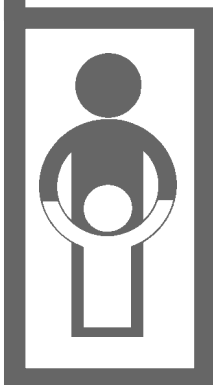


# Technologies for vaccine delivery in the 21<sup>st</sup> century

J. Lloyd



## DEPARTMENT OF VACCINES AND BIOLOGICALS



*World Health Organization  
Geneva  
2000  
in collaboration with*



**path**  
Program for Appropriate Technology in Health



UNICEF

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# 1. Vision

The scope of this vision of future change is limited to the technologies of vaccine delivery in developing countries during the next 10 or so years. The vision of change is driven principally by the need to make the delivery system more equitable, safer and more efficient. The 21st century brings us reformed health systems that better integrate preventive and curative services, new multivalent vaccines and technologies for safer administration and simpler distribution.

We can now envisage a vaccine delivery system that does not require refrigeration, is closely integrated with the delivery of drugs, utilizes safe prefilled injection devices containing single doses of thermostable vaccines and processes waste at the point of use without harming the environment.

The rationale for investing in these changes in technology is based on the conviction that they will help to achieve universal coverage with high quality immunization services and on the belief that the consequences of introducing new vaccines while attempting to maintain the current delivery system might include:

- continuation of low immunization coverage in hard-to-reach areas;
- wastage of costly vaccine in traditional multidose presentation;
- depression of public demand for new vaccines because of fear of unsafe injections;
- failure of governments or donor partners to continue bearing the cost and managerial burden of the cold chain.

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## 2. Strategy

The strategy for transforming vaccine delivery systems is aimed at the following critical success factors for immunization services:

- equity in access to new vaccines;
- safety of vaccine administration;
- simplicity and efficiency of vaccine delivery.

These factors can be significantly influenced by the application of new technologies and their associated training and management systems. The new technologies can be applied in three concurrent phases involving:

- safer multidose vaccine delivery, including the use of waste disposal technologies;
- the use of monodose prefilled injection devices;
- the use of thermostable vaccines delivered in the same way as drugs.

The most important anticipated impacts on immunization systems are shown in Table 1.

**Table 1:  
Impact of technology change on immunization services.**

	<b>Safer multidose vaccine delivery</b>	<b>Monodose prefilled injection devices</b>	<b>Thermostable vaccines delivered with drugs</b>
<b>Equity of access to new vaccines</b>	Safe injection devices and disposal technology assured for mass immunization. Lowest cost per delivered multivalent dose of new vaccine.	Ease of administration permitting community care providers to immunize. A single dose available to a single child always.	Vaccines carried to people wherever they live with no refrigeration impediment. Potency of vaccine assured for every child wherever he/she lives.
<b>Safety of vaccine administration</b>	No reuse of syringes possible. Reduced needle-stick risks. Sterilization assured by monitoring – or eliminated.	No reuse of injection devices possible. Vaccine dose integrity and sterility guaranteed to the point of use. No possibility of manual manipulation of vaccine.	Elimination of needle and consequent elimination of needle-stick hazard.
<b>Simplicity and efficiency of vaccine delivery</b>	Progressive elimination of complex and risky sterilization procedures. Progressive improvement in waste management systems. Higher cost for improved safety.	Elimination of administrative vaccine wastage, resulting in lower costs. Reduced reliance on refrigeration and ice-making at the peripheral level where 75% of distribution costs are concentrated. Less equipment maintenance. Easier stock control.	Reformed health systems able to integrate drugs fully with vaccines. Complete elimination of refrigeration in the distribution system, leading to reduced costs and managerial burden. Easier stock control.

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## 3. Technologies

As well as enabling change, technologies can catalyse it by focusing changes of behaviour on visible, tangible difference. The rationale, status and prospects of the following new technologies are discussed below:

- auto-disable (AD) syringes and safety boxes;
- monodose prefilled injection devices;
- needle-free injections;
- point-of-use sharps processing;
- thermostable vaccines and vaccine vial monitors.

### 3.1 Auto-disable syringes and safety boxes

#### 3.1.1 Rationale

The reuse of standard single-use disposable syringes and needles, which are employed for nearly half the immunizations given, is widespread<sup>1</sup> and there is a high risk of transmission of bloodborne pathogens between patients.<sup>2</sup> The resulting disease burden is believed to be higher than that arising from transmission between patients and health workers through accidental needle-stick and also higher than that caused by improper disposal. Reuse presents the highest risk in the category of unsafe injection practices in developing countries.

