Research and Development of New Vaccines Against Infectious Diseases

[Global Alliances for Vaccines]

Kieny, Marie Paule PhD; Excler, Jean-Louis MD; Girard, Marc DVM About the Authors: Marie Paule Kieny is with the World Health Organization, Geneva, Switzerland. Jean-Louis Excler is with the International AIDS Vaccine Initiative, Delhi, India. At the time of this study, Marc Girard was with the Foundation Biomerieux, Annecy, France.

Requests for reprints should be sent to Marie Paule Kieny, PhD, Initiative for Vaccine Research, World Health Organization, Avenue Appia 20, CH1211-Geneve 27, Switzerland (e-mail: kienym@who.int).

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Abstract

Infectious diseases are responsible for approximately 25% of global mortality, especially in children aged younger than 5 years. Much of the burden of infectious diseases could be alleviated if appropriate mechanisms could be put in place to ensure access for all children to basic vaccines, regardless of geographical location or economic status. In addition, new safe and effective vaccines should be developed for a variety of infections against which no effective preventive intervention measure is either available or practical.

The public, private, and philanthropic sectors need to join forces to ensure that these new or improved vaccines are fully developed and become accessible to the populations in need as quickly as possible.

THE IMPLEMENTATION OF large-scale and comprehensive national immunization programs, and the considerable successes that were achieved in the eradication of smallpox and the reduction of polio, measles, pertussis, tetanus, and meningitis, were among the most notable achievements of the 20th century. Even in the poorest countries, it has been possible to achieve significant progress in disease control by immunization.1 There is good reason to expect that these advances will be sustained and will progress even further in the 21st century.2

However, the world's poorest regions are still suffering a heavy toll of premature deaths and disabilities from infectious diseases for which vaccines do not exist, or need to be improved.3 Infectious diseases are still responsible for at least 15 million deaths per year, making them the largest contributors to the disparity in average life span between rich and poor countries (77 and 52 years, respectively). In addition to this high death toll, millions of children are suffering from disability and illness because they have not been
properly immunized. The most effective way to reduce disease and deaths from infectious diseases is to vaccinate populations at risk. Unfortunately, vaccines are still missing for a number of pathogens, and some of the existing vaccines are not completely protective. For these diseases, it is of crucial importance that research and development of vaccines be a priority.

The following is an overview of a few selected fields of current vaccine development.

**DIARRHEAL DISEASES**

Conservative estimates place the death toll from diarrheal diseases at 4 million to 6 million per year, with most of these deaths occurring in young children. In the long term, access to clean water, better hygiene, and improvement of sanitation would have the greatest impact on diarrheal diseases, but immunization against specific pathogens is the best hope for the short term and medium term.

The burden of diarrhea among children aged younger than 5 years in the developing world is estimated to be 1.5 billion episodes per year, leading to 3 million deaths. Enterotoxinogenic Escherichia coli is the most frequently isolated bacterial enteropathogen, followed by shigellas (Shigella flexneri and S sonnei) and cholera bacteria (Vibrio cholerae). Enterotoxinogenic E coli is also the most common cause of travelers’ diarrhea. The development of new vaccines against viral diarrhea caused by rotavirus, present in countries with high and low levels of hygiene, is the focus of intense international efforts.

Rotavirus is the leading cause of severe diarrheal disease and dehydration of infants in both industrialized and developing countries. By age 3 to 4 years, virtually all children have had the disease. Rotavirus is responsible for 25% of deaths associated with diarrhea and for 6% of all deaths in children younger than 5 years of age.

Rotavirus is a double-stranded RNA virus belonging to the Reoviridae family. In the United States, an oral live tetravalent rhesus-human reassortant vaccine was licensed in 1998; recommended for the routine immunization of infants, it was administered to more than 900 000 children. Efficacy estimates were around 55% against all cases of rotavirus diarrhea and over 70% against severe disease.

However, an increased frequency of a rare but severe vaccine-associated side effect, called intussusception, was demonstrated, leading to the vaccine’s withdrawal from the market in 1999. Unfortunately, the vaccine, which was undergoing testing concomitantly in Asia and Africa, could not be evaluated in terms of risk-benefit for children in developing countries since the trials were stopped.

