Global health science: a threat and an opportunity for collaborative clinical science

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We will never have a better opportunity to improve public health globally. The question is whether we are shrewd enough, bold enough, and committed enough to make it happen.

There is a tide in the affairs of men
Which, taken at the flood,
leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.
On such a full sea are we now afloat,
And we must take the current when it serves,
Or lose our ventures[1].

We are at a unique juncture in international science and health. As a result of major advances—an unprecedented political and philanthropic interest with deep global public support, and a realization that diseases do not respect borders, affecting us all whether rich or poor—we live in an era of unprecedented opportunity in global science and health. We are at the high tide: if we seize the opportunities presented, we can make a real difference to the lives of millions. The question, as in the words of Brutus to Cassius in Shakespeare's tragedy of almost 500 years ago, is whether we are shrewd enough, bold enough and committed enough to take advantage of the tide.

Major challenges in global health sciences

We now have the tools to truly 'roll back' malaria because of the development of artemisinin-combination antimalarial drugs and insecticide-treated bed-nets. Considerable progress has been made in the treatment of malaria, helminth infections, lymphatic filariasis, onchocerciasis, schistosomiasis and other 'neglected' tropical diseases through successful partnerships in the public sector and between the public and private sectors and with substantial increases in the implementation of proven interventions[2]. Human immunodeficiency virus in the 'rich' world does remain a chief public health problem, but with earlier diagnosis, access to safer and better antiretroviral drugs, and good clinical care, infection has gone from a rapidly progressive and universally fatal disease to a treatable chronic condition with which people have the opportunity to live a full and healthy life. But infection with this virus is mainly a disease of the 'poor world', where most people still have either sporadic or no access to life-saving antiretroviral drugs, no access to second-line agents and limited supportive clinical care. This is an unacceptable disaster today, and it has the potential to lead to an even bigger problem in the future with the inevitable development and spread of drug resistance.

Tuberculosis remains a major global health problem with no good new drugs available, a vaccine still a long way off and drug resistance spreading. There are also other important new infectious threats. Over 40 emerging diseases have been reported in the past three decades, including severe acute respiratory syndrome, avian influenza, new Ebola outbreaks and Nipah virus encephalitis. Others infections such as dengue and West Nile Virus have increased and have spread to new regions because of changing demographics, urbanization, zoonotic spread and an ever-changing environment. The future effect of climate change on human and animal health is difficult to predict, but such change will probably influence disease patterns directly or indirectly. As economies develop, urbanization increases and the structures of societies change. Alongside that change, the pattern of disease will also alter, with an increase in the prevalence of mental health problems, cardiovascular disease, cancer, and alcohol- and drug-related problems and injuries. We should also remember that most infectious diseases go undiagnosed, and as long as diagnostic facilities remain rudimentary in most parts of the world, these 'unknowns' remain a chief cause of morbidity and mortality.

In addition to the emergence of new pathogens, there is the insidious and steady increase in antibiotic resistance among the main bacterial pathogens, which is outpacing the rate of discovery of genuinely new antibiotic classes. The horrifying prospect of a return to a pre-antibiotic era remains a huge concern; indeed, antibiotic resistance may be the world's most important emerging health problem. It is possible that despite what we have at our disposal now for preventing and treating most of the world's public health threats (if we chose to use them), we are in fact living in a 'honeymoon phase' with greater challenges ahead. At present, most infectious diseases remain preventable with better sanitation and nutrition, safe and efficacious vaccines, and insecticide-treated bed-nets. Many infections are treatable if diagnosed early enough and the appropriate course of antimicrobial drugs is available. If we implemented what we know now, we would be able to 'roll back' or even eliminate many of the main global public health problems. We are often seduced by the promise of better interventions 'just around the corner'. We all hope and need for these to arrive, but we are failing to implement proven interventions that are now available and affordable. So how can the global scientific community work together internationally to ensure we put to best use the technological advances, public interest and available

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Published online 22 October 2007; doi:10.1038/ni1532

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There is no quick and easy solution to global health issues. More often than not, 'rich' countries intervene at the grass roots level. However, responses to health problems should be tackled locally by the affected country, with money and technology coming from the developed world as and when needed.

funding to bring the greatest benefit to the greatest number of people? And how can we build the scientific and clinical infrastructures to ensure that we are capable of meeting the threats of the twenty-first century? The World Health Organization is the only body with an international mandate to coordinate this, and it needs to be at the center of any such effort. But it also needs to provide the courageous leadership to set the right agenda and policies. At present the World Health Organization has a unique opportunity to provide this[3].