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<sup>1</sup> Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. *Bulletin of the World Health Organization*, 1999, 77 (10): 789-800.

<sup>2</sup> Kane A, Lloyd J, Zaffran M, Simonsen L, Kane M. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bulletin of the World Health Organization*, 1999, 77 (10): 801-807.

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The AD syringe, which has been assessed in the laboratory and the field,<sup>3</sup> presents the lowest risk of person-to-person transmission of bloodborne pathogen because it is designed to prevent reuse. It is the disposable equipment of choice for administering vaccines for mass immunization campaigns.<sup>4</sup> Although means for safe disposal are still inadequate in most developing country settings, the risk of noncompliance with sterilization procedures is considered much higher.

The risk posed to health staff and the general public by contaminated needles and syringes is reduced by the use of puncture-proof containers, known as safety boxes, for the collection and disposal of used disposable and AD syringes, needles and other injection materials.

### 3.1.2 Status

AD syringes are produced by five manufacturers for supply to immunization services either directly or through the United Nations Children's Fund (UNICEF). It is estimated that over 160 million of these syringes were used in 1999, twice as many as in 1998. Nevertheless, this represented only a small fraction of the injections given for immunization in developing countries during 1999, which totalled over a billion.

Fig. 1. Auto-disable syringes



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<sup>3</sup> Steinglass R, Boyd D, Grabowsky M, Laghari AG, Qavi A, Evans P. Safety, effectiveness and ease of use of a non-re-usable syringe in a developing country immunization programme.: *Bulletin of the World Health Organization*, 1995, 73 (1): 57-63.

<sup>4</sup> *Safety of injections: WHO-UNICEF policy statement for mass immunization campaigns*. Issued jointly by the World Health Organization, Geneva Switzerland, (Global Programme for Vaccines and Immunization, Division of Emergency and Humanitarian Action and the Division of Emerging and other Communicable Diseases Surveillance and Control) and the United Nations Children's Fund (UNICEF Programme Division, New York, USA and UNICEF Supply Division, Copenhagen Denmark). (Also the adopted practice of the International Federation of Red Cross and Red Crescent Societies.) WHO/EPI/LHIS/97.04 REV.1 (replaced by *Safety of injections: WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services*. WHO/V&B/99.25).



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The demand for the AD syringe has been limited because it cost US\$ 0.077 in 1999, whereas a typical standard disposable syringe costs only \$0.040 on the international market. In 2000-2001, simplified versions of the AD syringe will enter the market at significantly lower prices. Furthermore, efforts are being made to transfer AD technology<sup>5</sup> from two or more sources of intellectual property to five large developing countries.

Safety boxes are designed to contain 100-200 AD syringes at a cost per syringe disposed in the range \$0.006-0.01. They are supplied by UNICEF to all countries ordering syringes for immunization services and are flat-packed for easy distribution to the field.

### **3.1.3 Prospects**

For as long as multidose vials of vaccine continue to be used the AD syringe is likely to remain the injection device of choice for routine immunizations.

#### **UNICEF-WHO policy**

A programme for the use of AD syringes in immunization has been agreed between WHO and UNICEF.<sup>6</sup>

- The reuse of standard single-use disposable syringes and needles places the general public at high risk of disease and death.
- The AD syringe, which is now widely available at low price, presents the lowest risk of person-to-person transmission of bloodborne pathogens because it cannot be reused. The AD syringe is the equipment of choice for administering vaccines in both routine immunization and mass campaigns.
- Safety boxes, which are puncture-proof containers for the collection and disposal of used disposable and AD syringes, needles and other injection materials, reduce the risk posed to health staff and the general public by contaminated needles and syringes.
- WHO and UNICEF reaffirm the current policy that AD syringes, vaccine and safety boxes should continue to be supplied as a bundle for all elective and emergency campaigns.
- UNICEF reaffirms its current policy that its own programme funds cannot be used to procure standard disposable syringes for any immunization purpose.
- UNICEF procures supplies and equipment as a service to governments and other organizations but as of 1 January 2001 no procurement service contracts for standard disposable syringes will be entered into for immunization.

