Vaccine 35 (2017) 2265–2271

Contents lists available at ScienceDirect

Vaccine

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

Review

Exploring new packaging and delivery options for the immunization supply chain ☆

Darin Zehrung [a,*], Courtney Jarrahian [a], Birgitte Giersing [b], Debra Kristensen [a]

[a] PATH, 2201 Westlake Avenue, Suite 200, Seattle, WA 98121, USA
[b] World Health Organization, Avenue Appia 20, CH-1211 Geneva 27, Switzerland

ARTICLE INFO

Article history:
Received 22 September 2016
Received in revised form 11 November 2016
Accepted 28 November 2016

Keywords:
Delivery device
Immunization supply chain
Packaging
Cold chain
Intradermal injections
Sublingual administration

ABSTRACT

A variety of vaccine packaging and delivery technologies may benefit the immunization supply chain. These include alternative primary packaging, such as blow-fill-seal polymer containers, and novel delivery technologies, such intradermal delivery devices, microarray patches, and sublingual formulations of vaccines, and others in development. The potential timeline to availability of these technologies varies and depends on their stage of development and the type of data necessary to achieve licensure. Some new delivery devices are anticipated to be introduced in 2017, such as intradermal devices for delivery of inactivated poliovirus vaccine to stretch vaccine supplies due to a supply limitation. Other new technologies requiring vaccine reformulation, such as microarray patches and sublingual vaccines, may become available in the long term (2021 and beyond). Development of many new technologies requires partnership between vaccine and technology manufacturers and identification of the applicable regulatory pathway. Interaction with public-sector stakeholders early on (through engagement with forums such as the World Health Organization's Immunization Practices Advisory Committee Delivery Technologies Working Group) is important to ensure suitability for immunization program use. Key considerations for programmatic suitability of a new vaccine, packaging, and delivery device include cold chain volume, costs, and health impact.

Contents

Abbreviations: BFS, blow-fill-seal; CMC, chemistry, manufacturing, and controls; CTC, controlled temperature chain; DSJI, disposable-syringe jet injector; EPI, Expanded Programme on Immunization; ID, intradermal; IPV, inactivated poliovirus vaccine; ISC, immunization supply chain; LMIC, low- and middle-income countries; MAP, microarray patch; PQ, prequalification; PSPQ, Programmatic Suitability of Vaccine Candidates for WHO Prequalification; TPP, target product profile; V-TIA, Vaccine Technology Impact Assessment; WHO, World Health Organization.

☆ Open Access provided for this article by the Gates Foundation.

* Corresponding author.
E-mail addresses: dzehrung@path.org (D. Zehrung), cjarrahian@path.org (C. Jarrahian), giersingb@who.int (B. Giersing), dkristensen@path.org (D. Kristensen).

http://dx.doi.org/10.1016/j.vaccine.2016.11.095
0264-410X/

1. Background

In early 2016, 22 vaccines were recommended for delivery through the immunization supply chain (ISC) in low- and middle-income countries (LMICs) [1] as compared to the original four vaccines recommended against six diseases in 1974—vaccines against diphtheria, pertussis, tetanus, tuberculosis, poliomyelitis, and measles [2]. As the number of vaccines delivered through the World Health Organization (WHO) Expanded Programme on Immunization (EPI) has increased, so has the overall ISC burden. Gavi, the Vaccine Alliance, projected that by 2020, four times the cold chain capacity will be needed compared to 2010 [3]. Beyond 2020, new vaccines for diseases such as malaria and respiratory syncytial virus will likely be incorporated into the EPI, with likely expansion of the schedule in the second year of life. New packaging and delivery technologies that have either been developed or are currently being developed are urgently needed to reduce the ISC and cold chain burden, while simultaneously achieving or improving upon immunization program goals.

This article reviews the status of four different types of delivery or packaging technologies that may reduce overall cold chain volume, enable dose sparing, enhance thermostability, or facilitate a non-parenteral (needle-free) route of delivery. Representative examples of technologies and developers are described to illustrate the variety of devices and formulations in development. Additionally, we highlight the benefits of early consideration of such technologies in the vaccine development process, particularly for technologies that could improve vaccine accessibility in LMIC.

