Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Challenges of vaccine presentation and delivery: How can we design vaccines to have optimal programmatic impact?

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Vaccine
Delivery technologies
Programmatic suitability
Prequalification
Low- and middle-income countries
Product development

ABSTRACT

Immunization program delivery strategies that enable high vaccine coverage, particularly in inaccessible and remote areas, are critical to achieving optimal vaccine impact. In addition to demonstration of safety and efficacy, there are many factors that influence whether a newly licensed vaccine will be introduced into a country's national immunization program, particularly in resource-constrained environments. This paper describes three case studies of novel approaches that represent the potential for improved programmatic impact by increasing vaccine accessibility in different ways. However, the pathway to regulatory approval, policy recommendation, and program introduction in low- and middle-income countries is complex, requiring engagement with multiple, diverse stakeholders. Consideration of aspects that affect uptake in low- and middle-income countries, during the product development stage, will help better position new or second-generation vaccine products for successful implementation to achieve public health impact.

1. Introduction

The development and use of vaccines to protect against infectious disease is considered one of the most effective global public health tools of our time. In 1974, the World Health Organization (WHO) established the Expanded Programme on Immunization (EPI) to ensure that all children have access to six routinely recommended vaccines [1]. Since then, significant progress has been made in the development of additional vaccines, doubling the total number of vaccines in the routine EPI schedule and bringing to 25 the total number of vaccine-preventable diseases with licensed vaccines available [2].

While vaccination is estimated to save 2–3 million lives per year, there remains a significant immunization gap of 19.4 million infants in resource-constrained countries, resulting in 1.5 million deaths per year in children younger than 5 years [3]. The addition of new vaccines to the EPI schedule saves lives; however, there has been a corresponding increase in the cost and complexity of the immunization supply chain and vaccine delivery. In some cases, approximately half of the costs to vaccinate a child are associated with management of vaccine supply logistics and health care worker administration [4]. In order to reduce this burden and improve efficiencies, innovative technologies and approaches are needed to simplify vaccine delivery by removing the need for a cold chain, minimizing the packaging footprint, easing administration, and reducing waste [5,6]. In addition, quantitative tools that model the potential total health systems effectiveness of these innovations are acutely needed to assess the potential value proposition for these new products and approaches, and to effectively advocate for their development. Understanding the challenges of vaccination programs is critical to inform the development of products with the necessary attributes and design features that

Abbreviations: bOPV, bivalent oral poliovirus vaccine; CTC, controlled temperature chain; EPI, Expanded Programme on Immunization; fIPV, fractional dose inactivated poliovirus vaccine; GPEI, Global Polio Eradication Initiative; ID, intradermal; IM, intramuscular; IPAC, Immunization Practices Advisory Committee; IPV, inactivated poliovirus vaccine; LMIC, low- and middle-income countries; MAP, microarray patch; MR, measles-rubella; SAGE, Strategic Advisory Group of Experts (on Immunization); V-TIA, Vaccine Technology Impact Assessment (tool); WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.vaccine.2017.04.063
0264-410X/

may have real coverage impact. Generation of the data needed to support a policy recommendation will help to accelerate introduction and uptake of optimal, cost-effective vaccines and products.

The aim of this paper is to discuss current challenges for vaccine presentation and delivery and provide considerations as to how vaccines and technologies can be designed to have optimal programmatic impact. We provide three short case studies of technologies and strategies that are at various stages of development and implementation, that aim to address some of the programmatic challenges faced by immunization programs. We also discuss the respective considerations and pathways beyond regulatory approval, through policy recommendation to in-country introduction. We then introduce a novel quantitative vaccine technology impact assessment tool currently in development to assess new vaccine technologies. This model may ultimately inform vaccine and technology development decisions, donor investment strategy, and global- and country-level policymaking.

2. Case studies

2.1. Case study 1: fractional dose inactivated poliovirus vaccine (intradermal delivery) and development of other innovations in support of polio eradication

Inactivated poliovirus vaccine (IPV) is now recommended in all routine immunization programs in conjunction with three doses of bivalent oral poliovirus vaccine (bOPV), as part of the Global Polio Eradication Initiative's (GPEI) endgame strategy [7]. In recognition of the limited supply and high costs of IPV and following clinical demonstration of comparable immunity between two fractional IPV (fIPV) doses (each one-fifth of a full vaccine dose) by the intradermal (ID) route and a single full dose administered via the intramuscular (IM) route, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) concluded that IPV could be administered through a fractional dose strategy [8]. Consequently, two fractional doses are recommended for routine immunization and one fractional dose for campaigns (with bOPV). fIPV has been effectively implemented in India and Sri Lanka for both routine and campaign delivery.

