Closing the Global Immunization Gap: Delivery of Lifesaving Vaccines Through Innovation and Technology

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Objectives After completing the article, readers should be able to:

1. Review challenges of immunizing children in resource limited settings.
2. Discuss current successes and limitations of operational strategies in the development and deployment of vaccines to the areas of greatest need.
3. Introduce innovative approaches and future interventions to address key logistical challenges encountered with vaccine delivery in developing regions.

Abstract

One of every 5 children does not receive basic vaccines because of concerns related to storage and delivery in resource limited countries. Transporting vaccines over long distances in extreme temperatures is a common challenge. Issues that involve production and formulation, delivery technologies, cold chain logistics, and safety factors need to be addressed to properly adapt vaccines to resource constrained settings. Current successful field interventions include United Nation Children’s Fund cold boxes, which are used to store and distribute vaccine in disaster struck areas, and vaccine vial monitors, which allow health workers to gauge whether vaccine is still usable in areas with unreliable electricity and refrigeration. This review aims to provide a general overview of innovative approaches and technologies that positively affect vaccine coverage and save more lives.

STRENGTHENED INFRASTRUCTURE TO GET VACCINES WHERE THEY NEED TO BE

By preventing up to 3 million deaths and protecting more than 100 million lives from illness and disability, vaccines are one of the best investments in health. (1) Aggressive efforts against polio have decreased polio burden by 99.8%, and complete eradication would save an estimated US $50 billion by 2035. (2) The

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ABBREVIATIONS

CDC Centers for Disease Control and Prevention
DTP Diphtheria and tetanus toxoids and pertussis
PATH Program for Appropriate Technology in Health
WHO World Health Organization
VVM Vaccine Vial Monitor

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Expanded Programme on Immunization has contributed enormously to reduce the burden of debilitating vaccine-preventable diseases, such as measles, diphtheria, pertussis, tetanus, and polio. Vaccines have the ability to save and transform lives, allowing children to grow up healthy, attend school, and improve their earning potential. Simply put, vaccines create wealth for the world’s poorest regions, where infectious diseases account for almost half of all deaths. (3) However, 22 million infants are still not fully immunized with routine vaccines. Despite significant accomplishments in vaccine coverage, challenges leading to limited access to vaccination parallel many of the barriers similarly encountered in achieving access to health care in many of these settings. These obstacles include political instability, conflict, social and economic isolation, and traditional antivaccine beliefs. The novel strategies presented in this brief review represent examples of modern technologies that could be useful in helping eliminate one significant roadblock to immunizing all children.

CURRENT SITUATION AND CHALLENGES

Reaching marginalized communities in remote areas, poor urban settings, and politically unstable regions continues to be an obstacle in narrowing the immunization gap. Successful distribution in these areas requires the transport of vaccines in extreme temperatures over long distances between health centers. Even with improved global Expanded Programme on Immunization coverage rates, an estimated 20% of the world’s children 5 years and younger do not receive the full 3-dose course of the diphtheria and tetanus toxoids and pertussis vaccine (a common proxy for childhood vaccination rates) as a result of high vaccine prices, weak health care systems, and technical difficulties. (4) Unfortunate examples are highlighted in Indian states, such as Bihar, where the 3-dose DTP vaccine coverage rates of 40% lag at least 30% behind other states, such as Tamil Nadu and Kerala. Disparities in these vaccine coverage rates exist in countries such as Ethiopia, where figures by the World Health Organization (WHO) are reported as high as 86%, whereas the Ethiopia Demographic and Health Surveys have documented rates as low as 37%. (5)(6) Countries eligible for discounted pricing through the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) have seen the total cost for purchasing a full course of Expanded Programme on Immunization vaccines (initially targeting tuberculosis, diphtheria, tetanus, pertussis, polio, and measles) increase from US $1.37 per child in 2001 to more than US $38.80 per child in 2011. (4) These figures do not factor in programmatic or waste-related costs. Administration of vaccines in large multidose vials minimized costs for older vaccines and permitted wastage rates that exceeded 50% in some cases. (7) This high wastage rate was deemed acceptable, and even encouraged, as an alternative to delaying the opening of a new vial and potentially missing an opportunity to vaccinate.

The launching of the Decade of Vaccines collaboration and the validation of a new Global Vaccine Action Plan require a reenergized global effort to ensure increased political support, improved vaccine delivery, strengthened research and development of new vaccines, better supply security, and increased affordability. (8) The Decade of Vaccines collaboration represents a straightforward vision for major international multilateral organizations to work together to meet the challenge of achieving universal access to immunization set forth by the World Health Assembly in May 2012. To adapt vaccines to poor settings, critical topics to be discussed are production and formulation, delivery technologies, supply chain logistics, and safety factors. These innovations will play a central role in advancing the use and delivery of vaccines to hard to reach populations.