The two biggest hurdles to the successful implementation of proven interventions for human health are money and human resources. For decades, money has been the most critical issue; however, that is now slowly changing with the mobilization of substantial amounts of money from governments, nongovernmental and philanthropic organizations, and international agencies. For the first time, the problem may be our inability to use the available money efficiently rather than the amount of money itself that limits the effect. All people working in global health carry a huge responsibility to use the present funding, technology and public support wisely. The present interest may wane because political fashion is fickle, and this window of opportunity may not last forever. At this 'tipping point' in international health, human resources and the capacity of health systems will limit the ability to deliver what we know. There is a dearth of well trained, committed people throughout the health and scientific systems, as well as in the national and international authorities, who are equipped and able to deliver what we already know. Chronically underfunded universities throughout the developing world (including the lamentable policy of most international agencies of not supporting 'overheads' when grants are awarded to universities in resource-poor settings), lack of funding for a real career structure for health care workers and scientists, lack of sufficient senior mentors, the continued 'brain drain' from the resource-poor world to the 'rich' world, limited logistics, and corruption on all sides of the funding equation are all handicaps limiting successful implementation.

International collaboration on a local level

One of the issues highlighted by the rapid emergence of severe acute respiratory syndrome and the influenza virus H5N1 is the critical effect that a rapid local response can have on research and disease containment and the dangers when such a response is not available or forthcoming[4]. People and facilities are needed in the countries most affected to address the problem when it arises. In the era of science globalization, with a plethora of international agencies and stakeholders (unfortunately still mostly with their 'centers of gravity' in the developed world), we must not forget that it is mainly the local response that will determine the outcome of rapidly emerging infectious diseases. We must ensure that the clinical and scientific capacities are built and sustained where the threats are most likely to present themselves. Such facilities should not just focus on the threat of emerging infectious diseases but also address the day-to-day endemic issues of public health. Thus, it is essential to have the infrastructure and flexibility in place to respond when a new issue emerges. Small institutions with secure long-term funding can be important in this. There are many national and international institutions around the world that have been leading this for decades, and many of them have been critical in the early responses to emerging threats as well as addressing many of the less high-profile, but still important, endemic threats. The best such international collaborations are embedded in host institutions, with a method of operation and 'center of gravity' firmly set in the host institution. Such collaborations should foster excellent relations, with long-term commitments from all partners, driven by health needs and science. They should be unencumbered by political interference or excessive bureaucracy, with tough intermittent peer review, regular exchanges of people, flexible research, funding and service agendas developed in partnership with the benefits shared equally, and mutual friendship and respect.

The model for international collaborations will vary around the world and there is no set formula; funding agencies must allow these to develop with their own ethos and structure. There is no one size that fits all. Such collaborations provide a phenomenal (and in fact underused) resource for training and can enhance the capacity of a country to deal with health issues. There are many examples of such international partnerships, some with collaborations built up over decades: various enlightened Ministries of Health, the Wellcome Trust, the Pasteur Institute, the Li Ka Shing Foundation, the US National Institutes of Health, Rockefeller University,

the Aga Khan Foundation, the US Centers for Disease Control and Prevention, the Fogerty Foundation, the Medical Research Council (UK), the International Clinical Epidemiology Network, and an increasing number of 'south-south' partnerships such as the Pharmacology Network linking Asia, Africa and South America. Gerry Keusch and Carol Medlin have suggested these small institutions be linked and built on to provide a 'virtual global network' for health research[5]. I believe there are too many competing global networks and consortia consuming more in teleconferences, flying to meetings, and committees than they produce in real terms. Nevertheless, I do think the idea of a 'virtual network', as advocated by Keusch and Medlin[5], that builds on the notable success of many of the small institutions around the world is one network that could potentially deliver more than the sum of its parts. Keusch and Medlin's view was ahead of its time and should be taken forward.

