

VACCINATION IN DEVELOPING COUNTRIES: PROBLEMS, CHALLENGES, AND OPPORTUNITIES

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Summary

Vaccines are the most inexpensive means of improving health and lowering morbidity and mortality caused by infectious diseases in the developing world. However, and in spite of significant advances in science and technology, the implementation of global vaccination coverage remains a pipe dream. Many obstacles and challenges remain, and imaginative and bold solutions are required. Recent initiatives based on international cooperation, philanthropy, and goodwill promise a brighter future for those in need living in the developing world.

1. Introduction

The eradication of smallpox and the imminent demise of polio are clear reminders of the power of vaccination in dealing with the scourge of communicable diseases in the developing world. The World Health Organization's (WHO) Expanded Program for Immunization (EPI), which is focused on the six major diseases of childhood (diphtheria, pertussis, tetanus, polio, measles, and tuberculosis), succeeded in dramatically raising immunization coverage in developing countries from 5% in the 1970s to more than 80% of the birth cohort in the 1990s. Although it must be admitted that not all 80% were fully immunized, it is estimated that this effort saved two to three

million lives per year. A report from the U.S. National Institute of Allergy and Infectious Diseases (NIAID) stated that the twentieth century witnessed a revolution in immunology, microbiology, molecular biology, biotechnology, and vaccinology and saw the introduction of vaccines that led to the reduction or elimination of 21 infectious diseases. The development of improved vaccines and new vaccines against a variety of infectious diseases such as hepatitis B, bacterial meningitis, pneumonia, typhoid, and varicella are examples that have been added to the armory. More importantly, these advances in the biomedical sciences have provided novel approaches to future vaccines hitherto unimaginable (e.g. DNA vaccines, edible vaccines, and therapeutic vaccines).

Despite these impressive achievements, significant problems and challenges remain. The fragility of achievements by many developing countries is well illustrated by the impact of economic crises in various parts of the world in the 1990s. In many countries affected by these crises, immunization coverage fell and the ability to purchase vaccines was affected by depreciating currencies. For many major diseases affecting developing countries, vaccines are not yet available; HIV, malaria, and dengue are three important examples. Practically, however, the central question is how will these advances be implemented and thus benefit the people who need them the most: the poor living in developing countries? This article will discuss the key challenges, outline the major obstacles, assess possible solutions and mechanisms, and conclude with a discussion of recent initiatives based on international cooperation and goodwill that promises to make a significant impact on providing extensive immunization coverage to children in the poor countries of the world.

2. Challenges to Improving Vaccination

What are the challenges we face in implementing these scientific advances to improve effectiveness of vaccination as a primary preventive strategy against infectious diseases? Clearly, the wider implementation of the currently available vaccines against the major diseases that cause significant mortality and morbidity in the developing countries (e.g. hepatitis B, *Haemophilus influenzae* type b (Hib) meningitis, typhoid fever, and rotavirus) is a key challenge. Many of these vaccines have been licensed for more than 10 years, have been proven safe and efficacious, have been offered at low prices and yet have not been introduced as part of national mass immunization programs in many developing countries. In the face of economic difficulties, maintaining current immunization coverage is a major challenge for many governments. Political commitment to maintaining vaccination infrastructure in the face of competing priorities, and continued affordability of vaccines, needs to be maintained. Table 1 provides a summary of the major infectious disease problems in the developing world and whether vaccines are available against these infections.

No satisfactory vaccines available ^a	Satisfactory vaccines available ^a
AIDS (2285)	Hepatitis B (1000)
Tuberculosis (1498)	Measles (888)
Malaria (1110)	Rotavirus (800)
Pneumococcus (1100)	Typhoid fever (600)
Dysentery (bacillary) (600)	Hib (500)

Enterotoxigenic <i>E. coli</i> (600)	Tetanus (410)
RSV (160)	Pertussis (346)
Schistosomiasis (150)	Cholera (120)
Leishmaniasis (42)	Diphtheria (5)
Chagas disease (17)	Japanese encephalitis (3)
Dengue/dengue hemorrhagic fever (15)	Poliomyelitis (2)
Leprosy (2)	

