Rethinking global access to vaccines

Barriers to dissemination of life saving vaccines in low income countries can and should be overcome, argue **Dave A Chokshi** and **Aaron S Kesselheim**

Inadequate access to vaccines in low and middle income countries results in more than two million deaths each year.¹ Two thirds of these deaths occur in children under the age of 5. Hepatitis B virus and *Haemophilus influenzae* type b (Hib) vaccines are now starting to be used in low and middle income countries, but they were licensed for use in the industrialised world more than two decades ago. Our difficulty in disseminating well established vaccines casts doubt on our ability to promote widespread use of new ones, such as those for diarrhoea associated with rotavirus infection and for human papillomavirus (a causative agent of cervical cancer) (table). Currently, over 99% of the 440 000 annual deaths from rotavirus associated diarrhoea and 93% of the 260 000 annual deaths from cervical cancer occur outside the 60 wealthiest countries.^{2,3}

Challenging widely held beliefs

Three arguments have historically dominated discussions about the cause of unequal access to vaccines in poorer countries: the primacy of healthcare infrastructure; constraints imposed by insufficient funding; and the belief that vaccine approval in high income countries is a precondition for discussing access in other settings. Recent experiences have shown how each of these contentions is open to challenge.

Primacy of infrastructure

Must poor healthcare infrastructure be addressed before large scale vaccination can succeed? The claim that poor infrastructure is a more fundamental—and therefore more pressing—problem than access to vaccines must be distinguished from the claim that local logistical hurdles must be overcome to achieve equitable access. Those who agree with the former contention believe that ensuring supplies of food and clean water and building roads will do more for public health than isolated interventions like vaccines. For example, access to rotavirus vaccination has been questioned on the

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Accepted: 16 January 2008

grounds that it might undermine the urgency of providing clean water and sanitation for all.⁴

An exclusive focus on the primacy of basic public health interventions, however, can block the opportunity to build infrastructure through vaccination. Empirical analyses, most notably of polio eradication in the Americas, have documented how immunisation programmes can strengthen the infrastructure of health systems.⁵ Amartya Sen describes the broader effect as an “autocatalytic process” connecting health and development, whereby improving health through direct means such as vaccines unlocks the capabilities of populations to thrive economically.⁶ In addition, contact between the healthcare establishment and indigent people is often sporadic and usually related to an acute health problem. Vaccines are one of the few interventions that can save lives even when healthcare infrastructure is inadequate or non-existent. Clarifying the underpinnings of this infrastructure problem permits a rigorous examination of the local obstacles that make the delivery of vaccines difficult.

Funding

Are the costs of closing the global vaccination gap out of proportion to the funding available? The Global Alliance for Vaccines and Immunization (GAVI) has collected almost \$7bn (£3.6bn; €4.7bn) since its inception in 2000. A pilot “advance market commitment” to help speed the development and availability of a pneumococcal vaccine gained seed funding of \$1.5bn in 2007. Yet these commitments pale in comparison to the \$35bn that GAVI estimates it would take to carry out its existing programmes in the 72 poorest countries through 2015.

At the country and district level, acceptance of the cost-funding orthodoxy has been posited as a chief reason for the slow uptake of vaccines such as for hepatitis B vaccine in the past.⁷ One reaction to this imbalance is to calculate the funding shortfall and advocate for its

Development and dissemination of rotavirus and HPV vaccines

Vaccine	Institutions contributing to vaccine development	Regions where key phase III trials were conducted ^{17 18 39 40}	Disease burden ^{2 41}	Programmes for accelerating access in low and middle income countries ^{3 39-42}
Rotateq	Merck, Children's Hospital of Philadelphia, Wistar Institute	North America, Europe, Taiwan	440 000 annual deaths from rotavirus associated diarrhoea, 99% outside of 60 wealthiest countries	Rotavirus Vaccine Program (PATH, US Centers for Disease Control, WHO) funded by initial \$30m grant from Vaccine Fund and GAVI Alliance
Rotarix	GlaxoSmithKline, Avant Immunotherapeutics, Cincinnati Children's Hospital	South America, North America, Finland		
Gardasil	Merck, Georgetown University, University of Rochester, University of Queensland, US National Cancer Institute	North America, South America, Singapore	260 000 annual deaths from cervical cancer, 93% outside of 60 wealthiest countries	Cervical Cancer Vaccine Project (PATH, WHO, Harvard University, International Agency for Research on Cancer) funded by initial \$27.8m grant from Gates Foundation
Cervarix	GlaxoSmithKline, Georgetown University, University of Rochester, University of Queensland, US National Cancer Institute	North America, Europe, South America, Asia		

