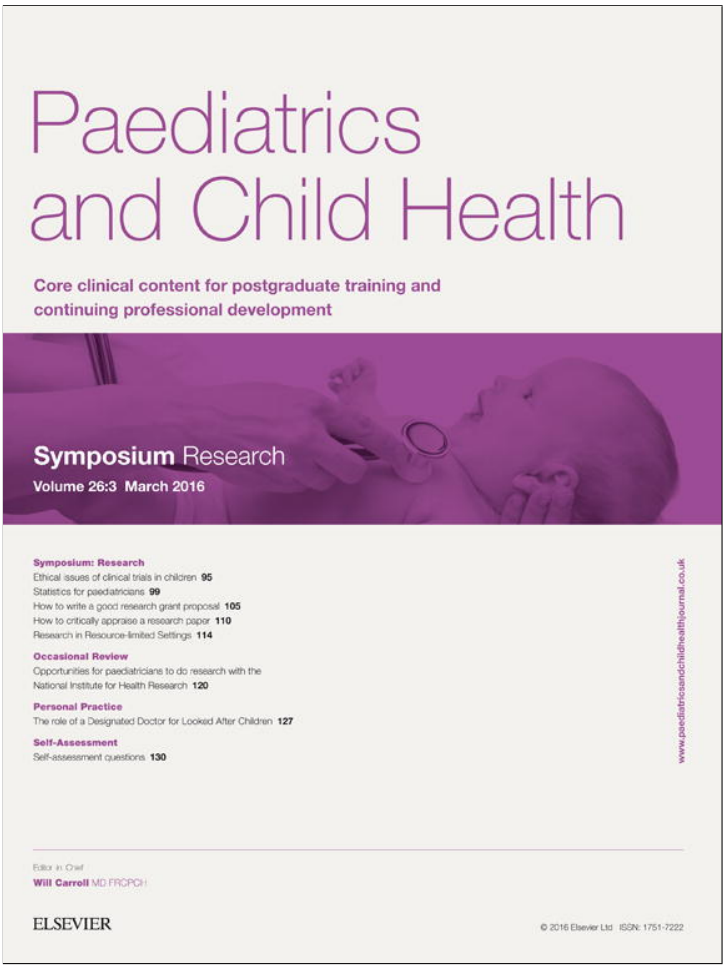

Research in Resource-limited Settings

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Abstract

After long periods of vast child health disparities between industrialized countries and Resource-limited Settings (RLS) a wave of research has started to address and reduce the gap. Major global collaborations have been mutually rewarding and have established funding and career structures unthinkable even 25 years ago. Despite this progress, work remains to ensure academic and funding equity and ethical parity. This paper outlines the background to and history of research in RLS, illustrates the current situation and points to potential future developments.

Keywords Millennium Development Goals (MDGs); research ethics; Resource-limited Settings (RLS); United Nations Children's Fund (UNICEF); World Health Organisation (WHO)

Introduction

Imagine that global health research resources: financial, academic and human, were distributed proportional to needs as defined by perinatal, neonatal and child morbidity and mortality. In that Utopia, those countries classed Lower and Middle Income (LMIC or alternatively Resource-limited Settings) would be swamped with the means to improve their health trajectories.

Despite the high ideals of the Millennium Development Goals (MDGs) and some recent if limited progress towards their targets, the world, sadly, remains inequitable. Typical sub-Saharan African and south Asian mortality rates of 60/1000 (perinatal), 100/1000 (infant) and 160/1000 (under five) of largely preventable causes compare starkly with industrialized rates in the order of 3, 5 and 10/1000 respectively. Data from global sources such as the WHO, UNICEF and the Global Health Council show consistent unacceptable differences in both infant and under-five mortality between industrialized and RLS from eminently preventable causes. This is compounded by malnutrition which contributes to 2 million childhood deaths (attributable to stunting, wasting and restricted intrauterine growth) half of which are at least partially attributable to micronutrient deficiencies Figures 1–3.

