of health aid should be for research.[100] A similar fate awaited the recommendations of subsequent reports on increasing research for health such as those made by the 2001 Commission on Macroeconomics and Health, the 2012

[100] World Health Assembly. Ministerial Summit on Health Research. WHA58.34. 25 May 2004. Available from: http://apps.who.int/iris/bitstream/handle/10665/20384/WHA58_34-en.pdf

CEWG and the 2013 Lancet Commission to increase funding by $3 billion annually. However, such targets, even if not acted upon, are often useful advocacy tools.

Rather, the major impact of these reports comes from encapsulating emerging new ideas. Thus, ENHR is a more memorable legacy of the 1990 Commission report in that its central concept, that every country needs the capacity to adapt health interventions to its own circumstances, influenced the debate on research for health and has been repeated in different ways by many subsequent reports. Its work in highlighting of the paucity of research devoted to the health needs of developing countries was also influential in focussing attention on how to address this gap, giving birth to COHRED and ultimately, the Global Forum for Health Research, as well as being the inspiration for the PDP initiatives. All subsequent reports have taken this as a starting point for their work.

The main impact of the 1993 World Development Report (WDR) has been its methodological contribution in relation to assessing the burden of disease and the application of cost-effectiveness analysis based on DALYs to the prioritisation of health interventions and of research for health, techniques that are now ubiquitous in health, globally and nationally. For instance, the growth of health technology assessment owes a great deal to the spread of these methodologies.

The 1996 Ad Hoc Committee report was in many ways an application of the WDR methodology to health research. Its notable concrete contribution was in the formation of the Alliance for Health Policy and Systems Research in 1999 whose work has been critical in developing this research area – giving birth later to Health Systems Global, a global network of researchers who have held biennial conferences since 2010. While there has been much progress, in terms of methodological development and popularising the use of this research, there still remains a need for greater domestic support for it, both in terms of funding and in convincing decisionmakers of the importance of integrating evidence in the delivery of health care.[101]

However, nearly three decades of reports and initiatives have failed to transform fundamentally the central problem referred to by the 1990 Commission. As revealed by G-Finder, funding for R&D on neglected diseases has been essentially stagnant or falling since 2009, although there was a significant upturn in 2017. A recent study estimated that the additional funding required to bring products for these diseases through the current pipeline, including needed 'missing' products not in the pipeline, would amount to $1.5-2.8 billion annually over the next five years.[102] The decade long discussion in the WHO following the CIPIH report, which produced the GSPA and the CEWG report, actually resulted in minimal concrete outcomes.

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[101] Bennett S et al. The evolution of the field of Health Policy and Systems Research and outstanding challenges. *Health Research Policy and Systems* 2018 16:43. Available from: https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-018-0317-x

[102] Young R et al. Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model. *Gates Open Research* 2018, 2:23 Last updated: 8 October 2018. Available from: https://gatesopenresearch.org/articles/2-23/v2#ref-4

The central question in all this is to identify the drivers of change, which often lie in the realms of political economy. While the CMH report's recommendations on research were not heeded, its objective of making investing in health integral to economic development was to a large extent successful. Yet this was principally because it caught the political mood of the time – it was, in the words of its chair Jeff Sachs, "science-based politics".[103] Its preparation came in the wake of the promulgation of the MDGs and the 2000 G8 Okinawa summit which, for the first time at a G8 summit, made extensive commitments on health and initiated discussions that led to the creation of the Global Fund.[104] It came at a time when G8 governments were concerned about those left behind by globalisation and the spectre of the HIV/AIDS epidemic. The demand of AIDS activists to make the new antiretroviral treatments available and affordable had a profound political impact which was instrumental in driving the creation of the Global Fund and the Doha Declaration on TRIPS and Public Health. At the same time globalisation provided the resources, as well as the willingness, to open the purse strings for global health.

In reality, by the time, the CMH was published in December 2001 much of its main messages had already been absorbed politically, mainly because some members of the Commission, particularly Jeff Sachs, supported by Gro Harlem Brundtland, the WHO's Director-General and other key WHO officials, were actively pushing those messages at the highest political levels.[105]

Similarly, the reports that followed the Ebola crisis were an integral part of the political pressure to make changes in global and national institutions that would avoid its repetition, and contributed to concrete outcomes including, for instance, a reorganisation of the WHO's emergency response capacity as well as initiatives such as CEPI and the R&D Blueprint. And the reports on antimicrobial resistance similarly reflected the political impetus that had been built up to address the problem, although concrete outcomes are, as yet, few.

Reports are therefore more effective where they can build on an existing political constituency for change, and preferably be backed by a powerful advocacy group. They can be successful in other ways in effecting incremental changes to current policies, as in the creation of the three new initiatives arising from the 1990 and 1996 reports, which may take forward continued work in support of their messages or recommendations. The PDPs are also a good example of quite significant institutional change. But radical changes that threaten the status quo and powerful interest groups (such as the pharmaceutical industry or the countries with pharmaceutical industries) or are seen to be very expensive, or both, are unlikely to make headway.

Whither Research for Health?

[103] Horton R. Offline: What makes a good professor? *Lancet* Vol 378 December 17/24/31, 2011. Available from: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140673611618837.pdf

[104] G8 Communique Okinawa. 2000. Available from: https://www.mofa.go.jp/policy/economy/summit/2000/pdfs/communique.pdf

[105] Liden J. The Grand Decade for Global Health: 1998–2008. Chatham House, 2013. Available from: https://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0413_who.pdf

Responses to the Survey

In this section we reflect the views of survey respondents.

What are the major achievements in research for health since 1990?

The introduction mentioned most of the concrete achievements referred to by respondents. The progress made in global health in the first decade of this century was widely noted. Beyond that, respondents referred to positive developments in the institutional arena. Many referred to the enduring contribution of the WHO's Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and Special Programme for Research and Training in Tropical Diseases (TDR), both established in the 1970s, and bracketed these institutions with the Alliance for Health Policy and Systems Research. Alongside the development of PDPs they pointed to the development of promising new partnerships, as well as new initiatives such as the Medicines Patent Pool. Several noted that research capacity in LMICs had increased, although progress was very patchy.

Moreover, there has been a significant flowering of influential NGOs which campaign and take action around issues to do with innovation and access. Much of this growth was stimulated by the HIV/AIDS epidemic. ACT UP[106] was influential in the early days in pressing the industry and regulators to accelerate the development of experimental AIDS drugs, followed by the Treatment Action Group[107] allied with many others, such as the Treatment Action Campaign[108] in South Africa and the International HIV/AIDS Alliance.[109] Since then other NGOs have campaigned effectively to press for innovation and access relevant to the needs of developing countries. These include the Médecins Sans Frontières (MSF) Access Campaign[110], Knowledge Ecology International (KEI)[111], Health Action International (HAI).[112] More recently the NCD Alliance[113] has been formed bringing together more than 2,000 organisations in 170 countries.

Respondents also pointed to increases in our understanding of global health issues, some of which emanated from reports – including the importance of global public goods, and the increasing focus on the importance of operational and health systems and policy research. There was much more recognition of the social, economic, political, environmental and commercial factors that contributed to ill health, but also a dilemma in the integration of these factors into healthcare programmes and their prioritisation.

Are there major areas in research for health since 1990 where progress has been insufficient? Which areas?

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[106] AIDS Coalition to Unleash Power. Available from: http://www.actupny.org/
[107] Treatment Action Group. Available from: http://www.treatmentactiongroup.org/
[108] Treatment Action Campaign. Available from: https://tac.org.za/
[109] International HIV/AIDS Alliance. Available from: https://frontlineaids.org/
[110] Médecins Sans Frontières Access Campaign. Available from: https://msfaccess.org/
[111] Knowledge Ecology International. Available from: https://www.keionline.org/
[112] Health Action International. Available from: http://haiweb.org/
[113] NCD Alliance. Available from: https://ncdalliance.org/

Most respondents pointed out that neglected infectious diseases remain neglected. In particular, many focussed on the startling lack of progress in addressing tuberculosis, the continuing need for effective vaccines for the big three and other diseases including a universal influenza vaccine. Many respondents felt high-burden and middle-income countries should assign much higher priority, in terms of both funding prevention and treatment and research, mentioning tuberculosis in particular. Other areas of concern were the research needs in relation to new antibiotics, as well as the need to research antibiotic stewardship, mental health, traffic accidents amongst others. It was noted that progress had been slower in areas not covered by the MDG agenda.

Most respondents thought that, although progress had been made, a glaring deficit was in the resources devoted to health systems, health services, health policy and implementation and operational research. The primacy of biomedical research was recognized but no one argued that less should be spent on it (rather there should be more in specific areas such as tuberculosis). But there were too many existing interventions demonstrated to be cost-effective and beneficial that were not being implemented and not just for lack of funding. In particular the rise of NCDs, highlighted the importance of researching lower cost means of prevention, diagnosis and treatment. In addition, it emphasized the importance of behavioural and other research to investigate the impact of political, social and environmental and commercial factors on health. Aging populations and rapid urbanization also raised the issue of how the built environment could be more sensitive to health needs, in terms, for example, of effects on nutrition and obesity, reduction of accidents and air pollution as well as being "aging-friendly".

Have some areas of research been overfunded, and some underfunded? Is the balance between biomedical research and other forms of research for health appropriate?

Respondents generally argued that there were no areas that were over-funded but pointed out that there was still a mismatch between the burden of disease and research funding. The areas featured in the MDGs (the big three and mother and child health) were generally best funded. Market conditions also heavily favoured investment in areas such as oncology for products which mainly had a very small impact on life expectancy – in 2017 about half of all clinical trials were for cancer drugs.[114] There is also evidence of inefficiencies through duplicating research and the pursuit of marginal benefits.[115] The inefficiencies and distortion of investment could be due to excessive returns from cancer medicines combined with market dominance. A common comment was that the system was still very disease- and technology-oriented including, for instance, new initiatives such as CEPI and the R&D blueprint, and CARB-X and GARDP, for biomedical countermeasures for epidemics and antibiotics, respectively. Moreover, the research on health impact arising from outside the

[114] Tay-Teo K et al. Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. *JAMA Network Open*. 2019;2(1): e186875. doi:10.1001/jamanetworkopen.2018.6875

[115] World Health Organization. Pricing of cancer medicines and its impacts. Technical Report. Geneva,2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1

health sector was under-funded. One respondent noted that the definition of research for health in this study was insufficiently broad as it ignored the broader determinants of health.

There was general agreement that implementation and other forms of non-biomedical forms of research were underfunded. However, it was also argued that the reasons for this were at root a question of political will. Powerful interest groups, the intellectual property system and market forces all favoured biomedical research as a matter of industrial as much as health policy, and also shaped the composition of that research to exclude areas with poor market prospects. Other forms of health research did not have the same political clout. But nor did they require the vast sums of money consumed in biomedical research. Rather the demand for this kind of research needed to come from decision makers and healthcare workers recognizing its value.[116]

Box 6 Social Prescribing

[W]e will create a National Academy for Social Prescribing to be the champion of, build the research base, and set out the benefits of social prescribing across the board, from the arts to physical exercise, to nutritional advice and community classes. A resource which GPs and other frontline health workers can draw on for guidance and expertise. Where they can learn what works, and what's available in their communities.

Because social prescription reduces over [pre]scription of drugs. It can lead to the same or better outcomes for patients without popping pills. And it saves the NHS money, because many of these social cures are cheaper or free.

Now, drug companies may not like that. And you can bet this multi-billion pound industry will use every tool at their disposal to lobby for the status quo and convince us drugs are better than free social cures. That's why we need a National Academy for Social Prescribing to be a champion for non-drug treatments. And it's the role of the state to sponsor the treatments that are often cheaper, better for patients, and better for society.

Source: Excerpt from speech by Matt Hancock, UK Secretary of State for Health and Social Care. 6 November 2018.
https://www.gov.uk/government/speeches/the-power-of-the-arts-and-social-activities-to-improve-the-nations-health

The point was made that this should not be regarded as a zero-sum game. The two kinds of research should be complementary. Ideally research would be designed on the basis of the following:

- **How big is the health problem?** This could be a disease, or a condition such as air pollution, or a behaviour such as alcohol abuse.
- **What are its proximate and root causes?**

[116] Jones R and Wilsdon J. The Biomedical Bubble: Why UK research and innovation needs a greater diversity of priorities, politics, places and people. Nesta, London, 2018. Available from: https://media.nesta.org.uk/documents/The_Biomedical_Bubble_v6.pdf

- **Why does it persist?** Is it because of a lack of knowledge or tools, a failure to use existing tools or knowledge, a failure in how we organize, finance and deliver health services, or a failure to understand how the determinants of a condition or behaviour could be addressed?
- **What therefore are the research needs?** If there are existing tools what research is required to put them into practice? If there are no tools what research is needed to develop them? If there is a lack of knowledge about determinants what research is necessary?

Looked at in this way, the issue of what kind of research is needed is problem-specific. The reality of course is far more complicated, but the mission-approach has recently been suggested as an appropriate way to address health problems. For example, two respondents raised questions as to whether the search for new tools in the fields of antibiotics and tuberculosis, which has proved largely unsuccessful over several decades, should be complemented by a much greater effort in improving antibiotic stewardship and a greater emphasis on addressing the causes of tuberculosis as well as improving the standard of care using existing tools.

The successes in respect of HIV/AIDS constituted a sort of unplanned mission approach addressing a) the shortage of tools, b) financing of R&D and access, c) pricing and affordability, and d) implementation research to scale-up access. The Apollo moon mission and the approach of the Defense Advanced Research Projects Agency (DARPA) in the US – responsible, for example, for GPS and the internet - are regarded as models by supporters of the mission approach. An analogous institution to DARPA – HARPA - has been proposed in the US[117] and the EU has shown interest in the subject.[118]

Since 1990 there have been significant changes in the institutional architecture that governs research for health. From your perspective what are the positive features of this architecture, and what are the areas that require improvement?

There was a recognition that there had been positive developments in increased funding and new funding sources, which was reflected in the number of new institutions in research and influencing research. There was also greater collaboration regionally and globally and also more focus on building capacity. Accessibility to new products had increased markedly through global procurement mechanisms and the actions of institutions such as Gavi, the Global Fund and Unitaid.

[117] Snyder A. The pitch for a health DARPA. Axios. 19 October 2017. Available from: https://www.axios.com/the-pitch-for-a-health-darpa-1513306295-11f899a8-7956-4ae0-b8a3-034e1c111a8c.html

[118] Mazzucato M. Mission-Oriented Research & Innovation in the European Union. Directorate-General for Research and Innovation, 2018. Available from: https://ec.europa.eu/info/sites/info/files/mazzucato_report_2018.pdf

However, there were many less positive aspects mentioned:

- Funding for research was still highly concentrated in a few large funders which gave them too much influence in *de facto* priority setting compared to e.g. the governments of LMICs.
- The increased number of particularly disease-focussed initiatives increased the dangers of lack of coordination and duplication (e.g. in clinical trials) and encouraged the fragmentation of effort and discouraged the adoption of a holistic approach to health improvement. There was insufficient sharing of data and knowledge. One recent initiative in respect of clinical trials is the Clinical Research Initiative for Global Health.[119]
- PDPs and funders tended to be too technology-focused and not geared up to consider issues connected with field level implementation – patients and health workers had no voice in the research agenda.
- The lack of free and speedy access to research data, methods, tools, and scientific publications hindered access.