redress.⁸ But the vaccine equation is more complicated than simply tabulating inputs and outlays. Rational policy making depends on analysis of both costs and benefits. A recent cost effectiveness analysis showed that a vaccination programme for hepatitis B was both cost effective and affordable in the Gambia, where the per capita gross domestic product is only \$300.⁹ Furthermore, vaccines can confer macroeconomic benefits such as improved labour productivity that may supersede the substantial directly measured health benefits.¹⁰ The International Finance Facility for Immunisation (www.iff-immunisation.org), which provides immediate aid from wealthier countries to GAVI, is a financial solution that represents a first step in accelerating the pace of investment in immunisation.

Prior approval

Must vaccines be developed for and approved by wealthier countries before they can be widely disseminated? Currently, availability of vaccines in low and middle income countries depends largely on prior evaluation by US or European drug regulatory agencies.¹¹ Pharmaceutical manufacturers receive the vast majority of their revenues from wealthier countries, so there is less financial incentive to make a product available if it is not being sold in those markets. Also, health agencies in poorer countries often take their cues from nations with more established regulatory systems before approving new products or when removing them from the market. In 2001, after Wyeth's rotavirus vaccine Rotashield was taken off the market in the US for a rare association with increased rates of intussusception, Wyeth stopped production and the product was eliminated from use in low and middle income countries, where the higher rates of morbidity from rotavirus associated diarrhoea may have made the low risk of that side effect more tolerable.¹²

Under this paradigm, intellectual property rights can slow the dissemination of vaccine technology. As a result of the TRIPS agreement (the World Trade Organization's agreement on trade related aspects of intellectual property rights), patents protecting drugs and other healthcare technology are becoming increasingly prevalent. Because patents provide manufacturers with full control over how their products are distributed, for innovative products such as human papillomavirus vaccines, global society is forced to ask: what is the manufacturer's plan for making its vaccine widely available?¹³ Differential prices offered by pharmaceutical manufacturers may still remain too high, and implementation of donation programmes has been slow.¹⁴

Instead, the public health community should better regulate intellectual property so that new vaccines can reach the people who need them. While protecting markets in wealthier countries to help provide incentives for research and development, we should work to accelerate international cooperation that can lead to improved distribution in needy settings. For example, many vaccines derive from publicly funded research, and the clinical trials used to support regulatory approval in wealthier countries are often conducted elsewhere. The

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There would be fewer deaths from rotavirus associated diarrhoea if vaccines were more widely available in poor countries

human papillomavirus vaccine Gardasil was originally researched by scientists at an Australian university, two American universities, and the US National Cancer Institute, and some of the early trials supporting its efficacy were conducted in Brazil, India, and Costa Rica. Wealthier countries' governments could use this leverage to make the approval of future vaccines contingent on the existence of robust plans for global distribution. Novel licensing schemes have been proposed to speed technology transfer from larger innovator companies to local or regional manufacturers as soon as efficacy has been established.¹⁵ Such arrangements could help meet international demand for low cost products and permit rapid clinical testing needed to determine if a product is indicated for use in low and middle income countries.

Capacity building: a strategy to improve global vaccine access

In moving from defining the problem to outlining solutions, multinational efforts should focus on building local capacity to scale up vaccination programmes. Specifically, capacity building consists of constructing a parallel clinical research pipeline for developing countries, lowering barriers to vaccine production in developing countries, and fostering local leadership in healthcare delivery.