BETTER VACCINE FORMULATIONS

Optimizing vaccine production methods will help in achieving stronger and broader immune responses, reducing adverse events, and improving stability in extreme heat and cold (Table 1). Traditional vaccines include components of infectious organisms, which provide stronger immune responses but at the cost of unacceptable adverse effects. Most newer vaccines consist of highly purified recombinant proteins, resulting in lower levels of immunogenicity. Consequently, new methods use highly purified synthetic adjuvants to provide enhanced protection without a generalized nonspecific immune response (Table 2).

VACCINE SUPPLY CHAIN AND LOGISTICS SYSTEMS

Vaccine Infrastructure and Thermostability

Countries have relied on the same storage and transport systems for more than 3 decades. High rates of wastage have

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of an Ideal Vaccine</th>
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<tr>
<td>• Single-dose regimen with prolonged duration of protection</td>
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<tr>
<td>• Simple to transport, store, and administer</td>
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<td>• Safe with no adverse effects</td>
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<tr>
<td>• Affordable and inexpensive</td>
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<td>• High stability against extreme heat and cold</td>
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been tolerated since traditional vaccines could be acquired in large quantities at a very low cost. With international vaccine prices reaching $5 to $7 per dose for vaccines against rotavirus, human papillomavirus, and pneumococci, there is clearly a new environment in maximizing efficiency. (9)

To minimize unnecessary wastage, new vaccines are packed in 1- and 2-dose vials bundled with syringes and other delivery devices. This results in a marked increase of price and amount of cold storage space required (Figure 1). The increased volume results in increased shipments and workload due to limited space in trucks and cold rooms. Increasing energy costs certainly compound pressure on the existing system.

Natural disasters, such as annual flooding, can cut people off from the outside world. Such events unfortunately are common in many resource limited areas and remind us of the need for a controlled temperature system, which is not reliant on electricity and adaptable to local health systems. Maintaining a 35.6°F to 46.4°F (2°C-8°C) cold chain can prove to be extremely difficult in these settings. Heat has the potential to damage vaccines in areas where power outages and fuel shortages can prevent refrigerators from operating, as well as settings where transportation of vaccine over long distances are required to reach remote populations. Aluminium adjuvant-containing vaccines, on the other hand, display an increased sensitivity to unintentional freezing, especially when vaccine is placed too close to the walls of ice-lined refrigerators or frozen ice packs. The effects of temperature damage are vast; suspected damaged vaccines are often discarded at great cost to the immunization program, whereas unnoticed damage results in children receiving potentially ineffective vaccine. Substantial advances in better passive cooling equipment, such as reengineered cold boxes, are being used to move vaccines in areas that require extended travel periods from 6 to 10 days without the risk of freezing. Both this and the prospect of battery-free solar refrigerators for use in isolated health centers and clinics are expected to save considerable expenses. The Centers for Disease Control and Prevention (CDC) offer a comprehensive toolkit on vaccine storage and handling that outline recommendations on cold chain maintenance and equipment, routine storage and handling, inventory management, and emergency procedures for protecting inventory. (14) Realizing that cost is a major barrier for poorer countries to achieve these best practice strategies, the CDC acknowledges that these are guidelines meant for interim guidance, encouraging practices that move toward full implementation of these recommendations. (15)

Laboratory and field studies have validated the feasibility of using certain vaccines outside the cold chain in ambient temperatures for a limited period immediately preceding dosing when used alongside vaccine vial monitors (Table 3), which is often the most logistically difficult and complex part of the cold chain to maintain. Early discussions with the manufacturer and countries with high meningitis disease burdens were instrumental in the success of achieving

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**Table 2. Role of Adjuvants in Vaccine Development (1)**

- Decrease the dose of vaccine
- Decrease the number of doses
- Shorten onset and prolong duration of response
- Induce mucosal immunity
- Enhance immune response in very young and old recipients

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**Figure 1.** Cumulative value and volume of vaccines used in routine childhood vaccinations in Ethiopia. (10)(11)(12) Reprinted with permission from Program for Appropriate Technology in Health. Building Next Generation Vaccine Supply Systems. December 20, 2013. All rights reserved. Available at: http://www.path.org/publications/detail.php?id=2175. (13)
TABLE 3. Vaccine Vial Monitors: Saving Money, Saving Lives (16)

A vaccine vial monitor (VVM) is a label that contains a heat sensitive material that is placed on a vaccine vial to register cumulative heat exposure over time. The inner square of the VVM is made of heat sensitive material that is light at the starting point and becomes darker with exposure to heat.

