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

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A B S T R A C T

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.

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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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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).

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 an 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.

Fig. 1. Interrelated elements impacting cold chain performance.
in three sections below: heat stability for vaccines used in routine immunization (RI), heat stability for vaccines used in campaigns and special strategies, and freeze protection. It should be noted that this analysis, although applied directly only to a small group of vaccines, actually provided clarity across a much wider group of vaccines and vaccine use cases.

2.1. Heat stability for vaccines used in routine immunization

Routine immunization in GAVI countries occurs continuously throughout the year, is mostly done in fixed health posts or via short outreach, and usually involves the administration of several vaccines together. Complete removal of all RI vaccines from the cold chain would lead to significant benefits in terms of coverage and total system cost. The fact that storage of RI vaccines is limited to health posts equipped with CCE forces some parents to travel large distances to immunization points or, conversely, requires that healthcare workers perform expensive outreach by traveling to remote villages. Removal of RI vaccines from the cold chain would enable storage at unequipped health posts and likely lead to increased coverage. It would also facilitate flexible use cases for RI vaccines, facilitating outreach to hard-to-reach populations. For some types of vaccines, such as live viral vaccines, thermostability could reduce the likelihood of lost potency and efficacy when exposed to high ambient temperatures. While most heat-damaged vaccines are thought to be identified through the use of vaccine vial monitors (VVM) and discarded, some are likely to slip through and be administered. Thus, a fully thermostable portfolio of RI vaccines might also have a positive impact on vaccine efficacy. Finally, a fully thermostable RI portfolio would likely provide a $125–150 million reduction in total system costs per year across GAVI countries (Fig. 4), driven by reductions in wastage (estimated at $15–40 million per year across GAVI countries, or 1–3% of total vaccine expenditures [Supplementary Information]) along with reductions in the cost of cold chain equipment (estimated at ~$110 million per year) [Supplementary Information]. However, fully capturing these benefits necessitates not just removal of almost all RI vaccines from the cold chain, but—critically—the removal of these vaccines for periods of time that are driven by the length of time vaccines typically spend at various levels of the country supply chain. Notably, the ability to harvest major benefits from increased thermostability of RI vaccines is driven by specific temporal thresholds, as outlined in Fig. 5 (see also Supplementary Information).

Certain benefits of thermostability can be achieved quite rapidly. RI vaccine stability outside of the cold chain (at 40 °C) for several days allows for reduced wastage and undetected loss of immunogenicity as well as, importantly, facilitating flexible
Fig. 4. Potential savings from fully stable RI vaccine portfolio: up to $150 M/year. Percentages represent percentage of 2020 total system cost. 1 Assumes closed vial wastage could be reduced by 20–60% depending on current VVM. Source: PATH Total Cost of Ownership working model from author correspondence with Project Optimize, PATH; “Cold Chain Equipment Manager,” Published January 2012, http://www.path.org/publications/detail.php?id=1569. Accessed July 2013 (extrapolated distribution of equipment for six countries to rest from expert interviews); see Supplementary Fig. 1 for wastage sources. CCE, cold chain equipment.

use cases such as use of RI vaccines in campaign and special strategy settings. Such short-term thermostability also allows simplification of outreach by eliminating the need to keep vaccines cool during day trips to remote vaccination sites (although there are logistical challenges in terms of avoiding vials being repeatedly taken out of refrigerators and returned).

A critical, larger breakpoint occurs around two months (at 40 °C), which is the typical maximum amount of time a vaccine vial spends at a health post before being used (Fig. 5). If RI vaccines were made to be thermostable for two months, CCE at health posts could potentially be removed, saving cost and reducing complexity. Vaccines could also be stocked in a broader set of health posts, potentially increasing coverage.

The third large breakpoint occurs around 12–18 months (at 40 °C), which is the typical amount of time vaccines currently spend across all levels of the supply chain in a standard 4-level supply system (Fig. 5). The actual amount of time is dependent on how efficiently the system is run—with significant investment in redesigning and speeding up of supply chains, this could potentially be brought down to 6–9 months in the future. Achieving this length of thermostability for the entire RI portfolio would enable removal of cold chain equipment at all levels of the supply chain, and a fundamental re-design of the supply chain, for example by merging with other supply chains. In turn, this would allow reaping of the full benefits of removing the RI portfolio from the country supply chain listed above (Fig. 4).