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<sup>5</sup> The WHO-UNICEF policy statement for mass immunization campaigns (WHO/EPI/LHIS/97.04 Rev.1) has now been replaced by *Safety of injections. WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services* (WHO/V&B/99.25). This extends the policy to routine immunization programmes on a phased-in basis.

<sup>6</sup> *Safety of injections: WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services* (WHO/V&B/99.25).

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- WHO and UNICEF urge that by the end of 2001 all countries should use only AD syringes or sterilizable syringes. Standard disposable syringes should no longer be used for immunization.
  - WHO and UNICEF urge that by the end of 2003 all countries should use only AD syringes for immunization.
  - All partners of immunization services are requested to finance not only the vaccines but also their safe administration, AD syringes and the safe management of waste. Partners should do this by planning and implementing the above strategy as well as by supporting related training, supervision and sensitization.

### **Other markets**

The development of other markets for AD syringes may improve their availability and reduce their price. Injectable family planning drugs are beginning to be delivered by means of AD syringes and there may be a market for a high proportion of skin-piercing injections provided through primary health care in developing countries.

In industrialized countries, on the other hand, markets are unlikely to develop for the AD syringe because it does not prevent accidental needle-stick, which is the main preoccupation in these countries. In response to this concern, various types of safety syringe have been marketed which either automatically or manually protect the needle by sheathing after injection. Automatic needle-sheathing syringes have the property of being effectively auto-disabling but they are costly (\$0.75 per unit) and comparatively difficult to destroy because of their bulk. Manual needle-sheathing devices are less costly (approximately \$0.012-0.025 additional cost per syringe unit) and may enter the AD syringe specification when price sensitivity no longer constrains the development of the AD market.

### **Quality assurance**

Most AD syringes are manufactured in industrialized countries where the International Standards Organization (ISO), CEN or the United States Food and Drug Administration provide some assurance of GMP. However, in spite of ISO certification, several manufacturers of ADs have demonstrated quality problems that have been reported from the field and by UNICEF Copenhagen. These problems are likely to multiply as new producers emerge in developing countries. During the next biennium, therefore, WHO plans to work with relevant authorities to ensure that there are independent mechanisms for monitoring syringe consistency and safety.

### **Needle-free reconstitution for multidose vials**

For the injection of reconstituted vaccine in multidose vials, AD syringes are now used in tandem with standard disposable 5-ml syringes and needles, these being employed at the rate of one per vial for the reconstitution process. However, there are needle-free reconstitution systems permitting consecutive pairs of vials of diluent and freeze-dried vaccine to be linked for the reconstitution process without the use of a syringe and needle. The costs and benefits will be evaluated in the field and, if satisfactory, these systems will be introduced into routine and mass immunization.

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## 3.2 Point-of-use sharps processing technologies

WHO recommends immunization services to destroy syringes and needles as soon as possible after injections have been given and as close as possible to the place where they have been given. It is rarely, if ever, possible to achieve destruction by incineration at an acceptable environmental standard in order to meet this recommendation. Clearly, therefore, if syringes and needles have to be stored and carried to the point of destruction the hazards of sharps and infection should be minimized.

### 3.2.1 Rationale

The hazards of storing and transporting infected syringes and needles to the point of final disposal can be reduced by de-fanging (i.e. separating, encapsulating or destroying the needles), disinfection and compaction. Once de-fanged the sharps can no longer cause accidental needle-stick. After they have been disinfected the probability of cross-infection is reduced, and after compaction the processes of storage and transportation become more feasible.

### 3.2.2 Status

A number of technologies exist or are in the process of development.

**Disinfectants** are corrosive, costly and have comparatively narrow spectra of inactivation. New liposome-based decontaminants hold some promise as very low-cost, highly effective and entirely safe products for use in developing countries and, following research and development, could be made available.

**Thermoprocessing**, or melting, is performed in the USA and could, with some modification, be made available wherever there is an electricity supply. Thermoprocessing disinfects, compacts and encapsulates needles within the plastic of the syringes. The resulting cake may be discarded in domestic waste, recycled or incinerated.

Fig. 2. Thermoprocessing technology on the USA market (“Demolizer”)



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**Fig. 3. Electrical model of needle destroyer**



A **needle destroyer** either destroys the needle entirely by means of an electric current or cuts the needle and hub away from the syringe for separate disposal by burying. The remaining syringe is thus less hazardous during disinfection and transportation. Some long-life devices are transportable but not easily portable while short-life devices are designed to be supplied, carried and discarded with the sharps safety box. Standard disposable syringes and newer AD syringes with separate needles can be de-fanged by one-handed removal of the needle into a sealed container with a V-slot opening.