A lamb-derived monovalent live-attenuated oral vaccine is licensed in China, but the vaccine cannot be distributed on the international market at present. Several new vaccine approaches are currently being pursued:

* A human-derived monovalent live-attenuated oral vaccine is being tested in phase III trials in Latin America and Asia and has undergone extensive testing in Europe, the United States, South Africa, and Bangladesh.

* A bovine-human reassortant pentavalent live-attenuated oral vaccine is currently in late phase III trials, but large efficacy trials in developing countries remain to be conducted.
* A human neonatal vaccine and 2 human-bovine naturally occurring neonatal-derived strains are also under development.

It remains to be seen whether intussusception will be associated with any of these new rotavirus vaccines, and several alternative vaccine approaches have been proposed to avoid this potential adverse event.

**ACUTE RESPIRATORY INFECTIONS**

Both viruses and bacteria are a common cause of acute lower respiratory infection (LRI) in children worldwide. The commonest pathogens causing acute LRI are respiratory syncytial virus (RSV) and Streptococcus pneumoniae. Dual infections with viral and bacterial pathogens are frequent and seem to increase the severity of the disease.

The sudden emergence in early 2003 of an epidemic of atypical pneumonia originating in China led to the identification of the severe acute respiratory syndrome (SARS) virus, a coronavirus unrelated to previously known coronaviruses. The virus was later recovered from Chinese masked palm civets and raccoon dogs, which might have acted as an intermediate host between an as yet unidentified natural virus reservoir and man. The development of a vaccine against SARS has been judged a global priority, but it is still only at the early clinical stage.

**RSV**

RSV infects nearly all children by age 2 years. The global annual infection and mortality figures for RSV are estimated to be 64 million and 160 000, respectively. The disease spectrum includes a wide array of respiratory symptoms, from rhinitis and otitis media to pneumonia and bronchiolitis, the latter 2 being associated with substantial morbidity. In industrialized countries, RSV is a well-documented cause of yearly winter and spring epidemics of bronchiolitis and pneumonia, which are responsible for 18 000 to 75 000 hospitalizations and 90 to 1900 deaths annually in the United States. Existing data clearly indicate that RSV also accounts for a high proportion (20% to 30%) of LRI cases in children aged 1 to 4 years in developing countries.

RSV belongs to the Paramyxoviridae family, genus Pneumovirus. Two subgroups, A and B, have been described, primarily based on differences in the antigenicity of the surface glycoprotein (G). Two factors have complicated the development of vaccines to prevent RSV infection. First, host immune responses appear to play a role in the pathogenesis of disease, as early studies with a Formalin-inactivated vaccine showed that vaccine recipients suffered from more severe disease. Second, naturally acquired immunity is neither complete nor durable and recurrent infections occur frequently. Purified fusion protein vaccines have been shown to be safe and immunogenic in 12- to 48-month-old children. A subunit vaccine containing the RSV F, G, and M proteins, now in phase II in Canada and Australia, has exhibited an excellent safety and immunogenicity profile. Another candidate vaccine is a synthetic peptide of the conserved region of the G protein administered intranasally. Live attenuated RSV vaccines based on temperature-sensitive, cold-adapted strains of the virus that could be delivered to the respiratory mucosa are probably among the most promising approaches.
**S pneumoniae**

Infections caused by pneumococci are a major cause of morbidity and mortality all over the world. Pneumonia, febrile bacteremia, and meningitis are the most common manifestations of the disease. The highest rates of pneumococcal disease occur among young children and the elderly. Pneumococci are estimated to cause over 1 million deaths, most of which occur in developing countries, where they probably are the most important pathogen of early infancy. In Europe and the United States, pneumococcal pneumonia is the most common community-acquired bacterial pneumonia, estimated to affect approximately 100 adults per 100,000 each year. In developing countries, infants aged younger than 3 months are especially at risk of pneumococcal meningitis. Even in economically developed regions, invasive pneumococcal disease carries mortality rates of 10% to 20%, and the rate may exceed 50% in high-risk groups.