To identify ways to reach these stability thresholds, our analysis investigated a wide range of technologies for each of the four selected RI vaccines. These technologies included re-labeling to better reflect the inherent stability of vaccines, re-formulation with various excipients, diverse drying technologies, and novel formulations (e.g., microspheres, nanoparticles, microcrystals, silk proteins, and sugar glassification). Currently, these RI vaccines are far away from the required stability for removal from the cold chain [9]. There is a potential path to achieving about 6-month stability with rotavirus vaccine and IPV within the next 5 years by leveraging novel lyophilization techniques. It should, however, be noted that the products of drying technologies are broadly disliked by health care workers and discouraged by global policy-making committees and LMIC vaccine programs due to complexity and errors in reconstitution [10]. Such techniques will be very challenging to apply to PCV or pentavalent vaccines, due to the additional complexity of these vaccines—the multivalency of these vaccines being associated with an unavoidable “weakest link” problem in which the thermostability of the vaccine is hostage to the least thermostable component. While there are some emerging technologies that might achieve the desired stability for PCV and/or pentavalent vaccines, these technologies are highly nascent and speculative. Further, as there is no licensable correlate of protection for pertussis vaccine, the regulatory path for a new thermostable pentavalent vaccine might well involve clinical studies with an efficacy endpoint—a challenging and expensive proposition. Therefore,

Fig. 5. Common vaccine supply chain structures: quantization of benefits of thermostability for RI vaccines. 1 For majority of facilities; approximately 20% of facilities (most very remote) will need up to 3 months, given 100% buffer stock policies; assumes facilities follow WHO FEPD (first expired, first out) policies. 2 Potential to reduce overall time to 6–9 months through system changes (e.g., informed push, de-layering). Source: observations in three large GAVI countries; unpublished working data shared by the Clinton Health Access Initiative.
at this point in time, there is no clear way to achieve the minimum threshold of 2 months with the full portfolio.

There is broader complexity at work here as well. As there are multiple manufacturers of each of these vaccines, technologies for stability improvement would need to be made available to all manufacturers or else we would run the risk of seriously constraining our vaccine supply base by limiting the availability of the desired thermostable vaccine to a small set of suppliers with access to the novel process or technology. This would raise the bar considerably for maintaining a robust and secure vaccine supply base. Looked at in this light, the complexities involved in achieving sufficient thermostability across the RI vaccine portfolio appear substantially greater than the complexities involved in improving supply and cold chains (vide infra), strongly suggesting that: (a) a major effort aimed at generating and applying the technologies needed to remove all RI vaccines from the cold chain, either at the health post level or entirely, is hard to justify at this point; and (b) attention to improvements in the supply and cold chains is likely to have greater impact, at least in the near to mid-term.

If thermostability sufficient to remove the Expanded Program on Immunization (EPI) RI vaccine portfolio from the cold chain is not achieved, what about removal of a subset thereof? The cold chain would still need to be maintained, and it would be significantly harder to capture the above potential benefits. Cost savings would be minimal (Fig. 6). Two strategies could be imagined, neither having clear value: (1) storing a subset of vaccines outside of CCE at health posts; health posts equipped with CCE could store stable RI vaccines at ambient temperature, while continuing to keep heat sensitive vaccines in CCE. There would be limited savings from being able to downsize some CCE, however, because there is a large fixed cost component to CCE. It could also potentially relieve bottlenecks at national and regional levels, although these account for a very small fraction of cold chain spend. Further, if drying is used as an approach to increase thermostability, this must be balanced by the fact that keeping vaccines and diluents in separate vials means that the total product is larger, heavier and less convenient to use. (2) Stacking a subset of vaccines at health posts with no CCE: an alternate strategy would be to bifurcate the RI system, with heat-sensitive vaccines being stored only at health posts with CCE, and heat-stable vaccines being stored at a larger set of health posts. This could potentially lead to higher coverage for this subset of vaccines. However, such a system is not attractive, being complex to manage and access (with different trips to different health posts being needed to get the full complement of vaccines) and involving clear increases in expense. While excursions would be eliminated for

