The Case for Investment in R&D for Three Immunization Technologies: Recommendations for GAVI Action

This report was prepared by the GAVI Working Group to summarize and build upon the findings of the New Technology Working Group (NTWG) and provide recommendations to the GAVI Board for research and development (R&D) for immunization technologies. Recommendations are provided both for development of each specific set of technologies (nested in the three sections of the report) and for GAVI's broader role in R&D for vaccines and immunization.

Background

During its meeting in Stockholm in March 2002, the GAVI Board reviewed a proposal by the R&D Task Force regarding priority technologies for improving the quality and reach of immunization services. Three priorities for technology development were identified:

- Reduced costs and improved efficacy through elimination of the cold chain;
- Performance monitoring through detection of biomarkers of effective immunization; and,
- Improved safety through improved management of infectious waste and/or elimination of the use of sharps.

In each of the three areas, the R&D Task Force chose one specific technology as a promising example for further study by the New Technology Working Group (NTWG) of the R&D TF. These included:

1. Sugar glass stabilization for elimination of the cold chain
2. Non-invasive tetanus antitoxin tests for performance monitoring; and,
3. Defanging devices for improved safety.

The NTWG prepared a detailed scientific report on these selected technologies that was discussed by the GAVI Working Group in June 2003. Before the presentation of these findings to the Board, the Working Group recommended the preparation of a succinct summary and the inclusion of additional analysis, including:

- The "landscape" of current R&D efforts for related technologies;
- The summary of data establishing the "public health case" and "business case" for investment in these technologies; and,
- Specific recommendations to the GAVI Board for action in the development of these and other new technologies for immunization.

Section 1: Sugar Glass Stabilization

Magnitude of the Problem

All current vaccines are thermolabile, requiring continuous storage and transport in a cold chain to ensure their potency and safety. This thermolability of vaccines, along with the cost and fragility of the cold chain in resource-poor settings, defines a substantial set of constraints to cost-effective immunization:

- Annualized direct costs of establishing and maintaining the logistics-intensive cold chain in the developing world, which are estimated at US $200 million [1];
- Frequent detection of breaks in the cold chain (including damage due to both heat and freezing) and resulting spoilage of vaccine, estimated to result in costs in excess of US $100 million per year [2];
- Further undetected failures of the cold chain (especially due to freezing, as the vaccine vial monitors - VVMs – that are currently in use detect only heat exposure), resulting in an unknown reduction in efficacy of vaccines, excess morbidity and mortality due to vaccine preventable disease, and damage to the public confidence in immunization[3];
- Additional logistical burden, costs, and compromise of safety due to the need to reconstitute those vaccines that are lyophilized to enhance stability.

Technical Landscape

Other Candidate Technologies

Several technologies are currently employed routinely to solve the problem of thermolability, by continuously maintaining a "cold chain" from the moment of release of vaccine from the manufacturer, through international transport and supply depots, to where vaccines are administered. These include technologies for refrigeration, insulation (such as cold boxes), and temperature monitoring (including vaccine vial monitors to detect heat-compromise). No acceptable technology is in use to detect freeze damage. Other current and potential candidate technologies to solve the problem of thermolability include:

Vaccine Vial Monitors (VVMs): VVMs enable the end-user of a vaccine to identify whether any heat exposure has endangered the efficacy of the vaccine. This permits minor breaks in the cold chain to be accommodated without undue vaccine wastage and ensures that heat-

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[1] Jodar LP, Aguado TM, Lloyd J, Lambert PM. Revolutionizing Immunizations. Gen Eng News 1998; 18:6.

[2] Martin to provide references

[3] In Australia, exposure to sub-zero temperatures occurred to nearly 50% of HepB vaccines [(6)], and freezing was identified as the greatest threat to vaccine potency [(7)]. A study in Indonesia (CM Nelson, et al. Hepatitis B vaccine freezing in the Indonesian cold chain: evidence and solutions. Bull WHO, 2003) showed up to 75% of liquid vaccine was exposed to sub-zero temperatures. In areas where climatic conditions are frequently sub-zero vaccine-freezing is a very significant problem and some studies have detected up to 40% of vials exposed to freezing temperatures [(9)], suggesting that winter-freezing of vaccines being a likely cause of the diphtheria epidemic (1998) in the Soviet Union (Ask Martin to provide references).

compromised vaccine is "flagged" to be discarded. While VVMs are not yet in universal use for all GAVI-procured vaccines, efforts are underway to clear the last remaining barriers.

