EXPERT REVIEWS

Introducing new vaccines in developing countries

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Vaccines offer the most cost-effective approach to controlling infectious diseases. Access to vaccines remains unequal and suboptimal, particularly in poorer developing countries. Introduction of new vaccines and long-term sustainability of immunization programs will require proactive planning from conception to implementation. International and national coordination efforts as well as local and cultural factors need to be known and accounted for. Adequate infrastructure should be in place for the monitoring of disease burden, vaccine effectiveness and vaccine safety, based on the common terminology and international consensus. This overview paper aims to raise awareness of the importance of introduction efforts for vaccines of special relevance to resource-poor countries. The target audiences are those involved in immunization programs, from planning or oversight roles to frontline providers, as well as health care professionals.

KEYWORDS: AEFI • developing countries • immunization • vaccines • vaccine introduction • vaccine safety

Background

Economically stabilized industrialized countries provide vaccine developers with the most financially advantaged markets for vaccines, but the largest burden of vaccine-preventable diseases lies within developing countries (FIGURE 1) [1]. Successful funding of vaccine programs in developing countries requires the support of international organizations, or public or private funding agencies. In recent years, innovative partnerships such as the Global Alliance for Vaccines and Immunisation and the International Financing Facility for Immunisation have been established to provide reliable funding arrangements [1]. Some countries such as Brazil, India, Cuba, Vietnam and Indonesia have also invested in their own research institutions for the purpose of large-scale vaccine manufacturing. For the purposes of this study, we are defining 'developing country' based on the 2013 United Nations World Economic and Situation and Prospects [2].

A vaccine is a biological preparation that contributes to immunity against a particular disease. The term vaccine derives from the use of cowpox (Latin: *variola vaccinia*), to inoculate humans, providing them protection against smallpox [3]. Vaccines have helped to reduce the incidence of many common diseases, led to the control of others, and have resulted in the global eradication of smallpox. Vaccination is cited as the most effective intervention in modern medicine [4]. It is universally accepted that adopting vaccines is the best use of scarce health care resources. More safe vaccines will become available and will protect people against a range of pathogens that cause misery and death. In contrast to industrialized countries, many people in developing countries lack adequate health care and cannot afford the cost of treatment needed for common infectious diseases. Infectious diseases are major causes of economic underdevelopment and poverty in these countries. Development and deployment of vaccines to protect against infectious diseases in developing countries is a high priority to improve global health.

The goal of any vaccination program is to reduce and ultimately control the target disease(s) by working in conjunction with public and private health care providers. Accomplishing this goal will require achieving and maintaining high vaccination coverage levels, improving vaccination strategies among under vaccinated populations, prompt reporting and thorough investigation of suspected cases and rapid institution of disease control measures. Also, a vaccination program should develop strategies for appropriate use of the vaccines, specifically in the high disease burden countries. To do this, we need to generate evidence

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Figure 1. Line in front of vaccination site in Batil, South Sudan.
Image courtesy of Petra Ruzickova, Médecins Sans Frontières.

on the effectiveness of the vaccine, and devise appropriate tools for the policy makers and public health experts in the country to guide them on the decision making and introduction of novel vaccines in developing countries [5].

Challenges in introducing a new vaccine

Introducing a new vaccine in a developing country may face several financial and logistical challenges [6–9]. Global challenges include the fact that newer generation vaccines are often too expensive to be introduced in developing countries. Several vaccines that were previously used both in developed and developing countries are being replaced with newer generation vaccines in the developed world (e.g., whole-cell pertussis vaccine being replaced by acellular pertussis vaccine) but continue to be used in developing countries due to their low cost. Major global vaccine manufacturers tailor their selection of vaccines to the needs of the developed world. There is little incentive for them to develop vaccines for diseases largely prevalent in the developing countries alone (e.g., Japanese Encephalitis, Dengue, Cholera, Tuberculosis, Malaria, etc.) [10].

The in-country challenges include uncertainty of local health officials with regard to when and how the vaccine should be introduced as well as how to evaluate the program. To address these challenges, the vaccine introduction program should develop epidemiological and laboratory methods to quickly assess the burden of the disease in the country. Health officials need to be engaged to consider the introduction of vaccine, and the experience from the vaccine introduction programs should be documented to understand if there is competition or synergy between existing and new vaccine introduction program. They also need to investigate how to maximize the synergies. Surveillance should document the burden of the disease in countries and regions in sufficient detail to allow local health officials to make informed decisions about the need of the vaccine. The introduction programs will also require to move from 'demonstration projects' to projects of increasing scale in regions with higher disease burden and to integrate 'operations evaluations' and 'effectiveness evaluations'. Results from these evaluations will then inform the further use of the vaccine in this and other regions. These evaluations will also add to the knowledge base of the use of the new vaccine, which can lead to improved delivery of the vaccine.

Introducing new vaccines into a country's immunization schedule is challenging, particularly in developing countries. A comprehensive document issued by WHO details the policy and programmatic issues that need to be evaluated before making the decision of introducing a new vaccine [101]. The issues include the disease burden in the country, the effectiveness of the vaccine, financial sustainability, public perceptions and community pressures especially equity issues in a heterogeneous population as well as programmatic impacts including human resources availability and program sustainability [11].

Less attention has been paid to the proactive monitoring of the safety of vaccines in developing countries. All countries, irrespective of the economic status of its population and technological advances, have room for improving vaccine safety monitoring. Vaccine safety concerns have existed for as long as there have been vaccines. The experience in countries with long-standing immunization programs tells us that, as vaccine-preventable diseases are brought under control and memories fade, public attention will shift to vaccine safety. Although the focus for many years has been on initiating and expanding vaccine programs for the progress to be maintained, it will be essential to pay close heed to public perceptions of vaccine safety [12–15].