Box 7 Practical barriers to undertaking research in Bangladesh

Although funding for research undertaken in LMICs has increased significantly in the past two decades, research infrastructure, such as laboratory equipment, has not kept pace. There are numerous practical barriers to undertaking research in LMICs, which researchers in high-income countries do not face.

Some barriers are logistical: Simple laboratory materials (examples given are PCR and bacterial growth media) can take months to source and deliver and may face long delays at customs.

For research supplies, the authors suggest that research funders such as the BMGF could work with local vendors of other organizations to support their grantees. Local offices of the US Centers for Disease Control and Prevention (CDC) and WHO surveillance initiatives have previously facilitated robust supply chains for research supplies. The WHO could also work with LMIC governments to review customs regulations relevant to laboratory supplies.

Other barriers are financial: Researchers are frequently unable to access full-text articles due to high journal subscription fees, and struggle to pay article processing charges, especially the higher charges often associated with open access publishing. The WHO HINARI Access to Research Initiative allows non-profit organizations in LMICs to access scientific literature for free or at low prices but is linked to GNP and excludes countries such as Brazil and India. However, the authors suggest that for sustainable, systemic change, a global push for universal access to scientific literature is needed.

Source: Saha S et al. Global Science: Barriers in Bangladesh. *eLife* 2018; **7**. DOI:10.7554/eLife.41926.

[119] Clinical Research Initiative for Global Health. Available from: https://ecrin.org/projects/crigh

Do you think the research for health system should be better coordinated? If so, how could this be done?

There was general agreement that research could be better coordinated but also a recognition that this could not be through a directive body. A number of steps were needed to move towards better coordination. It was felt that the WHO could play a larger normative role as, for instance, it had done recently in compiling a list of priority antibiotics where R&D was required and priority emerging diseases for R&D. It could develop and promulgate Target Product Profiles and Preferred Product Characteristics as well as standards for such things as contracting, setting priorities and data reporting and sharing. It was important to take a public health rather than a science-led approach in setting priorities although the value of investigator-driven research was also commented upon.

While the WHO could take a larger role in setting priorities and promoting more coordinated approaches it was noted that the recently established Global Observatory on Health Research and Development, intended to "to help identify health R&D priorities based on public health needs, by consolidating, monitoring and analysing relevant information on the health R&D needs of developing countries; building on existing data collection mechanisms [and] supporting coordinated actions on health R&D"[120] was severely underfunded and not in a position to fulfil its mandate. Similarly, the WHO has failed to implement the establishment of the Expert Committee on Health Research and Development which was seen as an essential complement to the Observatory and was meant to replace WHO's Advisory Committee on Health Research which has been defunct since 2010.

What more should be done to strengthen research capacity and capabilities, particularly in developing countries? Where and by whom?

There were several ideas as to how research capacity could be strengthened. Note was taken by several respondents of the good work done by the European & Developing Countries Clinical Trials Partnership (EDCTP) in building research capacity in Africa but limited to clinical research. Some success stories were noted such as H3D at the University of Cape Town in South Africa which is has a new anti-malarial drug in clinical trials.[121]

There was a strong sense that more should be done by LMICs themselves to support research capacity and indeed research in their own countries. There was scope for the BRICs countries and the G20 to take the initiative here.

There was plenty of advice for funding agencies. Funders were too prone to follow fashion and too keen to see immediate results – the absence of a research infrastructure was not being systematically addressed. A longer-term view was required in order to build capacity. And funders should not set up parallel systems but support country- and regional-led

[120] World Health Organization. About the Global Observatory on Health R&D. Available from: http://www.who.int/research-observatory/why_what_how/en/

[121] Sunday Times (SA). UCT professor named one of 50 World's Greatest Leaders for 2018. 23 April 2018. Available from: https://www.timeslive.co.za/news/south-africa/2018-04-23-uct-professor-named-one-of-50-worlds-greatest-leaders-for-2018/

approaches. There was too much money chasing too few researchers in LMICs. They should also build in-country capacity for training rather than training overseas.

Several respondents suggested that a way forward would be to establish regional research institutes to stimulate and support local research and build capacity.

What are the implications of the move towards universal health coverage and the attainment of the SDGs for research for health?

There was a broad consensus that the main implication of the move towards UHC was that it reinforced the need for implementation research to scale up the use of existing and new technologies. There would be a greater need for health systems and health policy research in considering different ways of financing and organizing health systems and services for UHC. There would also be a greater need for research on service quality (see Box 8). In addition, many respondents highlighted the need for research to address the other determinants of health – including social determinants, climate change, NCDs and city planning.

Box 8 New research is crucial for the transformation of low-quality health systems to high-quality ones

More than 8 million people per year in LMICs die from conditions that should be treatable by the health system. In 2015 alone, these deaths resulted in US$6 trillion in economic losses. Poor-quality care is now a bigger barrier to reducing mortality than insufficient access. 60% of deaths from conditions amenable to health care are due to poor-quality care, whereas the remaining deaths result from non-utilisation of the health system. High-quality health systems could prevent 2·5 million deaths from cardiovascular disease, 1 million newborn deaths, 900 000 deaths from tuberculosis, and half of all maternal deaths each year. Quality of care will become an even larger driver of population health as utilisation of health systems increases and as the burden of disease shifts to more complex conditions. The high mortality rates in LMICs for treatable causes, such as injuries and surgical conditions, maternal and newborn complications, cardiovascular disease, and vaccine preventable diseases, illustrate the breadth and depth of the health-care quality challenge.

Data on care quality in LMICs do not reflect the current disease burden. In many of these countries, we know little about quality of care for respiratory diseases, cancer, mental health, injuries, and surgery, as well as the care of adolescents and elderly people. There are vast blind spots in areas such as user experience, system competence, confidence in the system, and the wellbeing of people, including patient-reported outcomes. Measuring the quality of the health system as a whole and across the care continuum is essential, but not done. Filling in these gaps will require not only better routine health information systems for monitoring, but also new research, as proposed in the research agenda of this Commission. For example, research will be needed to rigorously evaluate the effects and costs of recommended improvement approaches on health, patient experience, and financial protection. Implementation science studies can help discern the contextual factors that promote or hinder reform. New data collection and research should be explicitly designed to build national and regional research capacity.

Source: Kruk M et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution *Lancet Glob Health* Published Online 5 September 2018. Available from: http://dx.doi.org/10.1016/S2214-109X(18)30386-3

Box 9 Excerpts from the Declaration of Astana 2018

We will promote multisectoral action and UHC, engaging relevant stakeholders and empowering local communities to strengthen PHC. We will address economic, social and environmental determinants of health and aim to reduce risk factors by mainstreaming a Health in All Policies approach. We will involve more stakeholders in the achievement of Health for All, leaving no one behind, while addressing and managing conflicts of interest, promoting transparency and implementing participatory governance. We will strive to avoid or mitigate conflicts that undermine health systems and roll back health gains. We must use coherent and inclusive approaches to expand PHC as a pillar of UHC in emergencies, ensuring the continuum of care and the provision of essential health services in line with humanitarian principles (Part IV).

Knowledge and capacity-building. We will apply knowledge, including scientific as well as traditional knowledge, to strengthen PHC, improve health outcomes and ensure access for all people to the right care at the right time and at the most appropriate level of care, respecting their rights, needs, dignity and autonomy. We will continue to research and share knowledge and experience, build capacity and improve the delivery of health services and care.

Technology. We support broadening and extending access to a range of health care services through the use of high-quality, safe, effective and affordable medicines, including, as appropriate, traditional medicines, vaccines, diagnostics and other technologies. We will promote their accessibility and their rational and safe use and the protection of personal data. Through advances in information systems, we will be better able to collect appropriately disaggregated, high-quality data and to improve information continuity, disease surveillance, transparency, accountability and monitoring of health system performance. We will use a variety of technologies to improve access to health care, enrich health service delivery, improve the quality of service and patient safety, and increase the efficiency and coordination of care.

Source: Declaration of Astana. From Alma-Ata towards universal health coverage and the Sustainable Development Goals. 2018. Available from: https://www.who.int/docs/default-source/primary-health/declaration/gcphc-declaration.pdf

Do you have views on how to address the tension between the rising cost of many of the products of R&D and the need to ensure affordability and access in both higher and lower income countries?

Inevitably this question resulted in a variety of views. There was some degree of consensus that PDPs were a good thing – mobilizing public and private sector resources to develop new tools to tackle neglected diseases. One solution was to look at ways to reduce the cost of R&D including, for instance, making regulation less stringent (e.g. by agreeing on new biomarkers

for regulatory approval, or approval subject to post-qualification trial evidence). Several made the point that middle-income countries graduating from GAVI or the Global Fund suffered from losing access to subsidized prices. It was suggested that on the one hand, these countries should allocate more of their own resources, but also the international community might help by organizing procurement regimes which ensured lower prices for those countries suffering from transition out of funding by global institutions. This took account of the fact that most poor people were now in graduating middle-income countries, and more would be as other low-income countries graduated.

For high-income countries, most respondents thought that governments were in a position to do more to restrain prices. Pharmaceutical companies continued to have very high returns (based on profit margins) compared to the average of other large companies, comparable also to software companies.[122] While the productivity of research investments (in terms of $ of R&D expenditure per new approved drug) have been in long-term decline, [123] profits have been sustained by the freedom to price that patents permit. Prominent examples include the very high price of new oncology drugs[124] and those for hepatitis C. Companies were able to charge prices that the market would bear but those markets were themselves either dominated by government spending or susceptible to government control. Several respondents remarked that the business strategies of these companies were dominated by maximizing profits to satisfy shareholders – to the extent that, for example, stock buybacks and shareholder dividends in the US in 2006-15 exceeded spending on R&D.[125]

Thus respondents thought governments could do more individually and collectively to bear down on prices. The WHO has argued that there should be a regime of fair pricing "affordable for health systems and patients and that at the same time provides sufficient market incentive for industry to invest in innovation and the production of medicines."[126] The problem is how to achieve this. Value-based pricing principles have enabled companies to justify very high prices. At the same time agencies, such as NICE in the UK, use similar principles to bear down on prices by securing confidential discounts to bring the price below the acceptability threshold. It was suggested that the WHO could do more to provide and promote health technology assessments globally and regionally to help countries, many of which have weak HTA capacity to make choices on the provision of products. One respondent believed that little could be done without fundamental changes in US policies on pricing.[127]

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[122] US General Accountability Office. Profits, Research and Development Spending, and Merger and Acquisition Deals. Washington, 2017. Available from: https://www.gao.gov/assets/690/688472.pdf

[123] Scannell J et al. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov.* 2012;11:191–200. Available from: doi: 10.1038/nrd3681.

[124] Workman P et al. How Much Longer Will We Put Up With $100,000 Cancer Drugs? *Cell* Volume 168, Issue 4, 9 February 2017, Pages 579-583. Available from: https://www.sciencedirect.com/science/article/pii/S0092867417301241

[125] Lazonick W et al. US Pharma's Financialized Business Model. 13 July 2017. Available from: https://www.ineteconomics.org/uploads/papers/WP_60-Lazonick-et-al-US-Pharma-Business-Model.pdf

[126] World Health Organization. Fair pricing of medicines. Available from: https://www.who.int/medicines/access/fair_pricing/en/

[127] PharmExec.com. Is the Price Right? An Overview of US Pricing Strategies. 25 October 2018. Available from: http://www.pharmexec.com/price-right-overview-us-pricing-strategies

Recent examples of new approaches include Australia's approach to funding hepatitis antivirals by providing one billion Australian dollars over five years for an unlimited supply of medicines.[128] A similar scheme is being implemented in the UK.[129] For different reasons the UK is also introducing a system of paying for antibiotics by subscription rather than per course as a step towards a global system to reward innovation.[130]

Conclusions

There are several key messages that emerge from analysing the reports and the responses to the survey.

- **Neglected diseases continue to be neglected.** The data on funding and the generation of new products strongly indicate that the problem identified in the 1990 report persists. While there have been some achievements, notably in HIV/AIDS, all the institutional innovations of the last twenty years or so have not been fundamentally transformative. Suggestions for making further progress such as calls for doubling funding, an R&D convention or delinking R&D costs from prices have largely fallen on deaf ears. In the current context, it was suggested that it might be appropriate to change the frame of reference from "neglected diseases" to "neglected populations", noting that these existed in both higher and lower income countries and that their needs in respect of healthcare should not be looked at in isolation from the social, economic and other determinants of their vulnerable health status.
- **There needs to be more health policy and health systems research, encompassing also the impact of other sectors on health.** Almost all respondents mentioned the importance of different forms of research for health. This was particularly emphasized in the context of implementing UHC, in addressing NCDs, in stimulating the scale-up of existing interventions, and in addressing the social, economic, political environmental and commercial determinants of health. It was also noted that research was too much organized around disease-focussed and technology-biased programmes and too little attention was paid to the pressing need to strengthen health systems, including ensuring quality, while also addressing the threats to health that came from outside the health sector. In that context, attention needed to be paid alongside SDG Goal 3 on Good Health and Well-Being, to Goal 1 on No Poverty, Goal 2 on Zero Hunger, Goal 5 on Gender Equality, Goal 6 on Clean Water and Sanitation, Goal 7 on Affordable and Clean Energy, Goal 8 on Decent Work and Economic Growth, Goal 11 on Sustainable Cities and Communities and Goal 12 on Responsible Consumption and Production.