Improved Refrigeration Systems: Several improvements in refrigeration systems are slowly being implemented as equipment ages and requires replacement. Central stores of vaccine stock can be protected with computer-based monitoring to reduce both detected and undetected temperature damage. Ice-lined refrigeration equipment with better temperature control is being introduced gradually in intermediate stores to protect against accidental freezing of vaccines. At the periphery, replacement of kerosene refrigerators with hybrid solar equipment will result in better temperature control. These improvements will further drive up the annual costs of refrigeration for vaccines in developing countries, already conservatively estimated at US $200 million per year[4].

Lyophilization: Lyophilization of vaccines (eg. Measles, HiB, Rotavirus, meningococcal polysaccharide) involves immobilizing in a cake of semi-crystalline sugar (lactose or sorbitol supplemented with mannitol, amino acids and, in older vaccines, proteins such as gelatin or bovine serum). This confers reasonable stability (typically several weeks at ambient temperature) and resistance to freezing but storage in the cold chain is still required. Unfortunately as soon as vaccines are reconstituted they begin to lose activity and must be kept cool. Vaccine not used within several hours is wasted. As mentioned above the increased logistical and safety problems associated with vaccines that require reconstitution make this approach problematic. Hence, although this approach could theoretically be applied to alum-containing vaccines to render them freeze-resistant, the gain is offset by the increased logistics.

Sugar Glass Stabilization

Instead of entrapping vaccine in crystalline sugar (lyophilization), it may be entrapped in an amorphous sugar (sugar glass) with a high transition temperature. Molecular mobility is thereby significantly reduced, resulting in stabilization. Despite the evidence of this effect from extensive pre-clinical studies, the vaccine industry has not pursued the final development of the technology. The cold chain is considered an inconsequential barrier in the primary market of the industrialized world, so that the expected benefits would not justify the costs of reformulation and re-licensure of existing vaccines. As long as the "traditional" vaccines require a cold chain, there is little incentive to apply the technology in the formulation of new vaccine products.

Most sugar glass technologies yield a dry product, such as a foamed glass or powder. At present, dry vaccines must be reconstituted for administration, bringing new logistical hurdles and safety risks with the requirement for field use of a sterile diluent and the needles and syringes required to introduce the diluent into the vial. Thermostability is lost after reconstitution, so that ice must then be available to keep the newly reconstituted vaccine cool prior to administration. Several vaccines (BCG, measles, yellow fever, and freeze-dried Hib) currently require reconstitution, however the conversion of currently liquid vaccines to dry formulations would not likely be an acceptable trade-off for thermostability.

[4] Jodar LP, Aguado TM, Lloyd J, Lambert PM. Revolutionizing Immunizations. Gen Eng News 1998; 18:6.

Sugar glass technology, therefore, would be most compelling in an injectable dry format or a thermostable liquid, so that no reconstitution is required. Ballistic delivery systems for dry vaccines have been developed, including for intradermal delivery of a powder formulation (such as Powderject© technology) and for subcutaneous delivery of vaccine that is micro-encapsulated in a projectile (such as the Injectile© technology). A sugar-glass stabilized vaccine could be delivered dry by either of these methods. Although this approach could offer the additional advantage of the elimination of sharps, there remain several technical hurdles to both formulation and delivery. Since these technologies are in earlier stages of development, this report focuses solely on the liquid form for which delivery systems already exist.

Sugar-glassified vaccine may be suspended in non-aqueous, liquid perfluorocarbons (PFCs) without sacrificing thermostability. PFCs have the advantage of having already been tested and approved for use as a blood substitute and as an injectable contrasting agent. In addition to being thermostable (to both sub-freezing and elevated temperatures), vaccines formulated in this manner do not require bacteriostatic agents such as thimerosol (since the liquid does not support bacterial growth), and require no reconstitution prior to injection.

Cambridge Biostability Limited (CBL) has developed a technique to suspend glassified vaccine microspheres in PFCs. To obtain a stable liquid, the density of the composite vaccine microspheres must be precisely matched with the high density of the PFC liquids. The resulting suspension does not require shaking before injection and is physically stable for years. After injection, the composite glass microspheres dissolve in body water and the PFCs are eliminated by evaporation through the lungs or skin.

Several vaccines, including hepatitis B, Hib, and tetanus toxoid, have been prepared as composite-glass microspheres and suspended in PFCs using the density matching process developed by CBL. Animal trials with the tetanus toxoid vaccine suggest that immune responses are greater and more sustained than with conventional vaccines. Studies of thermostability with the hepatitis B vaccine indicate stability improvement up to 60°C and the absence of heat damage after one week at -20°C, reflecting the conversion of a freeze-sensitive vaccine to a freeze-safe vaccine. Final, longer-term stability results will be available before the end of 2003.

