Vaccine 33 (2015) 3471–3479

Contents lists available at ScienceDirect

Vaccine

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

Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle-income countries

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ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 10 May 2015
Accepted 26 May 2015
Available online 6 June 2015

Keywords:
Thermostability
Cold chain
Freeze protection
Supply chain
System design

ABSTRACT

The need to keep vaccines cold in the face of high ambient temperatures and unreliable access to electricity is a challenge that limits vaccine coverage in low and middle-income countries (LMICs). Greater vaccine thermostability is generally touted as the obvious solution. Despite conventional wisdom, comprehensive analysis of the value proposition for increasing vaccine thermostability has been lacking. Further, while significant investments have been made in increasing vaccine thermostability in recent years, no vaccine products have been commercialized as a result. We analyzed the value proposition for increasing vaccine thermostability, grounding the analysis in specific vaccine use cases (e.g., use in routine immunization [RI] programs, or in campaigns) and in the broader context of cold chain technology and country level supply chain system design. The results were often surprising. For example, cold chain costs actually represent a relatively small fraction of total vaccine delivery system costs. Further, there are critical, vaccine use case-specific temporal thresholds that need to be overcome for significant benefits to be reaped from increasing vaccine thermostability. We present a number of recommendations deriving from this analysis that suggest a rational path toward unlocking the value (maximizing coverage, minimizing total system costs) of increased vaccine thermostability, including: (1) the full range of thermostability of existing vaccines should be defined and included in their labels; (2) for new vaccines, thermostability goals should be addressed up-front at the level of the target product profile; (3) improving cold chain infrastructure and supply chain system design is likely to have the largest impact on total system costs and coverage in the short term—and will influence the degree of thermostability required in the future; (4) in the long term, there remains value in monitoring the emergence of disruptive technologies that could remove the entire RI portfolio out of the cold chain.

1. Introduction

While vaccines have been integral to the dramatically declining rates of infectious disease morbidity and mortality enjoyed over the course of the last century, the health benefits of vaccines have not been shared equally across the globe. Since 2000, there has been a concerted effort to realize the full, equitable public health impact of vaccines in the process of meeting the Millennium Development Goals and the supporting goals of the Global Immunization Vision and Strategy (GIVS) and Global Vaccine Action Plan (GVAP) developed by WHO and UNICEF [1–3]. Three fundamental goals underlie the GIVS and many country-level immunization strategies: (a) increasing vaccine coverage: extending immunization to all children; (b) increasing vaccine effectiveness: ensuring that the vaccines delivered are optimally efficacious and simple to administer; and (c) minimizing the total system cost of immunization programs. Significant progress toward achieving these goals has been made by Global Alliance for Vaccines and Immunization (GAVI) Alliance Partners, including: an additional 440 million children immunized since 2000, which stands to prevent some 6 million future deaths and avert $63 billion in potential illness costs;

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http://dx.doi.org/10.1016/j.vaccine.2015.05.071

more equitable, accelerated access to new, innovative vaccines; and substantial reductions in vaccine prices [4–6].

Despite this, significant challenges remain. Some 20 million infants in GAVI countries, representing 26% of the birth cohort, still fail to receive all of their basic vaccines [7]. Further, the long-term financial sustainability of immunization remains a concern. The total cost of delivering immunizations in GAVI countries was approximately $2.2 billion in 2012, mostly funded through donors (Supplementary Information). With the continued increase of birth cohort size, continued rollout and introduction of new, more costly vaccines (rotavirus, pneumococcal conjugate [PCV] and human papillomavirus [HPV] vaccines) and the required investment in delivery systems to reach the remaining infants, the total cost of immunization programs is projected to increase to close to $4 billion per year by 2020 (Supplementary Information).

The temperature sensitivity of current vaccines, and the attendant need for a robust cold chain, suggests that improving vaccine thermostability could impact all three of the above goals. Development of fully thermostable vaccines could increase coverage by enabling the stocking of vaccines at facilities that do not have cold chain equipment (CCE) and by facilitating outreach. The development of such vaccines might improve efficacy by decreasing the probability of administering vaccines whose efficacy was impaired by heat and/or freeze exposure. Finally, total system costs could be reduced by decreasing vaccine wastage due to detected heat and freeze exposures, by decreasing the cold chain footprint, and by reducing the overall requirements for the vaccine delivery supply chain.