After an earthquake in Yogyakarta, Indonesia, much of the health infrastructure and electricity was lost for several days, resulting in nonfunctional refrigerators. Despite the heat, VVMs revealed that most vaccines were not damaged and were able to be used, resulting in the saving of 50,000 doses, which would have been otherwise needlessly discarded.

Since their introduction in 1996, more than 2 billion VVMs have been used. The World Health Organization (WHO) and United Nation Children’s Fund estimate that VVMs will allow health care workers to recognize and replace more than 230 million doses of inactive vaccine and to deliver 1.4 billion more doses in remote settings, saving at least US $5 million each year.

VVMs allow for use of a controlled temperature chain, which would achieve the following:
- Reduce costs and system constraints
- Reach more people
- Target appropriate groups
  - (Infants; hepatitis B birth dose; pregnant females: tetanus toxoid; and adolescent girls: human papillomavirus)
- Reduce the risk of vaccine freezing

Implementing web-based tools to track and report vaccine stock movements and collect data on immunizations given could positively affect accuracy and timeliness of vaccine stock records, reporting burden, and ability to track vaccines in case of a recall. Use of a digital immunization registry system using cell phone technology to help track the successful label revision of meningococcal type A vaccine in October 2012, stating the following: “In situations where maintaining the 2-8°C storage is not possible, both MenAfrivac™ and its diluents can be stored at temperatures not exceeding 40°C (104°F) for up to 4 days, provided the vaccine vial monitor has not yet reached its endpoint and the expiration date has not been reached.” (17) This controlled temperature chain strategy has been successfully used in other countries, such as Chad, China, India, Indonesia, Mali, and Papua New Guinea, and during the final legs of distribution. The examples of the new meningococcal vaccine and an experimental rotavirus vaccine in Table 4 serve to illustrate how the innovation of partnership can serve to overcome 2 of the biggest challenges in delivering vaccine throughout developing regions: the heat and high cost.

Information Systems and Immunization Logistics

For more than 30 years, ministries of health have created and maintained logistics systems that receive, store, transport, and refrigerate vaccines with the hopes that vaccines are available where they are needed. Regrettably, in many countries, half of all vaccine doses are never administered, and many more are wasted because of unintentional freezing, heat exposure, expiry, and other mishaps. (23) Innovative solutions are also required for inefficient management, paper-based tracking systems, and outdated policies that can disrupt vaccine delivery before they reach the people who need them. Many middle-income countries with sufficient electricity, telecommunication, and transportation often are using immunization systems designed before the advent of personal computers, the Internet, or cell phone networks. By efficiently managing information and storing vaccines, countries can enhance immunization logistics systems.

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TABLE 4. **Partnerships Leading to Significant Progress in Vaccine Delivery to the Field**

For more than a century, sub-Saharan Africa has been affected by meningitis outbreaks, with as many as 450 million people at risk. The hope of a vaccine became a reality in December 2010, when Burkina Faso became the first of 22 African “meningitis belt” countries to introduce an affordably priced meningococcal A vaccine for less than 50 cents a dose. Working together, the World Health Organization, Program for Appropriate Technology in Health (PATH), Serum Institute of India, and the Bill and Melinda Gates Foundation partnered to successfully produce an effective and affordable vaccine to curb this annual epidemic. By the end of 2012, it became the first vaccine approved to be kept at up to 104°F (40°C) for 4 days, making deployment easy for the local environment and leading to the successful vaccination of more than 100 million people thus far.

Accounting for more than 450,000 deaths in children younger than 5 years, Rotavirus is responsible for an estimated 37% of all diarrheal deaths worldwide in this age group. Two vaccines are currently licensed for use: RV5 (Rotaqev) and RV1 (Rotarix). Although these live attenuated oral vaccines have demonstrated lower efficacy in developing countries, they are expected to have a significant effect because of the high disease and mortality burden. (18)(19) Costs of these vaccines can often be prohibitive for lower-middle-income and least developed countries to self-finance, especially with an increased number of countries being phased out for funding eligibility by the GAVI Alliance. The Indian government, Bharat Biotech, and PATH have teamed together to deliver a new low-priced rotavirus vaccine (Rotavac, US $3 for a 3-dose regimen), which has demonstrated reasonable efficacy in a recent phase 3 trial. (20) Although further testing and implementation in real field settings are still required, the significant price decrease for an efficacious rotavirus vaccine has the potential to expand access to millions of children. The Meningitis Vaccine Project and the Rotavac collaboration are current examples of how successful collaborative efforts can bring together public and private entities to tailor an affordable vaccine suited for specific populations in need. (21)(22)