Choosing the right vaccine/formulation & logistics

The planning of the introduction of a new licensed vaccine starts with the right choice of vaccine and vaccine formulation as well as the accurate planning of the vaccine provision and logistics for the immunization program. During the introduction phase, infrastructure and systems established during prelicensure clinical trials should be reutilized to establish logistics for routine use of new vaccines including postmarketing surveillance [16]. Immunization plans should not be developed in isolation, but always in coordination with the global vaccine action plan [17]. Specific requirements regarding the use of multidose vaccines in warm climates with difficulties in maintaining the cold chain have to be considered.

Cost estimates should be conducted comparing the production/cost of single-dose vials and ready-to-use syringes versus multidose vials and the need to coordinate multiple immunizations from the same vial [18]. The exact mode of transportation from the airport/site of delivery or production to the vaccination clinic or site should be determined, making sure that an uninterrupted cold chain can be maintained, whether roads and trucks are available, the cool house has an emergency power unit and sufficient reuse prevention syringes and needles are available [19].

Regarding the stability of the vaccine, questions to be considered include how many people can get vaccinated, before the expiration date of the vaccine approaches? How will doses

be used without wasting the remaining vaccine in the multi-dose vial? What is the role of preservatives with respect to vaccine reactogenicity? The rule 'one needle per vaccinee' should have highest priority to prevent blood-borne infection, and immunization safety should be emphasized at all stages of the vaccine introduction. Depending on the vaccine composition, there may be cultural and/or religious implications. These have to be taken into consideration early on in the planning phase. Examples include whether a vaccine could be considered 'halal' under Islamic law; for example, a meningococcal (Group A, C, Y and W-135) conjugate vaccine that is commonly used to protect Mecca pilgrims. If aborted cells are used in the production process, a vaccine may have little acceptance in certain groups of the population.

Timing of vaccine introduction in relation to the existing national immunization program

Prior to the vaccine introduction, solid models should be built around the question how many individuals will likely benefit from the vaccine introduction, what should be achieved by the intervention and when. At the time when the introduction of a new vaccine is anticipated, there should be thorough consideration regarding the ideal timing of vaccine introduction in relation to the national immunization program. Sometimes it is necessary for a vaccine to be introduced before it has become an integral part of the national/local immunization recommendations or EPI vaccination schedule. The choice depends on the type of the vaccine and the prevalence of the disease. Countries should determine the objective of the vaccine introduction (disease elimination, decrease disease burden, decease hospitalization, etc.) to be able to model the best vaccine introduction option. Other factors to be considered include age of the recipient population, schedules (catch up immunizations in addition to routine immunizations or introduction into the national immunization program), urban, rural or regional population targets (including population density, population migration), transmission of the disease (hyperendemic or endemic outbreaks), dosing, onset and duration of protection (e.g., after one, two or three doses) and need for integration with other preventive measures (e.g., vector control). Modeling can help to plan for the optimal use of limited quality of the vaccines, used to estimate vaccine effectiveness and cost–effectiveness, required vaccine coverage to achieve program objectives at different levels of vaccine efficacy and used to determine the impact of the vaccination program [102].

Promoting a vaccine that is not already part of the national program may, however, provide an additional challenge. Clear public health messages need to be conveyed reassuring the general public that the vaccine is as safe and efficacious as the remaining vaccines in the immunization program.

Education

Technical assistants and local vaccine administrators have to be educated about new modes of vaccine administration, if applicable (oral, parenteral, others). Communication regarding the new vaccine should be prepared in close collaboration with field workers and community leaders [11]. Structured interviews and case scenarios may be used to support the construction of communication material. It may also be necessary to determine the existence of specific cultural and linguistic obstacles that could impact effective communication and vaccine uptake. Potential rumors and fears surrounding the new vaccine need to be addressed adequately, as does the safety of the vaccine workers and associate personnel [20].

Safe injection practices need to be taught along with simple techniques to prevent needle-stick injuries [21,22]. The training can be conducted in the format of a summer school addressing doctors, nurses and midwives, as shown to be successful in the Vaccine Safety, Attitudes, Training and Communication EU project [23] or in the format of the mid-level management training course conducted by WHO-AFRO in the African region [24]. In the future, E-learning tools will play a major role (where available), such as the materials for vaccine safety training, recently developed by the WHO in collaboration with the US centers for disease control and prevention [103].

Research & evaluation

Research and evaluation of a vaccine introduction project should include how the vaccine can be best deployed in various populations. Technical assistance should be provided to the local health officials dealing with the burden of disease, preparing informative and practical documents and designing interactive decision-making tools. The research, evaluation and technical assistance functions should help make evidence-based decisions to control the disease and prevent unnecessary deaths, facilitate collection of relevant data when undertaking a vaccine introduction program and serve as a repository of cost and coverage information based on data from the vaccine introduction program. The repository could also serve as a library where country and global policy makers can have access to the information on how to introduce a new vaccine efficiently in their countries. To amplify its impact, the project should disseminate knowledge gained from researches and evaluations on appropriate use of the vaccine in the country.

It cannot be overemphasized that vaccines should be introduced based on the same safety standards all over the world, double standards have to be prevented. Nevertheless, each country is different; hence, introduction programs need to adjust to local characteristics.