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[128] Moon S and Erickson E. Universal Medicine Access through Lump-Sum Remuneration — Australia's Approach to Hepatitis C. *N Engl J Med* 2019; 380:607-610. Available from: https://www.nejm.org/doi/full/10.1056/NEJMp1813728

[129] NHS England. NHS England's plan to eliminate Hepatitis C decisively backed by High Court. Available from: https://www.england.nhs.uk/2019/01/nhs-englands-plan-to-eliminate-hepatitis-c-decisively-backed-by-high-court/

[130] Matt Hancock. Antimicrobial resistance needs an urgent global response. 24 January 2019. Available from: https://www.gov.uk/government/speeches/antimicrobial-resistance-needs-an-urgent-global-response

- **Middle-income countries needed to do more to address their own health problems and the research needed to address them**. The view was expressed quite frequently that middle-income countries needed to take more responsibility for addressing their health problems. The 2013 Lancet Commission recommended that half of its proposed doubling of research funding for neglected diseases should come from middle-income countries. One respondent thought that the solution to tuberculosis had to be found in high-burden countries, rather than in international efforts to generate new technologies. Even so, the problems of graduation from international support were recognised (e.g. with respect to vaccines) and the international community should consider ways to mitigate these (e.g. through engineering price reductions for vaccines).
- **The rise of China** There are very large gaps in the information on what research is going on in LMICs, notably in China. This should be a role for the WHO's Observatory but it does not have the resources. There is a distinct lack of information on the exact scale of China's health research and its composition. Understanding these better might alter conclusions of research for health strategy.
- **The mission approach to health research needs further consideration.** As a methodology it has many attractions but in its application to health there remains a tension between industrial and health objectives. In the UK it has been proposed in the context of industrial strategy in the life sciences sector.[131] It is important that patients, clinicians, healthcare worker and carers rather than researchers or industrial interests drive the agenda but politically these are not the groups with political clout. A related suggestion was to consider the opportunities for new PDPs to pursue research on NCDs including addressing risk factors that lie outside the health sector, bearing in mind recent falls in life expectancy in some high-income countries.
- **Addressing issues of affordability while sustaining innovation.** These issues have to date only been partially addressed. The HIV success has been discussed and one can also point to the PDPs and the Medicines Patent Pool as tools to address the innovation/access conundrum. In vaccines too, Gavi has contributed along with others to making vaccines affordable and accessible in its LMIC recipients. In the antimicrobial sphere, proposals for delinking payments for R&D from the price of the product have gained a degree of official support but have yet to be acted on. The astonishing prices of some new treatments has attracted a lot of political attention in the US and Europe.[132] Many commentators argue that there is something intrinsically wrong with the pharmaceutical industry business model that requires more than

[131] Bell J. Life Sciences Industrial Strategy – A report to the Government from the life sciences sector. London, 2017. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/650447/LifeSciencesIndustrialStrategy_acc2.pdf

[132] McCarthy T. 'Supporting greed over needs': the group taking on big pharma in the midterms. The Guardian, 28 October 2018. Available from: https://www.theguardian.com/us-news/2018/oct/27/big-pharma-midterms-republicans-democrats

tinkering around at the margins.[133] A fundamental look at the incentive structure that drives the industry is perhaps required. Beyond that funders of research could introduce more conditionality related, *inter alia*, to ensuring that the outputs of research are accessible.

- **Utilize the opportunities that lie in digitalization.** Digital solutions, artificial intelligence and big data profoundly influence both the system of research for health as well as the health system. It will be important to develop global public goods in this space to speed up innovation and make its benefits accessible. These will be related to data infrastructures and other tools and digital platforms that can stimulate more open science and open innovation in research for health.
- **Improving coordination.** There is no demand for an elaborate new mechanism for coordination of research for health which experience has suggested is very difficult to achieve. But a relatively small investment in the WHO's Observatory and proposed Expert Committee on Health R&D could pay dividends in terms of identifying gaps in research for health and in promoting consensus on priorities.

[133] Lazonick W et al. US Pharma's Business Model: Why It Is Broken, and How It Can Be Fixed. 2017. Available from: http://www.isigrowth.eu/wp-content/uploads/2017/06/working_paper_2017_13.pdf

Annex 1: Survey Questions

Q1. What are the major achievements in research for health since 1990?

Q2. Are there major areas in research for health since 1990 where progress has been insufficient? Which areas?

Q3. Have some areas of research been overfunded, and some underfunded? Is the balance between biomedical research and other forms of research for health appropriate?

Q4. Since 1990 there have been significant changes in the institutional architecture that governs research for health; for example, new funders (e.g. philanthropic and other new funders), and new research organizations (e.g. product development partnerships, biotech firms and stronger capacity in developing countries). There are also new institutions that influence research for health (e.g. TRIPS, new funders of health products such as Unitaid, Gavi, the Global Fund and PEPFAR, health technology assessment organizations such as the UK NICE, the WHO Prequalification Programme, and regulatory agencies). From your perspective what are the positive features of this architecture, and what are the areas that require improvement?

Q5. Bearing in mind Q4, do you think the research for health system should be better coordinated? If so, how could this be done?

Q6. What more should be done to strengthen research capacity and capabilities, particularly in developing countries? Where and by whom?

Q7. What are the implications of the move towards universal health coverage and the attainment of the SDGs for research for health?

Q8. Do you have views on how to address the tension between the rising cost of many of the products of R&D and the need to ensure affordability and access in both higher and lower income countries?

Q9. Please provide any further comments you might wish to make on the proposed review of the global system for research for health and how it could be made an effective vehicle for improving the effectiveness of research for health and health outcomes?

Annex 2: Survey Respondents

Clemens-Martin Auer

Manica Balasegaram

Agnes Binagwaho

Janet Byaruhanga

Kalipso Chalkidou

Tim Evans

Julio Frenk

Maria Freire

Abdul Ghaffar

Mark Harrington

Peter Kilmarx

Marie-Paule Kieny

Sue Kinn

Alan Lopez

Andrea Lucard

Michael Makanga

Lenore Mandelson

Charles Stephen Mgone

Anne Mills

Suerie Moon

Hiro Nakatani

Kevin Outterson

Bernard Pecoul

John Reeder

John-Arne Røttingen

Robert F Terry

Els Torreele

Nick White

Gavin Yamey

Annex 3: List of reports

1990 Commission on Health Research for Development: Health Research: Essential Link to Equity in Development.
http://www.cohred.org/downloads/open_archive/ComReports_0.pdf

1993 World Development Report: Investing in Health.
https://openknowledge.worldbank.org/bitstream/handle/10986/5976/9780195208900_fm.pdf

1996 Ad Hoc Committee on Health Research: Investing in Health Research and Development. http://apps.who.int/iris/handle/10665/63024

2001 Commission on Macroeconomics and Health: Macroeconomics and health: Investing in health for economic development.
http://www1.worldbank.org/publicsector/pe/PEAMMarch2005/CMHReport.pdf

2004 World report on knowledge for better health: strengthening health systems.
http://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf

2004 Ministerial Summit on Health Research. The Mexico Statement on Health Research: Knowledge for better health: strengthening health systems.
http://www.who.int/rpc/summit/agenda/en/mexico_statement_on_health_research.pdf

2006 Commission on Intellectual Property Rights, Innovation and Public Health.
http://www.who.int/intellectualproperty/en/

2008 Bamako Call to Action on Research for Health: Strengthening research for health, development, and equity.
http://www.who.int/rpc/news/BAMAKOCALLTOACTIONFinalNov24.pdf

2009 World Health Organization: Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. http://www.who.int/phi/publications/gspa-phi/en/

2012 CEWG: Financing and Coordination: Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination.
http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

2013 World Health Report. Research for Universal Health Coverage.
http://www.who.int/whr/2013/report/en/

2013 Lancet Commission: Global health 2035: a world converging within a generation.
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(13)62105-4.pdf

2015 Harvard-LSHTM Independent Panel on the Global Response to Ebola: Will Ebola change the game? Ten essential reforms before the next pandemic. *Lancet* 2015; 386: 2204–21. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2815%2900946-0

2016 High-level Panel on the Global Response to Health Crises: Protecting humanity from future health crises. A/70/723. 9 February 2016. http://undocs.org/en/A/70/723

2016 Commission on a Global Health Risk Framework for the Future. The neglected dimension of global security: A framework to counter infectious disease crises. http://nam.edu/GHRFreport

2016 Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. https://amr-review.org/Publications.html

2016 United Nations Secretary-General's High-Level Panel on Access to Medicines: Promoting Innovation and Access to Health Technologies. http://www.unsgaccessmeds.org/final-report/

2017 WHO: World report on health policy and systems research. http://apps.who.int/iris/bitstream/10665/255051/1/9789241512268-eng.pdf?ua=1

2017 G-FINDER: Neglected disease research and development: Reflecting on a decade of global investment. Sydney, 2017. http://policycuresresearch.org/downloads/Y10_G-FINDER_full_report.pdf

2017 OECD: New Health Technologies: Managing Access, Value and Sustainability. http://www.oecd.org/health/managing-new-technologies-in-health-care-9789264266438-en.htm

2018 Lancet Commission: High-quality health systems in the Sustainable Development Goals era: time for a revolution. Published Online 5 September 2018. http://dx.doi.org/10.1016/S2214-109X(18)30386-3

2018 Lancet Commission: Alma-Ata at 40 years: reflections from the Lancet Commission on Investing in Health. *Lancet* 2018; 392: 1434–60. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32389-4/fulltext

2018 OECD. Pharmaceutical Innovation and Access to Medicines. Paris, 2018. http://www.oecd.org/health/pharmaceutical-innovation-and-access-to-medicines-9789264307391-en.htm

Appendix: The research for health ecosystem

Background

We used the term 'research for health' to describe the full spectrum of research that is relevant to health outcomes, both within the biomedical field and in other areas.[134]

The research for health ecosystem is complex. At its core are the funders and researchers in both the public and private sectors, but the volume, content, and impact of research are also influenced by a wide range of institutions, organizations and political and economic interests that are external to the core actors (the macro-environment).

This mapping exercise seeks to elaborate on these existing frameworks to produce an analysis of the research for health architecture that identifies key factors and institutions in the core system and in the macro-environment.

Annex A contains a number of visual frameworks from earlier analyses that seek to characterize the actors, processes, and interactions that constitute the system.

This analysis is based on a series of conceptual frameworks as illustrated in Figures 1-3.

Figure 1 is a conceptual framework for the research for health ecosystem from the point of view of funders. The framework conceptualises the process of research funding as flowing from the funder – public or private – through major prioritisation steps: first, prioritising among potential research subjects to be funded, and then prioritising among the potential recipients of the funding.

Figure 2 is a conceptual framework for the research for health ecosystem from the point of view of entities undertaking research. This framework focuses on the factors influencing the decision by a research entity to undertake a given research project. The concept of 'push' and 'pull' factors has been used in many other analyses.

Figure 3 is a conceptual framework for the dissemination of research results, where research results include both scientific knowledge and health products deriving from research. Three broad pathways for research outputs are presented: the sharing of research results, the non-sharing of research results, and product development. Aspects of product development will also fall into the sharing (e.g. descriptions of inventions in published patents) and non-sharing (e.g. trade secrets, internal know-how) categories.

[134] World Health Organization. The WHO strategy on research for health. Geneva, 2012. Available from: https://www.who.int/phi/WHO_Strategy_on_research_for_health.pdf

Many of the elements in the frameworks are mutually interrelated in one or more ways, directly and indirectly. For example, for-profit entities may directly influence what philanthropic funders do (for example, if the former formally feeds into the latter's strategy) and may indirectly influence what philanthropic funders do, for example, where philanthropic funders choose to prioritise disease areas that for-profit entities are less active in.

Below, we explore each of the areas identified in the conceptual frameworks. The text is organized to follow the process flow in Figure 1.

Figure 1. Research for health ecosystem from a funder perspective

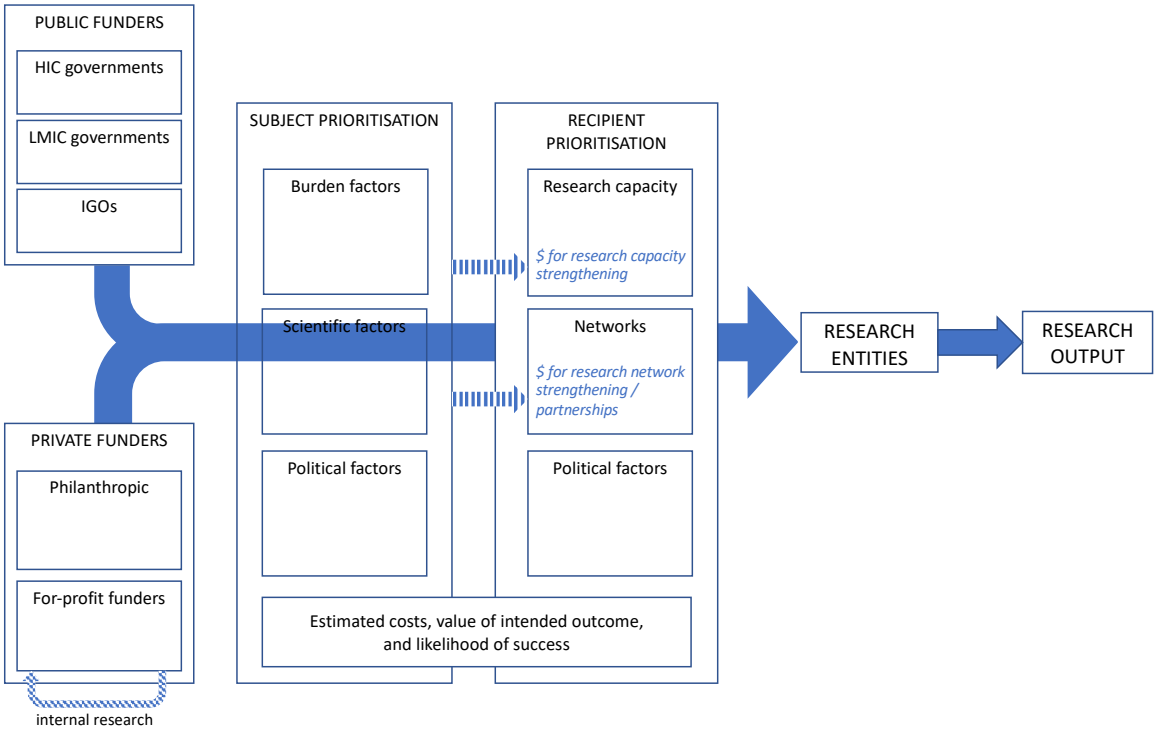


Figure 2. Research for health ecosystem from a research entity perspective.