The tide, however, does seem to be slowly turning and a number of recent measures have generated an impetus. These include: the Millennium Development Goals (part 'carrot', part 'stick'), high profile philanthropic donations typified by Bill and Melinda Gates, pharmaceutical assistance in the form of subsidized drug treatments, and greater weight to RLS research from the large research foundations.

There is no such entity as a definitive review of paediatric research in RLS but this review will set out to introduce the following: history, ethics, current activity and deficits, donor politics, and careers within such research.

For the sake of clarity we will define what we mean by LMIC using the World Bank 2013 criterion which considers countries by their Gross National Income (GNI) per capita. Economic criteria classifies countries as low income when its GNI is US $ less than 1035; lower–middle when it is US $ 1036–4085; higher middle when it is US $ 4086–12615; and high income when it is US $ more than 12,616.

History

Though the major tropical academic institutes, Liverpool, London and Amsterdam were founded over a century ago, research has, until recently been of lower profile than 'traditional' overseas expatriate work involving direct clinical care or education. Typical examples of the latter would be either a stable clinic or hospital often founded and supported by religious foundations. This was, and still is, most obvious in sub-Saharan Africa where the evangelical legacy remains very strong amongst all the previous European colonies. An alternative more recent approach is the rapid response style as typified by the International Committee of Red Cross (ICRC) and Mèdecins Sans Frontières (founded in the early 1970s) and numerous non-governmental organisations (NGOs) in reaction to war or natural disasters. For many such organizations, work continues beyond the resolution of the immediate humanitarian crises to improve the often paltry infrastructure and to assist in the creation of systems sustainable independently locally.

The evolution of the Liverpool School of Tropical Medicine (LSTM) illustrates the history of recent research well. The LSTM, the oldest tropical research institute in the world was established at the turn of the 20th century and built its first overseas research lab in Sierra Leone in 1921. After a wave of discovery including establishing the ground-breaking link between the black fly vector, filaria and river blindness, momentum slowed until after World War II.

Post war, a number of major Western institutions forged academic partnerships and research activity burgeoned. The research however was patchy and often disorganized. Studies were largely observational and when trials were conducted, ethical considerations such as consent and unnecessary enrolment beyond positions of equipoise were a commonplace.

Interest in conducting trials in RLS was also until recently largely driven by and dependent upon the perceived potential profit for pharmaceutical companies developing newer therapies. The classic example is HIV where huge amounts of money have been invested in drug development in the West, where profit is

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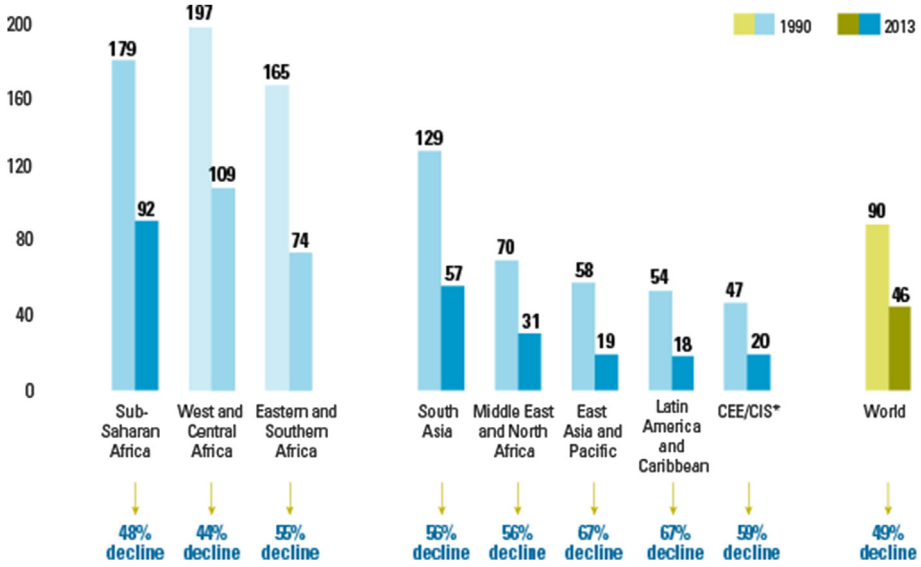

Figure 1 Despite progress, under-five mortality rates are still far higher in low-income countries than in high-income countries. Under-five mortality rates (vertical axis) and number of deaths (bubble size) by income level, 1990 and 2015. Note: The vertical axis refers to the under-five mortality rate and the size of the bubble is proportional to the number of under-five deaths. Source: Committing to Child Survival: A Promise Renewed, Progress Report 2015 (UNICEF, with permission)

guaranteed; while the majority of the world's HIV infected population in sub-Saharan Africa (SAA) was offered pitifully limited access to even the cheapest anti-retroviral drugs.