Building a knowledge base

There is a need to collect information from various vaccine introduction projects in the developing countries. Information on the introduction of a new vaccine is important, because the vaccine may need to be applied to many different situations. The information may be used to design appropriate strategies for the countries, who wish to introduce the vaccine in their disease control program. The experience from one area can then provide guidance for building a knowledge base on the use of the vaccines in another setting.

Importantly, building the knowledge base will need to be a dynamic process. The knowledge base acquired from various vaccine introduction projects will need to include specific information that will help make decisions. For example, different projects may use different strategies, but they may not necessarily document or even appreciate these differences. Building a knowledge base will require an understanding of the differences and documenting these differences so they can be evaluated, and future introduction programs can learn which approach will be best suited for a given situation. Additionally, many programs will choose to evaluate the effectiveness of the vaccination program, but unless similar methods are used, the results may not be comparable. Thus, the methodological issues for evaluation of the effectiveness of the vaccination program need to be properly documented, and the results of the evaluation interpreted with care.

Local opinion leaders and expert groups, who are knowledgeable about the need of vaccine introduction, should be actively engaged early in the process [25]. Health care providers, who are up to date on their own immunization, are usually better at motivating others to follow their example [26]. Focus group and qualitative sociocultural research on perceptions of the new vaccine among health care workers, parents, technical experts and political leaders should be conducted prior to implementation of the immunization program [27–29]. To this end, social media networks, expert panels and academic institutions, including medical students should all get informed to be on board with the planned program [30]. Interdisciplinary and multinational advisory and monitoring boards could be assembled to facilitate the accumulation of expertise from different viewpoints. Advisory boards could consist of representatives of the ministry of health, ministry of higher education, public health experts, private public partnerships with experiences in vaccination, clinical researchers, safety pharmacovigilance experts, WHO and other global partners (UNICEF, GAVI, Gates), possibly funders and religious leaders. National expert committees have successfully been engaged in the safety monitoring during the MenAfriVac introduction campaign across 33 sites in Niger [31]. Strategies need to be formulated on how opinion leaders can be identified and engaged, bringing them together with people who already have gathered experience with the new vaccine in other settings.

Background materials including protocols, reports, communications materials, etc. should be made available to the vaccine introduction program, so that health officials do not need to 'reinvent the wheel'. Availability of such materials will facilitate smooth introduction of a new vaccine. An important aspect for this documentation will be reports from staff to the sites to understand the type of programs and strategies that work well and the constraints of those, which did not. A standardized reporting and evaluation form may be used for this purpose. This document will then be able to describe the different vaccination programs in order to compare their costs, their logistical evaluations, their program effectiveness and potentially their cost–effectiveness – the knowledge base that will help making a successful vaccination introduction program.

Documenting crucial experiences and lessons learned from prior and existing vaccination programs are important. The documents can be used by the project implementers when they plan for a new vaccine introduction in order that they can benefit from past introductions. They, in turn, can contribute their lessons to this section for the next set of implementers.

Lessons learnt from existing immunization programs include the need to have rapid response emergency programs and panels in place that can respond to sudden outbreaks of vaccine-preventable diseases, such as the current measles outbreak in Wales, UK, as well as safety signals, real or perceived [32,33].

For instance, in a cholera vaccine introduction program in Batil, South Sudan, the vaccine recipients experienced some reactions (vomiting and nausea) on the first day of vaccination [34]. It turned out to be a psychological effect, as several women would collectively run away from the site and vomit or spit out immediately post vaccination. The vaccinators managed to stop them from running away and advised them to breathe deeply to prevent the nausea and vomiting. This worked effectively [34]. The tradition in many communities in the area is that a man cannot drink in front of his mother-in-law. The vaccinators had to assure the male vaccine recipients that they would not be seen by their mother-in-law while taking the vaccine. Another tradition is that newly married couples cannot eat or drink outside the house, thus they were given the (oral) vaccine inside their house [34].

Religious and cultural implications of immunization programs may need to be considered early on. In Muslim communities, for example, immunization programs – regardless of the route of administration – should not be planned for the month of Ramadan (fasting month). In some regions, it is wise to plan for male vaccinators to administer vaccines to males and use female vaccinators for the administration to female vaccine recipients.

In an area of Odisha, India, the vaccine introducers observed that participants did not like the 'taste and smell' of the cholera vaccine during a pilot introduction project. The communities described the taste as 'fishy' or 'rotten egg' in nature. Since many people in the area are vegetarians on a specific day of the week, the taste of the vaccine resulted in lower participation in the campaign [Binod Sah, IVI, Pers. Comm.]. Understanding community concerns and traditions and adequately addressing them are important when a new vaccine is planned to be introduced in a specific society.

Evaluation of the effectiveness & demand for a new vaccine

Assessing biological and programmatic effectiveness of a vaccine are important for wide use of the vaccine [35,36]. Use of a standardized protocol in this regard will help the national programs implement and evaluate their programs and promote cross program learning. Financial planners need to know this information for introduction of the vaccine. The costs of the vaccine program can largely be anticipated since they include items that are reasonably known. These include purchase of the vaccine, personnel and transportation costs and communications

and logistics cost. Costs of treating a patient with the vaccine-preventable disease can be determined from medical records. The more difficult costs to estimate are the costs of the disease in an outbreak situation. Typically, an outbreak leads to the disruption of health services with subsequent deterioration of other routine services. Further costs are related to effects on trade and travel. Cost–effectiveness calculations can also be influenced by the variations in target disease incidence from year to year. Since the cost–effectiveness calculation is related to the rate of the disease and the cost of the vaccine, the vaccine can be thought to have poor effectiveness when the disease incidence is low. However, since the vaccine program affects disease incidence, one must consider historical rates in the model and not just rates during the duration of the project.

