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COMMENTARY

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Presentation matters: Buffers, packaging, and delivery devices for new, oral enteric vaccines for infants

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ABSTRACT

Oral administration of vaccines is simpler and more acceptable than injection via needle and syringe, particularly for infants (Fig. 1) This route is promising for new vaccines in development against enterotoxigenic *Escherichia coli* (*ETEC*) and *Shigella* that cause childhood diarrhea with devastating consequences in low-resource countries. However, vaccine antigens and adjuvants given orally need buffering against the degradative effects of low stomach pH, and the type and volume of antacid buffer require special attention for infants. In addition, container/closure systems must be compatible with vaccine formulations, protect against water and gas transfer, and have minimal impact on the cold chain. Health care workers in demanding low-resource settings need an administration device that is easy to use, yet will accurately measure and safely deliver the correct vaccine dose. Developers must consider manufacturing capabilities, and immunization program managers want affordable vaccines. As new combination enteric vaccine candidates advance into clinical evaluation, features of the final vaccine presentation—liquid or dry format, diluent, buffer, primary and secondary packaging, and administration device—should be taken into account early in product development to achieve the greatest possible impact for the vaccine.

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Health impact of diarrhea

Diarrhea is the fourth-leading cause of death among children under 5 y of age worldwide, killing an estimated 530,000 and hospitalizing millions in 2015, mostly in developing countries.[1] Among the various causes of diarrheal diseases, *ETEC* and *Shigella* are the two most important bacterial pathogens for which there are no licensed vaccines.[2] Recent impact studies indicate that immunizing against these two causes of diarrhea could benefit global public health significantly, particularly if they could be combined into a single vaccine for efficient immunization.[3,4] Such a vaccine would improve the health of infants and children in developing countries, and also could protect travelers and military personnel in areas where these bacteria are endemic.

Oral vaccines usually require buffering

The oral route for administration of vaccines to infants is simpler, safer, and more acceptable than needle and syringe, and is particularly useful in developing countries that lack highly trained health care workers and face difficulty in disposing of sharps waste. The target tissue for oral vaccines is the mucosa of the small intestine; however, the low pH of gastric fluid can degrade protein antigens and some adjuvant components of vaccine formulations before they reach the gut. The ability of antigens to resist degradation during transit through the stomach environment can have a profound effect on their ability to induce protective antibodies. Because infants as young as 24 weeks gestational age are able to maintain the intragastric pH at the adult level—below 4—from the first day of life, even vaccines for young infants must survive this environment. Thus, oral vaccines typically require a buffer, which can be given with the vaccine or incorporated into the formulation. Oral enteric vaccine candidates in development include whole-cell inactivated bacterial and subunit vaccines—most of which require a mucosal adjuvant to improve efficacy.[5] Although neutralizing stomach acid may not be as important for inactivated vaccines as for live ones, the stability of mucosal adjuvants in stomach acid must be evaluated, as some of these are sensitive to pH.

The choice of buffer is important not only for maintaining vaccine efficacy, but also for avoiding unwanted side effects in infants. Sodium bicarbonate, a commonly used antacid buffer, has been reported to cause discomfort from release of carbon dioxide gas after neutralization of stomach acid. This gas build-up in the stomach can create pressure that results in reflux of stomach contents into the esophagus, causing spitting, and may require re-administration of the vaccine. Children can have reflux at any age, although it is more common in infants less than one year of age. Other antacid buffers, such as bicarbonate-ascorbic acid, have been evaluated in clinical studies in infants and have been reported to cause less bloating than bicarbonate buffer alone.[6] The phosphate-citrate buffer used in RotaTeq vaccine is another good candidate for the new enteric

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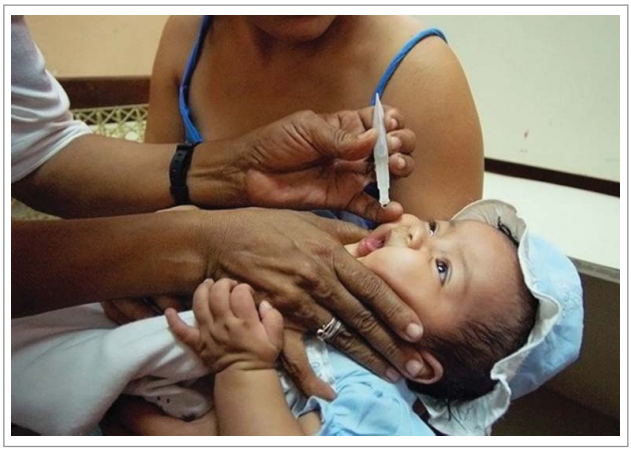

