Summary Report

Prepared for the Board of the Global Alliance for Vaccines and Immunization

By the New Technologies Working Group of the GAVI Research and Development Task Force

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INTRODUCTION

The Research and Development Task Force (R&D T F) of the Global Alliance for Vaccines and Immunization (GAVI) appointed a New Technologies Working Group (NTWG) to examine how recently developed technologies could be applied to improve the effectiveness and efficiency of immunization programs in developing countries. The R&D T F had beforehand, through extensive consultations, identified three "Immunization Technology Agendas" and specific "Technology Solutions"[i]. These were:

Agenda 1. Decreased dependence upon and streamlining of the cold chain
- **Selected technology** – Sugar glass stabilization.

Agenda 2. Improved tools to measure immunization services performance.
- **Selected technology** – Non invasive (oral fluid) field assays to measure protective levels of tetanus antitoxin (and other antibodies) in infants and toddlers as an objective measurement of the performance of immunization services.

Agenda 3. Reducing infectious wastes and ultimately eliminating the use of sharps.
- **Selected technology** – Devices to "defang" syringes.

The GAVI Board approved the three technology agendas and requested the R&D Task Force to prepare a report on the selected technologies and make suggestions on how they could be implemented in an efficient manner[ii]. .

Under the chairmanship of Francis Andre, the NTWG divided itself into three subgroups to each produce a report on one technology area. The elected leaders for each subgroup were[iii]:
- Sugar glass stabilization; Ms Debra Kristensen
- Non invasive field assay: Prof. Niel Constantine[iv]
- Defangers: Dr. Bruce Weniger

Highly detailed reports outlining the background and the issues to be considered in the development and introduction of each of the technologies were prepared by the subgroups.

These reports are available on the web at:

http://www.vaccinealliance.org/home/Resources_Documents/policy_Technical/Accelerating_RD/priority_technologies.php

A summary of the findings is presented below.

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[i] GAVI RDTF Paper #4
[ii] Seventh GAVI Board Meeting, Stockholm, 11 March 2002
[iii] A full list of contributors is provided in the background documents.
[iv] Replaced Dr. Helen Lee

SUGAR-GLASS STABILIZATION OF VACCINES.Health Needs

Vaccine stabilization through the use of sugar- or composite-glassification offers a means to improve both the *effectiveness* and *efficiency* of immunization programs in developing countries. The following specific benefits are possible:

Protection of Vaccines from Heat and Freeze Damage

The quality of most vaccines is highly dependent on keeping them at appropriately cool temperatures. Vaccines such as oral polio and DTP rapidly lose their potency when left at tropical temperatures. Freeze-dried vaccines such as measles are even more fragile as they quickly deteriorate after reconstitution unless kept cool. Additionally, freezing destroys certain vaccines (including tetanus and diphtheria toxoids, hepatitis B and *Haemophilus influenzae* type B) and instances of freezing in cold chains are well documented.[1-7] When temperature damage goes unnoticed, children may receive ineffective vaccine.[8, 9] Protection will be assumed, however, which could further jeopardize the health of these children. Prevention of temperature damage through thermostable formulations can help ensure immunization effectiveness.

Reducing Cold Chain Costs and Logistical Requirements

Costs associated with the cold chain are estimated to amount to $200 million per year.[10] Managers of cold chains in developing countries wrestle against a number of challenges, including power failures, faulty or inefficient equipment, fuel shortages, shortage of ice-making capacity, and changes in equipment due to global environmental concerns.[11, 12] In the midst of these logistical problems, additional demands are being placed on the systems due to the continual introduction of new vaccines. Because they can be safely stored at ambient temperatures, thermostable vaccines will lower shipping, storage, and temperature-monitoring costs and logistics, and will increase cold chain capacity for other vaccines. Of course, complete elimination of cold chain equipment will not be possible unless all vaccines become substantially more heat-stable.

Reducing Vaccine Wastage

In this era of uncertain supply of key vaccines for developing-country immunization programs, vaccine wastage is an issue that is being closely monitored. Vaccine wastage currently occurs due to discard of vaccines that have been left out of the cold chain, discovered frozen, expired, or reconstituted and not used within the number of hours allowed. UNICEF has estimated that more than 50 percent of vaccine is wasted.[12] Mechanisms to reduce unnecessary wastage are highly desirable. The proposed thermostable vaccines can greatly reduce or eliminate vaccine wastage through prevention of temperature-damaged discards and extension of shelf lives. With some formats, elimination of the need for reconstitution can also be achieved.