In the last quarter century emphasis has shifted towards trial based research and this has gathered momentum near exponentially since the millennium. This has been facilitated by support from philanthropic donors such as the Bill and Melinda Gates Foundation (the example par excellence), and enhanced funding of established institutions such as the Wellcome Trust, Department for International Development (DFID), the National Institute for Health (NIH) in the US. Contemporaneously, academic tropical research has developed a formal career structure and is no longer seen as the Cinderella 'overseas-see-the-world-experience' it was even a decade ago.

This progress has to be placed in perspective however, and Figure 4 illustrates the ongoing disparities in research activity.

Priorities of research in RLS

Limited financial resources make it necessary that the health authorities in developing countries set priorities in research as per the health needs. In this, again priorities need to be set for basic research, clinical research, vaccine trials, intervention studies and operational research. The MDGs, adopted by 189 nations in the United Nations Millennium Declaration in September 2000, have provided a source of priorities. Specific goals address the need to reduce burden of child and maternal mortality, and of HIV/AIDS, malaria and other diseases. The Partnership for Maternal, Newborn and Child Health (PMNCH) joins the reproductive, maternal, newborn and child health (RMNCH) communities into an alliance of more than 500 members, across seven constituencies: academic, research and teaching institutions; donors and foundations; healthcare

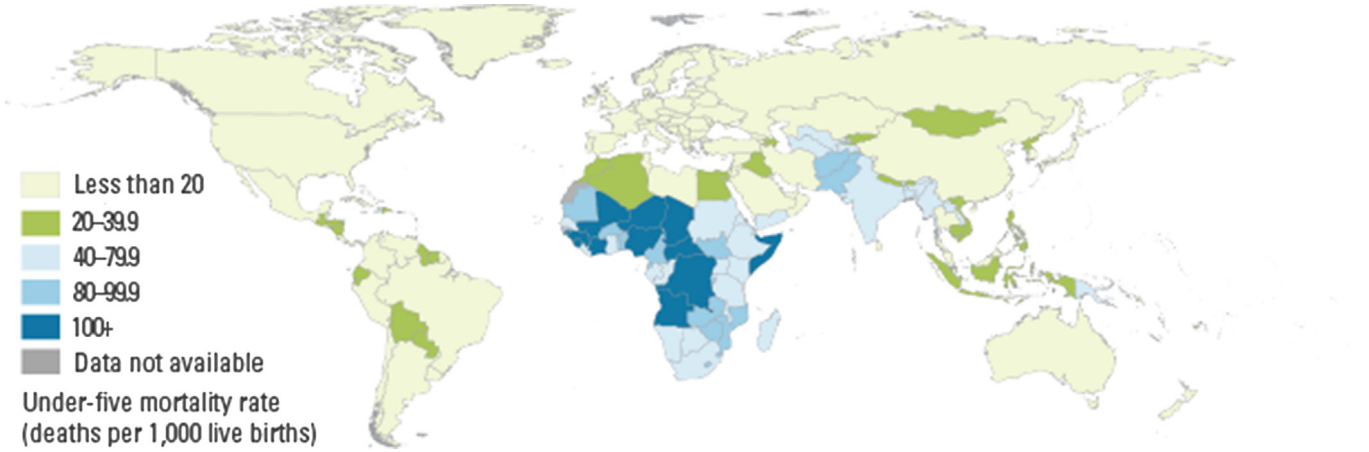

Figure 2 Under-five mortality rate and under-five deaths by country, 2015. The highest national under-five mortality rates are found in sub-Saharan Africa. Source: Committing to Child Survival: A Promise Renewed, Progress Report 2015 (UNICEF, with permission)