![Fig. 6. Potential savings are significantly lower if only a sub-set of the RI vaccine portfolio is thermostable. Percentages represent percentage of 2020 total system cost. Assumes closed-vial wastage is reduced by 20–60% for rotavirus vaccine and by 20–40% for IPV. Assumes 3-dose regimen of rotavirus vaccine with 17.1 cm³ per dose, and 1-dose regimen of IPV with cold chain footprint of 2.4 cm³; marginal cost per liter of CCE is $1.50–$2.00. Source: PATH Total Cost of Ownership working model from author correspondence with Project Optimize; PATH, “Cold Chain Equipment Manager,” Published January 2012. http://www.path.org/publications/detail.php?i=1569. Accessed July 2013 (extrapolated distribution of equipment for six countries to rest from expert interviews); see Supplementary Fig. 1 for wastage sources. CCE, cold chain equipment.]

![Fig. 7. 2020 cold chain equipment market segmentation: evenly split between on-grid and off-grid facilities. Based on baseline volume of 400 cc per fully immunized child; includes India. “Moderate mains”: at least 8 h per day, longest power cuts <48 h.]

| Potential cost savings with 2 stable vaccines (IPV and rotavirus vaccine) |
| Annual cost savings¹ | US $, M |
| Reduced wastage³ | 5-15 | <1% |
| Downsize Health post CCE² | 6-8 | <1% |
| Downsize CCE at upper levels | -1 | <1% |
| Total | 12-24 | ~0.1% |
those vaccines that were made stable, there is a risk of increasing excursions for non-stable vaccines due to added complexity of cold chain management.

It is acknowledged that the above analysis may not fit with the general intuition that any increase in vaccine thermostability is bound to be desirable. Thermostability in the range of days to weeks does in fact always have the potential to decrease wastage as well as allow for flexible use cases. In this vein, RI vaccines find important use in campaign and outreach settings. There is thus clear value documenting and exploiting the actual thermostability of existing RI vaccines. Further, while the benefits of reformulating existing RI vaccines to increase thermostability to serve these purposes are unlikely to outweigh the considerable costs involved in development and re-approval, the value proposition is quite different for new vaccines. There is clear benefit to ensuring that all high priority vaccines in development have their “early zone” (days to weeks) thermostability maximized, and to ensuring that the degree of such thermostability is clearly defined and included in the label.

The results of our analysis question the value of a major investment effort aimed at the development of high risk, disruptive technologies that could obviate the need for significant elements of the cold chain across the full RI portfolio. Such an effort is difficult to justify at the present time with the available landscape of technologies and, given past experience, investing in technology development not tied to a specific product is not recommended.

However, we recognize that targeted investments will be critical for achieving long-term thermostability goals. With that in mind, we recommend: (1) ensuring that labels for existing RI vaccines reflect their true thermostability in order to enable flexible use cases such as outreach and campaign use in specific geographies/situations. (2) Building and documenting heat stability into the development path of new vaccines to decrease wastage and enable flexible use cases. This includes defining—and potentially providing—the range of incentives that would encourage manufacturers to consider optimizing these aspects for priority vaccines currently in development. (3) Making seed investments in technologies with a high probability of technical and regulatory success to get appropriate threshold increases in the thermostability of specific RI vaccines. (4) Continuing to monitor the emergence of disruptive technologies with a view to moving the RI portfolio to greater heat stability when feasible. (5) Only limited investment in reformulating existing products until there is a line of sight to stabilization of the full RI portfolio.

2.2. Heat stability for campaign and special strategy vaccines

The above analysis of thermostability issues with RI vaccines has important implications for campaign and special strategy vaccines—and here it is useful to note that the campaigns that rid the world of smallpox and rinderpest were done with highly thermostable vaccines [11,12]. Vaccine campaigns (and special strategy immunization platforms) usually only involve 1–2 vaccines at a time and are of limited length, typically from a few days to one week. Thus while extended thresholds of stability are needed before major impacts are expected from increasing RI vaccine thermostability, this is not the case for campaign vaccines. As a result, better documentation and exploitation of the existing thermostability of such vaccines—enabling vaccine use at ambient temperatures in a controlled temperature chain (CTC)—can enable the administration of longer campaigns without the need for cold storage, thus making it easier to reach remote populations and increase coverage. Further, increased stability and leveraging of CTC can reduce the administrative burden on campaign workers. Evidence from a CTC pilot in Benin suggested reductions in both the administrative burden of health care workers as well as in cold chain costs. A modeling effort based on a larger sample in Chad suggested a 15% reduction in administrative burden as the result of setting up a CTC, along with a 79% reduction in cold chain costs [13].