Increasing Access

Many of the problems listed above are barriers to access to immunization services. The necessity of keeping vaccines within the cold chain limits outreach capabilities. Unnecessary vaccine wastage diverts funding that could be used on health care staff and facilities.

Proposed technology

Glass-forming sugars (such as trehalose and sucrose) and potentially other excipients can be added to vaccine formulations. As the vaccines are dried, glassy solids are formed that restrict molecular mobility and protect the actives. Dry glassified vaccine can be further developed into a variety of vaccine products with different routes of administration. The products envisaged can be stored without refrigeration for their entire shelf life.

Preclinical studies have demonstrated that this technology is promising for live, killed, conjugate and subunit vaccines (described in detail in the background document). For example: trehalose-stabilized DT vaccine has been shown to withstand 60°C for 1 year with no loss of activity, and measles vaccine has been stabilised to maintain activity for 2 months at room temperature (commercial vaccines lost 90% of their activity). Data demonstrating freeze-stability are available for glassified TT and influenza vaccines. In addition resistance to freeze-induced damage has been shown for trehalose-stabilised aluminium adjuvant.

- While extensive preclinical data exist, to our knowledge no clinical studies have been performed.

Important guidelines must be followed to ensure that appropriate vaccine formats and modes of delivery are selected for thermostable vaccines. Specifically, *the thermostable vaccine should not increase logistical complexity for national immunization programs and should not decrease safety for vaccinators or recipients*. For example, it is unacceptable to convert an existing liquid vaccine to a thermostable dry vaccine in a vial format. The resulting product would decrease safety and increase logistics via the reconstitution step and would not obviate the need for ice at the point of delivery if presented in a multi-dose vial as the thermostability characteristics of the vaccine would be lost after reconstitution. Priority must be given to formats that maintain or ideally improve upon existing logistical and safety standards

Development Plan

While there is optimism that thermostable vaccines can be achieved, multiple barriers to commercial availability exist and must be dealt with if these products are to become a reality for public sector immunization programs. From the perspective of a vaccine producer, barriers are likely to include lack of demand, lack of incentive to invest in low-margin vaccine products, substantial investment requirements, opportunity costs, perceived excessive risk due to the complexity of the intellectual property landscape, and potential

loss of market if resulting products reduce wastage during use. Potential incentives also exist for vaccine producers pursuing thermostable vaccine products including production efficiencies, reduction in shipping and storage logistics and costs during production and initial distribution, longer shelf lives for bulk and final product, and competitive advantages.

Advancement of thermostable vaccines is not proceeding and is unlikely to proceed without some measure of public- and private-sector risk sharing. Initial efforts should include achieving completion of clinical trials and, if successful, subsequent production scale-up with one or two priority thermostable vaccines. Ideally the efforts of such "forerunner" projects will demonstrate the possibilities to other industry partners.

The path to achieve technical proof-of-concept with a single vaccine would include the following steps:

1) Background research (technical, intellectual property, regulatory, etc.) and identification of priority vaccines and industry partners. Some of this work has already been carried out by the NTWG and other organizations, and is described in the background document.
2) Initial formulation, optimization of formulations, stability studies, and toxicology studies on new excipients.
3) Pre-clinical testing and clarification of regulatory issues.
4) Technology transfer (and required business agreements) if technology is acquired from a source other than the vaccine producer, establishment of production process, purchase of equipment if necessary, and production of GMP product for clinical trials.
5) Phase I, II, and III clinical trials. "Bridging studies" may be possible depending upon the product tested.

Because technical feasibility is probably not the major barrier to advancement of thermostable vaccines, other components of the strategic approach outlined in the detailed report should not be neglected by organizations pursuing these products. These include continued evaluation of the public health impact and commercial viability of proposed products, management of intellectual property issues, and characterization and development of the market.

The opinion of the NTWG is that of the currently available vaccines, multivalent vaccines[v] are prime candidates for stabilization. This was based on an initial attempt at prioritization of existing vaccines using the following attributes (not listed in order of importance): freeze-sensitivity, use in mass campaigns or supplementary immunization activities, potential to reduce cold chain needs for routine immunization programs if thermostable, potential for conversion from a freeze-dried multi-dose vial to a safer format, and price.

[v] Such as Diptheria-Tetanus-Pertussis-Hepatitis B- *haemophilus influenzae* type B (DTP-Hep B-Hib) vaccine and DTP-Hep B vaccine.

Please refer to the detailed document for a complete discussion of these issues.