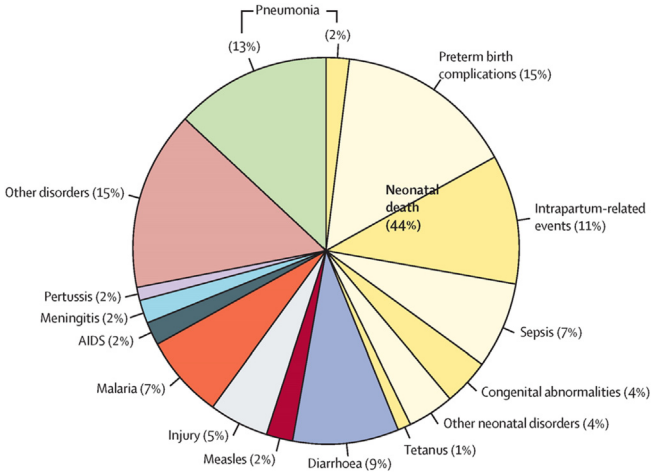

Figure 3 Global distribution of deaths among children under age 5 and among newborns, by cause, 2015. Pneumonia, diarrhoea and malaria are main killers of children under age 5; preterm birth and intrapartum related complications are responsible for the majority of neonatal deaths. Nearly half of all deaths in children under age 5 are attributable to undernutrition. A: Deaths among children under age 5. B: Deaths among newborns (0–27 days). Note: Estimates are rounded and therefore may not sum up to 100%. Source: Committing to Child Survival: A Promise Renewed, Progress Report 2015 (UNICEF, with permission)

professionals; multilateral agencies; non-governmental organizations; partner countries; and the private sector. This partnership aims to reduce child mortality and improve maternal health to the highest attainable standard in the years to 2015 and beyond (http://www.who.int/pmnch/about/en/).

With the Millennium Development Goals set to expire at the end of 2015 and the Sustainable Development Goals' framework is conceptualized, non-communicable diseases are being prioritized in the post-2015 global development agenda.

Research money is still inequitably polarized towards the 'big three': HIV/AIDS, malaria and TB. In 2007, R&D funding for HIV totalled US $ 1.1 billion (of which 64% was directed to vaccine development). A paltry US $ 1 million (0.1% of the total) was invested in drug development for resource poor settings, such as paediatric formulations and fixed drug combinations. Malaria commanded funding of US $ 468 million (50% of which was directed towards drug development) and TB US $ 410 of which the largest share, 35%, was invested in R&D, with 20% in vaccines. The poor relations remain the 'neglected diseases' a heterogeneous group of (largely) chronic vector borne illnesses including: guinea worm infection, schistosomiasis, lymphatic filariasis, leprosy, African trypanosomiasis (sleeping sickness), South American trypanosomiasis (Chaga's disease) and leishmaniasis. They affect 1 billion people worldwide but command less than 5% of R&D allocated funds. The Global Health Division of the Gates Foundation aims to harness advances in science and technology to save lives in developing countries, with focus areas