^a Numbers in brackets are the estimated number of deaths annually in '000s

Table 1. Availability of vaccines against major infectious diseases
(Source: World Health Report (Geneva: WHO, 1999))

There is also a need to prepare the way for improved vaccines (e.g. typhoid fever), promising new vaccines (e.g. pneumococcus, shigellosis, respiratory syncytial virus), and novel future vaccines (e.g. DNA vaccines against malaria and HIV/AIDS). Many of the newer vaccines are technologically sophisticated (e.g. typhoid Vi polysaccharide vaccines conjugated to a protein) and thus significantly more expensive than the original formulations. It is also likely that many future vaccines will be based on recombinant DNA technologies (e.g. genetic modification of live organisms, DNA-based vaccines, recombinant proteins, etc.) and present different concerns regarding safety and acceptability. Such concerns must be addressed if these vaccines are to be introduced into mass immunization programs.

Another important challenge relates to the HIV/AIDS epidemic that is primarily affecting developing countries, especially in Africa and parts of Asia. With 34 million people infected worldwide (25 million of whom live in Africa), and with the prohibitively high cost of anti-retroviral therapy, the development of an HIV/AIDS vaccine remains a very high priority. Vaccines represent an important component of future global strategies to combat the epidemic and perhaps the best long-term hope for the control of HIV/AIDS, especially in the developing countries. The other side of the coin is that the imminent eradication of poliomyelitis raises key questions on when to stop polio vaccination after eradication.

It is also timely, urgent, and important that we consider these challenges in light of recent developments. From a scientific viewpoint we need to consider several important issues. The excessive and indiscriminate use of antibiotics in many developing countries has seen the development and spread of antibiotic resistance among many bacterial pathogens (e.g. among *Salmonella typhi* and *Mycobacterium tuberculosis*). It is clear that the more widespread use of vaccines can essentially bypass this problem. One also has to consider the possibility of the appearance of emerging and novel microbial pathogens (e.g. the H5/N1 influenza strain in Hong Kong and the Nipah virus in Malaysia). Recent data have also highlighted disappointing results of some vaccine trials. For example, a major phase III efficacy trial of a new oral cholera vaccine in Indonesia involving 60 000 subjects showed no protective efficacy. Other clinical trials with a peptide vaccine against malaria (Spf66) in Asia and Africa also gave disappointing results. More recently, a newly licensed vaccine against rotavirus, a major

cause of diarrhea in the developing world, had to be withdrawn due to the serious complication of intussusception among vaccinated children. The rotavirus affair also raises important ethical issues as to whether a vaccine that has been withdrawn from use in the developed world should continue to be used in developing countries.

In addition to the scientific issues, there are also non-scientific issues affecting many developing countries, especially in Asia. A rapid rate of economic growth and development has often been accompanied by rapid urbanization. It has been estimated that, by the year 2015, of the 10 largest cities in the world, seven will be in or will border the tropical developing countries. This trend has often been associated with massive deforestation, overcrowding of cities, and poor sanitation. Rapid growth is also associated with the movement of migrant workers within regions. This has resulted in movement of pathogens (including resistant strains) between regions of high and low endemicity and problems with surveillance activities, as many of these migrants are illegal. The movement of migrant workers also has important implications for vaccine coverage, as illegal immigrants (and their families) may be missed by national immunization programs and may have come from countries with different immunization schedules. Economic crisis and political instability affected many developing countries in Asia, beginning in 1997, and has been associated with economic contraction, currency devaluation, inflation, business failures, and rising unemployment. Indonesia, one of the countries most severely affected by the crisis, has seen 68% inflation, 18% drop in school enrolment, 40% of its population (80 million people) living below the poverty line, 60% increase in maternal mortality, shortage of basic necessities, and social unrest. One of the key effects of the economic crisis has been a breakdown in the primary health care infrastructure (including vaccine delivery infrastructure) and reduced resources/funding for the purchase of vaccines.

3. Obstacles to Effective Vaccination

In addition to the challenges stated above, we also need to be aware of other, longstanding obstacles that need to be dealt with in order to achieve the ultimate goal of widespread immunization coverage against the major diseases. These obstacles are of four types: medical and scientific, structural and demographic, economic and political, and societal and cultural.