Operational Feasibility

Thermostable vaccines, if they can be successfully developed and proved affordable, would represent a solution to the daunting operational challenges presented by the thermolability of current vaccines. Preclinical data suggest that it is technically feasible to produce sugar-glass stabilized vaccines. Several late-stage R&D obstacles remain to be addressed, however, before this technology can be rolled out.

The Bill & Melinda Gates Foundation is preparing to fund a project, with implementation coordinated by PATH, to demonstrate the technical and operational feasibility of stabilizing GAVI vaccines using the CBL technology. The project will identify and address the current and potential hurdles to final development and application of this technology, including by:

- Comprehensively identifying and evaluating the optimal liquid suspension medium(s) based on required specifications, supply, cost, and environmental impact;
- Conducting formulation and stability studies with multiple vaccine producers;
- Identifying producers to whom the technology will be transferred;
- Clarifying regulatory issues and facilitating progress through these pathways;
- Enabling preclinical testing and clinical trials
- Addressing barriers to scaling up production;
- Assuring the intellectual property "freedom to practice" and back up rights for sustainable access to the products for public use;
- Demonstrating the value of thermostable vaccines for key stakeholders, including through strengthened cost-benefit evaluation; and,
- Identifying and exploring other potential applications of this technology, such as for new combination vaccines (which may reduce the number of injections needed) and for slow release of antigen (which may eliminate the need for booster doses).

The possible environmental impact of PFCs must also be considered since, although they are not highly volatile, they may contribute to the "greenhouse effect" and to global warming. Most countries have signed agreements to significantly reduce the use of PFCs. If applied to only 3 childhood vaccines, and used worldwide at a dose of 0.5 ml per dose per child, this corresponds to 500,000 liters of PFC, which would be excreted unchanged into the environment. Although regulations specify that PFCs may be used in cases where they are the only alternative available (on the basis of either performance or safety), expert opinion from environmental experts should be sought prior to initiating the development program.

Expected Cost-Effectiveness

The benefits of introduction of thermostable vaccines would accrue from:

- Reduction or elimination of the costs of the cold chain (savings would be substantial only if all routine childhood vaccines can be made thermostable);
- Increased safety, if the need for sterile reconstitution can eliminated (such as for measles vaccine, which is lyophilized to enhance heat stability);
- Increased efficacy due to elimination of freezing and heat damage; and,
- Reduced wastage and discard of vaccine due to detected heat damage and freezing, expiry, and discard of the unused portions of multidose vials.

The costs of introduction of thermostable vaccines would accrue from:

- The cost of the remaining R&D to proof of concept;
- The cost of reformulating, re-licensing, and modifying production of existing vaccines, ensuring sustainable access to products, and introducing the technology; and,
- The marginal cost of materials for application to new vaccines.

It should be acknowledged at the outset that there is little basis for estimation of the true extent of the health benefits due to increased efficacy of vaccines and improved safety if the need for reconstitution of lyophilized vaccines and/or the use of needles (through ballistic delivery) can be eliminated. For the following analysis, the benefits are limited solely to the economic benefits due to elimination of the costs of the cold chain and the reduced wastage and discard of detected heat damage and freezing:

One-time costs for late-stage R&D (US$40-60 million) and for change in production facilities (US$50-100 million) can be amortized over 10 years to yield an annual cost of US$15-30 million. With the expected production capacity of 100 million doses per year, this yields a per-dose cost of US$0.15 to US$0.30. The cost of the PFC (ranging from the US$60/L for non-GMP material to the current proposed price of US$1000/L for GMP product) will add $0.03 to US$0.50 per dose, assuming 0.5 ml will be used for each dose of vaccine. Other marginal recurrent costs are assumed to be negligible. Using the 100 million-dose annual production estimate, the material costs add US$3-50 million per year, yielding a total incremental cost per annum of $US18-80 million. Since this figure is most sensitive to the cost of the PFC, it is clear that substantial cost savings would be realized in the likely event that the cost of GMP PFCs is forced down over time.

Expected cost savings due to reduced wastage of vaccine will be most sensitive to the costs of the highest priced vaccines. For the pentavalent (DTP-HepB-HiB) vaccine alone (@ US$3.20/dose), cost savings of US$80 million (at a conservative wastage rate of 25%) to US$160 million (at the more likely wastage rate of 50%) due to heat damage, freeze-damage, and discard of unused portions of multi-dose vials. If all routing vaccines could be made thermostable, additional annual savings of US$200 million due to the elimination of the annual direct costs of the management of the cold chain[5] suggest a potential cost savings of US$280-360 million. Even without consideration of the substantial health benefits due to improved vaccine safety and efficacy, the net economic benefit of the development of this technology would be in the range of US$200-342 million annually.