To unlock the value inherent in CTC migration of these vaccines, there is a need to define and create market incentives to make CTC development attractive for vaccine manufacturers, to continue pilots to change behavior by demonstrating the benefits of CTC migration. Close attention will need to be paid to two issues: (a) the need for novel VVMs, as current VVMs are designed for vaccines kept in the cold chain and measure cumulative heat exposure. Vaccines in the CTC will require both cumulative and threshold VVMs because they will be handled outside of the cold chain. (b) The fact that optimal value will only be harvested when the temperature use range of the product label matches the actual thermostability of the product.

In addition to being able to easily unlock the benefits of incremental increases in campaign vaccine thermostability, the differences between RI and campaign style vaccine use cases outlined above also suggest that, for campaign vaccines as opposed to RI vaccines, there is likely to be considerable value in investing in the reformulation of specific, single campaign vaccines for increased thermostability. There is no need for the concerted development of a full portfolio of campaign vaccines past a specific threshold of thermostability in order for coverage and total system cost benefits to be unlocked.

2.3. Freeze protection

While in the cold chain, vaccines are frequently exposed to freezing temperatures, both in storage and in transport [14]. Although the real health impact of freezing on vaccine efficacy is unknown, it may well be underappreciated. Pre-clinical immunogenicity studies suggest that alum-adjuvanted vaccines are especially sensitive to freezing-induced degradation of immunogenicity (>80% reduction in some cases; unpublished data from PATH Freeze Protection Lab). Simple, cheap technological solutions—in the form of excipients with cryoprotective properties that are already approved for human parental use—are available [15].

For vaccines under development, the rational path forward is clear: cryoprotection should be built into the development pathway at the level of the TPP. As such, engagement and collaboration with vaccine manufacturers on this topic should be a priority. Secondly, freeze protection is a case where “retrofitting” existing vaccines may represent a high value. For example, if even 1% of PCV were compromised by freezing, the cost of delivering ineffective doses would cover the cost of re-formulation within a few years. However, such retrofitting would depend on there being incentives for manufacturers to pursue such reformation (e.g., preferential treatment by GAVI, and partnering to cover costs of reformation and regulatory submission). And finally, to justify these efforts, it will likely be critical to generate compelling data on how often vaccine freezing takes place, and what the loss of immunogenicity due to such freezing actually is.

2.4. Summary

Thermostability requirements and benefits vary by vaccine use case. The ability to harvest major benefits from increased RI vaccine heat stability is driven by specific temporal thresholds that are dependent, in turn, on the design of supply systems. Surprisingly, cold chain costs actually represent a relatively small fraction of the total system cost for RI vaccines—making it hard to justify large increases in expenditures for improving vaccine thermostability in order to provide savings on cold chain equipment expenditures. While considerable savings could indeed be achieved if the entire
RI portfolio could be removed from the cold chain for the minimum 2-month threshold, this is not possible with current technologies. For the present, there is clear value in defining the actual thermostability of both RI and campaign vaccines and including these data in their labels. There is also clear value in prospectively addressing thermostability issues (both heat and freeze sensitivity) for new vaccines at the level of the target product profile (TPP)—particularly for the temporal breakpoints described above. For campaign vaccines, enabling migration to CTC can provide substantial benefits quickly and at a relatively low cost.

3. Cold chain equipment analytics

Given the current challenges for wringing significant benefits from increasing the thermostability of the RI portfolio, addressing cold chain challenges—at the level of CCE infrastructure and country vaccine supply system design—appears to be a less risky and more cost-effective strategy to increase vaccine coverage, at least in the short term. A more informed focus on delivery systems, and specifically on the cold chain, should enable the community to meet goals for increasing vaccine coverage while minimizing overall costs. Historically, cold chain interventions have been partially constrained by lack of clear data on CCE performance. This has led to countries, global bodies and suppliers making critical decisions based on anecdotal information. To address this, a diagnostic was conducted to uncover key CCE challenges. The diagnostic included interviews with global experts on cold chain, health systems, and country infrastructure, in-depth country research to understand health system structure and evolution and to assess user needs, extensive modeling of facility catchment and electrification and cold chain inventory, and supplier research and assessment of the economics of key technologies.