The demand for a new vaccine is usually uncertain. Vaccine producers may not invest in initiating new vaccine production without an estimate of the potential demand. This has created a vicious circle in the past and has delayed the introduction of new and underutilized vaccines in developing countries. The uncertainty of demand has led to a reluctance among vaccine manufacturers to increase production resulting in a low supply and high prices [104].

The challenge to the global health community is to ensure that there is a predictable and growing demand, facilitated by donor funding and technical support, which could lead current vaccine manufacturers to increase their production capacity for the vaccine and possibly new manufacturers to enter the market. This would result in the growth of global production capacity, in turn leading to lower price of the vaccines. Note that financial and technical support from the GAVI Alliance and from several accelerated development and introduction plans have helped to create virtuous cycles for several newer vaccines in recent years, including hepatitis B, the pentavalent (DPT-HepB-Hib) and rotavirus vaccines [105].

Rational and effective use of the vaccine may also lead to an increased demand of the vaccine that may spur increased vaccine production. Consequently, there is a need to conduct research and evaluation of the vaccine introduction programs to increase the demand for vaccine. The program should include providing technical assistance, and focusing operations research to know how to overcome the barriers to introducing a new vaccine as well as achieving a good coverage of the vaccine. Dissemination of the important findings from introducing of a new vaccine in a developing country is also important for broader acceptability of the vaccine. Developing a forecast of the demand for vaccines provided through public health sector programs in developing countries is critical to encourage existing producers to invest further in their vaccine production capacity, as well as new manufacturers to acquire the technology to produce the vaccine. Vaccination coverage remains unsatisfactory in many parts of the world, often due to lack of funding and infrastructure, but also due to political and/or economic instability.

Gathering robust data on vaccine efficacy & safety

Robust data on safety, immunogenicity and efficacy (direct vaccine protection) are required by regulatory agencies to license a new vaccine. Such data are typically the only information used as product prescription information and advertising [37]. If data collected in Phase IV trials do not reach the public, vaccines might be underutilized because only direct vaccine protections are communicated to the general public and medical community. Community perceptions developed during vaccine trials can be studied to help in the planning of a general vaccine introduction [38]. Wide dissemination of the data on safety and efficacy is, therefore, important for promoting the use of a new vaccine. It is also good to have a well-developed vaccine safety monitoring system for collecting information on the safety of the vaccines [5,13,39]. Expanded use of vaccines in the absence of such monitoring system could be problematic. Several useful vaccine safety monitoring systems have been developed, including VAERS in the USA, the adverse drug reactions advisory committee database in Australia and several others [40–49]. Although hundreds of millions of doses of vaccines are used every year in developing countries, assessments of regulatory authorities conducted by the WHO demonstrate that few developing countries have programs with the ability to monitor and assure the safe use of vaccines [106].

Building a vaccine safety infrastructure

Although many developed countries have systems for spontaneous reports of adverse events following immunization (AEFI) through their respective national centers for pharmacovigilance (NCPV), these systems are just emerging in developing countries. WHO and its partners are actively engaged in developing or strengthening these systems [50]. The WHO program on international drug monitoring was established in 1968 [51]. Many developing countries have now joined the program and set up NCPV reporting to the WHO collaborating centre for international drug monitoring (now known as the Uppsala Monitoring Centre, UMC), as well as national advisory committees.

There are specific reasons for having a vaccine safety monitoring system in developing countries [52,53]. The vaccine may not be produced under good manufacturing condition [54]. The vaccine potency and safety may become impaired by improper storage or administration. Also, some adverse effects may not become apparent in prelicensure trials because they occur rarely and may not be measured in such trials. Assuring high-quality vaccine production and high-quality postlicensure surveillance for vaccine, adverse events are complementary and integral components of a well-functioning system of vaccine regulation and control. This would help gain public confidence. The introduction of a new vaccine in any setting will be more effective and sustainable if publicly known safety surveillance is already in place.

The processes for and completion of AEFI reporting from developing countries are highly variable. Some countries have no NCPV. In countries where NCPV are established, adverse drug reaction reporting is a regular activity. In contrast, AEFI may or may not be received and forwarded on to the UMC [55]. There may be dual systems for AEFI reports with

those involving adults being reported directly to the NCPV, whereas those involving childhood vaccines being reported via the national immunization program. Any AEFIs reported to the NCPV are likely to be sent on to the UMC, but when AEFIs are reported via the immunization program, they may be sent to the UMC directly, or via the NCPV, or not at all [13,39,55].

In the face of limited resources, active collaboration between NCPV and EPI programs is extremely important though recent assessments by WHO indicate that such collaborations are few. Although benefiting from improved collaboration between existing systems, vaccine safety surveillance systems will need to accommodate for and 'fit into' the very different public health and vaccine safety environments in developing countries.

The efficient implementation of pre- and postmarketing surveillance systems requires well-trained personnel. The process of economic globalization leads to a continued loss of human resources due to migration to industrialized countries creating acute shortages in developing countries [56,57]. The monitoring and reporting of AEFI in areas of low health practitioners' coverage will often be undertaken by laypersons. This may have an impact on the nature and types of AEFI reported as well as the quality of reports. Caretakers of children who have been immunized will have to be educated and informed about reporting mechanisms, including contacting personnel in the event of medical problems following immunization [58]. In areas where there are few health professionals, village healers or midwives are often asked to take part in mass immunization programs without legal protection. When there are programmatic errors or AEFI, these workers are left to fend for themselves – an issue of poor communication and poor governance. Adequate training for those who will engage in mass immunization programs will be crucial for the long-term success of such programs.

