CLINICAL TRIALS AND TRANSLATIONAL MEDICINE COMMENTARIES

Desirable Attributes of Vaccines for Deployment in Low-Resource Settings

DEXIANG CHEN, DARIN ZEHRUNG

PATH, Seattle, Washington 98121

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ABSTRACT: A number of product development partnerships are actively developing new vaccines to combat infectious diseases in developing countries. To be effective, the products under development should not only be safe, efficacious, and affordable, but they should also have additional desirable technical attributes, including enhanced stability, efficient packaging, and improved ease of delivery. New technologies are now available to achieve these attributes; however, many of the technologies have yet to be adopted by the vaccine industry. This commentary discusses the opportunities and challenges associated with advancing such attributes, especially vaccine thermostability and dose sparing strategies, and the critical issues that must be addressed to bridge the gap between technology development and product development. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:29–33, 2013

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INTRODUCTION

In the past decade, there has been a dramatic increase in global efforts to introduce existing vaccines and develop new vaccines for combating infectious diseases in developing countries. Broad support and participation from philanthropic institutions, academia, industry, and national as well as international governmental and nongovernmental agencies have enabled these efforts. With the endorsement of the Global Vaccine Action Plan by the World Health Assembly in May 2012, the momentum is likely to extend and accelerate through the next decade and beyond.

Investments in vaccines and immunization have produced enormous returns in global public health. The number of children under 5 years of age dying each year has declined globally from more than 12 million in 1990 to 7.6 million in 2010.[1] Worldwide, poliomyelitis is on the verge of eradication, expanded immunization coverage from 2000 to 2010 has resulted in a 74% reduction in mortality from measles,[2] and the 2010 introduction of a new conjugate vaccine specifically designed for sub-Saharan Africa has made controlling the meningitis A epidemic in the region a realistic prospect.[3] With the recent global introduction of pneumococcal and rotavirus vaccines, significant reductions in mortality from pneumonia and diarrheal diseases are also expected in the coming years.

A number of product development partnerships (PDPs) are actively developing vaccines for a range of disease targets including malaria, tuberculosis, and AIDS as well as diarrheal and respiratory diseases. However, success for the PDPs requires more than just developing products that are safe and efficacious. It also requires the development of products that can be deployed to the right place, at the right time, and in the right condition. These vaccines should ideally have specific product attributes such as enhanced stability, compact packaging, and improved ease of use—all of which are important for the efficient and effective delivery of vaccines.

The purpose of this commentary is to discuss the implications of enhanced thermostability and dose-sparing strategies for developing affordable vaccines intended for deployment in low-resource settings.

THERMOSTABILITY

Vaccine "thermostability" signifies that the vaccine is stable at temperatures that fall outside the

Correspondence to: Dexiang Chen (Telephone: +206-302-4692; Fax: +206-285-6619; E-mail: dchen@path.org)

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"standard" cold chain temperature range (i.e., 2°C–8°C). The positive impact of thermostable vaccines has been documented for the global eradication of smallpox in humans and rinderpest in cattle.

By the 1950s, smallpox was very much under control in the United States and Europe because of the widespread success of campaigns with vaccines that were strictly dependent on the cold chain. However, the disease still caused two million deaths per year globally. A turning point in the effort to eradicate smallpox worldwide came a few years later when Leslie Collier developed a "heat-stable" smallpox vaccine using a key stabilizer, peptone, and a freeze-drying process. The vaccine was stable for months to years at 37°C,[4] enabling the World Health Organization (WHO) to initiate its global smallpox eradication campaign in 1967. During the next 10 years, the campaign deployed thousands of healthcare workers to remote areas of Africa and Asia carrying the "heat-stable" vaccine in their bags to conduct immunizations.

Similarly, rinderpest was a deadly disease of cattle that caused repeated pandemics in the 18th and 19th centuries. The effort to eradicate the disease started in the early 1900s but was not fully achieved until a century later. The availability of a new "heat-stable" formulation of a preexisting vaccine in the early 1990s triggered a global eradication campaign in 1994 by the Food and Agriculture Organization of the United Nations.[5] The dual effort of developing a thermostable rinderpest vaccine and mobilizing farmers to vaccinate their own cattle helped to extend the reach of the campaign to all corners of the world, which raised the overall coverage rate and ultimately led to the eradication of the disease as declared in 2011.

Numerous studies have shown that the tail end of the cold chain is unreliable, with regular temperature excursions—either too cold or too warm.[6] In many developing countries, immunizations are routinely carried out in settings other than healthcare clinics, requiring healthcare workers to travel to villages and other remote locations to perform immunizations. Currently, vaccine vial monitors and the "shake test" are used to determine whether vaccines have been exposed to excessive heat or freezing temperatures. Thermostable vaccines would provide an additional level of "insurance" on the quality and potency of vaccines during cold chain breaks and help to ease logistics for outreach beyond the peripheries of the cold chain.

In the last few years, there have been tremendous efforts to advance stabilization technologies that could aid the development of vaccines with enhanced thermostability.[7,8] These advances include new tools for characterizing the structure of proteins to inform formulation design, biophysical assays for high-throughput screening of formulations, tools to analyze and optimize the freeze-drying process, and advanced novel processing technologies (e.g., spray drying) for developing thermostable formulations. There is a large body of literature that demonstrates the feasibility of stabilizing both subunit vaccines and live attenuated bacterial or viral vaccines using these new stabilization tools. If adopted by PDPs, these technologies could have an enormous impact on the cost, efficiency, and effectiveness of immunization programs in developing countries.

Despite these technological advancements, there exist few, if any, vaccines with enhanced thermostability in the marketplace or even in the late stages of clinical development. A disconnection seems to persist among the different stakeholders, including stabilization technology developers, vaccine developers, regulators, policymakers, and vaccine buyers. To remedy the situation, there is need for in-depth dialogue on the issues given below.

- **Priority vaccines for stabilization**: It would be ideal to make every vaccine thermostable for the duration of its shelf life. However, reformulating licensed vaccines, particularly older vaccines, may be unattractive because of the cost and time required to conduct laboratory, preclinical, and clinical studies to validate the safety and efficacy of the new formulations. It may be more practical to apply stabilization techniques to vaccines in the early stages of development. In addition, vaccines that are routinely used outside the clinical settings, such as human papillomavirus vaccine for immunizing students in schools, may be more important to stabilize than vaccines that are administered in a doctor's office. Stabilization technology developers and vaccine manufacturers need guidance from public health agencies on priority vaccines for stabilization.
- **Temperature targets**: Preferably, vaccines would be stable at "ambient temperatures" for all the countries in which they will be used. However, this may not be possible to achieve because ambient temperatures can range between −30°C and 40°C, depending on the location and time of day. Such a scenario would likely also require a package insert or label to specify the temperature range under which a particular vaccine is stable. A more achievable target might therefore be the controlled-temperature chain (CTC). In contrast to the traditional cold chain "refrigerated" temperature range of 2°C–8°C, the CTC specifies a broader temperature range (e.g., 2°C–37°C) or a threshold temperature (e.g., <37°C) under which vaccines can be stored. It should be noted that vaccine freezing may be as widespread a problem as heat exposure. Agreeing on stability targets at