*S pneumoniae* is a gram-positive encapsulated bacteria of which about 90 different polysaccharide capsule serotypes have been identified. Most pneumococcal disease in infants is associated with the 11 most common serotypes, which cause at least 75% of invasive disease in all regions. Pneumococcal resistance to essential antibiotics is a serious and rapidly increasing problem worldwide.

Protective immunity against pneumococci is provided by type-specific anticapsular antibodies. However, capsular polysaccharide vaccines do not regularly elicit protective levels of antibodies in children aged younger than 2 years, or in immunocompromised individuals. One of the currently licensed vaccines contains purified capsular polysaccharide from each of the 23 capsular types of *S pneumoniae*, which together account for most cases (90%) of serious pneumococcal disease in Western industrialized countries. Relatively good antibody responses are elicited in adults. In some countries, vaccination is recommended for elderly people, particularly those living in institutions.

Experience with Haemophilus influenzae type B conjugate vaccines has shown that the immunogenicity of polysaccharide can be improved by chemical conjugation to a protein carrier, thereby eliciting a T-cell-dependent antibody response. Unlike polysaccharide vaccines, conjugate vaccines induce high antibody levels and elicit an immune response in infants and in immunodeficient persons. Moreover, these vaccines induce immunological memory. Therefore, they could reduce bacterial transmission in the community. Introduction of a 7-valent conjugate vaccine in the United States resulted in a dramatic decline in the rates of invasive disease. The vaccine also showed moderate protection against otitis caused by vaccine serotypes. However, the decrease in vaccine-type otitis media was partially offset by an increase in disease caused by nonvaccine types of *S pneumoniae* and by *H influenzae*, a phenomenon referred to as "replacement disease."

The development and introduction in developing countries of a conjugate *S pneumoniae* vaccine is now one of the highest-priority projects. Several conjugate vaccines that provide more optimal serotype coverage in developing countries than the currently licensed 7-valent vaccine are in clinical development. They may be available by 2008 to 2010 for vaccination programs in developing countries, although presumably at a high price.
MENINGOCOCCAL MENINGITIS

Bacterial meningitis remains a serious threat to global health, accounting for an estimated 170,000 deaths yearly worldwide. Even with antimicrobial therapy and the availability of sophisticated intensive care, case fatality rates remain at 5% to 10% in industrialized countries and are higher in the developing world. Between 10% and 20% of survivors develop permanent sequelae. Since the introduction of H influenzae type b conjugate vaccines, Neisseria meningitidis has become the commonest cause of bacterial meningitis in the world. N meningitidis is spread by person-to-person contact through the airborne respiratory droplets of infected people. The disease affects mainly young children, but it is also common in older children and young adults. Serogroups A, B, C, Y, and W-135 account for 90% of all disease.

Group A meningococcus has historically been the main cause of epidemic meningococcal disease and still predominates in Africa during both endemic and epidemic periods. The highest burden of disease occurs in sub-Saharan Africa in an area extending from Senegal and Ethiopia, referred to as the "meningitis belt." Epidemics occur in irregular cycles, lasting for 2 to 3 dry seasons and dying out during the intervening rainy seasons. The size of these epidemics can be enormous: in 1996, around 200,000 cases were reported, with 20,000 deaths. In the last few years, the emergence of group W-135 as the cause of epidemics has added complexity to the epidemiological situation in the region.

Group B meningococcus accounts for approximately 50% of meningococcal meningitis cases in North America and Europe. In all countries, the incidence of group B disease is highest in infants. Group B epidemics have occurred in the United States, Cuba, Brazil, and Chile. Since 1991, New Zealand has experienced a large epidemic of group B meningococcal infection, with incidence rates up to 10 times the background incidence. Altogether, meningococcus serogroup B incidence may be estimated at between 20,000 and 80,000 cases per year, with 2000 to 8000 deaths.

Polysaccharide vaccines against N meningitidis groups A, C, Y, and W-135 are available worldwide, although in restricted quantities, and with a price for the tetravalent vaccine that does not allow widespread use in sub-Saharan Africa.

The emergence of the W-135 serogroup in some countries of Africa has prompted the development of a cheaper trivalent polysaccharide A/C/W-135 vaccine. However, polysaccharide vaccines are poor immunogens in young infants and fail to induce immunological memory. In 1999, meningococcal group C conjugate vaccine was successfully introduced into the routine British immunization program, opening the way for the development of conjugate vaccines against the other N meningitidis serogroups. Vaccine manufacturers are currently developing conjugate vaccine combinations incorporating groups A, C, Y, and W-135 polysaccharides.