Vaccines of importance to developing country immunization programs that are currently in development and not yet in clinical trials, are even stronger candidates for stabilization. It is also imperative that vaccine producers engaged in such research be either United Nations prequalified or deemed capable of such qualification.

Investment opportunity

Costs will vary depending upon the type of vaccine selected, the development status of the vaccine, stabilization materials used, required production and processing equipment, source of stabilization expertise, and types of clinical trials and other data required for regulatory approval. Assuming that appropriate industry partners can be identified, a substantial public sector contribution will be required if real progress is to be made with multiple vaccines from multiple suppliers. Of course, investments should be made in stages and progress reviewed to verify project worthiness as additional data are acquired.

Potential roles on behalf of the public sector include involvement as:

- A development partner and facilitator that can “push” the technology forward by directly conducting research, providing financial support, creating initial specifications, assisting with regulatory issues, or securing access to key component technologies for thermostable vaccines.
- A purchaser or influencer of demand that can assist with characterization and development of the market to “pull” the technology forward.

It is beyond the purview of the NTWG to suggest specific mechanisms for funding such a broad area of research and development. Ideally, projects will be undertaken with multiple stabilization technologies and multiple vaccine producers to spread risks and encourage competition. It is our hope that the information provided via the detailed document will serve to educate and guide those pursuing relevant vaccine stabilization technologies.

Budget:

During early discussions of the NTWG with members of the R&D TF, it was agreed that the resulting documents would not contain recommendations for specific funding mechanisms and budgets as such detail is best determined by implementing groups. The charter was to produce global strategies for each selected technology on behalf of the public sector.
At the request of the GAVI secretariat, approximate budgets were developed for the development of non invassive field assays and for the implementation of defangers.
For sugar-glass stabilisation, for which the technology is at an earlier stage of development and for which many parameters will influence costs. For this

reason it is felt that budget assesment should be performed by an implementation group.

The NTWG recommends that an implementation group be formed, tasked with elaboration of the business case, identification of issues such as intellectual property constraints, and elaboration of a budget for steps leading to proof of concept of the technology in the form of a clinical trial.
It is anticipated that such a task will require $50,000 and last six months.

In order to provide GAVI with an estimate of what a development plan leading to a phase 1 study might cost, the R&D Task Force has provided the following generic breakdown for a contract research program using an existing vaccine (eg DTP):
1. Preclinical formulation, and stability studies: 6-8 months, $350000 (includes analytics development).
2. Preclinical immunogenicity-stability studies: 6 months, $ 350000
3. GMP preparation, lead stability studies, GLP tox study: 12 months $ 1500000
4. IND preparation and phase 1 trial: $500,000

This cost of $2.7 million assumes a rapid ‘trouble-free’ development, which is highly optimisitic. A figure of $4 million is likely to be required to iron out development problems. This does not include time or cost for early research such as formulation optimisation, which can be lengthy but which may lead to a significantly superior vaccine. Given the very early stage of this research, and the many unknowns, it is not possible to provide a budget figure with confidence.

NON-INVASIVE FIELD ASSAY FOR TETANUS ANTITOXINS

The Working Group was asked to identify technologies that would offer a non-invasive means to assess the effectiveness of immunization programmes, while being appropriate for field use, as well as in laboratories that possess only basic capabilities.

Health Need

Programmes to immunize individuals, particularly those to immunize children in developing countries are many, but their ability to reach large numbers of persons, and the efficiency of the efforts are unconfirmed. Methods to actively monitor protection from infection after vaccination and to determine adequate antibody responses in vaccinees, currently include self-reporting or documentation at households. These methods may, however, not be sufficiently accurate and are labor intensive and costly. Additional methods to verify the efficiency of immunization efforts are needed to ensure that vaccinees, particularly children, are receiving adequate protection from vaccine-preventable disease.

Development of a test to rapidly and safely evaluate, under field conditions or at point of care facilities, what proportion of the pediatric population has received an effective vaccination regimen (e.g., immunization of DTP) is proposed. In addition, a test that can be performed without the use of an invasively collected blood sample, would address safety concerns regarding transmission of infectious agents through needlestick and other types of blood exposures. Such a test, as part of a coverage survey could be used to supplement and validate current DQA programmes while being safe for health care personnel.

Because the presence of antibodies to tetanus toxoid is rarely present in individuals who have not been vaccinated, the measurement of these antibodies would verify vaccination status. In addition, the identification of certain levels of antibodies would constitute verification of effective vaccination for the protection of individuals. Further, use of the assay in the field would enable identification of areas of sub-optimally immunized women at risk of maternal and neonatal tetanus.