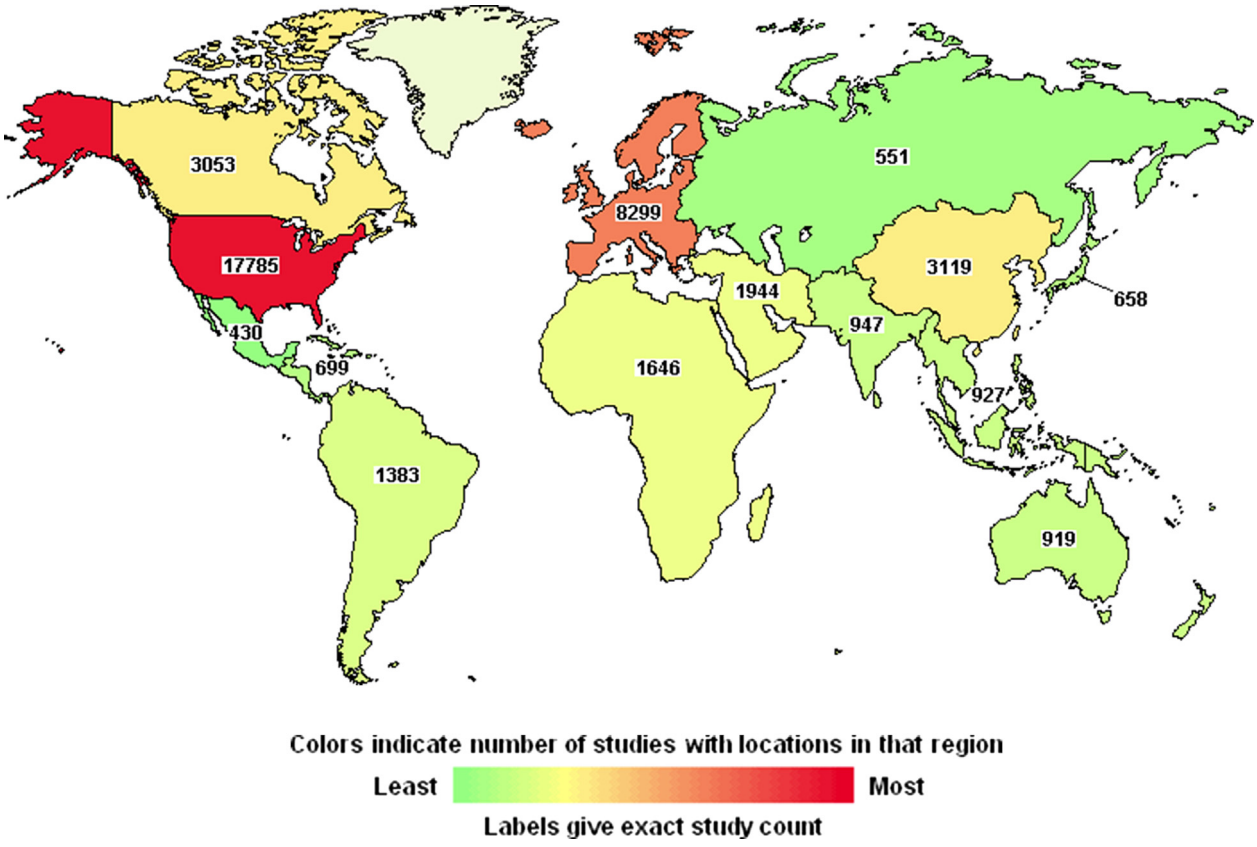

Figure 4 Global distribution of 39,459 studies shown on map, found using search term "children" at https://clinicaltrials.gov [Accessed on 5th March 2015]. Colours indicate number of studies with locations in that region. Labels give the exact study count.

such as vaccine discovery, drug discovery, maternal and child health, and control of disease-transmitting mosquitoes.

Though the disparity is well recognized, the tension between profit in drug development and need has not been resolved. Department of Biotechnology, Ministry of Science & Technology of Government of India in 2011 created a unique organization — **Biotechnology Industry Research Assistance Council (BIRAC)** — the first of the kind which would work with a focused mandate of strengthening and empowering the innovation research capacities of the biotech entrepreneur and provide an enabling, globally competitive ecosystem.

Ethics of research in RLS

Globalization, increasing awareness of human rights protection and greater scrutiny of all health research has given rise to a considerable debate in ethical conduct and regulation of international biomedical research.

The history of bioethics has evolved from the days of Hippocrates to Claude Bernard, to the development of the Nuremberg Code in 1960s. In 1964 the World Medical Association Declaration of Helsinki underscored 12 basic principles for the conduct of human biomedical research. The Council for International Organisation of Medical Sciences (CIOMS) in collaboration with the WHO proposed guidelines for international research in 1982, which were further amended in 1993 as the "International ethical guidelines for biomedical research involving human subjects".