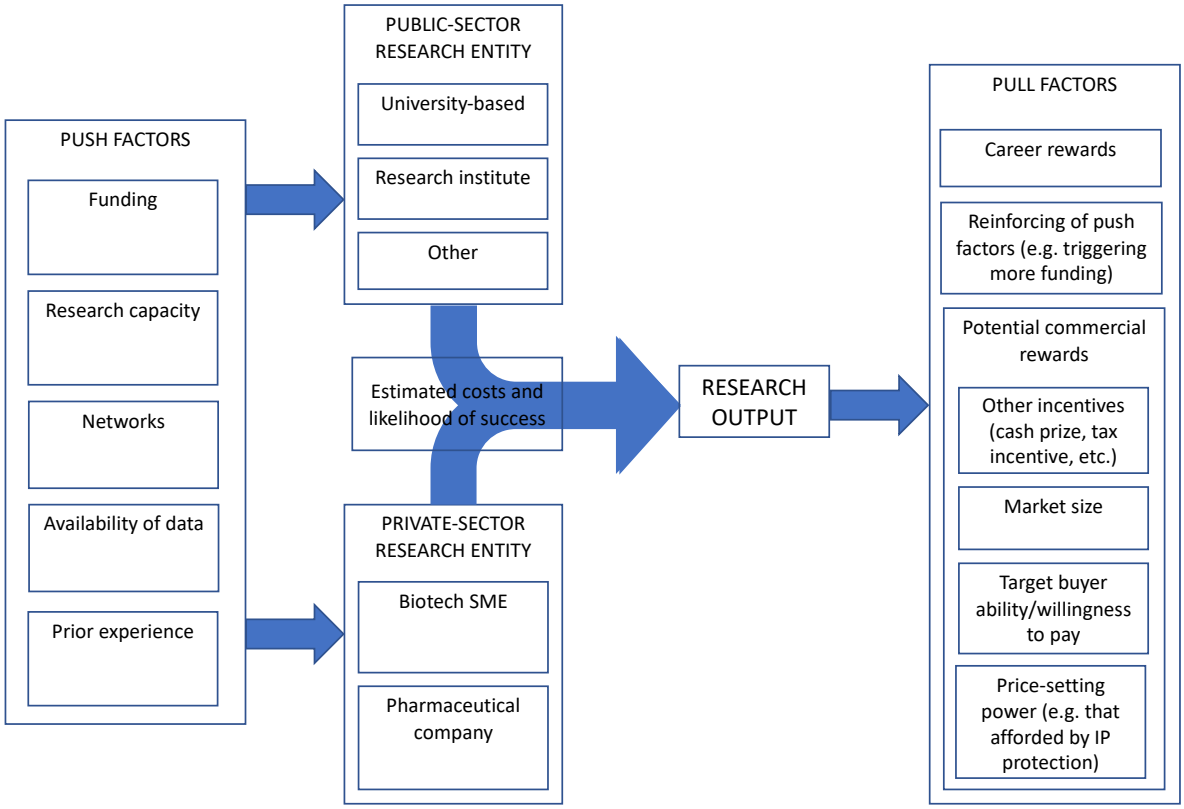
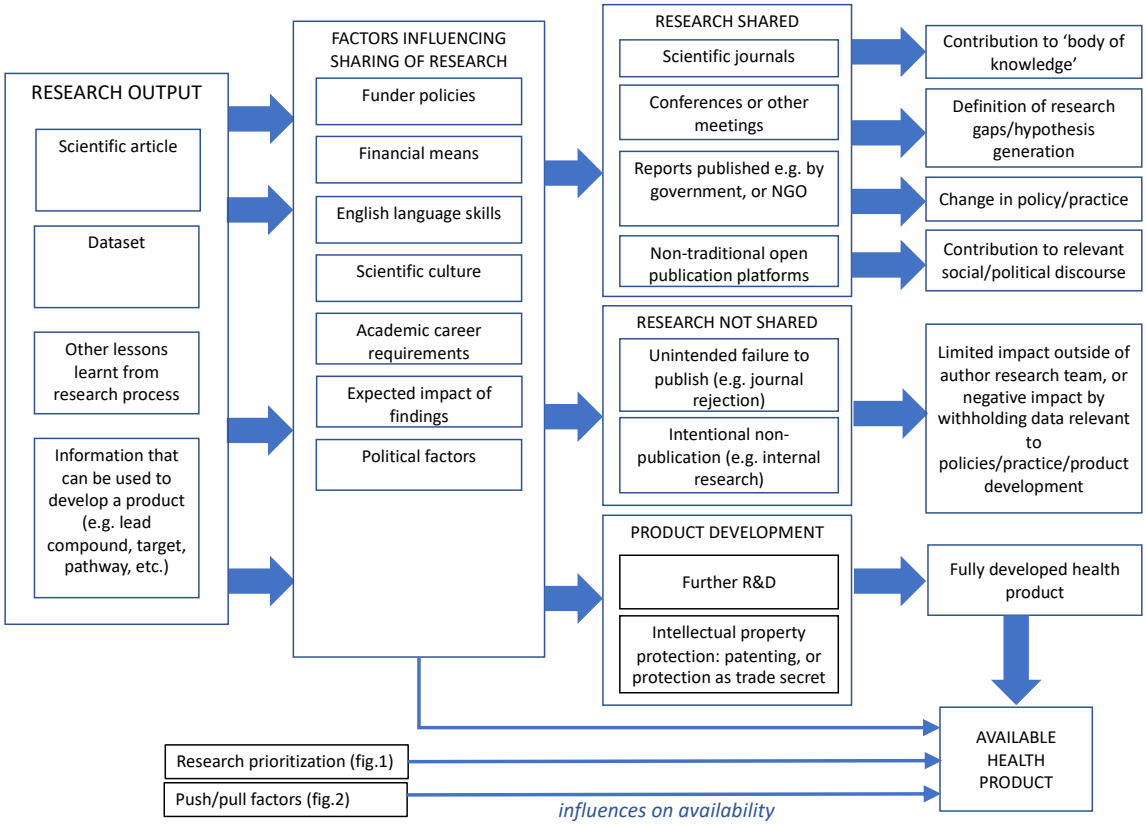


Figure 3. Research for health ecosystem: the dissemination of research results



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Research funders

Public funders

This category in general includes governmental funding and funding by intergovernmental organizations (IGOs). In some analyses, funding by charities may also categorised as 'public' funding.[135]

Although comprehensive data are not available, the most recent estimates suggest that the largest public funders spent about US$42 billion on health research annually (based on data from various years 2011-2014), disbursed through government research agencies (Table 1). An additional US$344 million was disbursed to health research by governments through overseas development agencies, and US$135 million are disbursed by the World Health Organization (2006 data).[136]

[135] For example, see Sussex J, Feng Y, Mestre-Ferrandiz J, *et al.* Quantifying the economic impact of government and charity funding of medical research on private research and development funding in the United Kingdom. *BMC Medicine* 2016; **14**. DOI:10.1186/s12916-016-0564-z

[136] Viergever RF, Hendriks TCC. The 10 largest public and philanthropic funders of health research in the world: what they fund and how they distribute their funds. *Health Research Policy and Systems* 2016; **14**. DOI:10.1186/s12961-015-0074-z.

Table 1. Health research expenditure by governmental funding agencies

Funder	Country	Total health research expenditures (2013 $ million)
National Institutes of Health (NIH)	USA	26,081.30
European Commission (EC)	EU	3,717.7
UK Medical Research Council (MRC)	GBR	1,321.5
Institut national de la santé et de la recherche médicale (Inserm)	FRA	1,041.2
United States Department of Defense (US DoD)	USA	1,017.7
Canadian Institutes of Health Research (CIHR)	CAN	883.6
Australian National Health and Medical Research Council (NHMRC)	AUS	777.6
Deutsche Forschungsgemeinschaft / German Research Foundation (DFG)	DEU	630.6
National Natural Science Foundation of China (NSFC)	CHN	621.3
Centre National de la Recherche Scientifique (CNRS)	FRA	531
UK Department of Health / National Institute for Health Research (NIHR)	GBR	491.2
Japan Society for Promotion of Science (JSPS)	JPN	472.5
Bundesministerium für Bildung und Forschung / Federal Ministry of Education and Research of Germany (BMBF)	DEU	472.1
Ministero della Salute / Ministry of Health of Italy	ITA	438.6
Instituto de Salud Carlos III (ISCIII)	ESP	388.2
Ministry of Health of China	CHN	371.7
Japan Science and Technology Agency (JST)	JPN	338.5
Singapore National Medical Research Council (NMRC)	SGP	220.7
Korean National Research Foundation (NRF)	KOR	191.5
Consejo Nacional de Investigaciones Científicas y Técnicas	ARG	184.4
Vetenskapsrådet-Medicine / Swedish Research Council	SWE	177.9
Swiss National Science Foundation (SNSF)	CHE	172.9
ZonMw / Netherlands Organisation for Health Research and Development	NLD	172.7
Sao Paulo Research Foundation (FAPESP)	BRA	154.2
Indian Council of Medical Research (ICMR)	IND	140.3
Fund for Scientific Research - Flanders (FWO)	BEL	136.9
Korea National Institute of Health (KNIH)	KOR	120
Forskingsrådet / Research Council of Norway	NOR	113.5

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)	BRA	110.8
Fonds zur Förderung der wissenschaftlichen Forschung / Austrian Science Fund (FWF)	AUT	99.5
South African Medical Research Council (SA MRC)	ZAF	63.2
Health Research Council of New Zealand	NZL	61.6
Danish Council for Independent Research / Medical Sciences	DNK	58.5
Russian Foundation for Basic Research (RFBR)	RUS	53.6
Danish Council for Strategic Research (two programmes: Individuals, Disease and Society & Health, Food and Welfare)	DNK	40.3
Consejo Nacional de Ciencia y Tecnología (CONACYT)	MEX	21.9
South African Department of Science and Technology (DST)	ZAF	13.5
Total		**41,904.20**

Source: Table adapted from Viergever et al.[137] Some caveats apply to the cited figures. Figures cited for most recent year for which data were available between 2011 and 2013. Some potentially important funders are not shown as the source study could not obtain data.

Funding from the US National Institutes of Health represents a substantial proportion of global health research funding – more than half of the total funding across around 40 agencies for which data could be obtained (Table 1). Among LMICs, it is likely that China represents the greatest funder of health research, followed by Argentina, Brazil, India and South Africa (note that the data in Table 1 are incomplete).

National governments channel funding to research in a number of ways, including through:

- Direct research grants made by government offices specifically for whom that is the primary role, for example, the US National Institutes of Health and the South African Medical Research Council.
- Direct research grants by development agencies, such as the Department for International Development in the UK.
- Research funding disbursed by departments for whom that is not the primary role, for example, ministries of education funding research undertaken at universities (e.g. through PhD studentships), ministries of defence funding research that aligns with their strategic needs, ministries of business funding research as part of developing businesses.
- Funding for research infrastructure, which may include, broadly conceived, funding of physical infrastructure such as laboratories, funding for any healthcare infrastructure that contributes to research such as hospitals and healthcare workers, funding for IT and data collection systems, and so on. One common manifestation of infrastructure

[137] See Viergever et al, above.

funding occurs in the funding of new 'centres' or 'initiatives' (usually coupled with direct research grants). However, nearly every government agency can potentially contribute to this component, with a cross-cutting factor being the extent to which governments and their agencies consider research when planning for infrastructure projects. For example, urban planning projects may plan to include elements of health research.

- Establishing incentive schemes that offer commercial rewards, such as establishing tax incentives, prize schemes or regulatory or intellectual property incentives.

Many of the largest public research funding entities have existed for many decades (Table 1).

However, some newer government-led funding initiatives can be highlighted as have been set up after 1990 aimed at filling gaps in the global research for health ecosystem (the following are examples, not an exhaustive list:

- Direct grants:
    - *Grand Challenges Canada (2010–present).* Grand Challenges Canada employs a challenge-oriented approach. In health research, Grand Challenges Canada finances, among other things, programmes on global mental health, maternal and child health, and humanitarian healthcare.[138]
    - *The US Biomedical Advanced Research and Development Authority (BARDA) (2006)* BARDA was established to support the development and manufacture of health products that could be used to mitigate the consequences of chemical, biological, radiological, and nuclear threats, as well as of pandemic influenza and emerging infectious diseases. BARDA is housed within the US Department of Health and Human Services and uses public-private partnerships to promote R&D. BARDA has contributed to 42 FDA approvals to date. BARDA had a budget of around US$500 million in 2018. Among other projects, BARDA is a key funder of CARB-X.[139]

- Prize schemes:
    - *The EU prize for innovative vaccine technology (2012-2014)* The European Commission offered a EUR 2 million 'inducement prize' to be awarded to a research team offering novel solutions to improving temperature stability of vaccines, a major challenge in many LMICs. Submissions were received from 49 competitors, and a jury of experts awarded the prize to CureVac GmbH.[140]
    - *The Horizon 2020 prize to reduce misuse of antibiotics (2015-2017)* The European Commission offered a EUR 1 million prize to be awarded to a

[138] Grand Challenges Canada. http://www.grandchallenges.ca/

[139] US Department of Health and Human Services. Biomedical Advanced Research and Development Authority. Available from: https://www.phe.gov/about/barda/Pages/default.aspx

[140] European Commission. German company wins EU's €2 million inducement prize for innovative vaccine technology. Available from: http://europa.eu/rapid/press-release_IP-14-229_en.htm.
CureVac AG. Available from: https://www.curevac.com/

research team that has developed a rapid point-of-care test to identify which upper respiratory tract infections can be treated without antibiotics. Such a test would support reduction in unnecessary use of antibiotics, a driver of antimicrobial resistance. The prize was awarded to Minicare HNL.[141]

- *The Longitude Prize (2014–ongoing)* The Longitude Prize has a £10 million prize fund, to be awarded to a research team that develops, similar to the example in the bullet point above, "a cheap, accurate, rapid and easy-to-use point of care test kit for bacterial infections". The Longitude Prize is run by Nesta (previously the National Endowment for Science Technology and the Arts) in the UK.[142]

Not-for-profit funding

Funding from four major philanthropic research funders – the Wellcome Trust, the Howard Hughes Medical Institute, the Bill & Melinda Gates Foundation, and Institut Pasteur – makes up a notable proportion of all global health research expenditure – around US$2.3 billion (Table 2). In research on neglected disease, philanthropic funding is disproportionately high, at US$692 million compared to US$2.3 billion disbursed by governments (Tables 3 and 4), and private non-philanthropic funding at US$554 million in 2017.[143]

Table 2. Health research expenditure by selected philanthropic organizations

Funder	Country	Total health research expenditures (2013 $ millions)
Wellcome Trust	GB	909.1
Howard Hughes Medical Institute (HHMI)	USA	752.0
Bill & Melinda Gates Foundation (BMGF)	USA	462.6
Institut Pasteur	FRA	220.9
Total		**2,344.6**

Source: As Table 1

Mixed public/private funding

Many of the large initiatives established since 1990 are public-private partnerships. Some examples include:

- *The European Commission's Innovative Medicines Initiative (IMI)* The IMI is a programme of public-private partnerships, set up initially as the European Technology Platform on Innovative Medicines (2005-2009), then as IMI1 (2008-2013), and currently as IMI2 (2014-2020). IMI2 – has a budget of EUR 3.3 billion. The research

[141] European Commission. Better use of Antibiotics. Available from: https://ec.europa.eu/research/horizonprize/index.cfm?prize=better-use-antibiotics
[142] Nesta. The Challenge: reduce the use of antibiotics. Available from: https://longitudeprize.org/challenge
[143] G-FINDER. Pubic Search Tool. Available from: https://gfinder.policycuresresearch.org/PublicSearchTool/

agenda for IMI covers a broad range of health topics, from infectious diseases to neurological disease, diabetes, and cancer.[144]

- *Coalition for Epidemic Preparedness Innovations (CEPI) (2016–present)* CEPI was established in reaction to the Ebola outbreak in 2014-15, to stimulate the development of vaccines for emerging infectious diseases. The majority of CEPI's funding is from governments, with additional funding from the BMGF and the Wellcome Trust. CEPI plans to use risk-sharing partnerships with industry and 'target investments to fill additional R&D gaps' to develop and manufacture vaccines.[145]
- *Global Antibiotic Research & Development Partnership (GARDP) (2016–present).* GARDP's mission is to work in partnership with the public and private sectors to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists.[146]

Table 3. Government funding for research on neglected diseases

Country	Total funding for neglected diseases research (2017 $ million)*
United States of America	1,598
United Kingdom	186
European Union	119
India	74
France	66
Germany	66
Multilaterals	52
Australia	24
Netherlands	24
Switzerland	18
Japan	18
South Africa	14
Canada	13
Brazil	9
Ireland	7
Sweden	4
Spain	4
Norway	4
South Korea	3
Mexico	2
Belgium	2
Other countries	11
Total	**2,318**

[144] Innovative Medicines Initiative. Available from: https://www.imi.europa.eu/

[145] Coalition for Epidemic Preparedness Innovations. Board of Directors Report 2016-2017. Available from: http://cepi.net/sites/default/files/CEPI_B1_16c_CEPI%20Annual%20Report%202017_final.pdf
Coalition for Epidemic Preparedness Innovations. Preliminary business plan 2017-2021. Available from: http://cepi.net/sites/default/files/CEPI%20Preliminary%20Business%20Plan%20061216_0.pdf

[146] Global Antibiotic Research & Development Partnership. Available from: https://www.gardp.org/

*Source: G-FINDER database. Policy Cures, 2018. Available from: http://policycures.org/gfinder.html *'Neglected diseases' as defined in the G-FINDER survey. **'Multilaterals' includes Unitaid, the United Nations Office for Project Services (UNOPS), the World Bank, and the World Health Organization.*

Table 4. Philanthropic funding for research on neglected diseases

Country	Total funding for neglected diseases research (2017 $million) *
United States of America	555.7
United Kingdom	104.4
Switzerland	19.5
Spain	5.2
Netherlands	3.1
France	0.8
Liechtenstein	0.7
Canada	0.7
Germany	0.5
Austria	0.5
Other countries	0.9
Total	**692**

Source: As Table 3

Private funders

Health research spending by for-profit entities significantly exceeds spending by governments and philanthropic organizations. It is estimated that, in 2018, pharmaceutical and biotech companies spent US$172 billion on R&D worldwide, compared to the US$42–64 billion spent by governments. The proportion of total revenues invested in R&D by pharmaceutical companies has been slowly rising over the past decades, with US pharmaceutical companies investing 14% of revenues in R&D in 1990, 16% in 2000, 17% in 2010, and 21% in 2018.[147] The top 20 pharmaceutical companies by R&D spending are shown in Table 5.