TABLE 5. **Field Questions to Be Addressed With Improved Information Systems**

- Who are the unimmunized children?
  - Which regions?
  - Can we find them?
- Where do we have the most wastage?
  - Why?
- Does one district have enough stock?
  - Is there enough to lend to another district for a short period?
  - If a specific lot needs to be recalled urgently:
    - Where is it?
    - Who are the children who received it?

Children, immunizations due, and vaccines received would allow information to be immediately available for better program management from the health center to the national level. Ideally, digitizing data at the point of contact with the patient would minimize staff time, errors, and delays and maximize accuracy and scalability. Some fundamental observations in the field that can assist in advancing these information systems are outlined in Table 5. The use of text messaging is even being piloted to monitor vaccine cold chain equipment to assess the benefits of remote alarm systems over traditional temperature loggers.

Current information can provide limited coverage data, stocking information from 1 to 2 months ago, but new systems will aim to provide up-to-date, pertinent data that can influence day to day decisions in national immunization programs. Streamlining systems within communities, within districts, and nationwide can result in fewer missed vaccinations, stronger public engagement, accurate demand forecasting, and stronger ability of policymakers to establish and adapt vaccination strategies to their setting.

**NEW DELIVERY TECHNOLOGIES**

**Safety**

Because vaccine recipients are healthy at the time of administration, any adverse event after immunization is highly scrutinized. This concern is further intensified when taking into account that hundreds of millions of children are immunized annually. As a result, rigorous safety evaluation measures will be applied to both the new vaccines and vaccine delivery technologies. An estimated 385,000 needle-stick injuries are reported by the CDC annually in US hospitals, whereas an estimated 2 million cases of needle-stick injuries occur globally, leading to considerable risk to health care practitioners. (24) Often, disposal of injection devices also serves as a challenge in resource limited areas. The WHO reports that approximately 16 billion injections are given each year, with vaccination representing 5% of this total. Unsafe injection practices in poorer countries have been attributed to 32% of hepatitis B cases, 40% of hepatitis C cases, and 5% of human immunodeficiency virus infection cases. (25) New delivery methods offer simple to use devices that improve safety and minimize immunization logistics.
Prefilled and Autodisable Syringes

Inexpensive, single-use autodisable syringes have been licensed and available for commercial use since the early 1990s (Table 6). Support for safe injection practices materialized after a joint WHO and United Nations statement recommending the use of autodisable syringes by immunization programs worldwide. (28) Prefilled autodisable syringes require no assembly or preparation and reduce vaccine wastage associated with multidose vials. These preparations are especially helpful for community health workers to bring along on their trips to poorly accessed regions, where they can deliver the tetanus toxoid vaccine to pregnant females and the hepatitis B birth dose vaccine to their newborn infants, because most pregnant females who live away from health centers deliver at home. New autoreconstitution injection devices with dried vaccine are under evaluation.

Neckel-Free Immunization

Concerns about the large number of vaccinations in infants and toddlers, as well as the significant problem of needle phobia in adolescents and adults, have driven the search for alternative and easier methods that involve needleless immunization. Current methods of needle-free vaccination include cutaneous and mucosal immunization techniques (Figure 2). Increased costs of these vaccine formulations must be weighed against savings gained with decreased logistics, injection supplies, and hiring of skilled personnel.

Intradermal Immunization

The skin, a vital component of the immune system, is enriched with an efficient network of Langerhans cells, which take up antigen and subsequently stimulate systemic (IgG and IgM) and mucosal (IgA) immune responses. (30) With reports of its use from the late 1930s, liquid jet injection is one of the oldest forms of needle-free immunization. (31) Liquid jet injectors generate a highly pressurized liquid stream that penetrates through the skin and can deliver all injectable vaccines at an intradermal, subcutaneous, or intramuscular level. Because vaccine spreads through a larger tissue volume compared with needle administration, jet injection may allow for a more pronounced and faster antibody generation before vaccine
degradation takes place. (31) These devices have had a long history of use and can deliver all injectable vaccines currently used in programs in developing countries at intradermal, subcutaneous, and intramuscular levels. Although the first-generation syringe jet injectors could allow for a rate of 1000 immunizations per hour, they fell out of favor in the 1990s because of concerns of cross-contamination. These injectors have since been modified to use disposable needle-free syringes. At full production scale, disposable syringe jet injectors may be comparable in cost to the current method if noninjectable delivery were to be decentralized via community health care workers, resulting in reduced program costs. Although further evaluation is necessary to address long-term protection, disposable syringe jet injectors could serve as an effective and feasible alternative to injectable formulations (Table 7).