In relation to medical and scientific challenges, it is well known that many developing countries have weak surveillance capabilities, limited data on disease burden, and a weak scientific base. The implication of this is that very often there is a lack of awareness that a problem even exists. Furthermore, many children in developing countries suffer from malnutrition (including zinc, vitamin A, and selenium deficiencies), parasitic infection, multiple infections with more than one pathogen, and mucosal abnormalities (e.g. in the gut, persistent rhinitis). There is also the problem of evolution of pathogens where in developing countries the selective pressure to change may be higher due to indiscriminate antibiotic use, high transmission rates, and immunodeficient hosts. Taken together, the implications include altered immune status among children and infants in developing countries and potential problems with the mucosal delivery of vaccines. The latter is an important criterion for the "ideal" developing world vaccine in addition to single dose, neonatal administration, combination of several vaccines, lack of cold chain requirement, and low cost.

Under structural and demographic obstacles, we find poor infrastructure, logistic problems, expanding populations, and diversity (i.e. developing countries are very diverse and cannot be categorized as a single entity) to be the features found in many developing countries that often contribute to problems of effective delivery of vaccines. The obstacles in the economic and political category include limited resources, the high cost of vaccines, competing priorities, and national pride. The latter is often overlooked (and underestimated) and may result in a fear of dependence on industrialized countries, suspicion of true motives and fear of exploitation, and a strong desire for equity and national autonomy. Taken together with high cost of vaccines and competing priorities, this translates into problems of access and affordability, low priority for immunization programs, and resistance to innovations.

As to societal and cultural issues, the major obstacles relate to poverty, illiteracy (especially among women), religious taboos, superstition, influence of traditional healers/shamans, and an overemphasis on curative, rather than preventive, medicine. The direct implications of the above include social problems, lack of awareness of the importance of vaccination, and false perceptions and irrational fears about the use of vaccines. For example, the false perceptions include the idea that immunization is curative, that healthy children do not need to be immunized, and that sick children should not be immunized. Irrational fears include the belief that disease is an act of God or the supernatural (and that immunization may anger the gods/spirits), that vaccination will make children dependent on Western medicine, that vaccines contain components prohibited by religion, and that vaccination of children reduces fertility later in life. There have also been recent controversies on the safety of pertussis vaccine associated with complications affecting the central nervous system, and the link between measles vaccine and autism. These controversies also illustrate the fact that irrational fears of vaccination are by no means restricted to the developing countries but are also found in industrialized nations.

Clearly, the obstacles described in the various sectors are interrelated and will influence and interact with each other. The situation is also a dynamic one that is changing all the time.

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Biographical Sketch

Dr. Tikki Pang, presently Director, Research Policy and Cooperation Department, WHO, Geneva, holds a B.Sc. (Honours) in biochemistry and a Ph.D. in microbiology/immunology from the Australian National University, Canberra, Australia. Professional accreditations include fellow, Royal College of Pathologists, United Kingdom; fellow, Institute of Biology, United Kingdom; Fellow, American Academy of Microbiology; fellow, Academy of Medicine of Malaysia; and member, International Molecular Biology Network. Previous employment as lecturer then associate professor, Department of Medical Microbiology, Faculty of Medicine, and then as professor of biomedical sciences, Institute of Postgraduate Studies and Research, University of Malaya, Kuala Lumpur, Malaysia.

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Dr. Pang has published six books and more than 180 scientific articles, and has been awarded eight major research grants from the National Science Council, Malaysia, in infectious disease research and a Collaborative Research Initiative Grant from The Wellcome Trust, U.K. Research and academic interests include epidemiology, pathogenesis and laboratory diagnosis of dengue virus infections, molecular epidemiology and genetic diversity of enteric pathogenic bacteria, immunology and pathogenesis of typhoid fever, novel diagnostic and immunization approaches in infectious diseases, vaccination against tropical diseases, prevention and control of infectious diseases and impact on economic development, development of research capabilities in developing countries, and impact and application of modern biotechnology on developing economies.