It is worth noting, in broad strokes, the areas of focus for private sector R&D. Forty-seven percent of clinical trials currently in progress are for cancer treatments. The next most common disease areas are neurology, followed by infections, and auto-immune disease (Figure 4). A rapidly increasing proportion of newly approved medicines are for rare (so-called 'orphan') diseases, representing 58% of approvals by the US Food and Drug Administration in 2018.[148]

[147] PhRMA 2018 Annual Membership Survey. Available from: https://www.phrma.org/report/2018-phrma-annual-membership-survey

[148] See: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf

Based on available data, about 0.3% (US$554 million) of total R&D spending by the private sector was for neglected diseases research in 2017, or 15% of all neglected diseases research funding.[149]

Table 5. Top 20 pharmaceutical companies in terms of R&D spending

Company	R&D spend (US$ billions, 2017)	R&D spend as % of prescription sales
Roche	9.2	22
Johnson & Johnson	8.4	24
Novartis	7.8	19
Merck & Co	7.6	21
Sanofi	6.2	18
Pfizer	7.6	17
GlaxoSmithKline	5.0	17
AstraZeneca	5.4	27
AbbVie	4.8	17
Bristol-Myers Squibb	4.8	25
Eli Lilly	5.0	27
Celgene	3.0	23
Amgen	3.5	16
Boehringer Ingelheim	3.1	22
Bayer	3.3	18
Gilead Sciences	3.5	14
Takeda	2.9	22
Novo Nordisk	2.1	13
Regeneron Pharmaceuticals	2.1	56
Astellas Pharma	2.0	18

Adapted from EvaluatePharma. World Preview 2018, Outlook to 2024. 2018. Available from: http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf

Research entities

A wide range of entities undertake health research. Examples illustrating the range of health research entities are described in Box 1, below. The various types of research entities that factor in the research for health ecosystem include:

- In the public sector:
    - Research teams based in higher education institutions
    - Research teams based in public sector research institutions
        - Dedicated research institutes
        - Hospitals and other health centres

[149] EvaluatePharma. World Preview 2018, Outlook to 2024. 2018. Available from: http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf, and Policy Cures Research. G-FINDER 2018. Neglected Disease Research and Development: Reaching New Heights. Available from: https://www.policycuresresearch.org/wp-content/uploads/2019/01/Y11_G-FINDER_Full_report_Reaching_new_heights.pdf

        - Government offices that collect and analyse data relevant to health, though not in the traditional academic ecosystem, such as analysis of urban air quality
        - Military research centres
    - Intergovernmental organisations
- In the private sector:
    - Market intelligence firms
    - Insurance companies
    - SME companies, including university 'spin-offs'
    - Originator pharmaceutical companies
    - Contract research organisations
- Philanthropic research institutes
- Non-profit organizations that undertake research

Some of these categories are relatively new. One such example is university spin-offs, which have become increasingly common since the Bayh-Dole Act in the US and similar legislation in Europe were enacted in the 1980s.[150] The number of university spin-offs has grown since then: In 2017, 150 new university spin-offs were created in the UK, and 1,080 were created in the US in 2017. [151]

Another example is contract research organisations (CROs). An increasing proportion of clinical trials are run by CROs – companies that provide research outsourcing services to biomedical companies. It is estimated that more than one-third of drug development will be outsourced to CROs by 2021.[152] Though most commonly discussed in the context of clinical trials, these companies undertake a wide range of research activities – from drug discovery to 'big data' analyses of insurance databases.

A growing number of clinical trials are done in LMICs, with numbers rising most rapidly in Asia.[153] Some of the suggested advantages of choosing Asia for clinical trials are the concomitant availability of 'large treatment-naïve patient pools' and 'knowledgeable physicians', as well as lower overall costs.[154]

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[150] Etzkowitz H, Webster A, Gebhardt C, Terra BRC. The future of the university and the university of the future: evolution of ivory tower to entrepreneurial paradigm. *Research Policy* 2000; **29**: 313–30.
[151] Universities UK. Higher education in numbers. https://www.universitiesuk.ac.uk/facts-and-stats/Pages/higher-education-data.aspx, and
Association of University Technology Managers. AUTM 2017 Licensing Activity Survey. https://autm.net/AUTM/media/SurveyReportsPDF/AUTM_2017_US_Licensing_Survey_no_appendix.pdf
[152] Landhuis E. Outsourcing is in. *Nature* 2018; **556**: 263–5.

[153] Drain PK, Robine M, Holmes KK, Bassett IV. Global migration of clinical trials: Trial watch. Nature Reviews Drug Discovery 2014; 13: 166–7.

[154] Frost & Sullivan. Asia: preferred destination for clinical trials. https://novotech-cro.com/sites/default/files/170217_FrostSullivan_Asia%20white%20paper_full.pdf

Box 1 The spectrum of entities undertaking health research

Public Health Foundation of India (PHFI), India, established 2005

PHFI is a public-private partnership that undertakes research, training, and policy development in public health, and supports five centres of excellence across India. https://phfi.org/about/

The Francis Crick Institute (FCI), UK, established 2015

The FCI was established by six leading biomedical organisations – Medical Research Council, Cancer Research UK, the Wellcome Trust, University College London (UCL), Imperial College London, and King's College London – as a new research institute with an emphasis on collaboration across disciplines and research translation. https://www.crick.ac.uk/

National Institute of Infectious Diseases (NIID), Japan, established 1947

The NIID undertakes research on, and surveillance of, infectious diseases, undertakes R&D in vaccines, antisera, and diagnostic materials, and provides quality control services for biological products. http://www0.nih.go.jp/niid/index-e.html

Fundação Oswaldo Cruz (FIOCRUZ), Brazil, established 1900

As well as being a research institute covering a wide range of infectious and public health areas, and housing a hospital, FIOCRUZ also includes the Drug Technology Institute (Farmanguinhos), a public pharmaceutical manufacturer that supplies 40% of medicines purchased by the Brazilian Ministry of Health, and the Immunobiological Technology Institute (Biomanguinhos), a manufacturer of biological products and the world's largest manufacturer of the yellow fever vaccine. https://portal.fiocruz.br/en

Korean Institute of Tuberculosis (KIT), South Korea, established 1970

The KIT runs bacteriological and epidemiological research projects on TB, as well as providing training on TB to healthcare workers and serving as a specialised TB diagnostic centre. The KIT provides technical assistance to China, Japan, Philippines, Vietnam and Mongolia on molecular epidemiology techniques relating to TB. https://europepmc.org/articles/PMC4301635

IQVIA, USA, established 2016 through the merger of Quntiles and IMS Health

IQVIA is one of the world's largest companies working in health data and outsourced clinical research, with around 55,000 employees in 100 countries. Among other things, IQVIA buys and sells data on physician prescribing and insurance claims. IMS Health has produced numerous reports for public sector clients, such as the European Commission and the WHO. https://www.iqvia.com/

Médecins Sans Frontières (MSF), international, established 1971

Although MSF is more widely known as an organisation that provides humanitarian medical aid, MSF undertakes extensive field research. MSF's research covers a wide range of disease areas and healthcare settings, from refugee camps to prison systems. http://fieldresearch.msf.org/msf/

Cambridge Antibody Technology (CAT), UK, established 1989

CAT, a biotech spin-off of Cambridge University, discovered adalimumab, the second highest-selling drug in history. CAT was acquired by the pharmaceutical company AstraZeneca in 2006.

Chiang Mai University, Thailand, established 1969

The university hosts a health research centre focussing on the health needs of northern Thailand and neighbouring regions, as well as a social sciences research institute.

Research capacity

A range of factors can influence the capacity to undertake research in a given setting. Research capacity in health is, in many cases, closely related to the strength and resources of the relevant health system: for example, many research tools are also used for clinical purposes, such as diagnostic laboratory equipment.

Apart from physical infrastructure and, perhaps, more importantly, research capacity relies on a skilled and empowered scientific workforce.

Research capacity strengthening can be defined as comprising "any efforts to increase the ability of individuals and institutions to undertake high-quality research and to engage with the wider community of stakeholders".[155] A wide range of recommendations have been made for strengthening research capacity in LMICs, which is seen as an essential component of strategies to improving the global research for health ecosystem.

Initiatives to combat 'brain drain' – the emigration of skilled researchers to wealthier countries – are also highly important. Viable career paths and recognition for their work is likely to be of substantial importance to most researchers and are recognised, for example, in the recommendations of the WHO's World Report on Health Policy and Systems Research.[156] As the potential for careers and recognition may vary by chosen research area, this factor can affect the effective research priorities (this is reflected in the conventional wisdom of some areas being more 'prestigious' than others). These factors will also be influenced by the ease of reaching a global audience, for example through academic journals and conferences.

Examples of initiatives to strengthen research capacity include:

- **TDR ESSENCE (2008–current)**
  TDR ESSENCE is an initiative that allows research funders to "align and harmonize their activities and procedures with national priorities to better streamline efforts aimed to support efficient and targeted capacity building." Members of the initiative include many major governmental and philanthropic funders of health research.[157]

- The **European Clinical Trials and Development Partnership (ECTDP) (2003–current)** funds and supports collaborative partnerships to undertake clinical research to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria, as well as other poverty-related infectious diseases in sub-Saharan Africa. These partnerships are between

[155] ESSENCE on Health Research. Seven principles for strengthening research capacity in low- and middle-income countries: simple ideas in a complex world. Available from: http://eulachealth.eu/wp-content/uploads/2014/08/ESSENCE_7Principles_Final.pdf
[156] World Health Organization. World Report on Health Policy and Systems Research. Geneva, 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/255051/9789241512268-eng.pdf?sequence=1
[157] TDR ESSENCE. ESSENCE membership. Available from: https://www.who.int/tdr/partnerships/essence/members/en/

African and European institutions, in collaboration with the pharmaceutical industry and other collaborators.[158]

- **Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) (1995–current)**
  MLW conducts internationally excellent science to benefit human health with a focus on sub-Saharan Africa. The guiding aims of the Programme are preventing death from severe infection and transmission reduction in infectious diseases. In partnership with the College of Medicine it aims to attract, train, and retain local and international senior scientists.

- **African Institutions Initiative (AII)** (2009)
  The AII is a Wellcome Trust research capacity initiative that funds 7 African-led research consortia. Among other things, the consortia have increased the visibility of African research leaders and increased training opportunities in Africa.[159]

Open science

The global research community has increasingly embraced 'open' approaches to science, meaning research approaches that seek to make the research process and its results maximally available to others, for example, through the free sharing of datasets and publication in 'open access' journals (where no subscription is required to access the content). A number of initiatives can be highlighted:

- ***DREAM Challenges*** *(2006)*
  DREAM Challenges is an online collaborative science platform where stakeholders will pose a scientific challenge (often providing a relevant dataset), and solutions are 'crowdsourced' from a large network of researchers. On the platform, researchers can share data, code, and other research materials. Findings made in the DREAM platform often lead to publications. DREAM Challenges notes that it is different to similar initiatives such as Kaggle or Innocentive in that participation is usually not driven by a monetary reward.[160]

- ***Open Source Malaria (OSM)*** *(2011)*
  OSM hosts openly accessible 'lab notebooks' as well as databases of lead compounds on the GitHub and Wiki platforms. Laboratory experiments on the compounds and related aspects are done by OSM collaborators most often in university laboratories. OSM states that 'there will be no patents' on its work.[161]

- ***TDR Targets*** – see above, under *Scientific feasibility*

[158] European Clinical Trials and Development Partnership. https://www.edctp.org/
[159] RAND Corporation. Evaluating the Wellcome Trust's African Institutions Initiative. https://www.rand.org/randeurope/research/projects/african-institutions-eval.html
[160] DREAM Challenges. http://dreamchallenges.org/
[161] Open Source Malaria. http://opensourcemalaria.org/

Prioritization among potential subjects of research

Prioritization among potential subjects of research is influenced by disease burden, scientific factors, and political factors.

Burden

Data on the burden of causes of ill health is central to any prioritisation exercise. Despite this, systematic collection of global data on disease burden has become available only relatively recently, and robust data is still not available in many disease areas. Very little data are available even for some common diseases, for example on the epidemiology of thrombotic syndromes (such as ischaemic stroke) and diabetes, in many LMICs.[162]

A number of organizations and initiatives have been created since 1990 to analyse disease burden and to identify gaps in research, research funding, and therapeutic tools.

Examples of initiatives aimed at improving health data collection include:

- *The Institute for Health Metrics and Evaluation Global Burden of Disease (GBD) study (1990–present)*
  The GBD study, started in 1990 as a project commissioned by the World Bank, is now one of the leading sources of epidemiological estimates, with countless research projects drawing on GBD data.[163]
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- *The WHO Global Dementia Observatory (GDO) (2017–present)*
  The GDO aims to support WHO member states in the measurement of progress on action points in the Global Dementia Action Plan on the Public Health Response to Dementia 2017-2025.[164]

Identifying neglected areas in global health research funding

Describing the relationship between disease burden and relative resources allocated to research by disease area could contribute to a range of different approaches to funding prioritization. For example, identifying historically underfunded disease areas may allow direction of funding to fill 'research gaps'.