New concepts have been developed recently, including the systematic analysis of vaccine safety inquiries from public health officials vaccine providers and the general public for the tracking of vaccine rumors [59], as well as safety monitoring systems developed in the context of the recent H1N1 pandemic [60]. Another recent approach developed by the London School of Tropical Medicine includes a monitoring system of social networks to measure vaccine confidence in different groups and regions [61].

Macro & micro planning

National authorities should be fully involved in introducing a vaccine in their country. In this regard, political commitment is essential. All key stakeholders involved in this program should be in agreement and a memorandum of understanding describing their tasks and responsibilities should be in place and signed by the different parties involved. The coordinating committee needs to engage all relevant individuals and departments at the level of the Ministry of Health, other Ministries and implementing stakeholders and partners. A subcommittee is also needed for planning and supervision of the activities, developing toolkits for information, communication and social mobilization, assessment of the logistics requirement and preparing the budget and finance for the activities related to introduction of the new vaccine. It is also important to ensure that the vaccine is registered by the national regulatory authorities. The vaccination program should establish an intersectorial coordinating committee and thematic subcommittees and analyze epidemiological data to determine the target areas and population. Again, scientists, religious/spiritual leaders, community organizers and patient advocacy groups should be involved. Individuals' responsibilities, task sharing and the schedule of activities are to be clearly defined for the program. Accordingly, a budget is to be made to procure the vaccine, store and maintain the cold chain. Social mobilization, vaccination outposts and staff and logistic requirement need to be finalized for the program. It is also important to develop strategy and operational guidelines, review the acute disease surveillance data base, conduct capacity building workshops, prepare tools for data management, strengthen and develop guidelines for AEFI collection, for monitoring, supervision, communication strategies, media management and field-test guidelines, field-test social mobilization and advocacy materials.

The success of a mass vaccination campaign depends on having an adequate number of vaccination teams [107]. A team usually comprises of vaccinators and volunteers, preferably chosen from the population to be vaccinated. Qualified health care workers should be drawn carefully from hospitals and/or health facilities to ensure the least possible disruption of essential services including routine EPI activities. Depending on the setting, an additional person may be needed to control the crowd. The composition of vaccination teams may also vary depending on the registration system. For a mass vaccination campaign linked to research studies, the number of team members should be increased.

Supervision is necessary to ensure the quality of planning and implementation of the program activities. The success of a campaign largely depends on the work of motivated supervisors who assist in preparation, support training and are able to identify and solve problems before referring issues to the next management level [107]. Supervisors at central level should visit all places before the start of the campaign and revisit the problematic places (in terms of logistics and social mobilization, etc.). Several households should be visited to verify whether the population is aware of the campaign, dates, target population and location of the nearest vaccination center. If the supervisory visit indicates that social mobilization is inadequate or ineffective, efforts should be intensified and effective messaging to the population reinforced. During immunization campaigns, the supervisors should verify that the teams follow set procedures, collect tally sheets and fill in daily summary reports. They should also take the responsibility of quality control.

There should be a provision for revising the budget in a new vaccine introduction plan, so that any incidental or unforeseen expenses can be included. Field guidelines at each point of immunization, receipt of cold-chain and immunization supplies

and review of the storage and logistic situation should be included in the micro plans. Just keeping the vaccines cool is tough in a tropical country where average daytime temperatures are 35–40°C, and rural electricity supplies are not reliable [108]. There is a need to develop supervisory checklists, tally sheets and summary forms. The authorities should prepare training materials on running an immunization session and develop radio and television announcements and press articles. They should also make social mobilization toolkits, advocacy materials and develop evaluation plans. The distribution of vaccines and other materials should take place at the planned time, from central to district level, from district to subdistrict level and finally to vaccination posts. The distribution plan should account for the distance that has to be covered to distribute vaccines and materials, the mode of transport and the costs, staff (drivers, technicians for cold-chain final checks and maintenance) and the time required for distribution.

Social mobilization

Prior to conduct a vaccination program, social mobilization should be done through culturally adaptive method [109]. The information regarding vaccination campaign such as target population, target areas, vaccination outposts and the scheduled dates of campaign should be disseminated. Key messages for prevention of the disease should also be disseminated in the communities. Local medias such as the radio, television, newspapers, mobile teams equipped with loudspeakers, posters, leaflets, etc. may be used in disseminating the information related to the new vaccine. Local health care providers should also be informed about the vaccination program and their cooperation sought during the campaign.

Enrolling prominent figures from the community such schoolteachers, religious leaders, sportsmen and women, singers and actors can help disseminate the message. In addition, social mobilization may also be conducted in places where people tend to congregate (e.g., railway and bus stations) and are available to listen to specific messages. The success of social mobilization strategies depends largely on local and cultural specificities and how well they are understood and integrated into strategy and message development [107]. Special care should be taken to avoid cultural misunderstandings that might jeopardize the success of the vaccination campaign. Campaign organizers should also be attentive to negative messages spread by opponents to the campaign. Specific strategies should be developed and attempts to enter into dialog with potential opponents should be undertaken. It is important that the population understand that the immunization campaign is a preventive measure. Special attention should also be paid to local customs, sociocultural determinants, literacy rates and languages. Social mobilization should start at least 2 weeks before the beginning of the vaccination session. The campaign itself should be launched with an opening ceremony in which high-ranking officials should participate.