These multivalent meningococcal polysaccharide-protein conjugate vaccines will be available in the United States and Europe within a few years. Nevertheless, it is unlikely that these new vaccines will be available at a price affordable to most of the countries in the African meningitis belt. Therefore, a public partnership between the World Health Organization (WHO) and the Program for Appropriate Technology in Health (a US-based nongovernmental organization), the Meningitis Vaccine Project, is
Currently developing a serogroup A conjugate vaccine tailored for Africa that will be available at a price of less than US $1 per dose.

Serogroup B capsular polysaccharide is a poor immunogen, probably because it is structurally identical to glycoproteins expressed by host tissues. Consequently, vaccine research directed against serogroup B meningococcus has focused largely on cell-surface protein antigens (outer membrane proteins). The 2 most-studied outer-membrane-protein vaccines are those produced in response to outbreaks in Norway and Cuba. Both have been used for epidemic control in their respective countries and were found to be 50% to 80% effective.

HIV/AIDS

More than 40 million adults and children are living with HIV/AIDS worldwide and close to 5 million people (including 800 000 children) become infected each year. HIV infections are now almost equally distributed between men and women, with an estimated 17.6 million women aged 15 to 49 years living with HIV/AIDS. HIV/AIDS is the leading cause of death in sub-Saharan Africa and the fourth biggest killer worldwide. Asia currently experiences the world's fastest-growing HIV/AIDS epidemic. Highly active antiretroviral therapy has reduced progression to AIDS, deaths, and HIV transmission from mother to child in North America and Western Europe. However, success with treatment has not been matched by progress toward prevention, and evidence of rising HIV infection rates is emerging, particularly in marginalized communities. A new determination to fight the epidemic emerged following the United Nations General Assembly Special Session on HIV/AIDS in July 2001, and a general effort is being made to make antiretroviral drugs available to the underprivileged populations. A new initiative (called "3 by 5") launched by WHO in 2003 aims at providing effective therapy to at least 3 million patients by 2005. However, despite these encouraging trends, a preventive vaccine is needed more than ever, particularly in developing countries.

Human immunodeficiency viruses belong to the Lentivirus group of the Retroviridae family. Two types have been described: HIV-1 and HIV-2, the former appearing more aggressive and spreading more rapidly. The development of a safe and effective HIV vaccine is hampered by the tremendous genetic variability of the virus and the paucity of knowledge on possible immune mechanisms of protection. The first clinical trial of an HIV vaccine was conducted in the United States in 1987. Since then, over 30 candidate vaccines have been tested in over 80 phase I/II clinical trials, involving over 10 000 healthy volunteers. Most of these trials have been conducted in the United States and Europe. A few trials also have been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Thailand, Trinidad, and Uganda). The effort to develop and evaluate HIV vaccines will be strengthened by the African AIDS Vaccine Programme, which was established following an initiative of WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), and by a new initiative involving, among others, the Bill and Melinda Gates Foundation, the International AIDS Vaccine Initiative, and the US National Institutes of Health.

Only 2 efficacy trials have been completed so far, both using the same approach of a subunit gp 120 envelope glycoprotein, one in the United States (with sites in Canada and Europe) and the other in Thailand. The 120 kDa glycoprotein (gp 120) is the major antigenic determinant present on the surface of HIV particles.
Definite results from both trials were reported in 2003, demonstrating that immunization did not result in a statistically significant reduction of HIV infection within the study populations. A third efficacy trial involves a live recombinant vector (canarypox-HIV) expressing the gag, env, and pol genes of HIV-1 and combined in a prime-boost vaccination regimen with a gp 120 subunit vaccine; begun in Thailand in late 2003, it aims to include 16,000 volunteers. Other interesting approaches being tested in humans are based on DNA prime and recombinant poxvirus boosts. These vaccines are not intended to prevent HIV infection but to elicit a T-cell immune response that could prevent or delay the occurrence of the disease.