**Plasma-melting** and **small-scale incineration** may not be practical or economical in today's clinics but could serve for district-based waste destruction. Plasma-melting requires electricity but has the important advantage over small-scale incineration that no emissions enter the atmosphere. This technology is currently being developed for use at district level.

### ***3.2.3 Prospects***

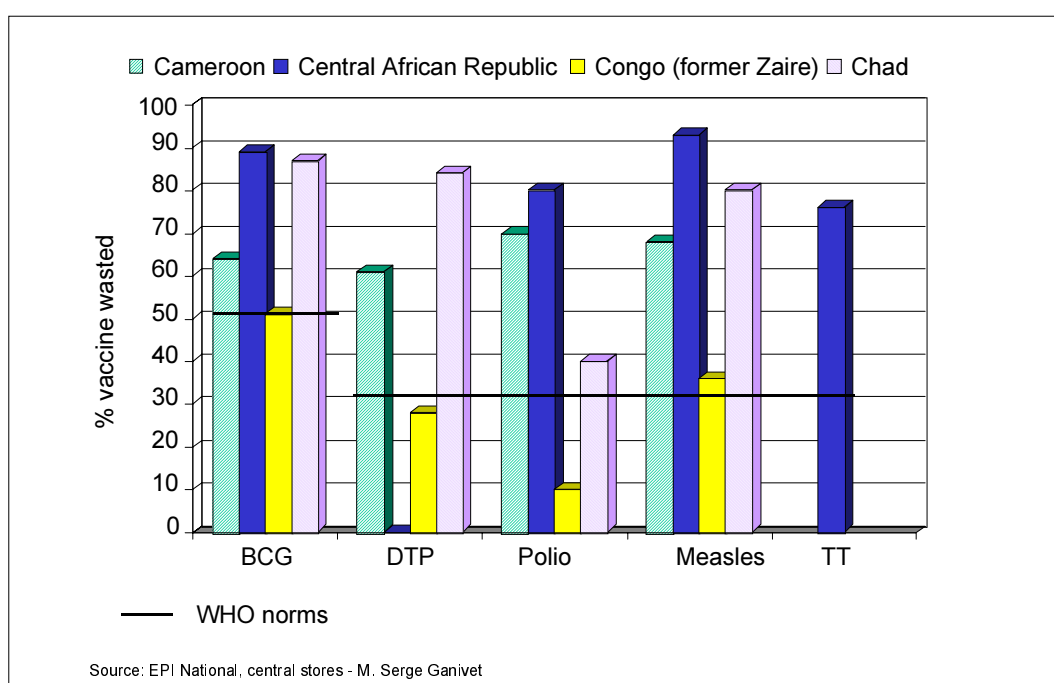
Until a practical technology becomes available for the final destruction of syringes and needles at the point of use in developing countries, waste-processing technologies will remain critically important for eliminating the hazards of storage and transportation. Technologies for final disposal will have to meet environmental standards that are stringent enough for future acceptance. This implies that greater investment and higher technologies than are currently available at district level will be needed to achieve the required standards.

### 3.3 Monodose prefilled injection devices

#### 3.3.1 Rationale

Multidose vials have been the standard presentation of almost all vaccine used in developing countries. However, as immunization sessions have become more frequent and more accessible they have become smaller and approximately 50% of vaccine is wasted because partly used vials are discarded when sessions are completed. A recent change in global policy<sup>7</sup> permits vials of certain vaccines to be used over a month so as to control wastage and ensure that when very few children attend sessions they are not refused vaccine. The evidence supporting this change is strong but there has been reluctance to adopt it. Recent actions in the USA and Europe have questioned the use of thiomersal, the bactericide that permits multidose vials to be used. The safety of multidose vial presentations of vaccine is likely to come under increasing scrutiny in the future.