2. New technologies

2.1. Blow fill seal

Blow-fill-seal (BFS) technology is an automated primary packaging process by which polymeric containers made from polyethylene or polypropylene material are formed, filled, and sealed in a continuous operation, thereby reducing risk of contamination and batch loss. In the BFS process, (1) polymer resin is extruded into a mold forming the container, (2) a filling mandrel fills the target pharmaceutical into the container, (3) the mandrel is retracted, and (4) the top of the container is sealed. BFS manufacturing can potentially be lower cost than filling in glass vials and preformed polymer tubes, especially at high production volumes; however, it requires significant investment by manufacturers. Cold chain volume savings might be realized with BFS in comparison to other single-dose containers, as BFS containers can be designed to be compact and pack efficiently. BFS containers are widely used for pharmaceuticals, including ophthalmic and injectable medications, and are undergoing evaluation with live attenuated rotavirus and influenza vaccines [4]. BFS squeeze tubes can directly deliver vaccines via the oral or intranasal route (Fig. 1A). For parenteral delivery, needles and syringes could deliver vaccines from BFS polymer ampoules and vials, or compact, prefilled, autodisable devices could be produced using BFS (Fig. 1B).

2.2. Intradermal delivery devices

Intradermal (ID) delivery targets the dermis layer of the skin, rich in antigen processing cells. The traditional Mantoux injection technique using a needle and syringe is currently used for ID delivery of bacillus Calmette–Guérin vaccine for tuberculosis and in some developing countries for rabies vaccines; and influenza vaccine is available in a prefilled mini-needle ID delivery device [5]. However, the Mantoux technique may be challenging to use in all immunization scenarios, particularly in campaign settings, and the available prefilled ID devices are not suitable for use in LMIC immunization programs due to cost and large cold chain storage requirements. A number of novel ID delivery devices have been developed to simplify the process of delivering an ID injection. These include adapters for conventional needles and syringes (Fig. 1C), hollow microneedle hubs for syringes (e.g., NanoPass MicronJet600™ device), mini-needle syringes (e.g., BD Soluvia™ prefillable microinjection system and the Star ID Syringe), and needle-free disposable-syringe jet injectors (DSJIs) (Fig. 1D). Based on clinical research of ID delivery of inactivated poliovirus vaccine (IPV) [6–8], WHO recommends that two fractional doses of 0.1 mL of trivalent IPV delivered intradermally can substitute for a single 0.5 mL intramuscular dose, which is currently being provided along with bivalent (poliovirus types 1 and 3) oral polio vaccine in routine immunization to provide immunity against vaccine-derived type 2 poliovirus [9]. Due to recent supply limitations [10], countries such as India and Sri Lanka are introducing ID delivery of IPV in routine immunization [11], and it has also been used in large-scale campaigns [12]. Although novel ID devices are generally more expensive than autodisable needles and syringes for ID delivery, dose sparing may enable cost savings, particularly for relatively expensive vaccines, and can reduce the cold chain burden. No vaccine reformulation is needed, and use of needle-free ID devices will reduce needlestick injuries [13,14].

2.3. Microarray patches

An alternative technology for delivering vaccines to the skin is microarray patches (MAPs; also known as microneedle patches) (Fig. 1E). These use dry formulations of vaccine antigen, either coated on an array of solid micro-projections or molded into a dissolving array. Phase I clinical studies have been completed for influenza vaccine on dissolving microarrays [15,16], and preclinical studies have demonstrated feasibility of microarrays for vaccines including IPV [17,18], measles [19,20], rotavirus [21], human papillomavirus [22], and pneumococcal conjugate vaccine [23]. MAP delivery has shown potential for dose reduction in animal studies for some vaccines [18], though this has yet to be assessed in humans. Patches may also enable increased thermostability [19,24], potentially enabling storage in a controlled temperature chain (CTC) [25].[1] Increased acceptability, ease of delivery by lesser-trained health care workers, and reduced or eliminated sharps waste are other potential benefits of MAPs which could help expand access to vaccination. However, MAPs are currently in an early stage of development. Their clinical efficacy and cost to produce at large scale has yet to be established; attributes of increased immunogenicity and thermostability may not apply to all vaccines. If a

[1] A CTC allows vaccines to be kept at temperatures outside of the traditional cold chain of 2–8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen. A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding 40°C for a duration of a specific number of days just prior to administration.