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[162] ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. Journal of Thrombosis and Haemostasis 2014; 12: 1580–90. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jth.12698
World Health Organization. Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016. Available from: http://www.who.int/about/licensing/%5Cnhttp://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

[163] Institute for Health Metrics and Evaluation. Global Burden of Disease (GBD). Available from: http://www.healthdata.org/gbd

[164] World Health Organization. Global Dementia Observatory. Available from: http://www.who.int/mental_health/neurology/dementia/Global_Observatory/en/

Examples of initiatives have been established to improve understanding of research funding flows include:

- *G-FINDER (2008–present)* The G-FINDER project publishes reports on global investment into neglected disease R&D and maintains a public database of such investments.[165]
-
- *The Institute for Health Metrics and Evaluation Financing Global Health (FGH) study (2009–present)*
  The FGH study reports on trends in development assistance for health, as well as other health spending, and provides a public database of spending data.[166]

- *The WHO Global Observatory on Health R&D*
  The Observatory "aims to help identify health R&D priorities based on public health needs" by collating and analysing data on health R&D needs and R&D spending.[167]

- *Treatment Action Group's (TAG) Pipeline Reports (2006–present)*
  TAG, a civil society organisation that has its roots in the HIV activist organisation ACT UP, tracks annual spending on HIV, tuberculosis and hepatitis C R&D by surveying entities with known or potential investments. [168]

In addition to public sector and philanthropic research funding, assessment of what disease areas the private sector is investing in may help inform prioritization. Data on private R&D investments broken down by disease area or technology are not generally available publicly. However, information on the so-called 'pipeline' of products in development is normally published by larger companies.

Overviews can be generated, for example, using data in clinical trial registries, such as in Figure 4.

[165] Policy Cures. Available from: http://policycures.org/gfinder.html
[166] Institute for Health Metrics and Evaluation. Financing Global Health. Available from: http://www.healthdata.org/policy-report/financing-global-health-2017
[167] World Health Organization. Global Observatory on Health R&D. Available from: http://www.who.int/research-observatory/en/
[168] Treatment Action Group. Pipeline Report. Available from: http://www.treatmentactiongroup.org/pipeline-report

Figure 4. Ongoing clinical trials by disease area (2016)

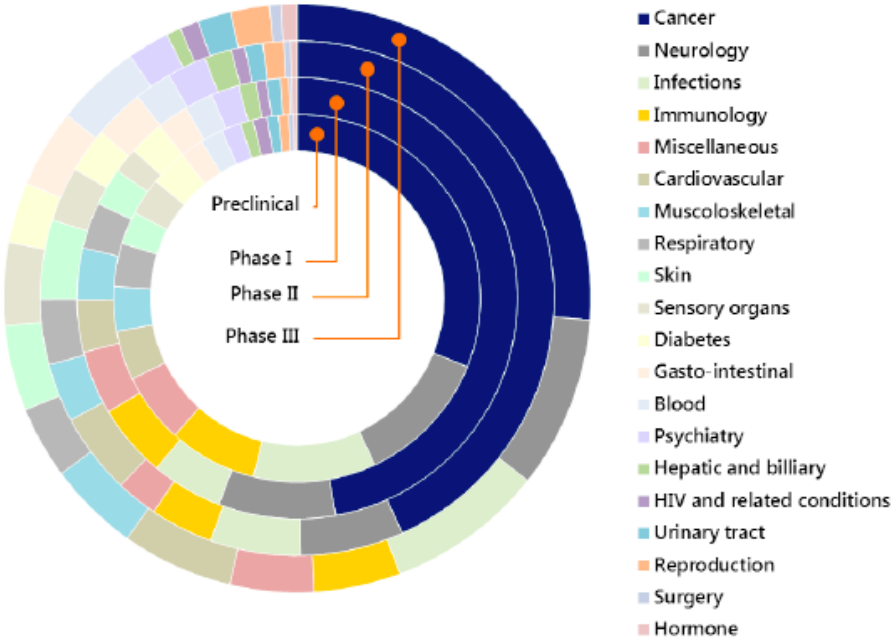

Figure from World Health Organization, 2018. Pricing of cancer medicines and its impacts. Available from: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1

Scientific factors

Scientific factors may include identifying areas with low-hanging fruit (for example, repurposing older medicines), identifying key pathogens to target with research, and developing target product profiles – rigorous descriptions of the technologies to be developed. Examples of initiatives that contribute to scientific elements in prioritization include:

- *WHO Antibacterial agents in clinical development (2017–present)*
  In 2017, the WHO published an analysis of the global R&D pipeline for antibacterial agents, describing the various agents in development with regard to their (likely) spectrum of efficacy, mechanism of action, and other important criteria.[169]

- *WHO Global Priority List Of Antibiotic-Resistant Bacteria*
  The WHO has prepared a list of antibiotic-resistant bacteria that require high priority in R&D efforts, which represents the first such effort.[170]

- *WHO R&D Blueprint and the Blueprint list of priority diseases (2015–present)*
  The R&D Blueprint is a plan to allow rapid R&D activation in response to epidemics. Among other things, as part of the R&D Blueprint, the WHO develops a list of

[169] World Health Organization. Antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline, including tuberculosis. Available from: http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/
[170] World Health Organization. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics. Available from: http://apps.who.int/medicinedocs/documents/s23171en/s23171en.pdf

pathogens to prioritise for R&D, in the context of potential public health emergencies.[171]

- *High-priority target product profiles for new tuberculosis diagnostics (2014)* The WHO Global TB Programme convened a meeting of experts and stakeholders to describe the targets and specifications that developers of a new TB test should strive to meet in product development.[172]

- *TDR Targets (2005–present)* The TDR Targets provides a public database that allows researchers to find and prioritize drug targets for neglected diseases pathogens.[173]

This sort of prioritization is also effectively undertaken by entities that produce clinical treatment guidelines, because, among other reasons, their stated criteria for choosing one therapeutic alternative over another have a normative importance in signalling what characteristics a new product would need in order to be considered an improvement. Examples of such organisations include WHO departments that issue treatment guidelines (such as in HIV and TB), the European Society of Medical Oncology (ESMO), and the UK National Institute for Health and Care Excellence (NICE).

Political factors

Politics may influence prioritization among potential research subjects and potential funding recipients.

Public opinion and civil society

To some extent and in some areas, research priorities are sensitive to the opinions of taxpayers. Disease-specific campaigns and patient groups regularly lobby for increased research into their respective areas of interest. Some examples of such campaigns and groups include ACT UP,[174] the British Heart Foundation,[175] and the National Organization for Rare Disorders.[176] Another angle of the importance of taxpayers' opinions can be seen in the substantial amount of research funding raised through private donations. For example, in 2015, 44% of non-industry health R&D funding in the UK came from charities.[177]

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[171] WHO R&D Blueprint. List of Blueprint priority diseases. Available from: http://www.who.int/blueprint/priority-diseases/en/

[172] World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. Available from: http://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf?sequence=1

[173] TDR Targets. Available from: http://tdrtargets.org/

[174] ACT UP New York. Available from: https://actupny.com/

[175] British Heart Foundation. Available from: https://www.bhf.org.uk/

[176] National Organization for Rare Disorders. Available from: https://rarediseases.org/

[177] Office for Life Sciences. Chart 10: 2015 non-industry spend on research and development. In: Life Science Competitiveness Indicators. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/606651/life-science-competitiveness-indicators-report-2017.pdf

NGOs working on the topic of health research more broadly directly lobby for changes in priorities and prioritization processes. Some examples include the Treatment Action Group, Knowledge Ecology International, and Médecins Sans Frontières.

Apart from organized civil society lobbying efforts and fundraising, taxpayers' opinions may affect priority setting by encouraging decisionmakers to make investments they believe will be popular. For example, nationally, politicians may 'champion' large research investments – for example, the National Cancer Moonshot to be led by US Vice-President Joe Biden, announced in 2016,[178] or UK Prime Minister David Cameron positioning himself as a leader on antimicrobial resistance globally.[179]

International relations

Research has long held substantial geopolitical importance in many countries. Perhaps the main reasons for this can be summarised as the link of research to industry and economic growth, and the importance of research to national security and the military. For example, the new UK Industrial Strategy, launched in 2017, places R&D front-and-centre in the government's economic strategy and the life sciences are a key component.[180] Reports that China is growing rapidly in terms of R&D generally and in health R&D led US federal agencies to call for increased research funding,[181] and the Wall Street Journal to opine that the 'tech arms race [is] driving the US-China trade dispute'.[182]

Most of the largest pharmaceutical companies are based in the US, Switzerland, Japan and the EU.[183] There are often tensions between countries' industrial objectives and public health considerations.[184]

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[178] Office of the Press Secretary, The White House. FACT SHEET: Investing in the National Cancer Moonshot. Available from: https://obamawhitehouse.archives.gov/the-press-office/2016/02/01/fact-sheet-investing-national-cancer-moonshot.

[179] Reuters. G7 told to act on antibiotics as dreaded superbug hits U.S. Available from: https://www.reuters.com/article/us-g7-summit-britain-antibiotics-idUSKCN0YI0MY

[180] HM Government. Industrial Strategy: Building a Britain fit for the future. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/730048/industrial-strategy-white-paper-web-ready-a4-version.pdf .

[181] National Science Foundation. U.S. science and technology leadership increasingly challenged by advances in Asia. Available from: https://www.nsf.gov/news/news_summ.jsp?cntn_id=137394.
Wu Y, Yin D, Abbasi K. China's medical research revolution. BMJ 2018;360:k547.
Chakma J, Sun GH, Steinberg JD, Sammut SM, Jagsi R. Asia's Ascent — Global Trends in Biomedical R&D Expenditures. New England Journal of Medicine 2014; 370: 3–6.

[182] Wall Street Journal. American Tech Firms Are Winning the R&D Spending Race With China. Available from: https://www.wsj.com/articles/american-tech-firms-are-winning-the-r-d-spending-race-with-china-1540873318

[183] See above, EvaluatePharma 2018.

[184] The Wire. Exclusive: Draft UN Text on TB No Longer Carries Provisions on Affordable Medicines. 21 July 2018. Available from: https://thewire.in/health/united-nations-tb-declaration-affordable-medicines

National security and defence

In recent years, arguments using the language of 'national security' objectives have regularly been made to recommend greater investments in research tackling antimicrobial resistance. The CDC argues that global health in general is a matter of US national security concern.[185] Other examples include HIV/AIDS,[186] Ebola virus,[187] and Zika virus.[188] The 'national security' argumentation underlies, for example, the substantial investments in the US Biomedical Advanced Research and Development Authority (BARDA) in the US, which was established to "develop and provide medical countermeasures for Chemical, Biological, Radiological, and Nuclear threats, pandemic influenza, and emerging infectious diseases" (see above under *Mixed public/private funding)*.[189]

The military itself may also undertake important health research. For example, the US Walter Reed Army Institute of Research has developed a number of innovative vaccines over last two decades and has run an HIV Research Program since 1986.[190]

Market factors

Where research is done with the aim of profiting commercially from the end-product, the factors that affect the magnitude of the expected profits are obviously of great importance. These factors may be divided broadly into those that determine the size of the (potential) market, those that determine the length of time that the proprietor will hold a monopoly on the product, and the willingness and ability of potential buyers to pay.

Market intelligence firms are highly relevant to understanding these factors and should not be overlooked in the health research ecosystem. Governments, for example, may rely in certain ways on data from firms such as IQVIA (previously IMS Health) to inform pharmaceutical market regulations.[191] Other examples include Clarivate Analytics, Evaluate, and Thomson Reuters.

Market size

Market size is affected by:

- The demand for products from patients or payers

[185] Centers for Disease Control and Prevention. Why Global Health Security Is Essential to U.S. National Security. Available from: https://www.cdc.gov/media/releases/2017/p0921-global-health-security.html
[186] Katz R, Singer DA. Health and security in foreign policy. Bull World Health Organ 2007; 85: 233–4.
[187] Politico. Obama: Ebola a 'security priority'. Available from: https://www.politico.com/story/2014/09/obama-ebola-global-health-security-agenda-summit-111355
[188] TIME. Zika Prevention Is a Matter of National Security. Available from: http://time.com/4449287/zika-prevention-national-security/
[189] Biomedical Advanced Research and Development Authority. BARDA Strategic Plan 2011-2016. Available from: https://www.phe.gov/about/barda/Documents/barda-strategic-plan.pdf
[190] Walter Reed Army Institute of Research. Available from: http://www.wrair.army.mil/
US Military HIV Research Program. Available from: https://www.hivresearch.org/
[191] National Pharmaceuticals Pricing Policy, 2012 (NPPP-2012). The Gazette of India, 7 December 2012. Available from: http://apps.who.int/medicinedocs/en/d/Js20106en/

- Epidemiology; with key actors being those that work to describing disease burden (noted above), but also those that bring unmet health needs to the attention of researchers or investors.
- Health system characteristics, such as the ability to diagnose a given disease (a market size may be small if only few cases are diagnosed of a disease with high theoretical prevalence), and the ability to follow-up diagnosed cases.
- The availability of therapeutic alternatives (a product will be used little if similarly effective products are already well-established).

Exclusivity

As described extensively elsewhere, factors that enable a (temporary) monopoly – through intellectual property, market exclusivity, data exclusivity, and other supplementary protections – are a highly important incentive for research investments in the dominant life sciences business model.

Instruments offering exclusivity include:

- Patents, which by default expire 20 years after the filing date. The range of what is 'patentable' is an area of jurisprudence that has actively evolved with the pharmaceutical industry.
- Patent term extensions (US) and supplementary protection certificates (EU), which extend monopoly rights beyond the default 20 years protected by patent, to compensate for what is argued to be effective loss of time under patent protection due to regulatory delays and time in clinical trial testing.
- Paediatric investigation incentives, which provide an additional period of monopoly rights if the proprietor undertakes clinical trials for paediatric use. Paediatric testing has historically been neglected by drug makers, perhaps due to comparatively small market size.
- Data exclusivity, in which generic applicants are barred from referring to the originator's clinical trial data for a certain number of years following approval. As undertaking new clinical trials would be duplicative and costly, this in general prevents applications for generic approval from being filed until data exclusivity expires. Data exclusivity is often coupled with market exclusivity, during which generic versions can be approved by regulators on clinical grounds but cannot be granted authorization to be sold on the market. These protections are a parallel mechanism to patent protection and can extend monopolies beyond patent expiry.
- Orphan drug exclusivity is one of many incentives provided in the US and EU to developing medicines for rare diseases (orphan drugs). Orphan drug exclusivity provides seven years of market exclusivity (see above) from the date of approval in the US and ten years in the EU.
- GAIN (Generating Antibiotic Incentives Now) exclusivity,

In this context, important actors include:

- National, regional, and international patent offices

- Regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency
- The World Intellectual Property Organization and the World Trade Organization

- The World Health Organization, where it influences the above policies, and where it recommends regulations affecting generic small-molecule medicines and biosimilars

Buyer ability and willingness to pay

Key actors in this regard include, at the national level, government agencies charged with health technology procurement, insurance companies and retailers, and the growing number of authorities undertaking health technology assessments (HTAs), such as the UK's National Institute for Health and Care Excellence (NICE), Thailand's Health Intervention and Technology Assessment Program (HITAP), and the International Network of Agencies for Health Technology Assessment (INAHTA).