### Mucosal Immunization

With 90% of microbial pathogens having a mucosal port of entry, mucosal vaccination offers protective immunity via locally secreted antibodies. In addition, these vaccines would be easier to administer, carry less risk of transmitting infection, and possibly simplify the manufacturing process, potentially increasing local vaccine production in developing countries. (35) Currently, internationally licensed mucosal vaccines used in humans exist for polio, typhoid fever, cholera, and rotavirus in oral forms, whereas one nasally administered influenza vaccine is being used in industrialized nations.

Because of its ease of administration, high patient compliance, and long history of use, oral delivery of vaccines is an attractive mode of immunization. The main challenges

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**TABLE 7. Liquid Jet Injection in the Global Context**

Disposable syringe jet injectors (DSJI) may play a critical role in global polio eradication efforts. Inactivated polio virus (IPV) would likely represent a preferred alternative to oral polio virus (OPV) because it is a killed virus and has demonstrated increased immunogenicity in areas where repeated OPV has failed to achieve adequate immunity in the community. Although IPV’s high cost (20 times higher than OPV’s cost) remains a major obstacle, it would be preferred to OPV because it contains killed virus (no risk of vaccine-derived virus transmission) and has demonstrated increased immunogenicity in areas where repeated OPV has failed to achieve adequate immunity in the community. (32)

- Investigators in Oman have found that using just 20% of the standard IPV by jet injection induced similar levels of seroconversion as intramuscularly administered IPV in 400 infants. (33)
- Although an earlier study in Cuba reported mild redness and induration in some infants, (34) 93% of parents in the Oman study preferred the DSJI method because of the simple observation that “the baby does not cry.”

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Disposable syringe jet injector use in action (Program for Appropriate Technology in Health, Patrick McKern. All rights reserved.)
faced by oral vaccines include gastrointestinal deactivation, high doses required, and the variability of clinical response. Because higher doses result in higher costs, one promising solution is the use of transgenic plant vaccines to minimize the need for refrigeration and allow inexpensive production. (36)

Dissolvable tablets, wafers, and thermostresponsive gels are under active development for oral and sublingual delivery. These formats transform into a viscous gel, enabling it to adhere better to mucosal surfaces, as well as provide protection from degradation caused by salivary enzymes.

In addition to being one of the main sites for airborne pathogens, the nasal route offers easier access to mucosal membranes. However, adjuvants are usually required for intranasal vaccines because of their short contact time and the limited use for those with active upper respiratory tract infections. (37) Other mucosa under evaluation for specific pathogens include ocular (herpes simplex virus), pulmonary (measles), and vaginal or rectal (human immunodeficiency virus) routes. (38)

FUTURE STRATEGIES TO ADVANCE INNOVATION

Scientific, commercial, and programmatic challenges are some of the key obstacles to clear to convince policymakers and manufacturers of the liability issues and feasibility of field implementation. Solutions will require increasing dialogue between the public and private sectors, adapting vaccine products and programs to the local context, and basing vaccine purchase decisions on immunization costs rather than price per dose alone. Another important issue that underlies global vaccine efforts relates to how much imperfection is acceptable. In areas with low mortality attributable to vaccine preventable diseases, such as the United States, we expect vaccines to have 90% or greater efficacy and to be delivered in a 100% effective manner. However, in resource limited areas, vaccines with lower efficacy have the greatest potential for large-scale effects, specifically related to the much higher rates of mortality, as seen with rotavirus. (39)(40) Furthermore, herd protective effects observed in reanalysis of field trials with oral cholera vaccine have revealed an amplified protective effect for both vaccinees and neighboring nonvaccinees. (41)

Future innovations are essential to continue moving forward in improving and expanding vaccine access—from production to protection. Implementation of computer and cell phone technologies to digitize health information systems provides a feasible method to improve registry management and maximize benefits of an efficient vaccine supply chain. Effective and cost-saving immunization programs can prevent and replace expensive “catch-up” schemes of outbreak responses. For it is only when affordable vaccines are delivered to the right place in the right conditions that they can save the greatest number of lives.

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