If ballistic delivery of a dry powder formulation is undertaken instead, the recurrent cost savings (due to the lack of need for the PFC solute) could be substantial. However, in view of the larger technical hurdles and likely longer timeline for R&D, it is difficult to estimate costs and benefits for this alternative.

Conclusions: Sugar Glass Stabilization

Thermostable vaccines would enable elimination of the cold chain, profoundly simplifying logistics and enhancing vaccination efficacy and efficiency. Technologies to achieve thermostability would provide disproportionate benefits to the developing would, so should receive targeted attention by GAVI and its partners. Sugar glass stabilized vaccines, delivered in a liquid format, show promise of reducing costs due to vaccine wastage and maintenance of the cold chain and of reducing threats to vaccine safety and efficacy. The full health and economic benefits of the rollout of this technology cannot be reaped until sugar glass stabilization of all routine vaccines can enable elimination of the cold chain altogether.

[5] Jodar LP, Aguado TM, Lloyd J, Lambert PM. Revolutionizing Immunizations. Gen Eng News 1998; 18:6.

The findings of the NTWG and the analysis by the Working Group regarding these technologies enable the following conclusions specific to sugar glass stabilization technologies:

- GAVI should continue to assess priorities for R&D in this important area and make specific recommendations for technology development to mitigate the tremendous cost of vaccine thermolability.

- High priority is already assigned to R&D for both liquid and solid sugar glass stabilized vaccines. It is appropriate that initial attention by GAVI partners should be focused on liquid formulations, since ballistic delivery systems for solid formulations still need to be developed. Although delivery of solid formulations would enable further improvements in safety through elimination of sharps, this R&D is likely to be an area of investment for industrialized world markets (in view of the special needs for delivery of several DNA vaccines currently under development). Urgent attention should be focused on further R&D for this technology to address questions of the feasibility of industrial scaling and validation of the products and processes for production.

- Mitigation of the pressing problem of freeze damage through development of freeze-detectors or addition of cryoprotectants should be a further priority for R&D, especially if sugar glass stabilization should prove less than feasible.

- GAVI should promote further studies to identify the health and economic costs of cold-chain efficacy. Special attention should be given to the measurement of excess morbidity and mortality due to safety breaches, reduced vaccine efficacy, and the effects of undetected breaks in the cold chain.

Section 2: Non-Invasive Tetanus Antitoxin Test

Magnitude of the Problem

GAVI's performance-based release of funding has relied upon country-level information systems and GAVI-conducted Data Quality Audits (DQAs). But service statistics are often a poor reflection of actual coverage[6]. Furthermore, vaccination rates may not correlate fully with actual immunization, such as when breaches in the cold chain result in delivery of ineffective vaccines. The ultimate measure of the impact of immunization, the incidence of vaccine-preventable disease, is also subject to factors unrelated to immunization, including social patterns, climate change, and natural variation of the pathogen. Disease incidence measures are particularly unsatisfactory as an indicator of immunization systems performance when coverage levels are low.

Technical Landscape

Tests for biomarkers of immunization systems performance have therefore been proposed in an effort to measure both coverage and quality. Most currently available tests of antibody induced by vaccination require blood to be drawn, with attendant economic costs and safety risks. Processing of samples generally requires separation of serum and testing that requires laboratory support.

Other Candidate Technologies

Routine Health Information Systems: The most viable alternatives to serological tests are measures of vaccination coverage provided by health information systems. Since reliable denominator data are rarely available, routine service statistics frequently provide substantial overestimates of coverage. Data quality audits (DQAs) have been introduced by GAVI to provide some measure of the credibility of the information system, but DQAs cannot correct for the absence of reliable denominator data. Population-based surveys provide a more credible measure of true coverage[19], however these figures do not reflect other aspects of system performance, including variations in functional immunity (such as due to effectiveness of the cold chain).

Serological Tests: The gold standard for detecting TT antibody level is an animal-based toxin neutralizing assay: this assay is complicated, expensive and time consuming. The best-known ELISA-based laboratory test is Baxter's double-antigen ELISA test, which detects and quantifies antibodies to tetanus or diphtheria toxoid[7]. The assay results correlate well with the toxin-neutralizing assay and is specific for IgG antibodies. It uses a biotin-streptavidin system for amplification of the signal followed by ELISA detection. These tests have showed a remarkably sensitive detection limit of 0.00002 IU/ml for both antibodies, high validity, and are suitable for quantifying antibodies in blood samples collected on filter paper as well as from serum.

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[6] Murray, et al, 2003.

