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Review

Vaccines for low-income countries☆

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ABSTRACT

Low-income countries typically lag behind industrialised nations, where the introduction of new vaccines is commonly tailored to the pressures of the commercial market. Happily in recent years this paradigm has started to change with the introduction of a univalent meningococcal A conjugate vaccine that is specifically targeted for the prevention of epidemic meningitis in Africa. The declaration of the 2010s as a New Decade of Vaccines, together with Millennium Development Goals 4 and 5, provide a strong mandate for a new approach to the development of vaccines for low-income countries, so that there has never been a more exciting time to work in this field. This review considers the opportunities and challenges of developing these new vaccines in the context of innovations in vaccinology, the need to induce protective immunity in the populations at risk and the requirement for strong partnership between the countries that will use these vaccines and different elements of the vaccine industry.

1. Introduction

Vaccination has had an unrivalled impact on global health [1] and vaccines have the greatest potential for further improvement in health in the poorest countries of the world. Infectious diseases account for around half of all deaths in these countries with around 90% of this mortality being attributed to diarrhoeal and respiratory diseases, AIDS, tuberculosis, malaria and measles [2]. In addition to the direct benefit of vaccines in preventing disease and death, there is growing evidence that their widespread implementation leads to much-needed economic development [3,4].

Vaccination is very much on the global agenda and underpins two of the United Nations' Millennium Development Goals: the reduction of child mortality (Goal 4) and improvement of maternal health (Goal 5) [5]. The establishment of the Global Alliance for Vaccines and Immunizations (GAVI) at the World Economic Forum in Davos, Switzerland, in 2000 has been key to the deployment of vaccines in low income countries. This public–private partnership has a mission to save children's lives and improve global health by increasing access to vaccines in low-income countries [6]. Ten years later, again at the World Economic Forum in Davos, the Bill and Melinda Gates Foundation (BMGF) pledged US$10 billion to support the research, development and delivery of vaccines for the poorest countries in a New Decade of Vaccines [7].

Despite the acknowledged importance of vaccines for low-income countries, there are major challenges to their effective implementation and the realisation of the enormous potential benefits of vaccines. This review will discuss the opportunities for developing and implementing vaccines for low-income countries. The challenges this poses will be considered along with the potential for exploiting new technologies and innovations in this field of vaccinology.

2. The Expanded Programme on Immunisation

The greatest benefit to date from the use of vaccines in low-income countries has been achieved through the Expanded Programme on Immunisation (EPI). This was introduced in 1974 by World Health Assembly resolution WHA27.57 to build on the success of smallpox eradication by making vaccines available to children in all countries [8]. Vaccines to prevent diphtheria, tetanus, pertussis, measles, poliomyelitis and tuberculosis were the first to be introduced into the EPI, with the aim of immunising children at between two and six months of age. By 2009, with the support of GAVI, now renamed the GAVI Alliance, 82% of infants worldwide had received three doses of diphtheria, tetanus and pertussis vaccine through the EPI [9].

More recently, the EPI has been used to deliver vaccines to prevent infection with hepatitis B virus (HBV), *Haemophilus influenzae* b (Hib), *Streptococcus pneumoniae* and rotavirus. The high coverage

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rate of the programme makes it an attractive platform for the delivery of new childhood vaccinations to low-income countries. There are problems associated with this. The crowding of the EPI schedule with more vaccines involving more injections and the possibility of immunological interference threatens to diminish vaccine effectiveness. Also, the immaturity of immune system at the young age when EPI vaccines are administered can result in sub-optimal responses compared to those of older children. This may necessitate multiple doses of vaccine in the primary vaccination schedule and booster doses when children are older. Finally, maternal antibody transferred to the infant transplacentally or through breast-feeding can potentially impair the response to vaccines given in the EPI schedule. This particularly applies to live attenuated viral vaccines such as the measles vaccine [10].

3. Requirements of new vaccines for low-income countries

Several factors are important when considering the suitability of new vaccines for low-income countries. The vaccine itself needs to be safe and immunogenic. It needs to induce an immune response in the target population that provides broad protective coverage against the prevalent strains of the pathogen targeted by the vaccine and new strains that might emerge following the introduction of the vaccine. Ideally the vaccine will induce life-long immunity following one dose without the need for subsequent boosting. It should also be thermostable and amenable to needle-free delivery. The results from clinical trials of new vaccines in industrialised countries do not necessarily predict the responses that will be elicited or the protection afforded by the same vaccines in low-income countries. This is well recognised for the live oral vaccines including those against polio [11], rotavirus [12] and cholera [13]. It may be due to a number of reasons including chronic environmental enteropathy, malnutrition, maternal antibodies and host genetic factors [14].