This diagnostic revealed that ∼17% of facilities targeted for CCE are unequipped, that a further ∼17% of installed refrigerators are non-functioning, and that much of the rest suffer from significant technology flaws, including high operating costs and poor temperature control [16]. Combatting these problems will involve: improving the understanding of user needs (especially how these vary within and across countries); enhancing the management of suppliers, including providing clear TPPs; expanding in-country expertise on how to set up and manage cold chain systems; and addressing the projected funding gap of $350 million from now to 2020 [17]. These issues are explored in greater detail below.

3.1. Equipment needs and market segmentation

Additional cold chain funding will need to be targeted at specific facility needs. Two major factors drive the need for a specific type of CCE at a health post: electrical grid access and required refrigerator capacity. For the first time, to our knowledge, detailed in-country data on user needs and implications have been gathered through country visits, health post observation and in-depth interviews with EPI managers and health post healthcare workers. An estimated 50% of target health posts are on-grid, with at least 8 h of electricity per day (Fig. 7). Based on current trends, this proportion will not change dramatically in the coming years. 2 This segment of the market is best addressed with ice-lined refrigerators. There has been confusion as to the amount of holdover time (time for temperature maintenance in the absence of energy input) required, but the current analysis indicates that for this segment power cuts very rarely exceed 48 h: ∼3 days holdover should be sufficient for the vast majority of on-grid health posts (Fig. 7). Some other critical but relatively simple improvements will also be required for existing products (e.g., built-in voltage regulators to avoid compressor burnout, and user-independent protection from freezing).

The ∼50% of health posts that remain off-grid (either fully or functionally), have traditionally been serviced through gas-powered absorption refrigerators or, more recently, solar battery refrigerators. However both these technologies have proven to be unreliable, and in the case of absorption refrigerators have large operational costs for fuel [16]. Several new technology options are emerging, including battery-free solar direct drives, passive devices that can keep cool for up to 30 days with a single load of ice, and thermoelectric devices that leverage the Peltier effect to create a cooling device with no moving parts. The two latter technologies are limited in capacity to below 15 L, but we estimate that at least 60% of functionally off-grid facilities will require 15 L or less [16]. These facilities are therefore good candidates for passive and thermoelectric devices, whereas larger off-grid facilities are best served with solar direct drives (although it would also be possible to service all off-grid facilities with solar direct drives). A tailored approach to facility needs could equip all target facilities with functioning, optimal equipment, but requires closing the funding gap of $350 M [17].

3.2. CCE supply-shaping interventions

Incentivizing the production of optimal CCE will be key to improving performance and lowering cost. Recently, WHO, GAVI, UNICEF and BMGF collaborated to create TPPs for each of the key CCE technologies in order to establish design parameters and costs for addressing market needs [18]. Several manufacturers have expressed both willingness and ability to meet these TPPs. Ultimately, the aim is for these TPPs to be worked into pre-qualification requirements.

Another important intervention to shape the supply of CCEs is to work with manufacturers to guide the design and manufacturing of new products to reduce prices. For example, we estimate that the price for a typical solar direct drive refrigerator can be reduced significantly through a combination of increased scale and improved product design. Such manufacturing collaborations will help ensure facilities have affordable products that match their needs.

3.3. Country decision support

Countries vary widely in terms of their infrastructure, and therefore their CCE needs. For example, India mostly has large on-grid health posts [19], whereas Tanzania is almost fully off-grid with very small health posts. Therefore, it is critical to help countries make nuanced decisions based on a robust analysis of their local needs. This should involve creating a CCE inventory, assessing current and future facility needs, evaluating and selecting various equipment types, and applying for funding and procurement support including ensuring appropriate systems and budgets for installation and maintenance.