Clinical research capacity

Efficacy trials for vaccines could take place in parallel in several epidemiological settings to account for differences in disease ecology. The key phase III trial submitted for approval of one rotavirus vaccine (Rotarix) did

not include any patients in Africa or Asia¹⁶; the key trial for another (Rotateq) included patients from Taiwan but no other Asian or African patients (table).¹⁷ Such decisions can have direct bearing on availability of vaccines—for example, 20 months after the publication of these landmark rotavirus vaccine trials, the World Health Organization stated, “Until the full potential of the current rotavirus vaccines has been confirmed in all regions of the world, WHO is not prepared to recommend global inclusion of rotavirus vaccines into national immunisation programmes.”¹⁸

Such caution can be well founded. In 1989, WHO recommended the high titre measles vaccine for use in low income countries. The vaccine was subsequently found to be associated with a twofold increase in mortality among girls and withdrawn from WHO recommendations.¹⁹ Such examples highlight the need to conduct parallel clinical research in low and middle income countries of both vaccine efficacy and overall mortality, and also to ensure that introduction of vaccines is organised so that individual and population outcomes can be assessed systematically. Responsibility for monitoring of vaccine research and development should fall to the public sector—or public-private partnerships—to minimise delays in cases where vaccine manufacturers did not pursue efficacy testing in countries where diseases are endemic. Such parallel research would expand scientific capacity, encourage performance of more appropriate and ethical clinical trials,²⁰ and produce results that would better inform governments’ risk-benefit calculations for investing in the vaccines. The Serum Institute of India demonstrates the necessary components of a parallel research enterprise: vaccine development in partnership with the public sector (the Indian government), rapid transfer of innovative technology (as with production of its Hib vaccine using a novel process from the Netherlands Vaccine Institute²¹), and scalable production extending internationally (seen in its collaboration on a vaccine against meningococcus for the “meningitis belt” of sub-Saharan Africa²²).

Local vaccine production

Once a vaccine is developed, prompt and adequate distribution requires inexpensive scaled production. Production capacity becomes even more important if the vaccine is produced from a non-traditional research partnership like the Malaria Vaccine Initiative rather than a large pharmaceutical company. Achieving necessary production capacity may require reliance on pharmaceutical manufacturers based in low and middle income countries.²³ Many such manufacturers have embraced a business model specialising in high volume, low margin production, which—with cost advantages in raw materials and labour—leads to lower cost products.²⁴ Some, including those in India, China, Brazil, and Indonesia, are successfully competing in the generic drug market in wealthier countries and have begun to invest in novel research and development.²⁵

The public health community could take better advantage of progress in manufacturing processes

and the production scale of local manufacturers. For example, in addition to affordable licences for intellectual property protecting end products, as vaccines grow more biologically complex, manufacturers in developing countries may need access to specialised technology. The US National Institutes of Health has pioneered a programme to transfer manufacturing technology to public and private institutions in low and middle income countries and has transferred early stage technologies for meningitis, rotavirus, typhoid fever, dengue, and varicella vaccines, building innovative capacity as well as production capacity.²⁶ If other public sector groups, such as universities, and private sector manufacturers emulate such technology transfer, intellectual property can serve as a tool to manage research collaborations rather than an impediment to access.²⁷

Procurement organisations must communicate with vaccine manufacturers to reduce uncertainty in demand. To preserve competition in the vaccine supply market, this communication could take the form of evidence based forecasting of disease burden and available funding rather than contractual agreements.²⁸ Providing manufacturers with information about new market potential could facilitate the efficient allocation of resources for developing, producing, and marketing new vaccines.