Co-infections, particularly with HIV, can have a major impact on the immune response to a vaccine and its clinical effectiveness. A dramatic example of this was in a clinical trial of 23-valent polysaccharide pneumococcal vaccine among HIV-infected adults in Uganda. The trial found no protection against invasive pneumococcal disease (including disease caused by serotypes included in the vaccine) and a higher rate of all-cause pneumonia in vaccinees compared with the control arm [15]. Reduced vaccine effectiveness at preventing disease can also result from differences in disease-causing serotypes and prevalent strains in low-income countries compared to high-income countries. This problem is well exemplified by the relatively low coverage of the 7-valent pneumococcal conjugate vaccine in Africa [16].

Affordability is key for the introduction of new vaccines into low-income countries. Development of new vaccines is a time-consuming and costly process involving several steps. Many of the newer vaccines that have been or are being developed primarily for industrialised markets are considerably more complex than the traditional empirical vaccines. Their multiple components drive up the basic cost-of-goods of the vaccine. The clinical trials required during vaccine development, especially Phase 3 clinical efficacy trials that involve thousands of participants, are particularly expensive. Therefore, it is important to seek to use simplified and affordable technologies and innovations that minimise the cost of development and the ongoing production costs of new vaccines to be used in low-income countries.

Vaccines for low-income countries must be seen to address a clear public health need in the target countries and represent a clear benefit for the cost incurred by their implementation. In order for this to happen, involvement of the developing countries in the vaccine development process is essential with early interaction between vaccine companies, the public, healthcare professionals and local as well as global health policy decision makers (Section 9).

4. Introduction of vaccines developed for high-income countries into low-income countries

New vaccines for which there is a need in high-income, as well as low-income countries, present a more attractive commercial incentive to the pharmaceutical industry than vaccines that will only be used in low-income countries. A recognised need in high-income countries led to the development of the first Hib polysaccharide–protein conjugate vaccines in the 1980s and pneumococcal polysaccharide–protein conjugate vaccines in the 2000s for the prevention of lower-respiratory tract diseases. Although of clear usefulness for low-income countries, where lower-respiratory tract diseases have been the commonest cause of childhood mortality, there were delays of between 10 and 20 years between the first use these vaccines in industrialised countries and their introduction into low-income countries [17]. It is important to strive to prevent similar disparities in the introduction of new vaccines. More recently, the Rotarix vaccine (GlaxoSmithKline) against rotavirus, an infection that is responsible for diarrhoeal diseases in high- and low-income countries, was released simultaneously in Latin America and high income countries [18].

A number of reasons can underlie the delay in the use of vaccines in low-income countries including the necessary financing for their implementation and the clear recognition of their public health benefits. These problems have been addressed by a new strategy of financing through the GAVI Alliance known as Advanced Market Commitments [19], together with accelerated development and introduction plans for pneumococcal and rotavirus vaccines in 2003, and Hib vaccine in 2005 which filled information gaps on these vaccines [17]. While Hib conjugate vaccines are monovalent, pneumococcal conjugate vaccines are polyvalent and consequently are an example of a modern complex vaccine with higher associated cost-of-goods. The initial 7-valent pneumococcal conjugate vaccine was replaced with a 13-valent vaccine including the three commonest pneumococcal serotypes causing disease in Africa. Nevertheless, there is ongoing evidence of replacement of disease-causing serotypes following vaccine introduction [20]. This has led to attempts to develop protein-based vaccines against pneumococcus [21].

5. Development of vaccines only needed in low-income countries

Development of new vaccines that are only required in low-income countries present a major challenge due to the absence of a clear commercial return to the vaccine manufacturer. Despite this, a new monovalent conjugate vaccine against meningococcus serogroup A was developed in the 2000s [22] specifically for use in the African Meningitis Belt where this serogroup has been responsible for the majority of meningitis epidemics. The vaccine, MenAfriVac, came from a new global health partnership, the Meningitis Vaccine Project [23]. This is a joint effort between the Programme for Appropriate Technology in Health (PATH) and the WHO, with financial support from the BMGF. The vaccine is priced at less than US$1 per dose. Mass immunisation campaigns began with the new vaccine in 2010 in Burkina Faso, Mali and Niger, and the vaccine is subsequently being rolled out across the entire African Meningitis Belt.

By developing a new low-cost vaccine that, from the outset, was specifically targeted at low-income countries, the Meningitis