Going forward, plans should be created and implemented for targeted support to countries with the ability to shape the CCE market, including India, Tanzania, Nigeria, Ethiopia, Uganda, DRC

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2 Several large investments in electricity have been announced in sub-Saharan Africa (The White House, “Power Africa: Fact Sheet,” June 30, 2013, http://www.whitehouse.gov/the-press-office/2013/06/30/fact-sheet-power-africa. Accessed July, 2014), but the focus is primarily on generation rather than expanded grid access, and most investments will anyway take 10+ years to bear fruit.

3 Assumes a volume requirement of 400 cc per immunized child, which includes actual vaccine volume as well as ancillary factors such as buffer stock, seasonal variations, wastage, and packing efficiency.
3.4. Funding and procurement

CCE is a relatively small portion of routine yearly immunization costs (~4% when vaccine costs are included [Supplementary Information]). Cost reduction, especially for newer improved technologies, is important to ensure that countries do not face distorted incentives. Currently, funding and procurement for CCE is very disjointed, leading to high prices, lack of transparency, fragmented messaging to suppliers, and limited ability to shape the market and influence country decisions. However, over 80% of funds come from donors [17], thereby presenting an opportunity to influence decision-making toward increased consolidation and transparency. We estimate that an extra $650 million will be required from now to 2020, assuming current procurement patterns continue, but here is potential to reduce this gap to $350 million if market-shaping interventions are successful [17]. Going forward, the community should continue its efforts to define alternate funding and procurement mechanisms to alleviate these issues, and to engage donors to fill the funding gap.

There is a clear continued need for CCE over the coming decade. The cold chain today suffers from challenges that are relatively affordable to overcome, particularly when compared to the cost of some of the thermostability changes discussed earlier. Thus a better understanding of facility needs and investment in products that meet them will be a crucial part of improving vaccine delivery in the near future.

4. Country vaccine supply design

Vaccine thermostability needs and CCE infrastructure needs are ultimately grounded in the overall design of country immunization supply systems. Most countries still rely on antiquated 4- or 5-level supply chains that were designed in the 1960s and 1970s, and have not been thoroughly revisited since. These systems are frequently slow, burdensome and unreliable, and it often takes a year or more from the time a vaccine enters the national stores until it gets used (Figs. 5 and 8). This drives up the required thresholds for thermostability, and also increases the necessary cold chain capacity since large buffer stocks are kept at each level.

The way that vaccines are delivered to lower levels of the supply chain provides a critical lever for change. In many countries, replenishment of stocks typically takes place by health posts sending workers to pick up vaccines from upper levels of the supply chain. This is in contrast to some more innovative models where the stocks are pushed down to lower levels of the supply chain in a data-driven way that takes into account existing stocks, typical use patterns, and estimated levels of wastage factors. Finally, there is an opportunity to re-think the role of private parties in the vaccine supply chain. For instance, using private distributors can help leverage existing channels and reduce the need for additional public investment. As country systems improve, the key temporal thresholds for vaccine thermostability might well decrease.

5. Summary

These analyses of the interrelated elements of vaccine thermostability, cold chain technology and country level supply system design led to findings that were surprising (the rather small relative cost of the cold chain—expected to decline further as equipment reliability improves; the specific duration thresholds required to unlock the benefits of vaccine thermostability) as well as expected (the value of migrating to CTC for campaign vaccines; the fact that unlocking the value of increased thermostability for RI vaccines is more complicated). Key recommendations, aimed at optimizing the public health impact of vaccines and fulfilling the global health equity agenda, that follow from these analyses include: (1) the full thermostability of existing vaccines should be defined and included in their labels; (2) for new vaccines, thermostability goals (including both heat and freezing stability) should be addressed up-front at the level of the target product profile; (3) improving

![Fig. 6. Time vaccines spend within country before use. X-axis: months, Y-axis: % vaccines. Countries blinded for confidentiality (all sub-Saharan). ](image)

Source: Unpublished working data shared by the Clinton Health Access Initiative.

and Ghana. These countries represent 30–50% of demand for each major CCE technology segment [16]. In addition, a lighter-touch model should be created for other countries, including easier access to up-to-date technical information and clear tools to evaluate technologies and total system cost implications.
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 vaccine 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.

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Appendix A. Supplementary data

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References