Local leadership

Calls for strong, country level leadership on vaccine introduction are common, but they are seldom followed by inquiries into why immunisation is not a higher priority for national leaders. One explanation is the poor quality of evidence about the value of introducing vaccines into low and middle income countries.²⁹ More data are therefore needed on disease burden, economic consequences of vaccine introduction, and use of vaccines in existing public health programmes. The 2002 launch of accelerated development and introduction plans (ADIPs) by GAVI for pneumococcus and rotavirus vaccines sought to address these knowledge gaps.³⁰ These programmes have had some success building evidence bases, but they have drawn criticism by focusing on a few products developed by large pharmaceutical companies, while excluding others that may be more appropriate in low and middle income countries. In the case of human papillomavirus vaccines, the non-profit organisation PATH launched a pilot project in 2006 to gather evidence to support introduction of the vaccine in India, Peru, Uganda, and Vietnam.³¹

Bridging the “implementation gap” between our growing knowledge of disease control and the implementation of that knowledge³² requires real time operational research, which focuses on processes as well as outcomes. Research on improving healthcare delivery systems creates widely applicable knowledge that addresses fundamental questions across various contexts.³³ One such question for vaccines is: how can immunisations be effectively packaged—both with other immunisations and different types of interventions—to take advantage of economies of scale and prevent the

fragmentation of health systems into disease specific programmes? Implementation studies turn attention to health systems improvement as a measure of success, not just efficacy of a particular intervention.

The non-profit organisation Partners in Health (www.pih.org/home.html) provides two striking examples of success in changing the research paradigm: the use of community health promoters to provide antiretroviral therapy in resource poor settings,³⁴ and a novel therapeutic delivery system for multidrug resistant tuberculosis.³⁵ However, recent estimates are that less than 0.02% of health expenditure in low and middle income countries is devoted to implementation of health services research.³⁶ Research institutions in both the developed and developing world—and, in the best case scenario, collaborations spanning both—must enhance their commitment to this area.

The ultimate aim of any effort to improve global access to vaccines must be to show local leaders in health care and government the benefits of vaccination.³⁷ Local political leadership, when combined with international financing mechanisms, can increase investment in health, prioritise disease prevention, and raise awareness about the individual benefits of vaccination.³⁸ The way forward—building immunity by building capacity—would help save and improve the lives of millions of patients around the world.

Contributors and sources: Both authors contributed to the research, writing, and revision of the manuscript. This article arose via dialogue with Adel Mahmoud, Brian Strom, Art Caplan, and Heidi Williams. DAC is guarantor.

Funding: None.

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

- World Health Organization. *World health report 2005: make every mother and child count*. Geneva: WHO, 2005. www.who.int/whr/2005/en/index.html.
- Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006;12:304-6.
- World Health Organization. *Revised global burden of disease: 2002 estimates*. Geneva: WHO, 2004. www.who.int/healthinfo/bodgbd2002revised/en/index.html.
- Birn AE. Gates's grandest challenge: transcending technology as public health ideology. *Lancet* 2005;366:514-9.
- Major efforts for disease eradication. In: Knobler S, Lederberg J, Pray L, eds. *Considerations for viral disease eradication: lessons learned and future strategies*. Washington, DC: Institute of Medicine, 2002:33-63. http://books.nap.edu/openbook.php?record_id=10424&page=33.
- Sen AK. *Development as freedom*. New York: Knopf, 1999.
- Clemens JD. Thinking downstream to accelerate the introduction of new vaccines for developing countries. *Vaccine* 2003;21(suppl 2):S114-5.
- Peny JM, Gleizes O, Covillard JP. Financial requirements of immunisation programmes in developing countries: a 2004-2014 perspective. *Vaccine* 2005;23:4610-8.
- Kim S-Y, Salomon JA, Goldie SJ. Economic evaluation of hepatitis B vaccine in low-income countries. *Bull World Health Organ* 2007;85:821-900.
- Bloom DE, Canning D, Weston M. The value of vaccination. *World Economics* 2005;6(3):25.
- Brooke S, Sherris J. *HPV vaccines: regulatory issues*. London: PATH, 2006. www.rho.org/files/StopCxCa_regulatory_2006.pdf.
- Cohen J. Medicine. Rethinking a vaccine's risk. *Science* 2001;293:1576-7.
- Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries—key challenges and issues. *N Engl J Med* 2007;356:1908-10.
- Médecins Sans Frontières. *Gilead's Tenofovir "access program"*

SUMMARY POINTS

Delay in distributing vaccines where they are needed most has a devastating human cost. Many of the reasons proffered for the disparity in vaccine distribution between rich and poorer countries can now be challenged with new evidence and better understanding of the underlying problems. Wider global availability of affordable vaccines can be achieved through building local or regional clinical trial and vaccine production capacity. Implementation research, by directly demonstrating the benefits of vaccination, can spur country-level leadership

for developing countries: a case of false promises? February 2006. www.doctorswithoutborders.org/news/hiv-aids/tenofovir_briefing_doc.cfm.