[7] Kristiansen et al., 1997. Improved ELISA for determination of anti-diphteria and/or anti-tetanus antitoxin antibodies in sera. APMIS 105:843-853

Non-Invasive Tetanus Antitoxin Tests

The development of a non-invasive test for tetanus antibody has been proposed in order to enable rapid, population-based assessment of the efficiency of immunization delivery systems. Detection of antibody to tetanus toxoid (TT) has the advantage that antibody derived from immunization differs from that induced by natural infection (although, in view of the high mortality rates associated with tetanus, survivors with naturally occurring antibody are rare). A oral fluid-based test was proposed to address the costs, logistical hurdles, and safety risks associated with serum sampling. Oral fluid-based assays have been successfully developed to detect infection with HIV, measles, rubella, and hepatitis B[8].

The NTWG report proposed specific technologies for development of a rapid test for anti-TT antibody in oral fluid. Design and cost assumptions were based on an expected number of tests per year of 40,000. It was proposed that a commercially available and relatively expensive oral fluid collection device be used, along with an immunoassay capable of detecting 0.01 IU/ml standard protective level of antibody. Since the level of antibody in oral fluid is 400 to 1000-fold lower than that found in serum, sensitivity must be very high to detect protective levels of antibody. Studies suggest that rates of fall-off in antibody levels after immunization are so variable that tests may be useful only within a relatively short period (less than one year) after immunization[9].

The available information regarding the proposed test is presented in the table below along with data for a serum-based rapid test kit under development by PATH and Baxter's commercially available ELISA test. Although some estimates can be offered, the data regarding actual costs and performance characteristics for the PATH test and the oral fluid-based test proposed by the NTWG are inadequate to permit valid comparisons.

	Oral fluid-based TT Ab test kit	**Serum-based TT Ab test kit**	**ELISA**
Sensitivity	unknown	unknown	0,00002 IU/ml
Specificity/validity	unknown	unknown	high
Ease of use	easy	easy	difficult
Safety	high	medium	medium
Operational feasibility	high	medium	medium
Unit cost (per test)	unknown	Less than 2 $	?
Start-up costs (Infrastructures etc.)	low	low	very high

*Compliance for oral fluid collection of the samples reported roughly 15% higher than for blood sample collection[10]

[8] NTWG report, http://www.vaccinealliance.org/site_repository/resources/NTWG_global.pdf. 2003.
[9] WHO Publication: WHO/EPI/GEN/93.13 (edited by A. Galazka).
[10] Tamshiro et al. Serological diagnosis of HIV injection using oral fluid samples. WHO Bulletin, v.72, 1994.

The market for tetanus toxin antibody detection is limited to those few cases in which there may be relative contraindications to tetanus vaccination or presumptive post-exposure prophylaxis with tetanus antitoxin. Although Baxter has successfully developed the serum-based double-antigen ELISA test (which detects immunity to both diphtheria and tetanus), the added value of a oral fluid-based test is unlikely to offer adequate comparative advantage in order to justify commercialization. A public sector market of only 40,000 tests per year would be inadequate to compel commercial development.

Operational Feasibility

The sole potential application for such a test is population-based surveys. Although the desired performance criteria might be different for research applications (e.g., cost control would be a lower priority), the NTWG assumed a primary purpose of routine monitoring of program effectiveness. The following target product profile can be defined for a TT antibody detection test, in order to specify the optimal and acceptable ranges of product performance characteristics:

- Easily performed on infants (in addition to older children and adults),
- High specificity (detecting antibody levels that correlate with full protection),
- Requires little or no training for reliable use and interpretation,
- Rapid (results available in minutes to enable immunization of those whose antibody levels do not correlate with protection),
- Available in a multiple test format for population-based surveys with a shelf life of years, and,
- Reliably detect antibody among those who are "fully immunized" according to recommendations for tetanus immunization.

Expected Cost-Effectiveness

Since the proposed test is a management tool, rather than an individual health care intervention, it is impossible to calculate classical cost-effectiveness values based on years of life saved. In view of the proposed target product profile, it is unlikely that the price of the test would be within an acceptable range for routine use for performance monitoring. The NTWG report estimates a cost per test between US$5 and US$15. It is possible, however, especially using a cheaper method for oral fluid collection, that the cost per test could be substantially reduced. It was pointed out in the report, for example, that the oral fluid collection tools for HIV tests had a more affordable unit price of $0.50 to US$1.50. Nonetheless, even with this reduced cost of the oral fluid collection device, the cost per test would unlikely be less than US$3.00-$5.00. Within the current technological and cost parameters, the proposed test does not compare favorably with the other available methods for immunization program performance monitoring.