Introduction of a new vaccine requires a long-term trustworthy and respectful relationship between the vaccine implementers and the community members. There could be a gap in understanding between implementers and the participants due to inequalities in social, structural and physical environment [62]. Sometimes, there could be rumor regarding the vaccine (e.g., the vaccines to be used are of low quality, will be used post their expiry dates or are intended to cause sterility). To combat these rumors, the program implementers have to work with the community prior to introducing the vaccine. Lack of adequate political will among the community leaders may affect smooth conduct of vaccination campaign [63]. The implementers should be cautious to make sure that personal political views did not affect the participation of the individuals during the campaign. Holding discussions with the community leaders, informing them about the benefit of the vaccine and seeking their cooperation are necessary. Many people in developing countries do not have the necessary minimum literacy to understand the mechanism of action of the vaccine, and the risk and benefits while participating in a vaccination campaign. Thus, community and youth engagement strategies are essential for the introduction of a new vaccine [64,65]. Such community engagement should involve bringing together people affected with the target disease, community stakeholders, school officials, educators and health providers to develop partnerships, address service gaps and difficulties and support families and individuals to increase awareness about the prevention of the disease.

Decision-making at the country level

Experience suggests that introducing a new vaccine into a national immunization program is influenced by multiple factors [102,110]. Activities need to be designed which will demonstrate the public health impact and need for the vaccine in the country and assess means of ensuring vaccine access for people at risk. The data generated can be used for other countries that subsequently introduce the vaccine.

Generating research evidence for decision-making

The following key aspects are required to evaluate the budget requirements for the program, allocate government and partner funding, evaluate affordability of the program for the government and individuals and assess program sustainability:

Epidemiological surveillance: surveillance should include analyses of disease burden, incidence and prevalence, pathogenicity and seroprevalence, disease vector and transmission, distribution of the disease (agent and area) and the morbidity and mortality associated with the disease.

Economic studies: solid data should be obtained on the cost of the vaccine-preventable disease divided into public and private sector, disease severity, individual and household cost, indirect cost of illness (including absenteeism, loss of productivity) and willingness to pay for a preventive measure.

Policy studies: strategic assessment includes scheduling, coadministration, target age groups, duration of protection, herd effect, programmatic aspects, such as supplies and logistics, as well as risk–benefit analyses.

Social studies: social scientists should be involved early on to address the public opinion and the demand for vaccine.

Mathematical modeling: mathematical models should be employed to help estimate the impact of the vaccine on the disease and costs, assess public health impact.

Regulatory aspects: the country's National Regulatory Authority (NRA) should be able to licensee and control the safety and quality of the vaccine. The NRA should ideally be WHO recognized and be capable of approving and overseeing the Phases III and IV trials conducted in the country, be able to license novel vaccines, develop and validate lot testing for the novel vaccines, ensure the vaccine is manufactured to GMP conditions and be able to review AEFI from the clinical trials and vaccination campaigns.

WHO has played a key role in establishing the WHO Biological Reference Materials necessary to standardize biological materials and developing WHO guidelines and recommendations on the production and control of vaccines to ensure safe and effective products. These standards, based on consensus achieved through international consultations, assist WHO Member States in ensuring that the vaccines produced and used in their country conform to current international standards. This also involves close collaboration with the international scientific and professional communities, regional and national regulatory authorities, manufacturers and expert laboratories worldwide [111].

By prequalifying vaccines, WHO provides a service to UNICEF and other UN agencies that purchase vaccines, with regards to the acceptability, of vaccines from different sources for supply to these agencies. Vaccines are added to the list after the evaluation of relevant data and the manufacturing sites being audited by WHO. This list is updated regularly. These vaccines are considered suitable for the target population, at the recommended immunization schedules and for use with appropriate concomitant products. This also ensures that there is independent and appropriate regulatory oversight of the vaccine by a responsible functional NRA [111].

Among other aspects, decision-makers will need information on affordability and relative cost–effectiveness, to determine the value for money of the new vaccine. Other important considerations are the availability and market price of vaccines, the safety and suitability of available vaccine products for national programs and logistical considerations of how the new vaccine should be introduced. Different possibilities exist, such as a phased introduction into specific risk groups first, followed by the general population versus one-time preventive campaigns in the at risk groups by routine vaccine introduction in at risk areas, in the national immunization programs, etc. [66]. Lately, WHO has focused on providing technical information packages, promoting the establishment and strengthening the capacity of national immunization advisory bodies and providing models and estimates of cost–effectiveness to help with the national or regional decision-making process. In this regard, the WHO has developed a comprehensive resource [101], proposing a generic framework that can be used by the health officials working on immunization program. The WHO Vaccine Introduction Brochure [101] is available online, website provides useful information regarding programmatic aspects of introducing a new vaccine. Numerous vaccine and product-specific guidelines have also been developed to facilitate introduction, and WHO Position Papers are also available for all new vaccines [112].

Surveillance post vaccine introduction

As countries begin to introduce newly approved vaccines into routine childhood immunization programs, monitoring the vaccines performance in real-world settings should be a high priority. Key considerations in the postlicensure period include: how the vaccine will perform against the target disease under routine public health use; how routine vaccination will impact the epidemiology of the disease with regard to the burden of severe disease and death, seasonality, serotype distribution and age distribution of cases; whether the vaccination will have a sufficient impact on transmission to reduce disease burden in unvaccinated individuals living in the vaccination area; whether the vaccine will confer protection through the initial years of the infants life, when most severe disease and mortality typically occur. Monitoring of the vaccine impact with focus on these public health considerations will allow public health authorities, health care providers, parents and decision makers to appreciate the health benefits of vaccination in reducing the burden of severe disease. It will also allow assessment of the cost and effectiveness of vaccines in programmatic use and the need for modifying vaccination formulations or schedules to enhance the performance of the vaccine [67,68].