The holistic approach to clinical science

In addition to the opportunities afforded by the present interest in international health and the funds that have begun to flow, we are also going through a 'golden age' of scientific advance. The genome revolution has changed the nature of science and in some cases has already brought real benefits to people's lives, and more will undoubtedly follow in the medium to long term. However, as a scientific community, we need to guard against overstating the speed at which such innovations will come to fruition and we need to be careful not to exaggerate the potential benefits for fear of alientating patients and the public with false promises. Breakthroughs will undoubtedly happen, but they will take longer and will probably have less effect than some of the more optimistic claims being made. This is not an argument against basic science; indeed, it is the opposite. I believe that investment in basic science is absolutely fundamental to ensure that we meet the greater challenges we will undoubtedly face in the future. The danger is that in the understandable excitement of the genomic revolution, we have left the patient behind.

Practice-orientated clinical research has not been given the funding it requires, and, even worse, we have managed to make it so cumbersome, complicated and bureaucractic that it has become easier to forget the patient and to focus solely on their genes or immune response[6]. This will come back to haunt us in the future when we will need to put all the major laboratory-based advances in the context of a human being. There is a very real danger that by the time we need these skills, we will have lost those people with such 'holistic' skills. In seminal research from Kenya, subsequently repeated in other settings, clinical scientists have defined how important and common bacterial septicemia is in the context of 'severe malaria'[7]. This work is of fundamental importance in terms of making patients better, but it also underpins how crucial patient-orientated clinical research is to our understanding of laboratory science. In terms of understanding pathogenesis, immunity and host genetic susceptibility, we need to define the clinical phenotype if we are to understand the genotype. It is now apparent that our ability to describe and analyze the molecular genotype far outstrips our ability to describe accurately and understand the clinical phenotype. By failing to define what is wrong with the patient with sufficient precison, we will fail to make the most of the genomic revolution. This imbalance must be addressed. This means greater support for integrated clinical research that breaks down the artifical barriers between clinicians and scientists and encourages a holistic approach to clinical science and the patient[6].

We must address the issue of bureaucracy and over-regulation (neither of which has ever been the subject of any scientific assessment in terms of the benefits of the process versus risks in preventing crucial research) before it stops all clinical research[8]. This is particularly true for diseases of the developing world and for rapidly emerging disease threats that the pharmaceutical industry (which has the resources to afford to pay for the administrative and bureaucractic costs) on the whole are not interested in. It means that even basic patient-orientated clinical research in resource-poor settings can be done only when there is a rich partner to support the often unnecessary bureaucractic hurdles that commonly do little to ensure that the fundmentally important issues of good clinical practice, good patient care and respect for the patient are in place. A new global agreement is needed on clinical research guidelines based on evidence and an appreciation of just how dangerous over-regulation can be to human health. Laurie Garrett has also raised an important issue in a thought-provoking article on public health. She questions whether the present funding available in international health and the current age of generosity might actually make things worse than better[9]. It is to be profoundly hoped that she is wrong, although there is undoubtedly truth in that thesis, which we must strive to guard against.

Conclusions

We will never have a better opportunity to combine the present availability of funding, widespread political and public support, and fruits of scientific research to make tangible differences to people's lives for the present generation and to provide a sustainable infrastructure for future generations. The 'center of gravity' in research needs to move from being mainly in the developed world to a 'center of gravity' in resource-limited settings addressing issues of local importance. If we are to fully realize the opportunities of the present scientific revolution, we must bring clinical and laboratory research back together and take a holistic approach that combines the best of practice-orientated clinical research with the best of laboratory sciences. We must not make patient-orientated research so difficult that we prevent critical research from being conducted. We are at a crucial juncture in international health; as in Shakespeare's play, we must grasp the opportunity the flood offers and take the current where it serves or we will lose our ventures[1].

This article is part of the Global Theme on Poverty and Human Development, organized by the Council of Science Editors. All articles from the Nature Publishing Group are available free at http://www.nature.com/povhumdev. The content from all participating journals can be found at http://www.councilscienceeditors.org/globalthemeissue.cfm.

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