Figure 1. Image of an infant receiving oral rotavirus vaccine from a prefilled polymer squeeze tube.

vaccines for infants. This buffer has sufficient stomach acid neutralizing capacity in a 2-mL dose volume, without unwanted side effects, and has shown good compatibility with different types of delivery containers.[7]

The final presentation should permit a small dose volume

Keeping the dose volume of vaccine formulation and buffer low is important for infants, since swallowing is slow and uncoordinated, and this can lead to spitting or vomiting of the vaccine. The total volume of the vaccine/adjuvant formulation and the buffer should not exceed 2 mL. The trivalent oral polio vaccine (OPV) that requires 2 drops per dose is a gold standard formulation in terms of keeping the volume minimal; however, OPV is resistant to gastric acid and does not require an antacid buffer, allowing for this small dose volume.[8] This will probably not be the case for new enteric vaccine candidates, such as a possible combination vaccine against *ETEC* and *Shigella*, where the final vaccine presentation—with multiple antigens, a mucosal adjuvant, and a diluent/buffer—may result in a large oral dose volume.[4] For vaccines formulated with antacid buffer, the largest contribution to overall dosing volume comes from the buffer component. The final formulation, comprising the vaccine and the adjuvant components, requires physiological pH and isotonicity; thus, the buffer component must have low salt concentration to maintain viability of the antigens. At isotonic salt concentration, there is insufficient or low buffering capacity, which means large dose volumes of the formulation would be needed to effectively buffer the stomach acid. One way to maintain the low dose volume requirement for new combination vaccines is by separating the vaccine components. For example, antigens and adjuvant can be combined in one primary container, and the buffer—concentrated in a low dose volume—can have its own primary container. These two components can be distributed together within secondary packaging. In this case, multiple administration steps are needed to fully vaccinate the infant, introducing greater risk of incomplete or improper administration of the full dose.

Key features of effective containers and delivery devices

Requirements for containers and delivery devices for new oral vaccines include protection of and compatibility with the vaccine formulation, performance and ease of use in dose administration, safety, manufacturability, immunization program suitability, and cost. These are discussed below.

Protection of and compatibility with the vaccine formulation. The stability of any new vaccine must be established for the specific material, design, and filling process for the intended container. Glass vials are a common primary container for many injectable vaccines, and are also used for OPV and some oral rotavirus vaccines. Vials for oral administration are generally packaged with droppers to be attached at the point of use; this approach is most suitable for very low-volume doses delivered by counting drops. Polymer containers also are widely used for pharmaceuticals and for vaccines; these include preformed containers that are sterilized and shipped to vaccine manufacturers for filling and sealing and blow-fill-seal containers that are formed, filled, and sealed in a single operation.

Polymer squeeze tubes are used as primary packaging for several OPV and rotavirus vaccines and have the advantage of acting as the vaccine administration device, eliminating the need for an additional component for delivery. However, some adjuvants may adsorb to polymers, which would require modifying excipients to minimize this risk. Polymer materials also are more permeable than glass to water vapor and oxygen transmission, and to leaching of label materials. Protective secondary packaging, such as a foil pouch, may be used to prevent water and gas transfer through the container, and labeling can be applied to a tab rather than to the body of the container to minimize leaching of ink and adhesive components into the drug substance—although both of these will increase the container's cold chain volume. Inclusion of a vaccine vial monitor (VVM) in the vaccine's labeling is a requirement for vaccines assessed for World Health Organization (WHO) prequalification, in accordance with the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ), which provides guidelines on vaccine characteristics that will be considered during the prequalification process.[9] For presentations requiring protective secondary packaging, placement of the VVM is important. If multiple doses of vaccine are packaged together in the same pouch or overwrap, the VVM should be placed on the primary container so that it remains with the vaccine until each dose is delivered. However, in this case the VVM may be obscured by the secondary packaging, which could present challenges for inspection during storage.

Performance and ease of use in dose administration. Many of the features discussed here also provide safety and program suitability in low-resource settings, in addition to ease of use. For all new oral vaccine presentations, human factors and usability evaluations should be performed to assess ease of use, correct dosing, and any potential risks or errors resulting from the presentation. One important ergonomic factor for delivery of oral presentations is squeezability of the delivery device, which is determined by container shape, material stiffness, and viscosity of the vaccine. Optimal usability and safety are achieved by minimizing the steps (and subsequent risks) associated with preparing and delivering the vaccine at the point of use, and by giving the vaccinator fine-tuned control over the dispensing speed. Presentations requiring reconstitution or mixing of vaccine components at the point of use increase the time required for and the complexity of the delivery process,