Monitoring disease trends in order to assess vaccine impact can be done using primary data sources, such as an active disease surveillance system or secondary data sources, such as national data on hospitalizations for disease. Although these data are often incomplete, monitoring data from 1 to 2 years before and after vaccine introduction, comparing rates in vaccinated age groups with those in unvaccinated age groups and assessing changes in seasonal and age patterns, may allow for a reasonable assessment of potential vaccine impact.

It is also necessary to ensure that long-term data on the safety of the vaccine is collected through postmarketing surveillance of AEFI to identify and manage safety concerns that could emerge after vaccine introduction. Efforts should be made to enhance disease surveillance in countries where the vaccine is introduced as cases of severe disease are less likely to be captured by the current AEFI surveillance systems in many endemic countries. The collection and long-term storage of serum or other samples from vaccinees would facilitate further studies (e.g., for correlates of protection and possible booster needs).

There is close collaboration needed between licensing national regulatory authorities and the vaccine sponsors [69,70].

The importance of the measures listed above can be gaged from the example of India that is a leading producer and exporter of vaccines but has one-third of the world's

unimmunized children. There are a number of reasons why India lags behind its less developed neighboring countries in terms of vaccination rates. These include huge population with relatively high growth rate, geographical diversity and hard to reach populations, lack of awareness regarding vaccination, inadequate planning and delivery of health services, inadequate supervision, monitoring and intersectoral coordination and weak vaccine-preventable disease (VPD) and post vaccination AEFI surveillance systems. Increased political and bureaucratic will, increasing demand for vaccination by using effective information, education and communication, proper monitoring of the VPD reduction, demand creation and successful AEFI and postmarketing surveillance systems are urgently needed. There is a need to strengthen the regulatory capacity of the country. Restructuring of the expanded Program of Immunization with the introduction of new vaccines and a clear-cut policy on the introduction of newer vaccines is required [7,71].

Conclusions

According to UNICEF, the past 20 years have seen an exponential increase in the number of available and new vaccines [113]. However, there is a concern that inadequate access to vaccines is responsible for over 2 million deaths annually in low- and middle-income countries [72]. These suggest that additional work needs to be done to meet the Fourth Millennium Development Goal, that is, to reduce, by two-thirds, between 1990 and 2015, the under-five mortality rate [114].

The global immunisation vision and strategy (GIVS), established in 2005, aims to facilitate the achievement of this goal.

The GAVI Alliance has been instrumental in funding new vaccines in the poorest countries. Vaccines against Hepatitis B and Haemophilus influenzae type b (Hib) have been widely introduced. An increasing number of countries are now offering pneumococcal conjugate and rotavirus vaccines in their programs, thus offering protection against some of the leading causes of child mortality: pneumonia and diarrhea. Poliomyelitis is on the verge of eradication [73], measles deaths have been reduced by 74% between 2000 and 2010 [74] and maternal and neonatal tetanus have almost been eliminated as a public health disease [115].

Several global health initiatives have been established to promote immunization within the context of the other primary health care interventions. So far, over 70 countries have developed comprehensive Multi-Year Plans, outlining their plans for implementing the GIVS strategies [75,76]. The GAVI, established in 2000, provides financial support for immunization to the poorest countries of the world. [77] Initiating in 1990, the accelerated vaccine introduction Priority Project is an effort to find mechanisms for accelerating the introduction of new as well as underused vaccines of public health importance in the developing world. The project finds barriers to new vaccine introduction in developing countries includes lack of efficacy, burden and cost–effectiveness information for developing country settings, the need for technical assistance with introduction, logistics, supply and quality control issues and lack of funding for vaccines. The accelerated vaccine introduction project also focuses on critical points in the vaccine evaluation and introduction continuum at which WHO activity can make a substantial difference. The project involves activities in each of Vaccines and Biologicals teams, and addresses the following areas – efficacy, burden and cost–effectiveness, vaccine quality, vaccine supply and financing and introduction into immunization programs. social network analysis can be employed prior to vaccine introduction to improve the understanding of structural and relational features of the network of actors involved [78].

The Johns Hopkins Bloomberg School of Public Health has been awarded a 4-year, US$5 million grant from the Bill & Melinda Gates Foundation to promote the effective use of oral cholera vaccines around the world [116]. The endeavor under the delivering oral vaccine effectively (DOVE) program will provide local health officials with technical assistance on how to use a vaccine (currently focusing specifically on the cholera vaccine), evaluate current vaccine-use practices and develop new field surveillance methods for monitoring and controlling outbreaks of the disease. In partnership with the WHO, UNICEF and other national and international agencies, the delivering oral vaccine effectively project will provide the knowledge, technical assistance and encouragement to bring a life-saving vaccine to those who need it the most, in particular the high-risk people of the developing countries. The program will greatly facilitate the appropriate use of the new cholera vaccine, and the knowledge will help facilitate introduction of the other new vaccines in the developing countries.

Lessons learned, guidelines for implementation and relevant data from successful previous vaccine introduction campaigns should be compiled and shared in a national, regional and global context. The decision of a national government to introduce a vaccine can significantly influence the decisions of other countries in the region.