Conclusions: Non-Invasive Tetanus Antitoxin Test

Improved tools for assessment of immunization service performance remain a highly desirable R&D goal. The NTWG developed a "roadmap" for development of an oral fluid-based tetanus antitoxin assay, suggesting a contract with an academic institution with an industrial partner. The research required to develop such a tool is, however, more "upstream" than for the other two technologies that were the focus of the NTWG report. GAVI should continue to monitor the development of this technology along with the landscape of other emerging technologies for opportunities to develop tools that would achieve the desired goal.

Section 3: Defanging Devices

Magnitude of the Problem

Millions of unsafe injections are given each day. WHO estimates that unsafe injections each year cause 32 million cases of hepatitis B, 7 million infections with hepatitis C, and 98,000 new infections with HIV[11]. It is further estimated that unsafe injections cause 1.3 million premature deaths annually – resulting in the loss of 26 million years of life and an annual economic burden of US$535 million in direct medical costs[12]. While injections for immunization are, by far, safer than most other injections given in the developing world, the delivery of vaccines by injection incurs an ethical obligation to take all reasonable steps to ensure injection safety, including safe disposal.

National and district health authorities in many developing countries demonstrate little interest and commitment for the safe disposal of needles and syringes, as illustrated by experience in Cambodia[13], the Eastern Mediterranean[14], India [15] and Africa [16].

Technical Landscape

Proper containment and disposal of sharps medical waste, in conjunction with auto-destruct (AD), or other safety syringes containing re-use prevention features, can reduce needlestick injuries, prevent improper reuse of needle-syringes, and reduce volume of medical waste and its risk to the community and environment[17]. While this report focuses primarily on defanging devices, a brief review of the technology "landscape" is provided.

Existing Sharps Management Technologies

Sharps boxes: Burnable sharps disposal boxes are a temporary storage device for used needle and syringes, and only one step of the disposal process. They are often not supplied or are available in insufficient numbers, are frequently found dangerously overfilled because they are not removed promptly, and are occasionally pilfered to improperly "recycle" non-A-D needle-syringes. If the boxes are to be burned in an incinerator, further operational problems are introduced by the requirement for transport to the incinerator site and storage before incineration.

Incineration: Incinerators that reach at least 800º C can nearly completely eliminate sharps waste, except for a small residue of sterile ash and metal. Their limitations include their cost, occasional community resistance to potential pollution, and lack of transport and fuel to deliver waste to centrally located units. Open burning at lower temperatures of certain

[11] Safe Injection Global Network (SIGN), Annual meeting report, 2002. Kane, A.J. et al. Unsafe injections in the developing world and transmission of blood-borne pathogens: review of the literature and regional estimates. Technet Consultation, WHO (1998).
[12] State of the World's Vaccines and Immunization, WHO, Geneva (2002).
[13] Laurent, 1998.
[14] Zghondi, 2002.
[15] Rajasekara et al. Injection practices in Southern part of India. Public Health 117 (2003) 208-231.
[16] Dicko et al. Safety of immunization injections in Africa. Bulletin of the World Health Organization 2000 78(2).
[17] Prüss, 1999.

plastics can release toxic pollutants[18]. To minimize pollution from improper burning, some Indian states forbid waste generators to operate their own incinerators; rather, they must bring waste to centralized approved ones[19].

Disposal pits: Digging pits in the ground is an option for local disposal of the residue of sharps waste from either burned disposal boxes, from the incomplete combustion of incinerators, or the direct deposits of unprocessed needle-syringes. Such disposal pits have the potential disadvantages of susceptibility to exposure through erosion or excavation, introduction of the risk of contamination of ground water used for drinking, and requiring a large amount of space if they contain bulky syringes.

Defanging Devices

Defanging devices limit exposure of the sharp hazard at the point of use by removing the needle and containing it until it is destroyed.

Electric Needle Destroyers: Most destroyers operate on mains (wall) electric current and apply a direct current electrical voltage across the needle in order to destroy it. Others use mains current to recharge 5-to-10 ampere-hour sealed lead acid batteries, which make them quite heavy. Prices of basic models range from approximately $100 to 200. More complex models may cost $800. Drawbacks to existing electric needle-destroyer technology include: (1) downtime due to frequent power shortages, (2) high price, (3) immobility of heavy tabletop models, (4) need for frequent replacement of worn electrodes, (5) inconsistent or incomplete destruction of the needles, leaving sharp stubs, (6) splattering or misting of blood, (7) generation of obnoxious fumes, noise, and sparks, and (8) the resulting prohibition of their use in explosive atmospheres where oxygen and anesthesia are in use[20].