Over the years, amendments in Helsinki Declaration have been complemented by individual efforts in industrialized as well as developing countries, such as consultations of the Nuffield Council for Bioethics in the UK, the National Bioethics Advisory Commission in the USA, and Ethical Guidelines for Biomedical Research by Indian Council of Medical Research, India.

Much of the debate about research ethics in RLS surrounds the area of "informed consent", "standard of care" and use of "placebo" in research trials.

In developing countries, where literacy is low, researchers should develop culturally and socially appropriate methods for obtaining informed consent. Participants should get an opportunity to seek advice or permission from a third person, such as a spouse or head of family. Local community leaders may need to be consulted before implementing a study. The research study objectives, procedures, risks and benefits need to be discussed in local language. Even then, a doubt remains if many of these communities are able to give 'truly' informed consent.

Applying the notion of "global standard of care" may look right, but standard therapy in one health system may be totally inappropriate in another setting with limited resources. The development of protocol for managing acute respiratory infections among children in developing countries has been proven to be of great benefit. It can be argued that none of these developments could have taken place had studies employed the "standard of care" in developed countries for treating lower respiratory tract infections or pneumonia with parenteral third-generation cephalosporins.

The Central Drugs Standard Control Organization (CDSCO), India's regulatory agency for clinical research, has recently made a series of announcements and corrections that moves India towards alignment with global clinical research practices. Reasonable direction is now available for regulatory review timelines, the role of ethics committees, the consent process, safety reporting process and the compensation process. Also it has been made mandatory that "standard of care" should be provided to all subjects taking part in placebo controlled trials.

The Wellcome Trust, UK, promotes attention to ethical considerations in international research through their collaborative sponsorship of conferences focused on ethical concerns in scientific research in RLS. It also has a grants award programme to fund investigations on the ethics of biomedical research in developing countries.

The good and the bad

In this section we illustrate examples of both failures and successes in recent research history.

A combination of ethical regulation, obligatory trial registration in the international registry, standardized methodological reporting (CONSORT) and improved detection of research fraud have improved research globally for the better over the last two decades. Recent examples of ground breaking work notable for rigour and collaboration, which has and will save numerous lives include the following.

'AQUAMAT'

A multicentre, multinational African randomized controlled trial (RCT) involving 5000 children showed unequivocally that artesunate is superior to quinine in reducing mortality from severe malaria, with 25% fewer fatalities in the artesunate group.

'DOTS'

Directly observed treatment for tuberculosis, a WHO initiative, has improved recovery rates and reduced multidrug resistance in areas with notoriously poor drug compliance.

Outpatient treatment of protein energy malnutrition (PEM)

A number of studies have demonstrated excellent recovery rates from PEM using novel, locally or centrally produced, high energy, hard-to-contaminate nutritional supplements, where previously prolonged inpatient treatment was deemed necessary.

There are many more successes but the next recent examples illustrate that complacency would be unwise.

Manipulating treatment and data falsification: the trovafloxacin scandal

In more than a decade long-run court case a pharmaceutical company Pfizer was held to account for a trial purporting to test the then new antibiotic oral trovafloxacin ('Trovan') in meningitis against the standard ceftriaxone treatment in Kano, Nigeria in 1996. Not only was ethics' approval falsified and the children therefore unlawfully recruited but the control group was manipulated by giving a smaller than standard dose thereby showing a spurious benefit of trovafloxacin.

Unnecessary trials

By 1994, it had been established through trials in the US and France by the AIDS Clinical Trials Group (ACTG 076) that by treating HIV positive pregnant women with a combination of third trimester oral zidovudine, peripartum intravenous

zidovudine and short term neonatal treatment, vertical HIV transmission rates could be reduced by two thirds. In 1997, however, Lurie and Wolf writing in the New England Journal of Medicine had amassed a total of 15 studies in RLS involving, amongst others the WHO, CDC and NIH again testing the zidovudine regimen against the controls. There was no justification from the point of view of equipoise, and there is no doubt that these trials led to unnecessary exposure and death to and from HIV infection in the study children. This groundbreaking paper simultaneously exposed the double standards then operating, and led to a universal code of "standard of care" in trials.