Proposed Technology

Oral fluids, collected from the oral cavity, are composed of saliva and crevicellular fluid that is derived from blood and contains antibodies at a concentration proportional to the concentration in plasma, though reportedly between 400 and 1000 less concentrated. Oral fluid samples can be collected easily, with little instruction, and can be administered by a variety of health care workers without the need for special training. The utility and accuracy of oral fluid tests are exemplified by an FDA-licensed oral fluid assay for the detection of antibodies to HIV. A number of oral fluid collection devices are commercially available, and matched test kits have proven effective for the identification of antibodies to mumps, measles, and other vaccine-preventable

diseases. Finally, rapid test technology is clearly effective, and has been in use for detecting infectious diseases for over a decade. Rapid test technology, coupled with the testing of non-invasively collected oral fluids can be exploited to offer a test with attractive attributes for monitoring the response to vaccination. Such a test would use a collection device similar to those commercially available and be modified to identify specific anti-tetanus toxoid antibodies. Although a low-cost, simple test to detect tetanus toxoid antibodies is under development by PATH with support from UNICEF, it requires the use of sharp lancets to acquire fingerstick blood that can compromise the safety of others. The proposed test would permit monitoring the response to TT-containing vaccines, using oral fluid tests.

Advantages

The advantages of the proposed non-invasive assay are clear, and include (1) the elimination of sharp instruments to collect blood, (2) rapid turn around time for results, (3) the utility for point of care testing, particularly in areas where more sophisticated tests cannot be supported, and (4) a simple collection and testing procedure that can be conducted by a variety of health care workers who have limited training.

Development Plan

Prior to investing in R&D, a market analysis should be conducted to ensure that sufficient demand exists for a non-invasive test. If the results verify the importance of having a simple, non-invasive and rapid means to verify the effectiveness of vaccination programmes under field conditions, the Group recommends that such test development be pursued, most effectively through an RFA. This could be accomplished by providing funding to complete a “proof of concept” study. If encouraging results are obtained, pursuit of full test development should be undertaken.

It is envisioned, based on past experience, that the development of an oral fluid based rapid test would require about 2 years, and would entail:

A. Verification of demand (contract analysis of market need), and preliminary business case analysis. Estimated cost: $50,000
B. Proof of Concept: Estimated cost: $80,000; Time: 4 months; Task: collection of appropriate oral fluid/serum sample pairs to be used as calibrators for test development
C. Test Development: Estimated cost: $500,000 - $750,000; Time: 1-2 years; Task: assessment of different oral fluid collection devices: for their ability to effectively collect samples rich in crevicular fluid, modification of the blood tetanus test, evaluation of different rapid test formats, optimization of all test components, standardization, preliminary validation.
D. Test Validation: Estimated cost: $100,000; Time: 6 months; Task: collect large number of blood/oral fluid pairs for comparison, assess interferences, perform reproducibility and precision challenges, test standardization.

E. Manufacturing: Estimated cost: $15-25 per test.

Investment opportunity

Currently available oral-fluid collection devices cost under $10, and the oral fluids obtained by these methods are presumed suitable for the detection of antibodies to tetanus toxoid (i.e., they have been used successfully for the detection of antibodies to at least 5 infectious agents). Rapid tests, already proven effective for the detection of antibodies in oral fluids, might be easily adapted for the detection of protective levels of tetanus antibodies, thereby verifying effective immunization programmes. Therefore, the successful development of an oral fluid based test for tetanus is likely. It can be closely estimated that a rapid test would cost less than $10, bringing the total for collection and testing to about $20 per subject.

Risks:

The technical risks appear low, based on the previous success of oral fluid collection devices, rapid tests, rapid tests that use oral fluids, and the availability of effective blood tests for tetanus toxoid antibodies (that can be modified). The greatest risk is not in the development of an effective test, but in identifying a manufacturer who is willing to pursue its development and marketing. This is especially true since the market need for a non- invasive serological assay for tetanus toxoid antibodies is not known. Current estimates of need vary from 40,000 devices required per year for geographic coverage surveys, to orders of magnitude greater if applied globally for all individuals at risk and performed annually. The final cost will be volume dependent.

DEFANGERS

The GAVI board requested plans for R&D spending for further development of technology in its priority area of ***"reducing infectious waste and ultimately eliminating the use of sharps"*** in immunization programs. Among various technologies considered, the GAVI R&D task force requested the NTWG first to address one that removes used needles from syringes (referred to as "defanger" devices).