Unquestioned optimism about the value of increased vaccine thermostability led the Bill & Melinda Gates Foundation (BMGF), and the global public health community in general, to make large investments in improving vaccine thermostability. These investments have led to some benefits, including the development (if not the deployment) of novel freeze protection technologies and a gratifying move to better exploitation of the actual thermostability of existing vaccines through label changes that allow migration to controlled temperature chains (CTC) [8]. However, to date, these investments have failed to result in the development and deployment of any commercial vaccine product with improved thermostability. We believe the reasons for this failure are several, including: (a) lack of a systematic approach centered on the specific use conditions of specific products; (b) lack of strategic alignment between projects and unmet public health needs, or by the needs identified by those involved directly in vaccine delivery; (c) directing funds to academic approaches to technology development that were neither designed to develop a specific vaccine product nor informed by an understanding of the end-to-end research, development and launch costs and their relationship to the relative value of particular vaccine products; (d) inability to overcome technical challenges; (e) lack of attention to vaccine development issues and industry motivations and incentives; and (f) lack of understanding of total systems costs, and the impact that specific interventions could have on such.

2. Thermostability analytic process

An analysis was performed that was designed to better define the potential benefits of increased vaccine thermostability. The guiding hypothesis was that the probability of success—of impact—would be substantially increased by systematic end-to-end analysis of the value proposition for the development of specific technological solutions to increasing the thermostability of specific vaccines with specific use cases. This was done in the overall context of considering three critical, interrelated elements: vaccine thermostability itself, CCE infrastructure, and country-level vaccine supply system design (Fig. 1).

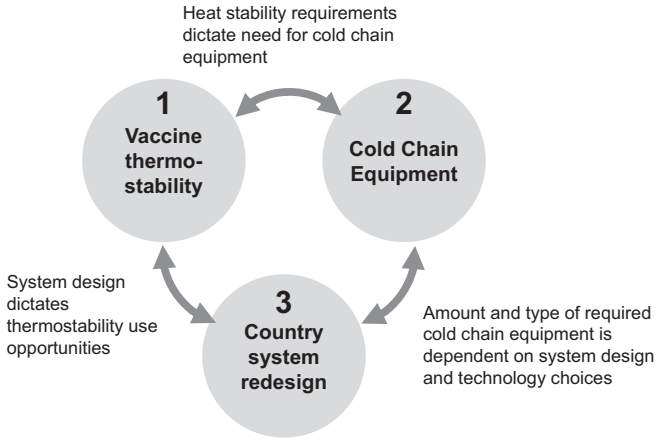

Fig. 1. Interrelated elements impacting cold chain performance.

In order to ground the analysis, we focused on four high priority vaccines: pneumococcal conjugate, inactivated polio (IPV), rotavirus, and pentavalent vaccines. These vaccines were chosen because: (a) they are relatively expensive and represent and increasing proportion of vaccine spending in LMIC; (b) they have or will have an outsized footprint in the cold chain; (c) they have high priority, given ongoing and/or imminent introductions; and (d) there is the potential for rapid impact (versus vaccines in the research and development pipeline that have not achieved proof of concept in humans). The analysis was rooted in real use cases including routine immunization and campaigns/special strategies, and focused on both heat and freeze as sources of damage.

An upstream landscaping was performed to assess the technical feasibility, research and development costs, and timelines of producing more thermostable vaccines. This involved generating catalogs of vaccines, thermostable formulation technologies, and attendant alternative administration system technologies where appropriate. These catalogs were used to analyze the risk, timing and potential benefit of each vaccine-technology pair to judge the probability of technical and regulatory success. Finally, candidate vaccine-technology pairs were identified that could reduce cost per dose and/or increase health impact.

In parallel, a corresponding downstream analysis was performed to assess the potential incremental benefit of the development of specific, more thermostable vaccines on total system costs, including effects on cost of goods, wastage, transport costs, cold chain equipment costs and healthcare worker costs. A model for the total end-to-end systems costs associated with delivering routine immunization vaccines was first generated, building on and integrating prior work from WHO, PATH, the Decade of Vaccines and others (Figs. 2 and 3; Supplementary Information). This model was then used to estimate the impact on the total system costs for the candidate vaccine-technology pairs identified in the upstream analysis. Integration of these work streams aimed to create an end-to-end analytical framework, founded on vaccine delivery needs and integrating vaccine discovery and development considerations, in order to define the value proposition for specific product development. The analysis focused heavily on economic impact—a function of the data at hand. That said, the impact of increased thermostability on coverage (e.g., ease of administration, potential for multi-day outreach, potential for offering vaccines at health posts without CCE), safety (e.g., delivery methods that require no sharps), and efficacy (e.g., impact of improved heat stability and freeze protection on efficacy) was integrated, qualitatively, into the analysis. The findings of the analysis are presented