Recombinant adenoviruses represent another promising approach of the same type, especially when combined with a recombinant canarypox in a prime-boost vaccination regimen. Other candidate vaccines include other recombinant bacterial or viral vectors, some of which have shown some promise in controlling viral replication in preclinical studies in nonhuman primate models. Subunit HIV vaccines based on engineered recombinant envelope glycoproteins alone or combined with the nonstructural Tat, Nef, and Rev proteins, DNA vaccines and peptides also are under development.

There is no doubt that the development of a safe, effective, and affordable HIV vaccine remains the scientific and public health challenge of this new century.

**HUMAN PAPILLOMAVIRUS**

Human papillomavirus (HPV) causes cervical cancer, the second biggest cause of female cancer mortality worldwide with 288,000 deaths yearly. Approximately 500,000 cases of cervical cancer are reported each year, with nearly 80% occurring in developing countries. In the absence of screening programs, cervical cancer is detected too late and leads to death in most cases. The highest incidences are found in some countries of Latin America (93.8 per 100,000 women in Haiti, the highest national incidence in the world), in Africa (61.4 per 100,000 women in Tanzania), and in Asia (30 per 100,000 in India). Epidemiological studies have reported that 75% of the 15- to 50-year-old population in the United States is infected with HPV, with 1% presenting clinical lesions. The prevalence of HPV infection among sexually active women may range from 18% to 25%, especially in some populations of sexually active teenagers.

HPV belongs to the Papovaviridae family. More than 30 types of HPV have been identified that can infect the genital mucosa. It has been established that over 95% of cervical cancer biopsies contain HPV DNA, with oncogenic HPV-16, -18, -33, and -45 comprising more than 80% of the cases. The association of cervical cancer with the presence of sexually transmitted HPV DNA has substantiated the basis for vaccine development. Viral recombinant proteins are being studied as antigenic components of vaccine candidates. Prophylactic vaccine candidates are based on the recombinant capsid proteins L1 and L2, which selfassemble into viruslike particles (VLPs) that can induce virusneutralizing antibodies, while therapeutic vaccine candidates, based on viral oncogenic proteins E6 and E7, are designed to induce cell-mediated immune responses able to eliminate infected cells.

The results of a controlled efficacy trial of HPV-16 VLPs became available recently and showed that the incidence of persistent HPV-16 infection and HPV-16-related cervical intraepithelial neoplasia was reduced in vaccinated women, with a 100% efficacy rate
over a 1.7-year follow-up period. These results suggest that immunizing HPV-16-negative women will eventually reduce the incidence of cervical cancer. Two prophylactic vaccine candidates are at the level of phase III efficacy evaluation: a bivalent HPV-16/18 VLP vaccine produced in insect cells using a recombinant baculovirus, and a tetravalent HPV-6/11/16/18 VLP vaccine produced in recombinant yeast.

**CONCLUSION**

The biotechnology revolution, culminating in the sequencing of the genome of a great many pathogens, together with increased knowledge of the immune responses to infections, has allowed the unprecedented rational development of new recombinant vaccines that will hopefully help control infectious diseases, including those that appear most complex, such as HIV/AIDS, tuberculosis, and malaria. However, despite these new tools, the challenges remain formidable. The development and registration of a new vaccine can take more than 10 years and cost $200 million to $500 million. The world vaccine market is estimated at approximately $6.5 billion, a meager 2% of the global pharmaceutical market, making vaccine research and development considerably less attractive to private investors than drug development. Moreover, many of the diseases for which new vaccines are urgently needed mainly affect developing countries whose market characteristics fail to attract private capital investment.

It is nevertheless vital to continuously develop new vaccines and to improve existing ones. In this context, a new paradigm needs to be developed to include and coordinate the actions of the WHO, international and national funding agencies, the pharmaceutical industry and manufacturers in emerging developing countries, nonprofit foundations, and nongovernmental humanitarian organizations. Working together, these organizations could harness existing potentials and accelerate the development and testing of new vaccines and the improvement and implementation of existing vaccines. The goal is to offer better safety, efficacy, and delivery methods with lower costs of production, leading to a more efficient distribution and better availability of vaccines, especially in developing countries.

**Contributors**

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**References**