Advantages of international collaborations

Academic partnerships and capacity building

Research collaborations between developing countries and international organizations are thought to produce higher quality results. An analysis has shown that evaluations of population level health interventions and policies in India are commissioned mostly by international organizations. As anywhere in the world, the majority of the funding for life sciences research in India comes through the government. Much of the funding for health research is channelled through the Central Government's Department of Health Research (which also oversees activities of the Indian Council for Medical Research), Department of Science and Technology and the Department of Biotechnology. These departments also have various extramural funding schemes.

The increasing health research funding is evident from the proportion of published papers from India in PubMed, which has increased from 0.4% of the global total in 1988 to 1.8% in 2008.

Human resources account for approximately 70% of recurrent expenditure in most of the health systems. Developing countries have a shortage of healthcare providers and also unequal distribution within the country. A lack of stewardship from highest level to human resources at individual facilities is of concern in RLS. Achieving balance between "demand and supply" is a great challenge in low and middle income countries.

The WHO's Task Force on Health Systems Research included human resources for health (HRH) at both "the district level and below" and " higher management levels" as two of the 12 research categories important for attaining the MDGs.

The Biomedical Research Career Programme for India, a new initiative jointly funded by the Indian Government's Department of Biotechnology and the Wellcome Trust, is planning to increase its emphasis on public health research in India.

Collaboration is also reflected at funding level notably from the following: NIH, the Gates Foundation, US Defence Association, the Wellcome Trust and the Medical Research Council. The philanthropic zeal of these donors cannot be overstated and has been perhaps the major driver in improving research in RLS.

Academic partnerships between European and North American institutions and African and Asian centres are mutually beneficial but not free of conflict of interest both financially and areas of research focus. As Costello and others have observed, that despite good intentions, the need for an industrialized university to cover the high costs of a collaboration can result in a disproportionate amount of partnership funds being diverted towards itself. In terms of focus there is potential conflict in publication profile. Western universities tend to concentrate on biomedical academic research and publication in high impact factor journals volume of which is of course essential for their own funding and status. However, the most important issues in resource poor settings are often organizational at public health and health system level areas of lower publication prominence. A notable example of a very fruitful collaboration between a western partner (MRC Lifecourse Epidemiology Unit, Southampton, UK) and a number of Indian academic centres (King Edward Memorial Hospital, Pune, Holdsworth Memorial Hospital, Mysore, Delhi Birth Cohort, Christian Medical College, Vellore, and Institute of Social Change, Mumbai) has seen a world class research being promoted in an area of mutual interest and of great benefit to the Indian partners. This also led to formation of a society (SNEHA) which is the first of its kind in the world, and which hosted the first world conference on Fetal Origins of Adult Disease (now called, Developmental Origins of Health and Disease, DOHaD).

Careers

There is no set career pattern through which to enter academic tropical paediatric research. The creation of academic clinical fellowships as part of run through training and support from one of the large donors (Wellcome Trust, MRC, NIH) have rationalized training for some. Others reach the same point by starting work in NGO health systems before branching into formal research. Progress as in UK/US academic work is dependent on a higher research degree (MD or PhD). The Wellcome Trust-DBT India Alliance, launched in 2008, is an £80 million initiative funded equally by The Wellcome Trust, UK and Department of Biotechnology, India with an aim to build excellence in the Indian biomedical scientific community by supporting biomedical research and the medical humanities.

Summary

Times have changed. Research in RLS is now conducted within a formal ethical framework and with the application of the same rigour in methodology and reporting expected in industrialized settings. On the other side, the bewildering "hype" in guidelines, regulations, declarations and recommendations for international research is looked upon by some as a hindrance to resolve the uncertainties about the effects of treatments. The differing circumstances in industrialized world vs. LMICs need to be rightly interpreted by the ethicists and investigators so as to improve health of the vulnerable populations. ◆

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Practice points

- Research in RLS is flourishing with academic and funding collaborations on a steep rise
- Ethical practice is now tightly regulated
- There remain tensions in terms of research focus, and perceived 'universal' standards of care
- Non-communicable diseases are getting attention in the post-2015 global development framework