Manual Needle Removers: Several non-electric needle cutters are marketed throughout the world, many of them produced in developing countries. Drawbacks of some of the devices are their short blade life, which requires frequent cutting blade replacement, and the lack of portability for use in outreach settings. Other technical drawbacks can include fluid splashing and contamination[21], and ease of access to the infectious needle shafts. Improved designs of manual needle removers are now available that disable the syringe as well as the needle. These have been shown to have a longer blade life and be free from splatter. Technical challenges remain to minimize handling of the contaminated needles by health care workers and waste disposal personnel, and to improve portability for outreach.

Two manual needle removers have been developed and are on the market (Balcan, NoMoreSharps). In addition, a number of other manufacturers have prototype devices under development (Chitsein, NoMoreSharps, BD).

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[18] MRC, 1999.
[19] Dalal, 2001.
[20] Muller, 2001a; PATH, 2000; PATH, 2003.
[21] Hersh et al. Ensuring Injection Safety during Measles Immunization Campaigns. Journal of Infectious Diseases 2003; 187 (Suppl 1): S299-306.

Current R&D landscape

Since 1998, PATH has assessed sharps disposal needs and available technologies, with funding from the U.S. Agency for International Development's HealthTech program, the Bill & Melinda Gates Foundation Appropriate Technologies in Health Program, and the Children's Vaccine Program. PATH evaluated electric and chemical needle destroyers[22], provided technical background of a luer-slip needle removal device to five manufacturers and to WHO, conducted bench evaluations of six different manual needle removers in various stages of development and marketing from four external manufacturers and developers, commissioned a study to examine splatter and surface contamination from needle remover use[23], commissioned a market study of needle removers in India[24], introduced needle removers to immunization programs in India, Mozambique, Senegal, Cote d'Ivoire and Indonesia, and designed two needle removal devices.

In May 2003, PATH began a formal evaluation of three needle removers (Balcan and two PATH designs) in India in 9 project sites to assess safety and acceptability of the devices to health care workers and waste disposal personnel; the disposition of both the contained needles and the defanged syringes; and the reliability, maintenance, and durability of the devices in the evaluation. This evaluation will last six months, and is expected to record the experience of 30,000 injections. The project will observe and track the total number of injections as well as numbers of needlestick injuries to the health worker and waste handler in all project sites. According to US experts on needlestick among health workers, it is difficult to obtain reliable injury data for rate calculations because of the high degree of underreporting and variability of reporting over time[25]. There is no consensus, even in the US, regarding the best denominator to calculate injury rates for comparisons. And, most significantly, the sample size required to detect reductions in needlestick rates ranges from 94,000 to 4.6 million injections. Because of the lack of reliable needlestick baseline data, and the large number of injections and needle stick incidents required to show a statistically significant difference, this project will not be able to make comparisons on needlestick rates. PATH has adapted the evaluation protocol from India to a generic format for application in other countries.

One PATH needle remover design, focused on the particular needs of outreach immunization, is being released to interested commercialization partners, with the ultimate goal of placing the design in the public domain. This will allow for local adaptations to be made from the core technology.

[22] PATH, 2000.
[23] NAMSA, 2002.
[24] Dalal, 2001.
[25] Pugliese, 2001.

WHO has drafted an equipment performance specification for needle removers, cutters or destroyers. In addition, WHO developed a checklist of issues to monitor in demonstration projects making use of needle removers in developing country setting (the PATH protocol addresses these issues). WHO/EA is planning an evaluation in Eritrea of sharps disposal systems, including needle removers, to begin in November 2003. A pre-pilot was carried out during a measles campaign in Eritrea at the end of September. Other WHO evaluations are under discussion in Ukraine, Kenya and Uganda.

WHO specifications and guidelines for use are important market incentives to potential manufacturers. Given the local variations that are likely to arise from the simplicity of this technology, application of WHO specifications and guidelines for needle remover use would enable local manufacturers to provide products, much as locally made safety boxes are being used.

Operational Feasibility

"Defanging" must occur immediately after the injection has been completed, before the needle-syringe leaves the hand of the person who performed the injection. Therefore, the needle remover must be located within one step of all loci where vaccinations are administered.

All waste handling technologies must fit into an overall framework of administration and management, involving policy guidelines, supply chain logistics, training for behavioural change, and supporting legislation. Ideally, final destruction or disposal of waste should occur as near as possible to the point where the waste is generated. No solution will fit all circumstances—it is likely that a number of solutions will be needed to meet the specific conditions of different sites. Options for processing of infectious sharps waste differ according to the site. It is useful to consider these options in terms of rural outreach, rural clinic, and urban clinic settings with low-to-medium infrastructure. (It is assumed that urban clinics in high infrastructure environments would have transitioned to specialized collection and disposal systems for hazardous waste.) Portability is the critical constraint for outreach. Use of a portable needle remover would enable the contained needles and the used syringes to be safely transported back to the rural clinic for disposal.