GPEI is also exploring the use of alternative delivery technologies to ease IPV delivery [9]. ID devices (e.g., adapters for needle and syringe, disposable syringe jet injectors) are currently available, and may simplify administration of fIPV compared to the standard ID injection technique with a needle and syringe. Novel microarray patches (MAPs; also known as microneedle patches) are in development for IPV, and may allow non-health care workers to administer IPV in house-to-house campaigns as part of an outbreak response. Preclinical studies evaluating patches with different vaccine antigens, including IPV, have shown that MAPs generate robust immune responses, similar to those by IM injection, and may enable dose-sparing [10–12]. IPV patches involve vaccine reformulation and are considered a novel combination product, requiring a full development pathway that is acceptable to national regulatory authorities. Preliminary cost modeling by PATH has found that the costs per dose for an IPV patch are likely to be higher than conventional IM or ID injection, but this may be offset by lower delivery costs if the technology enables dose-sparing or storage at ambient temperatures. If development is successful, IPV patches could become available in the early 2020s.

2.2. Case study 2: meningitis A vaccine delivery through controlled temperature chain

Since 2012, numerous countries across the meningitis belt of Africa have successfully implemented a novel cold chain strategy as part of meningitis A vaccine introduction, known as the controlled temperature chain (CTC). This approach allows storage and distribution of the vaccine out of the traditional 2–8 °C cold chain in ambient temperatures up to 40 °C, for three days or more, depending on the antigen. WHO is promoting this initiative for all vaccines that may be eligible, in order to relieve low- and middle-income countries (LMIC) of the "last mile" vaccine delivery constraints associated with cold chain infrastructure and access.

The criteria for CTC compatibility are defined mainly by how they can best benefit immunization programs, including through cost and time economies, while minimizing any associated risks such as a possible increase in wastage or health worker confusion. It is recognized, however, that not all vaccines will meet CTC requirements, leaving some still in need of the end-to-end cold chain. Consequently, vaccines used in campaigns or single-antigen special delivery strategies are currently prioritized for CTC over those used in routine administration, which are typically delivered as a bundle. Furthermore, CTC practices constitute on-label use of a vaccine, and a key requirement is that a vaccine be fully licensed and labeled as per its demonstrated heat stability.

The removal of a vaccine from the cold chain within the context of CTC occurs only once, in the days just before the vaccine is administered. CTC therefore does not replace the conventional cold chain, but operates in conjunction with it. The implementation of CTC must also be carried out in accordance with WHO's antigen-specific CTC guidelines, which stipulate the appropriate context, as well as the necessary tools (particularly for temperature monitoring), training, technical support, and supervision required for the effective application of this approach for a given vaccine [13].

As of the end of 2016, only three vaccines have the appropriate licensure and WHO prequalification allowing for use in a CTC: the meningitis A vaccine, a pneumococcal conjugate vaccine, and a human papillomavirus vaccine. While the potential systems benefits are significant, some countries remain reluctant to adopt this approach given that experience to date is still relatively limited and there is a persistent need for more data to build on existing evidence in support of CTC. However, with further advocacy and demonstration of measurable total systems and cost effectiveness, opportunities and thereby momentum will increase. This, in turn, should boost demand, with the expectation that more manufacturers will be willing to generate the data required to license more existing and new products for CTC.

2.3. Case study 3: microarray patches for measles-rubella vaccine delivery

The mission of the global Measles & Rubella Initiative is to achieve measles and rubella elimination in five WHO regions by 2020, in preparation for future global eradication [14]. While cases have significantly declined due to immunization, and many countries have achieved elimination, progress has stalled [15]. One challenge for measles and rubella elimination efforts is the vaccine's presentation. Measles-rubella (MR) vaccine is lyophilized, and must be stored in the cold chain before reconstitution with a supplied diluent, before injection [16]. The usual presentation is in ten-dose vials, and once reconstituted, the vaccine must be stored in the dark and discarded within 6 h. Reconstitution errors have occurred, including use of an incorrect diluent, which led to adverse events following immunization and deaths [17]. Likewise, concerns over vaccine wastage led some immunization program managers to recommend that vaccinators not open multi-dose vials if too few children were present, requiring caregivers to return on another day [18,19]. Ultimately, such practices may reduce vaccine wastage, but they also lead to reductions in vaccine coverage.

New tools for MR vaccine delivery, such as MAPs, have the potential to contribute to achieving measles and rubella

Please cite this article in press as: Giersing BK et al. Challenges of vaccine presentation and delivery: How can we design vaccines to have optimal programmatic impact? Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.04.063