Some of the lessons learnt include the fact that the introduction of new vaccines should include sufficient time factored in for technical and regulatory approvals (which are often time-consuming in developing countries), interdepartmental coordination and communication between different national government departments are key to successful vaccine introduction, training helps in strengthening the vaccine-specific AEFI and the country's AEFI monitoring systems, improving vaccine and logistic forecasting improves procurement of the vaccine, improving the vaccine supply chain minimizes vaccine wastage due to vaccine expiry, strong monitoring and supervision leads to scare in-country financial and human resources being utilized well, need-based revision of budgets leads to better vaccine campaign implementation and continued epidemiological assessments of the disease burden in different population strata, operational research, surveillance to better understand the disease burden (including the disease incidence, age distribution, case fatality rates, sequelae, disability-adjusted life years averted) and cost–effectiveness analysis is helpful in policy making. Economic evaluations can help determine appropriate resource allocation and design services.

Information on the disease burden, vaccine supply and sustainable financing are prerequisites to a successful vaccine introduction campaign. It is necessary to adequately estimate the programmatic time and resources costs of the vaccination program as this is often underestimated by countries. This includes the transportation of the vaccine, training and supervision, surveillance, waste management, monitoring for AEFI and cold-chain maintenance. It is importance to have standardized procedures for clinical case evaluation, consistent specimen collection, assessment of disability, national laboratory and regional reference laboratories to aid in confirmatory testing, evaluated assays and national uninterrupted supply of validated diagnostic kits.

Sensitization of key stakeholders, regular media updates and public awareness campaigns help in addressing concerns regarding the new vaccine. Political support and support from the National and Local communities is required. Communication plans should be developed for the different stakeholders including the public health experts, policy makers, health community, general public and the media. Well-developed and rapidly implemented crisis communication plans to ensure immediate clarification to vaccine-related concerns are critical.

International procurement support to developing countries to ensure access to safe and affordable vaccines, technical assistance and the regulatory experience of neighboring countries is important for reviewing available information, generating data for product licensure and helps speed up introduction efforts.

Dedicated advocacy helps keep the disease burden and the importance of the vaccine on the national, regional and international agenda. Advocacy efforts can help highlight the impact of regional diseases to the funding agencies and global health bodies.

New vaccine introduction and immunization strategies (including vaccine transition in the country) help in improving the countries health system infrastructure, enhance disease surveillance and strengthen AEFI monitoring.

Although there may not be a 'one-fits-all' solution for all developing countries, a consensus protocol can be developed to cover common issues and priorities in different parts of the word.

In conclusion, the key to success of introducing a new vaccine in a developing country is how it can be integrated with other intervention programs of the country.

The program should protect synergistically with other interventions, but this synergy needs to be documented in a variety of situations where the vaccine will be used. Mechanisms of the synergy include both biological and logistic synergy. Biologically, the vaccine may induce herd protection by reducing the environmental contamination of the pathogen [79] making other intervention programs activities more effective. In turn, the other interventions reduce the inoculum that potential patients consume and this increases the effectiveness of the vaccine. Further activities include the functions of policy advice, process guidance, other quantitative assessment and experience sharing and planning. The need to make important decisions about the use of new vaccines provides an excellent opportunity for countries to consider the use of broader advisory committees to deliberate and address strategic issues and health priorities at national level. These activities are important for a developing country for introducing a new vaccine, though they should be carefully tailored to meet the different needs of the individual country.

Expert commentary

There is an urgent need for more global consensus and a tightly coordinated, comprehensive and compassionate approach to vaccine introduction. Vaccine-preventable diseases do not respect political borders!

The impact of World Wide Web and social media on vaccine acceptance cannot be overestimated. Intelligent tools for the monitoring of vaccine acceptance and vaccine safety will have a major impact. The Internet is a double-edged sword as it is used for spreading rumors but also as a tool to monitor and counteract rumors and fears.

Need for improved rapid diagnostics and effective real-time monitoring of VPD prior to vaccine introduction. The results of this research on the overall disease burden and costs to society as a whole, as well as the VPD risk to the individual, should be communicated to local health care workers as well as the general population prior to introduction of a new vaccine. A proactive rather than reactive approach should be pursued.

New vaccine designs and delivery systems need to be promoted. Preventing blood-borne infections are an important aspect of improving immunization safety. More vaccines of relevance to developing countries are under development. The specific demands of resource-poor settings should be considered at the design stage.

Last, but not the least, the question should be discussed openly how vaccine effectiveness will be defined in the context of low-resource settings. The strategy should move from 'number of lives saved at the end of the day' toward the 'prevention of suffering/disease burden'. New epidemiological models may be warranted to measure and adequately describe the real-world impact of vaccines.

Five-year view

Country and regional stakeholders should collaborate closely in determining the most suitable and appropriate vaccines to be selected for introduction to maximize the effect of the immunization program. Priority lists should be updated continuously based on consensus processes. This might help to limit the cost of vaccines. Vaccines high on the list for the introduction to developing countries should include human papilloma virus vaccines, rotavirus vaccines, as well as pneumococcal and cholera vaccines in endemic areas. Additional research is warranted on the impact of influenza in developing countries. A universal flu vaccine is urgently needed to allow effective disease prevention in low-resource settings.

New business models and market incentives should be developed for the introduction of more licensed vaccines in low-

resource settings. Innovative ways of financing will be sought, including the mobilization of public–private initiatives, crowd financing, on-demand financing and innovative fundraising models from different areas.

Innovative IT tools need to be implemented. The comprehensive analysis of large databases will enable enhanced safety and efficaciousness analyses as well as real-time monitoring of disease and vaccine safety signals. Real-time monitoring of vaccine rumors via social media networks is useful. Issues that need to be resolved include ownership of individual-level patient data, ethics and liability, data protection and stewardship.

The dissemination of vaccine know-how should be enhanced. Lessons learned, guidelines for implementation and relevant data from successful previous vaccine introduction campaigns should be compiled and shared in a national, regional and global context.

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