Health Need

The use of needles to administer vaccines has many drawbacks and disadvantages. These include improper reuse and consequent iatrogenic transmission of bloodborne diseases between patients, and needlestick injuries to health care workers and others. The WHO estimates unsafe injections cause 21.7 million new HBV infections and 2 million HCV infections annually in developing and transitional countries. Anecdotal reports and formal studies among health care workers in developing countries reveal astounding rates of reported needlestick injuries -- upwards of several hundred injuries per 1000 workers per year. The growing utilization of auto-disable (A-D) needle-syringes, although helping make injections safer, is resulting in an increasing volume of "sharps" (needle) medical waste that must be properly disposed.

Proposed Technology

Both existing commercial defangers and investigational devices in development are designed to destroy or separate used needles from their attached syringe. If designed to desired specifications (see below) and operated correctly, they *may*:

- Reduce the overall volume of used needle-syringes by approximately 40 percent. Used syringes take up less space in sharps boxes and disposal pits if their projecting needles have been removed and disposed separately.
- Prevent millions of iatrogenic infections from the improper reuse of unsterile conventional needle-syringes (A-D ones would already be non-reusable). Immediately disabling conventional needle-syringes would reduce the risk of their improper pilferage, "recycling", resale, and unsterile reuse, a common habit in many developing countries.
- Reduce the risk of needlestick injuries. Immediately capturing the needle in a puncture-proof container can protect those who work with or become exposed to medical waste.

Existing commercial defangers range in cost from approximately US$100 to $800 for the electric models and approximately US$24 to $300, depending on features, for manually operated models. PATH predicts, however, that appropriately simple devices could be manufactured for less than $20 each.

Technology Issues

The desirable outcomes listed above which are claimed for the use of defangers remain theoretical and undocumented by careful scientific studies. In worst case scenarios, the additional manipulation involved in using defangers (versus dropping the intact needle-syringe into a sharps box) may result in an increase in needlestick injuries to the health worker giving the injection. Or, for other reasons, defangers may simply end up not being used by health workers. A suitable research agenda to confirm these claims is recommended as the initial step of a research and development (R&D) plan by GAVI (see below) before proceeding to widescale introduction and promotion of this technology.

The following specifications were developed by the "defanging" sub-group of the NTWG for consideration by WHO, other GAVI partners, and appropriate stakeholders[vi].

The defanger(s) should: (1) not require electricity or batteries; (2) defang all common syringes (A-D or conventional) of sizes from 1 mL up to 25 mL; (3) defang syringes with either Luer cone (slip), Luer lock, or snap-on type interfaces with needle hubs; (4) render unreusable non-A-D syringes; (5) leave no needle stub on the defanged syringes that could produce a percutaneous injury; (6) provide a clearance (or a safety shield) for the operating hand of at least 15 cm from the axis of needle entry; (7) demonstrate a lifetime of at least 25,000 defangs; (8) use disposable, fill-level-marked, transparent or translucent needle containers with permanently locking closures; (9) minimize splatter of the liquid contents of the needle; and (10) be easy to clean and maintain.

Market issues and size

Defangers might be considered analogous to A-D syringes, which had no inherent market demand until their use became normative behavior as a result of statements by WHO and UNICEF. Their market was created by donors of vaccine who accepted the "bundling" policy that a safe injection device should be provided with each dose of vaccine.

As with A-D syringes, if defangers are proven useful to GAVI, their supply in sufficient numbers might become an obligation upon UNICEF and donors of vaccine and A-D syringes, so as to render less harmful the medical waste which results.

In India, the growing and apparently successful existing market for defangers evolved from government regulations that needles must be rendered non-reusable. India also severely restricts the incineration of medical waste, which serves as an incentive to reduce its volume.

[vi] WHO Department of Vaccines and Biologicals in collaboration with the UNICEF Supply Division are already in the process of developing a performance, quality and safety system. This system will, *inter alia,* develop equipment specifications, and norms and standards for design and development of equipment and devices for immunization. This system will bring together not only WHO and UNICEF, but industry, key partners and users in the development process

Assuming proper defanger use requires one to be located within reach of every health care worker administering a vaccination, the theoretical global demand for defangers is estimated at 0.5 to 1.0 million defangers needed for the 75 Vaccine Fund-eligible countries, or 1.0 to 1.25 million for all 165 developing countries.