Fig. 4. Vaccine wastage in Africa, 1998



**Monodose presentations** of vaccine eliminate the risks of cross-contamination and wastage of vaccine, although they cost more and are more bulky to store than multidose presentations. If, in addition, the vaccine dose is prefilled into an injection device, the integrity of the dose is guaranteed up to the moment of use. This represents a great improvement in safety relative to the manual filling of a syringe. Furthermore, the cost of the device is largely offset by the replacement of both the vaccine container and the syringe. The relative costs also depend on the cost of the vaccine in single and multivalent format (Table 2). Monodose prefilled presentations of new vaccines guarantee safety and appear to be economically viable, although good cost data are not yet available.

<sup>7</sup> WHO policy statement: the use of opened multidose vials of vaccine in subsequent immunization sessions. WHO/V&B/00.09 (replaces WHO/EPI/LHIS/95.01).

**Table 2. Comparative system costs of hepatitis B presentations and injection devices.**

	Syringe + multidose		Syringe + monodose		UniJect™	
	US\$ high	US\$ low	US\$ high	US\$ low	US\$ high	US\$ low
Vaccine	1.175	0.820	1.410	0.950	1.520	1.064
Vaccine waste	0.588	0.164	0.000	0.000	0.000	0.000
Device	0.100	0.084	0.100	0.084	0.170	0.130
Device waste	0.002	0.002	0.002	0.002	0.000	0.000
Cold chain*	0.240	0.240	2.400	0.500	0.050	0.000
Disposal	0.045	0.025	0.045	0.025	0.028	0.015
Cost per dose administered	2.150	1.335	3.957	1.561	1.768	1.209

\* Portion of cold chain costs incurred at peripheral level.

Source: Based on device, vaccine and waste costs presented in cost study PATH-MOH Indonesia, 1997.

### 3.3.2 Status

Prefilled monodose injection devices, for both liquid and lyophilized vaccines, have been on the USA and European markets for 20 years. However, they incorporate glass containers and are often more costly than the vaccine itself. Moreover, they are not packaged so as to prevent their being used more than once. They typically occupy more than 20 times the storage volume of 10-dose presentations and twice the volume of single-dose vials, although a new plastic pouch-and-needle device, developed by the Program for Appropriate Technology in Health (PATH), USA, with support from the United States Agency for International Development (USAID), is being marketed by BD Inc under the trade name UniJect™. This device has been extensively field-tested in Bolivia and Indonesia, where health workers found it easy to use for the injection of tetanus toxoid and village midwives could administer the birth dose of hepatitis B vaccine, thereby raising coverage with this vaccine.<sup>8</sup>

BD Inc and UNICEF are engaged in a project to immunize 20 million women in risk areas for neonatal tetanus using UniJect™. In addition, PATH is working on the application of UniJect™ with multiple partners in studies on the delivery of the injectable contraceptive Cyclofem. In a study in Brazil, UniJect™ has shown such high levels of safety and user acceptance that the government has declared the device to be suitable for the delivery of all injectable contraceptives.

This device guarantees the integrity and sterility of the vaccine dose up to the moment of use. It generates 30% less volume and weight of waste than the 2-ml syringe and monodose vial, possesses the auto-disable property and occupies less than half the volume of the syringe and vial in distribution. However, the needle-stick hazard remains.

<sup>8</sup> *Achieving universal childhood immunization with hepatitis B vaccine: policy and cost-effectiveness issues.* Prepared for the Ministry of Health, Indonesia; PATH; April 1996.

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### 3.3.3 Prospects

Clearly, the convenience of UniJect™ facilitates a high public health impact in areas that are difficult to reach. The cost of administering tetanus toxoid with the device rises from around \$0.10 to around \$0.22, which means that only a niche market is likely to be available for this presentation. However, when more costly vaccines, such as hepatitis B vaccine or multivalent vaccines are considered, the presentation is economically viable as well as safe and convenient.

As new, more costly vaccines are introduced and as current antigens are incorporated into them, monodose prefilled injection devices such as the UniJect™ are likely to become mainstream presentations. Indonesia has begun to fill hepatitis vaccine in UniJect™ for distribution to several provinces for routine immunization. Studies are being conducted by other vaccine manufacturers on the use of monodose prefilled devices that require compatibility testing for long-term storage in plastic.

**Fig. 5. UniJect™ monodose prefilled injection device**



## 3.4 Needle-free injections

### 3.4.1 Rationale

Non-parenteral routes of vaccine administration involve a smaller risk of transmission of bloodborne pathogens than that associated with injections. However, with the exception of oral polio vaccine, which has a limited horizon, most vaccines emerging during the coming decade will be injected. Needle-free injection delivers the dose of vaccine at high velocity into the dermal and subcutaneous layers without the penetration of a needle. Needle-free injectors eliminate the risk of accidental needle-stick after injection and during the process of waste management. They also generate the least waste. Technologies are being developed for both multidose and monodose presentations of vaccine.