Large international procurement agencies such as the Global Fund, Gavi, and the PAHO Strategic and Revolving Fund can have substantial market-shaping power. One example is Gavi's pneumococcal vaccine advance market commitment (AMC), which offers a guaranteed procurement volume at a set price over a set time period, 'de-risking' the market for prospective suppliers.[192]

Authorities that undertake health technology assessment may influence how health research is carried out, as product developers may adapt their research approaches to fit the criteria that authorities use to measure value. For example, the growing use of cost-effectiveness analysis to inform health product procurement may influence the design of clinical trials to include more endpoints that can contribute to a 'cost savings' argument, such as length of hospitalization (reducing this is cost saving) or measuring the 'total cost of care' in the intervention and comparator arms.[193] Another way in which HTA authorities may have influenced health research is by, indirectly, reinforcing broader use of cost-effectiveness analysis. The WHO, for example, now promotes, and offers technical assistance for, greater use of cost-effectiveness analysis in LMIC health systems and disease treatment programmes.[194]

Regulation of health research

This area includes entities that set the rules for how research is done.

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[192] Gavi, the Vaccine Alliance. Pneumococcal AMC. Available from: https://www.gavi.org/funding/pneumococcal-amc/

[193] Jeremy Schafer. Adapting Clinical Trials For The Upcoming Oncology Value Wave. *Clinical Leader* 2017; published online June 8. https://www.clinicalleader.com/doc/adapting-clinical-trials-for-the-upcoming-oncology-value-wave-0001 (accessed Nov 4, 2018).

[194] World Health Organization. Cost effectiveness and strategic planning (WHO-CHOICE). http://www.who.int/choice/en/

Regulatory and reporting requirements may have a substantial influence on the cost of doing research and may pose barriers to doing research. Perhaps the most widely applicable such entities across various types of health research are institutional ethics review boards. Many countries have government offices that oversee research conduct at the national level, such as the Office for Human Research Protections in the US, and the Health Research Authority in the UK. A number of other aspects of the regulatory environment, broadly conceived, may impact the performance of research, such as customs rules.[195]

Numerous initiatives of the past two decades have been aimed at increasing bioethics review capacity in LMICs.[196] The EDCTP, for example, works to develop a Pan-African Clinical Trials Alliance, creating a network between the regulatory and ethical oversight stakeholders.[197] Other examples include the WHO Global Training Network and African Vaccine Regulators Forum (AVAREF).

Clinical trial registries, which provide a public database of both planned and completed clinical trials, are a relatively new phenomenon, with most established since the mid-2000s. Examples include: ClinicalTrials.gov (established in 2000), the WHO International Clinical Trials Registry Platform, and the European Clinical Trials Database.

Regulation of health products

For health research that is aimed at bringing to market a new health product, the eventual need to pass regulatory review will influence many decisions in the research process.

Interrelation of regulation and clinical trial design

The standards, guidelines, and practices of regulators such as the US Food and Drug Administration and European Medicines Agency have substantial influence on how clinical trials are designed, and these regulators regularly hold meetings with pharmaceutical companies to discuss how clinical trial should be designed to meet their requirements.[198]

Health product developers may take cues from previous decisions by regulators, influencing, for example, what types of drug candidates are chosen for further development, and what indications are sought. One aspect is the well-described 'orphanisation' of the drug pipeline

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[195] Saha S, Saha S, Saha SK. Barriers in Bangladesh. *eLife* 2018; **7**. DOI:10.7554/eLife.41926.

[196] Ndebele P, Wassenaar D, Benatar S, et al. Research Ethics Capacity Building in Sub-Saharan Africa: A Review of NIH Fogarty-Funded Programs 2000–2012. Journal of Empirical Research on Human Research Ethics 2014; 9: 24–40.

[197] The European & Developing Countries Clinical Trials Partnership. EDCTP2 work plan 2018. www.edctp.org/web/app/uploads/2018/06/EDCTP2-Work-plan-2018-web.pdf

[198] US Food & Drug Administration. Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf

European Medicines Agency. Scientific advice and protocol assistance. Available from: https://www.ema.europa.eu/human-regulatory/research-development/scientific-advice-protocol-assistance

– the dramatic increase in the proportion of medicines that are approved for 'orphan' indications,[199] that is, for rare diseases or for use in rare cases for more common diseases.[200]

Similarly, mirroring increasing acceptance by regulators of surrogate endpoints, their use in clinical trials is increasing,[201] and the FDA publishes a table of surrogate endpoints used in successful applications, to guide developers.[202] In a less formalised way, clinical trial development may be influenced by how professional societies, which are the main source of clinical practice guidelines in many disease areas (for example, the European Society of Medical Oncology), historically react to certain types of evidence.

Geographical differences in regulatory requirements

Different regulatory requirements may also result in some medicines being developed that are marketed only in selected countries. There are examples of medicines that have approved in only a handful of countries – for example the type 2 diabetes medicine teneligliptin, almost unheard of in the West, is approved in Japan, India, South Korea, and Argentina.[203]

Regulatory incentives to shift the focus of R&D

Policymakers have sought to leverage the costs and delays associated with regulatory requirements to encourage R&D for certain types of medicine, by designing incentive mechanisms that allow easier or faster drug approval. These incentives split roughly into two approaches: incentives that effectively lower regulatory requirements and incentives that allow submissions to 'skip the queue'.

Examples in the 'lower requirements' category include lower evidentiary thresholds for medicines for orphan indications. For example, French, Swedish, and UK regulators accept lower evidence quality for orphan medicines,[204] and FDA approvals of orphan drugs for cancer

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[199] Kinch MS, Merkel J, Umlauf S. Trends in pharmaceutical targeting of clinical indications: 1930–2013. *Drug Discovery Today* 2014; **19**: 1682–5.

[200] The specific definition of 'orphan' diseases varies by jurisdiction.
European Medicines Agency. Orphan designation. Available from: https://www.ema.europa.eu/human-regulatory/overview/orphan-designation
US Food & Drug Administration. Developing Products for Rare Diseases & Conditions. Available from: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

[201] Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Medicine* 2017; **15**. DOI:10.1186/s12916-017-0902-9.

[202] US Food & Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. Available from:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm

[203] Swami O, Sharma SK, Panneerselvam A, Singh KP, Parmar G, Gadge P. Teneligliptin in management of type 2 diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2016; Volume 9: 251–60.

[204] Young KE, Soussi I, Hemels M, Toumi M. A comparative study of orphan drug prices in Europe. Journal of Market Access & Health Policy 2017; 5: 1297886.

2004-2010 were based on a lower quality of evidence (e.g. single-blind clinical trials) substantially more often than for other cancer medicines.[205]

With regard to 'skipping the queue', a well-known example is the FDA's Priority Review Voucher (PRV) system, where developers may be awarded a PRV upon approval of a treatment for a 'tropical disease'. The PRV may then be used to obtain priority review status (i.e. accelerated review) for any future submission. PRVs may also be sold, with their value estimated in the hundreds of millions of dollars.[206]

Dissemination of research

The end-products of research can include, for example, raw data, new knowledge described in a research articles, and new health products. Effective dissemination is of primary importance to maximising the societal benefit of the research.

Dissemination of research results

Access to academic literature

In its most familiar form, research is disseminated in the form of academic articles. The movement to enable free, public access to academic articles has transformed the landscape of academic publishing. The European Commission estimates that about 28% of all academic publications were open-access in 2016 (within health-related fields the proportion ranged 20–38%), with the proportion growing.[207] Recently, the Wellcome Trust, Bill & Melinda Gates Foundation, and 13 European research funders announced Plan S to ensure all of their funded research projects are published open-access by 2020.[208]

Before the rise in open-access publishing, the WHO set up the Hinari Access to Research for Health Programme in 2002 to encourage publishers to voluntarily provide access to articles online for free or at very low prices for non-profit institutions in developing countries. The initiative included 1,500 titles at launch, and now includes 14,900 titles.[209]

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[205] Kesselheim AS. Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer. JAMA 2011; 305: 2320.

[206] US Food & Drug Administration. Tropical Disease Priority Review Vouchers: Guidance for Industry. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf.
Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. Health Affairs 2016; 35: 776–83.

[207] European Commission. Trends for open access to publications. https://ec.europa.eu/info/research-and-innovation/strategy/goals-research-and-innovation-policy/open-science/open-science-monitor/trends-open-access-publications_en. This figure includes 'green' open access, which describes articles that are not freely available from the publisher, but are freely available elsewhere, such as in the authors' institutional repository.

[208] Nature. Wellcome and Gates join bold European open-access plan. https://www.nature.com/articles/d41586-018-07300-5?error=cookies_not_supported&code=9a5f3ddc-fc35-4f45-b9f7-5b0f98c9103c

[209] World Health Organization. Hinari Access to Research for Health programme. http://www.who.int/hinari/en/

In addition, new publishing models have emerged – such as the *F1000Research* model, where articles are published within days of submission, without a competitive editorial selection, and are peer-reviewed non-anonymously after publication. BMGF, the Wellcome Trust, and MSF, among others, have established their own portals on this platform, to publish research they have funded.[210]

Contractual requirements regarding dissemination

Funders and institutions can develop policies to ensure adequate dissemination of the research they fund/undertake. The funder initiatives to support open access, mentioned above (by the Wellcome Trust, BMGF, and others), in general require authors to publish in journals that are either open-access or allow author self-archiving (i.e. authors making a version of their article freely available online).[211] In terms of health-related products, such as medicines, vaccines, and diagnostics, funders and institutions can similar implement systems to promote equitable access to health products developed from their research, through contractual clauses. Such mechanisms in general aim to include in contracts licensing intellectual property to third parties clauses that would require, for example, non-enforcement of IP rights in certain territories to allow generic manufacture of the product in question. This approach has variously been termed 'socially responsible licensing', 'equitable access licensing', 'humanitarian licensing', and similar terms. A number of universities have implemented such policies,[212] and some research funders, such as the Wellcome Trust, have policies along these lines.[213]

Data collected outside of academic research

Data that is relevant to health research may be collected by governments or other entities outside of the academic context, and, thus, may not be published in academic journals. Examples of such data could include air pollution data and water quality data. To make these data available for research, governments (or other applicable entities) must maintain mechanisms to publish the data. In many cases, these mechanisms come under wider transparency initiatives. Examples of such publication mechanisms include the CDC's National Health and Nutrition Examination Survey.[214]

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[210] F1000Research. https://f1000research.com/
Médecins Sans Frontières F1000Research Gateway. https://f1000research.com/gateways/MSF
Gates Open Research. https://gatesopenresearch.org/
Wellcome Open Research. https://wellcomeopenresearch.org/
[211] Wellcome Trust. Complying with our open access policy.
https://wellcome.ac.uk/funding/guidance/complying-our-open-access-policy
Bill & Melinda Gates Foundation. Bill & Melinda Gates Foundation Open Access Policy.
https://www.gatesfoundation.org/How-We-Work/General-Information/Open-Access-Policy
[212] Nguyen T-Y, Shahzad M, Veras J. Recent Experiences In Policy Implementation Of Socially Responsible Licensing In Select Universities Across Europe And North America: Identifying Key Provisions To Promote Global Access To Health Technologies. Les Nouvelles: The Journal of the Licensing Executives Society International. Sep 2018.
[213] The Wellcome Trust. Policy on intellectual property. https://wellcome.ac.uk/funding/guidance/policy-intellectual-property
[214] Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm

Non-technical audiences

There is increasing recognition that greater efforts should be made to effectively communicate research findings to stakeholders that may not have the relevant technical knowledge, including healthcare workers, policymakers, and the general public.[215] One approach to this is to require plain-language summaries (PLS) for items of technical writing (such as research articles). For example, EU Clinical Trials Regulation 536/2014 (Article 37) will require from 2019 all clinical trial sponsors to provide plain-language summaries, which will be made available in a public database.[216]

However, news media may be the most abundant stakeholder in translating research findings for the general public.

Dissemination of research as health products

When research is used in product development and is thus (most often) part of a profit-seeking business project, the ways and extent to which the research knowledge is disseminated change. Such research could be categorised as

- Research that is not shared, that is, which is kept private. Examples include trade secrets and internal know-how.
- Research that is shared but that cannot be used to full extent due to legal, technical, or practical barriers. Examples include patented subject matter, in which some of the findings are disclosed in the published patent, and entities can use this information to develop their own versions of the product in question, but the product cannot be brought to market before patent expiry. Patents may also interfere with research where the research process may be subject to a patent infringement suit.[217]
- Research that is shared following normal academic research pathways, such as journal publications describing the process of identifying a lead compound.

Many of the entities relevant to this aspect of research dissemination are outlined above, under 'Exclusivity'. Another important stakeholder in this context is the technology transfer offices (TTO) of universities and other public research institutions. TTOs undertake activities relevant to commercialisation of research outputs that are potentially relevant to product development. In some cases, TTOs have become private companies that hold 'pipeline agreements' with one or more universities. For example, Imperial Innovations, which serves as the TTO for Imperial College London, is a private company that holds an exclusive 'pipeline agreement' on research generated at the

[215] For example, see WHO. The WHO strategy on research for health. 2012.

[216] Phogat P, Vashisht V. EMA's Demands for Plain-Language Summaries for Clinical Trial Results that can be Understood by Anyone Could Create new Challenges for Sponsors. Applied Clinical Trials. http://www.appliedclinicaltrialsonline.com/ema-s-demands-plain-language-summaries-clinical-trial-results-can-be-understood-anyone-could-create

[217] Notable examples include gene patents (Merz JF, Cho MK. What Are Gene Patents and Why Are People Worried about Them? Public Health Genomics 2005; 8: 203–8.). Legal exceptions to patent rights exist for research purposes, but there is some debate as to whether they are sufficient and effective, which is beyond the scope of this paper.

university.[218] Imperial Innovations is in turn a subsidiary of IP Group plc, which holds stakes in a large number of university research endeavours around the world.[219]

Translation of evidence into policy and practice

Efforts in this area can be split into efforts to make governments and health systems more responsive to evidence generally, and into efforts to generate specific policies based on evidence.

One common example of evidence translation to policy is seen in clinical practice guidelines. Such guidelines are most often produced either by national governments, the World Health Organization, or regional professional societies such as the American Thoracic Society and the European Society for Medical Oncology.

It is likely that such guidelines are far less available for areas of public health policy outside of the scope of traditional clinician-oriented practice guidelines.