- Outterson K, Kesselheim AS. Putting patients first: a market-based licensing proposal for HPV vaccines and other patented medical products in developing countries. *Health Affairs* 2008;27:130-9.
- Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11-22.
- Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23-33.
- WHO position paper on rotavirus vaccines. *World Health Organ Weekly Epidemiol Record* 2007;82:285-96.
- Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, Bennett J, et al. Sex-specific differences in mortality after high-titre measles immunization in rural Senegal. *Bull World Health Organ* 1994;72:761-70.
- Basu S, Andrews J, Smith-Rohrberg D. Populations who test drugs should benefit from them. *Nature* 2006;440:605.
- The Hib Initiative. Serum Institute of India obtains first ever Indian license for its Hib vaccine developed through technology transfer from the Netherlands Vaccine Institute. 2007. www.hibaction.org/news/2007/05-03.php.
- Meningitis Vaccine Project. Improved meningitis vaccine for Africa could signal eventual end to deadly scourge. 2007. www.meningvax.org/files/press-0706-improved-phase2.html.
- Milstien JB, Kaddar M, Kieny MP. The impact of globalization on vaccine development and availability. *Health Aff (Millwood)* 2006;25:1061-9.
- GAVI External Stakeholder Advisory Board Meeting. *Global vaccine supply: the changing role of suppliers*. 24 June 2005. www.gavialliance.org/resources/BCG_24_June.pdf.
- Morel CM, Acharya T, Broun D, Dang A, Elias C, Ganguly NK, et al. Health innovation networks to help developing countries address neglected diseases. *Science* 2005;309:401-4.
- Salicrup LA, Fedorkova L. Challenges and opportunities for enhancing biotechnology and technology transfer in developing countries. *Biotechnol Adv* 2006;24:69-79.
- Chokshi DA, Rajkumar R. Leveraging university research to advance global health. *JAMA* 2007;298:1934-6.
- Sekhri N. Forecasting for global health: new money, new products, and new markets. 2006. www.cgdev.org/doc/ghprn/Forecasting_Background.pdf.
- Clemens J, Jodar L. Introducing new vaccines into developing countries: obstacles, opportunities and complexities. *Nat Med* 2005;11(suppl 4):S12-5.
- GAVI Alliance. Accelerated development and introduction of priority new vaccines (ADIPs). 2007. www.gavialliance.org/vision/policies/new_vaccines/adips/index.php.
- PATH. Cervical cancer vaccine project. 2006. www.path.org/files/RH_cc_vacc_proj_fs_update.pdf.
- Sanders D, Haines A. Implementation research is needed to achieve international health goals. *PLoS Med* 2006;3:e186.
- Madon T, Hofman KJ, Kupfer L, Glass RI. Public health. Implementation science. *Science* 2007;318:1728-9.
- Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis* 2004;38(suppl 5):S429-36.
- Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus." *BMJ* 1998;317:671-4.
- Alliance for Health Policy and Systems Research. *Strengthening health systems in developing countries: the promise of research on policy and systems*. Geneva: AHPSP, 2004.
- Buekens P, Keusch G, Belizan J, Bhutta ZA. Evidence-based global health. *JAMA* 2004;291:2639-41.
- Mahmoud A. The global vaccination gap. *Science* 2004;305:147.
- Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.
- Paavonen J, Jenkins D, Bosch FX, Naud P, Salmeron J, Wheeler CM, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007;369:2161-70.
- Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;9:565-72.
- Rotavirus vaccine program: a PATH affiliate. 2007. www.rotavirusvaccine.org/index.htm.