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**Multidose** injectors draw vaccine from multidose vials and can give sequential injections rapidly, with no risk of accidental needle-stick, no sharps waste burden and the lowest cost per dose delivered.

**Monodose** injectors draw vaccine from single-dose containers. Each container is either an integral part of an entirely disposable injector or is a cartridge fitting inside a reusable injection device. In both cases the fluid pathway of the injector is entirely disposable and non-reusable.

### **3.4.2 Status**

Tests on animals and humans have shown current models of **multidose** injectors to be a potential source of cross-infection with bloodborne pathogens. These injectors are no longer recommended. Fortunately, the testing appears to have revealed the contamination pathway. Modified multidose injectors are now being tested.

**Fig. 6. Multidose needle-free injector**

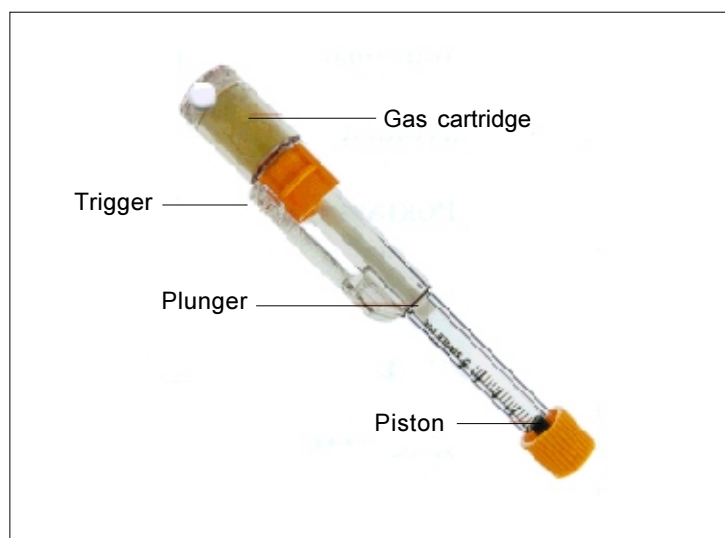


Several models of **mono-dose** injector are on the market, including both the entirely disposable type and the cartridge type. The main constraint for immunization services in developing countries is that new vaccine products must be regulated for storage in these devices. This is not a serious obstacle if a standard cartridge is established, and the cost per shot could be low because the price of the injector is amortized over its lifetime. If, however, a proprietary cartridge is to be developed for each injector, or if the entirely disposable type is to be used, the costs will be very high (\$1-1.50 per shot for the device only) and it is not clear how such diversity could be handled by either the vaccine industry or the public sector consumers for the developing countries.



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**Fig. 7. Monodose needle-free injector**



For this reason, Aventis-Pasteur in France and Am-O-Jet in the USA are collaborating on a new initiative to advance a standard low-cost cartridge that would be available to all vaccine manufacturers and would fit a wide range of reusable needle-free injection devices. Such a delivery system, while not self-contained and requiring the wide availability of well-maintained injection guns, could be both economic and practical for use in many developing country settings.

### ***3.4.3 Prospects***

If it can be demonstrated to be safe the **multidose** needle-free injector will reduce the cost and raise the safety and speed of injectable immunization campaigns. A very high priority is therefore given to accelerating development work aimed at making such an injector available as soon as possible.

The **monodose** cartridge system has the potential to be used for mass immunization where thousands of injections are given daily with heavy-duty reusable injection devices. With compact, hand-held devices that last for around 25 000 shots without any need for maintenance and are then discarded, it could also be used for routine immunization where only a few doses per day are given. It is not yet clear whether the costs, logistics and safety benefits will favour monodose prefilled needles or the monodose needle-free injection systems.

The time required to develop, validate, register and gain acceptance by vaccine manufacturers and the international health care community of new delivery systems can be 7 to 10 years or more. It is possible that other needle-free technologies currently being developed will compete with prefilled unit-dose jet injection for precedence in public health strategies aimed at reducing injections. These technologies involve transcutaneous, transdermal and transmucosal approaches.