Some examples of international initiatives to strengthen the use of evidence in policymaking include:

- ***The Asia Pacific Observatory on Heath Systems and Policies (APO) (2011–present)*** The APO is a partnership of governments, international agencies, foundations, and researchers that collates and analyses evidence to inform health systems policymaking and strengthen regional research capacity.[220]
- ***The World Health Organization Evidence Informed Policy Network (EVIPNet) (2005–present)*** The objective of EVIPNet is to "promote the systematic use of health research evidence in policy-making", with a focus on LMICs, by encouraging partnerships between policymakers, researchers, and civil society. EVIPNet engages in, among other things, capacity strengthening, exchanging experiences, monitoring and evaluation, as well as producing specific policy briefs and establishing priority-setting mechanisms.
-

Monitoring and evaluation of research activity

In many cases, governments and research funders undertake some monitoring and evaluation of the research activities they fund. However, easily usable metadata on research grant applications, grants, and outputs are not widely available and are do not follow harmonized formats. Metadata would include, for example, the main topic areas of the research, the type of analysis, time period, expenditures, and so on.

In recent years, with regard to governments, evaluations of research have in some countries become more formalized. Some examples include:

- ***The Research Excellence Framework (REF), United Kingdom***
  First conducted in 2014, the REF required higher education institutions to submit case studies describing their successful research projects, which are evaluated by a panel of experts with regard to outputs (e.g. publications), impact beyond academia, and an environment supportive of research.[221]

[218] Imperial Innovations. https://www.imperialinnovations.co.uk/
[219] IP Group plc. https://www.ipgroupplc.com/
[220] Asia Pacific Observatory on Health Systems and Policies. Available from: http://www.searo.who.int/entity/asia_pacific_observatory/en/
[221] Research Excellence Framework. https://www.ref.ac.uk/

- ***The National Research Foundation (NRF), South Africa***
  The NRF evaluates and ascribes a rating to the output of individual researchers, with the aim of incentivising high-quality research.[222]

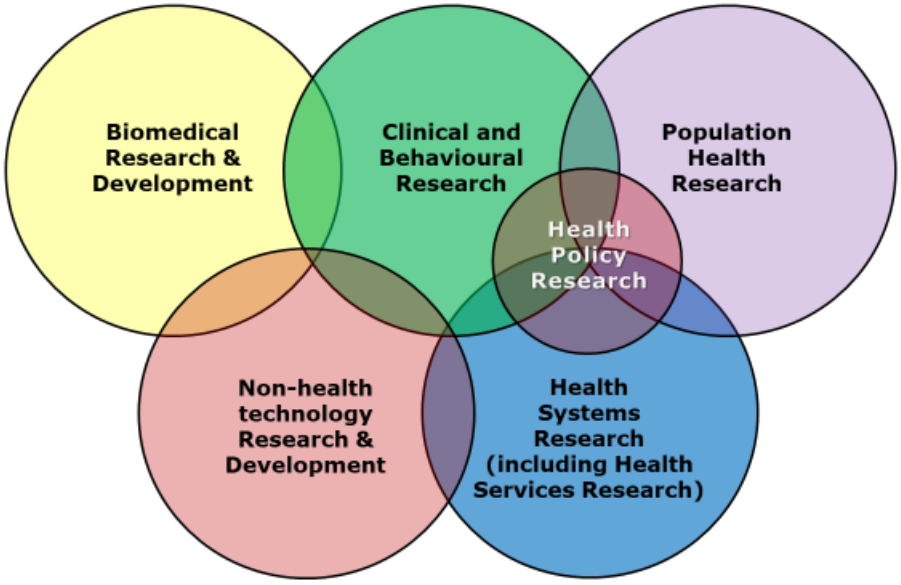
However, on the whole, the evaluation of research activity – as distinct from research funding, discussed earlier in this document – remains an area where there is little independent analysis.

[222] National Research Foundation. NRF Rating. https://www.nrf.ac.za/rating

Annex A: Conceptual frameworks for research for health

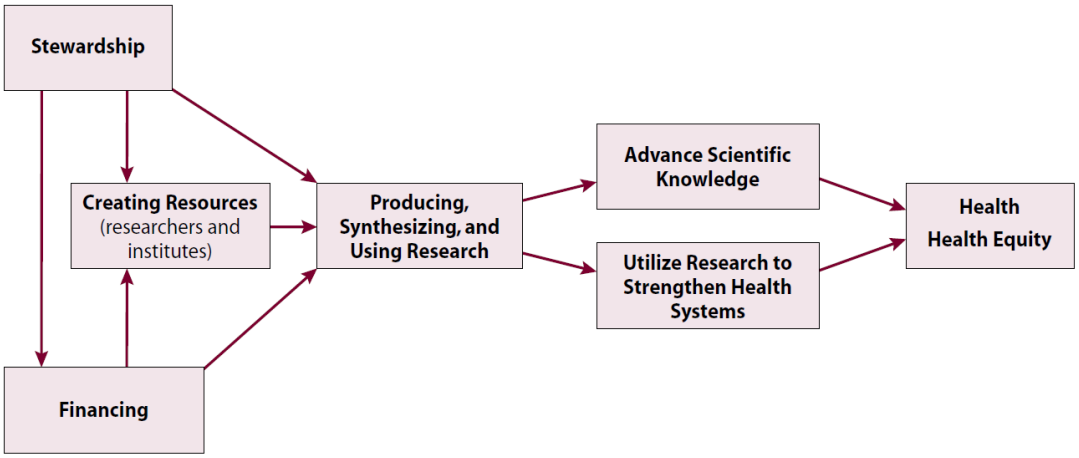
Figure 1 defines the different kinds of research that constitute the research for health system – one may debate where these circles should best overlap. Figure 2 is a simplified model of how research should be translated into health and health equity through its role in strengthening health systems. Figure 3 is a more detailed description of the chain from funding to research to the dissemination of new knowledge (including the importance of journals and patenting) but omits the interactions with health systems and the wider environment. Figure 4 emphasizes that research for health is part of a wider research system as well as the health system, and that all are located in the wider macro-environment, while Figure 5 places emphasis on the pathways by which the results of research can be utilized by policymakers and practitioners and thereby translated into health outcomes.

Figure 1 Types of research for health



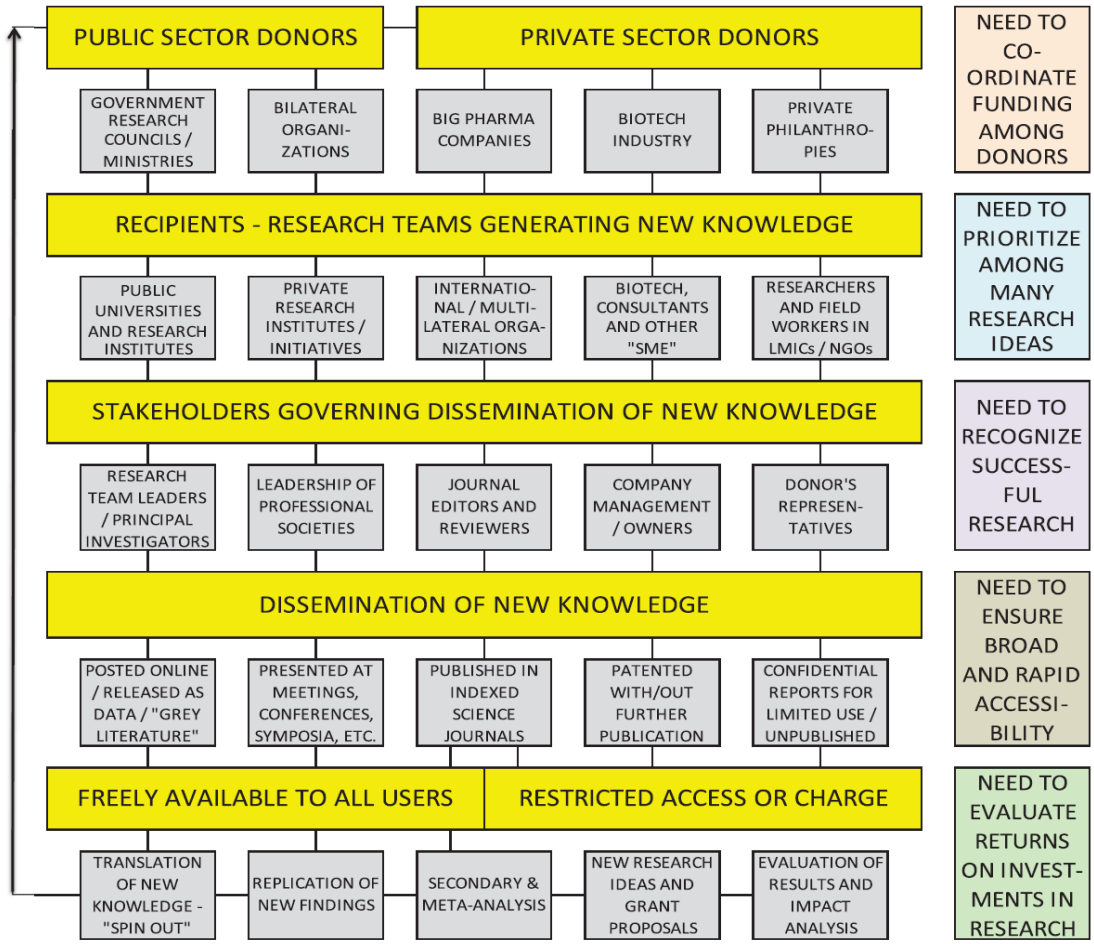
Source: Adapted from slide produced by the Research Council of Norway

Figure 2. Linkages between functions and goals of health research systems



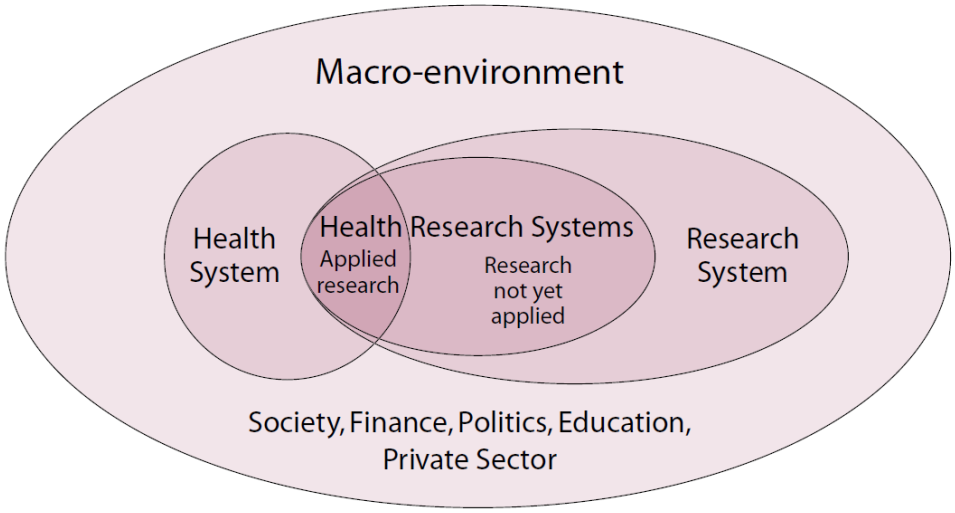
Source: World Report on Knowledge for Better Health: Strengthening Health Systems. World Health Organization, 2004. http://www.who.int/rpc/meetings/world_report_on_knowledge_for_better_health.pdf?ua=1

Figure 3. The structure of the global health research system and the five basic needs to ensure its efficient performance



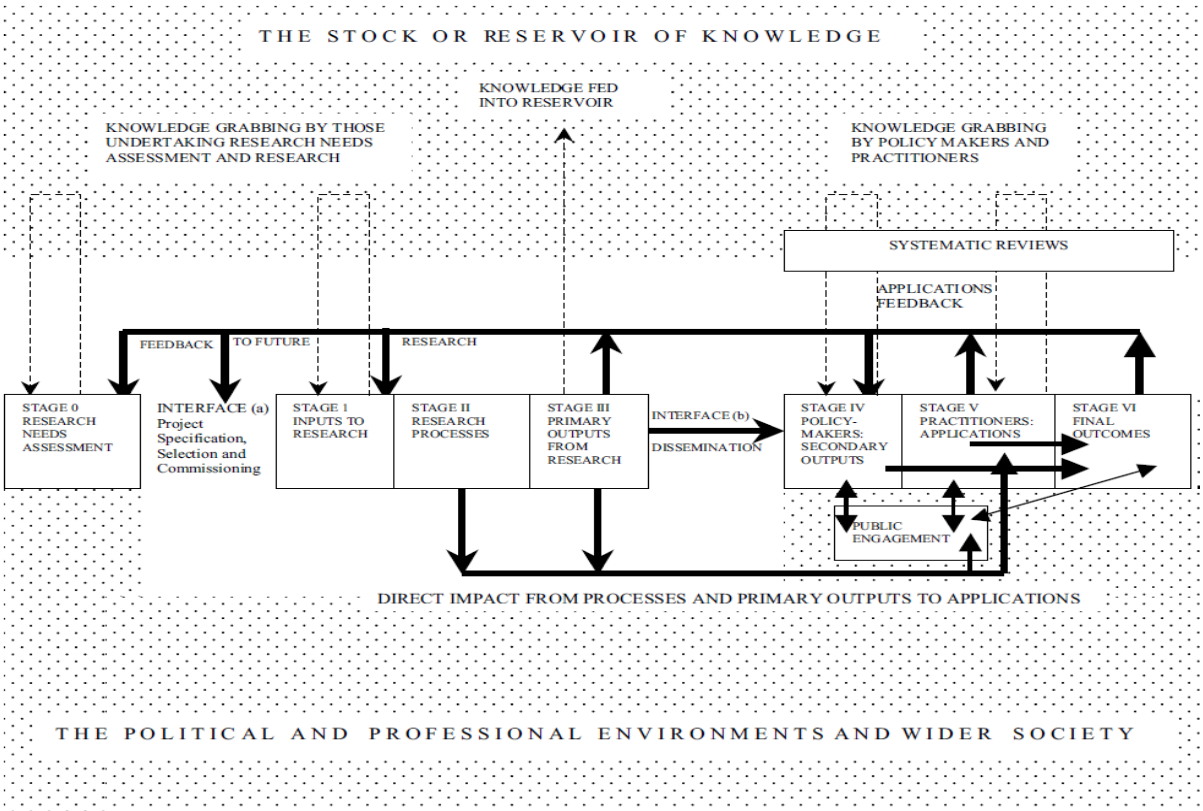
Source: Rudan I, Sridhar D. Structure, function and five basic needs of the global health research system. *J Glob Health* 2016; 6. DOI:10.7189/jogh.06.010505

Figure 4. Linkages between the health, health research and research systems and the broader macro-environment



Source: World Report on Knowledge for Better Health: Strengthening Health Systems. World Health Organization, 2004. http://www.who.int/rpc/meetings/world_report_on_knowledge_for_better_health.pdf?ua=1

Figure 5. The Place of Policy-Making in the Stages of Assessment of Research Utilisation and Final Outcomes



Key: Direct lines within the flow or feedback. Indirect lines of communication. Primary Outputs – Publications, trained researchers. Secondary Outputs – Policies from national, local and professional bodies. Final Outcomes – Health and equity gains, cost-effectiveness and economic benefits.

Source: Hanney SR, Gonzalez-Block MA, Buxton MJ, Kogan M. The utilisation of health research in policy-making: concepts, examples and methods of assessment. *Health Res Policy Syst* 2003; **1**. DOI:10.1186/1478-4505-1-2.