Development Plan

Bench Testing

Given the unproven claims for defangers, it is recommended that defanger developers and manufacturers be given approximately 4 months to modify their products or prototypes in order to satisfy the proposed specifications and submit them to GAVI. If this program is properly publicized to reach the defanger industry and other interested parties, it is probably not necessary for GAVI to finance such preliminary work unless too few qualifying devices are submitted. These should then be tested at the bench by independent testing laboratory(ies).

Scientific Field Trials

Defangers found to meet the specifications should then be evaluated in field trials in a variety of settings in representative developing countries of Africa, Asia, and the Americas. The field evaluations should be conducted by competent institutions or agencies which do not have any compromising relationships to defanger developers, intellectual property holders, or manufacturers. The evaluations should include passive (uncontrolled) studies, as well as controlled trials (and head-to-head, if multiple devices are submitted) in both routine immunization settings and special (mass) vaccination campaigns. They should use objective, quantitative research endpoints such as rates of needlestick injury, proportions of needle-syringes defanged, and frequency of defanger breakdown and other causes of non-use, such as loss, theft, disappearance, or deliberate intention to “recycle” non-A-D needle-syringes. Subjective health care worker experience and preferences towards the devices, as well as economic analyses should also be studied. The methodological challenges to carrying out this research agenda might be addressed by a specially constituted committee.

Program for Appropriate Technology in Health (PATH) has worked for several years to advance defanger technology for all injection settings and has developed its own proprietary devices. It has been getting user feedback on needle removers, and working with multiple needle remover manufacturers to optimize their devices to respond to developing country needs and to reduce prices. In 2003, PATH began a field demonstration project in India to assess the roles of different needle removal devices as part of sharps management practices, and to observe and document needlestick injuries to health workers and waste handlers. The purpose of their project is to document the contribution that existing and new needle remover devices can play in sharps

disposal systems, and to obtain information that would be used by WHO to develop performance specifications based on field use. The evidence that they are accumulating will be taken into account for the design and implementation of subsequent defanger evaluations. The proposed NTWG program is different from PATH's in that it first develops device specifications, then urges manufacturers to meet those specifications, and then provides for independent, scientific trials with specific device comparisons. Once defangers are proven to make a contribution to immunization programs, their promotion and/or implementation by GAVI would greatly enhance the likelihood of success.

Budget: *Research Phase Duration and Costs*

The bench and field research outlined above is estimated to require from 12 to 24 months to conclude, and to cost from US$0.5 to $1.5 million.

Investment Opportunity

GAVI Decision re: Implementation

Upon review of the results of careful, scientific field trials as described above, GAVI would decide whether and to what extent defangers should be promoted for use in eligible Vaccine Fund countries. It could then select an implementing organization or entity to carry out the program, including purchase, promotion, distribution and/or bundling with donated vaccine, design and management of training syllabi, and other rollout materials and ancillary needs.

Defanger quantities, costs, and rollout

- **Quantities needed.** Based on the estimates of “market” need summarized above, it is assumed 1 million defangers hypothetically would be needed to completely serve every Vaccine-fund eligible country. However, a realistic assumption would be that research would find defangers of practical use in only half (500,000) of all immunization loci.
- **Replacement quantities.** In addition, to replace devices as they reach their service life of 25,000 defangs, new devices would be needed in perpetuity at a ratio of 1 for every 25,000 doses of injectable vaccine supplied.
- **Purchase costs.** Costs to manufacture each device meeting the specifications above are estimated to range from a low of US$10.00 to a high of $20.00.
- **Ancillary costs.** Costs of shipping, training, administration, etc., might constitute 25 percent of purchase cost, or an additional $2.50 to $5.00 per device.
- **Recurring/disposable costs.** Disposable needle containers which hold 100 needles and satisfy other specifications might cost US$0.25 each, which converts to $0.0025 per injection.

- **Overall costs.** Thus, the hypothetical cost of purchasing devices to reach half (500,000) every immunization locus in Vaccine Fund countries would total as follows:

Initial device purchase -	$5 million to $10 million
Initial ancillary costs -	$1.25 m to 2.5 m
Replacement devices (incl. ancill.) -	$0.0009 to $0.0018 per injection
Disposables costs -	$0.0025 per injection

- **Rollout estimates.** A realistic expectation would be that such costs would be spread out over several years. An implementation program is likely to distribute only 100,000 devices in year 1 of a rollout ($1.25 to $2.5 million), another 100,000 in year 2 and succeeding years (same annual costs). Thus, complete rollout would require 5 years.

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