and have resulted in errors such as use of incorrect diluents or administration of the diluent alone by practitioners who mistake it for the complete vaccine.[10] To this end, a critical characteristic of the PSPQ is that oral vaccine formulations be in a ready-to-use format (no reconstitution needed) for developing-country, public-sector immunization programs.[9] Compliance with this requirement is compulsory, but requests for exceptions are reviewed by the PSPQ Standing Committee, taking into account the public health need. If preparation steps are necessary, the mixing process and containers should be easy to use and should minimize the risk of errors, and all required components should be disposable and packaged with each dose of vaccine. This co-packaging requirement applies to water for reconstitution as well, as clean water may not be available at immunization sites in low-resource settings.[10,11] Integrated reconstitution technologies—in which multiple liquid or dry vaccine components are packaged within the same primary container and mixed within the device prior to administration—can simplify the preparation process and reduce the risk of errors, but can also be costlier.

Safety for recipients and health care workers. As noted above, some features that impart ease of use to containers and delivery devices—such as ready-to-use formulations—also increase safety of use. An inherent safety feature of oral vaccines is that they are administered without needles, and thus needlestick injuries and sharps disposal can be avoided. Another safety consideration is the use of packaging and delivery-device designs that reduce the risk of accidental injection of an oral vaccine, which can cause adverse events and render vaccination ineffective. This error has occurred with oral rotavirus vaccines, particularly those in packaging that appear similar to vaccines for injection.[12] The risk of injection precludes use of oral vaccine presentations in glass vials intended for delivery with a syringe with the needle removed.

Manufacturing feasibility. Manufacturing feasibility and cost are also important for selecting containers and delivery devices for oral vaccines. For vaccines that may be marketed to adult travelers as well as provided to infants in low-resource settings, different presentations—and different final manufacturing processes—may be needed. Polymer containers may have lower per-unit costs than glass vials and be easier to use, but since manufacturers are likely to have glass-vial-filling facilities in place, using an alternative fill-finish process will entail start-up costs, could require building or repurposing facilities, and might increase a company's technical burden and risks. For vaccines needing reconstitution, integrated reconstitution devices can simplify delivery but may increase manufacturing complexity and device costs. If a manufacturer is contracting with other companies for packaging or delivery components, having only a single source supplier is a risk, since a problem at this source could hold up the entire production process.

Immunization program suitability. Many characteristics that address program suitability overlap with other product requirements. For example, accurate dose preparation and measurement, as well as simple, controlled vaccine administration are desirable not only for ease of use but for program suitability in low-resource settings where health care workers may have minimal training. Use of a polymer squeeze tube as the primary container and delivery device increases safety, addresses ease of use, and reduces packaging volume—all of which contribute to program suitability. In some instances, however, contradictory needs are at play. Single-dose presentations offer advantages in ease of use, as they do not require measurement of doses; however, they can increase manufacturing costs and cold chain storage volumes. Multi-dose presentations reduce space needed in the cold chain, but they increase vaccine wastage, particularly if the vaccine is at risk of contamination or is not stable for more than one immunization session after opening.[13] Tradeoffs such as these must be assessed in determining the optimal primary container for a new vaccine. Vaccine manufacturers as well as developers of packaging and administration components can get feedback on the suitability of proposed presentations of vaccines in development from the Immunization Practices Advisory Committee's Delivery Technologies Working Group and from the WHO prequalification group.[14,15]

Cost containment. Immunization program managers should ideally assess the overall program cost to deliver a vaccine in different presentations, in addition to vaccine price itself. Some technologies may increase safety or ease of use, but likely will increase vaccine purchase costs and the burden on the cold chain, so these attributes must be balanced in selection of a vaccine presentation.[16,17] Developers will want to design primary containers and delivery devices with the needs of manufacturers and immunization programs in mind, in order to maximize suitability while minimizing costs. For example, for polymer tubes, a multi-mono-dose configuration—in which multiple, conjoined, single-dose containers share a single label and VVM—can reduce manufacturing costs and demands on storage space.[7] However, this approach requires a design that prevents users from removing a single container without the label information.

Summary

In summary, oral vaccines against bacterial pathogens such as *ETEC* and *Shigella* that cause diarrhea in millions of children in low-resource countries could save lives and reduce the burden of serious illnesses. But creating efficacious vaccines is just the first step toward this goal. New oral enteric vaccine candidates must be buffered against stomach acid, formulated in minimal dose volumes, filled into containers that protect antigens and adjuvants but minimize the load on the cold chain, and can be safely administered in the correct dose by minimally trained vaccinators working in challenging environments—all within the constraints of manufacturability and attention to cost. Product designers who take these features into account in their development processes will be able to position new oral vaccines for implementation in routine immunization programs, and these programs in turn will achieve optimal vaccine impact.

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