The two waste streams that are created from effective needle removal—contained needles and 'defanged' and disabled syringes—need to be disposed of properly. It is recommended that the contained needles be emptied into a protected needle pit. These pits can be located at primary health care facilities, and therefore, transport of the hazardous sharps is avoided. The defanged syringes can be collected in various ways—in a safety box, or handled along with other "infectious waste" in less expensive yellow plastic bags until disposal. Depending on location, ultimate disposal of the syringes may be incineration, burning, plastic reprocessing, or via regular municipal waste. There is some uncertainty about the need for disinfection of the syringes as a reprocessing step or before the syringes could be disposed in regular municipal waste.

Expected Cost-Effectiveness

Use of needle removers, even in conjunction with safety boxes for syringe body disposal, is no more expensive than using safety boxes alone. For example, assuming 20,000 injections, a $30 needle remover, and considering that a $0.66 5-liter safety box holds 150 syringes with needles or 235 syringes without needles, associated costs are:

Needle remover + Safety boxes		Safety boxes alone	
Needle remover	$30	No needle remover	
Safety boxes needed: 86	$57	Safety boxes needed: 134	$88
Total cost	$87	Total cost	$88

This calculation will vary depending on the size of the syringes, how the safety box is filled, the cost of the needle remover, and the cost and need for replacement needle containers. If syringe bodies were disposed of in yellow plastic bags instead of safety boxes, then the total cost would be much less.

WHO staff modeled the number of needle removers that might be needed. Details of their approaches and data are provided in the New Technologies Task Force report (Section 7.2.2). They conclude that approximately 1.0 to 1.25 million devices could be needed for immunization programs in all developing countries. For all injections (10% immunization, 90% curative), they estimate that 10 to 12.5 million devices could be needed.

Operational effectiveness remains to be fully measured—in terms of effects on safety and waste disposal systems. Country-level data are needed on the extent of improper disposal and rate of needle-stick injury to both health workers and community members. With such data, the risk of disease transmission can be fully determined. Impact on the waste disposal systems can be measured by cost per volume or weight of the disposed waste.

If needle removal devices are designed and used appropriately, their impact may:

- Reduce the overall volume of sharps waste by 90 percent; and,
- Prevent millions of iatrogenic infections from the improper reuse of unsterile disposable needle-syringes.

Conclusions: Defanging Devices

GAVI partners are already working to evaluate the role of needle removers and to encourage the supply of appropriate and low cost devices. This analysis suggests the following conclusions specific to defanging devices:

- Ongoing work by partners to documents the effectiveness and safety of needle removers should continue, with complementary work to develop training materials, job aids, and evaluation tools as indicated.

- WHO's work on equipment specifications should be given priority and guidelines for sharps disposal should be adapted as needed, based on emerging findings, to include needle removers.

Summary of Priority for Immunization Technology Development

	Sugar Glass Stabilization	Defanging Devices for Sharps Removal	Non-invasive Assay for TT Antibody
Magnitude of the Problem Addressed	+++	++	+
Technical Feasibility	++	+++	+
Field Operational Feasibility	+++	++	++
Expected Effectiveness	++	++	+
Cost/Savings	+++	++	+
Overall Priority	+++	++	+/-

Recommendations for R&D for Immunization Technologies:

Based on the work of the NTWG and the subsequent analysis by the GAVI Working Group, the following recommendations are made:

- With their uniquely comprehensive view of global and country immunization activities, GAVI and its partners are well positioned to identify emerging needs and opportunities to develop and introduce new immunization technologies. GAVI should develop a systematic mechanism to undertake biannual "scans" of the landscape of emerging technologies, to conduct cost-effectiveness analysis, to make recommendations, and to advocate for R&D efforts.

- GAVI should continue to rely primarily upon partners to fund and implement R&D efforts. GAVI should strengthen links with donor and technical partners who can:

    - Convene the periodic reviews of emerging needs and opportunities for immunization technology development; and,
    - Design and fund programs of R&D to address these needs and opportunities.

- GAVI should work particularly closely with WHO to ensure that global guidelines and policies are developed and put in place to ensure the smooth introduction of needed immunization technologies. Once promising technologies are ready for broad introduction, GAVI should accelerate the process by endorsing WHO recommendations, providing incentives in support of introduction and diffusion of these innovations, and (where appropriate) using Vaccine Fund resources to initiate progress toward sustainable funding for these technologies.

WG technology sub-group members

1. Sally Stansfield, Gates Foundation (Chair)
2. Mark Kane/Janet Vail , CVP/PATH
3. Martin Friede/Teresa Aguado, WHO
4. Steve Landry, VF
5. Irina Serdobova, GAVI Secretariat (Secretary)