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### 3.5 Thermostable vaccines and vaccine vial monitors

Strict regulations stipulate the refrigerated storage and transportation of vaccine products, even though certain new monovalent products are very heat-stable and certain multivalent products contain some very stable antigens. To conform with these regulations a cold chain system has been established all over the world which increases the cost of immunization by around 14%. This figure will rise if new monodose vaccine products are to remain in the cold chain. Vaccine vial monitors (VVMs) enable health workers and managers to react appropriately to weaknesses in the cold chain and they make it possible to use vaccines where ice and refrigeration are unavailable. They do not, however, allow for the elimination of the cold chain.

#### 3.5.1 Rationale

Vaccine distribution without a cold chain would considerably simplify the delivery system and make it easier to integrate with drug distribution in developing countries.

Fig. 8. Vaccine vial monitors



Sugar-glass drying technology allows vaccines to be made which can be stored and transported routinely at tropical room temperatures or in freezing climates. Extremes can be monitored by VVMs. New multivalent vaccines stabilized with this technology would be regulated for shelf-life storage at temperate or tropical room temperatures.

Clearly, while some vaccines are still regulated for refrigerated storage the cold chain must be retained for them. But many multivalent vaccines now incorporate both new and traditional bacterial vaccines, such as DTP. Once all vaccines have been stabilized there will no longer be a need for refrigerated equipment and the associated maintenance. As a consequence the global savings annually will amount to approximately \$200 million.

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### Why sugar glass?<sup>9</sup>

Research studies conducted in industry have shown that the long-term stabilizing ability of certain sugars is vital for a vaccine's high-temperature stability. The first hint of the potential of sugars as vaccine stabilizers came from the cryptobionts, organisms that can dry out completely under stressful physicochemical conditions and regain full metabolic activity when subsequently exposed to water. Cryptobionts contain high concentrations of trehalose, a simple yet unique disaccharide. Trehalose is among the most chemically unreactive and stable of sugars. The two glucose moieties are joined through their reducing carbons and the resulting  $\alpha$ -1,1 glycosidic bond has a very low energy, less than  $10^{-1}$  kcal/mol. This makes trehalose not only non-reducing but very stable to hydrolysis. Other non-reducing sugars have also been used effectively for the preservation of biological materials.

A sugar-based drying and stabilizing technology has already been developed and applied to a number of vaccine antigens. For example, dried measles vaccine stabilized with trehalose suffered no loss of activity after two months at room temperature, whereas a commercial freeze-dried measles vaccine lost over 90% of the original titre in the same time. In another study the stability of a trehalose-dried combination of diphtheria, tetanus and acellular pertussis antigens (DTaP) adsorbed to aluminium hydroxide adjuvant was compared with the conventional vaccine. After storage at 60°C for up to 12 weeks the trehalose-dried DTaP antigens and adjuvant were biologically and chemically unaltered. Preclinical investigations have demonstrated the immunogenicity and potency of the trehalose-dried candidate vaccine.

Only live polio vaccine failed to dry<sup>10</sup> successfully. This was because the complex molecular structure of the virus prevented full penetration of trehalose.

#### 3.5.2 Status

Intellectual property in sugar-glass drying processes for vaccines is held by a small number of companies and individuals, including:

- Durer Chemical Corporation, USA;
- Quadrant Health Care, United Kingdom;
- Commonwealth Scientific and Industrial Research Organization, Australia;
- Universal Preservation Technologies, USA;
- B. Roser, Anglia Research, United Kingdom.

These sources of intellectual property have been used by the vaccine industry to develop sugar-glass dried versions of their products. The results have been encouraging but the high cost of regulation and the lack of a sure market have prevented any sugar-dried vaccine product from being licensed.

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<sup>9</sup> Advances in parenteral delivery of vaccines as solids may revolutionise immunization campaigns worldwide. *Genetic Engineering News*, 15 February 1998.

<sup>10</sup> *Development of a dry and thermostable oral polio vaccine*. RIVM-Kampinga et al., WHO-funded research, 1993.

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### **Automatic reconstitution**

With a view to enabling sugar-dried vaccine to be administered as a liquid, work is in progress to develop the automatic reconstitution of such vaccine in a type of needle hub that can be fitted to a standard syringe or a monodose plastic reservoir such as the UniJect™. The vaccine, dried as a foam, reconstitutes during the process of injection as the syringe or pouch forces diluent through the needle hub and down the needle.

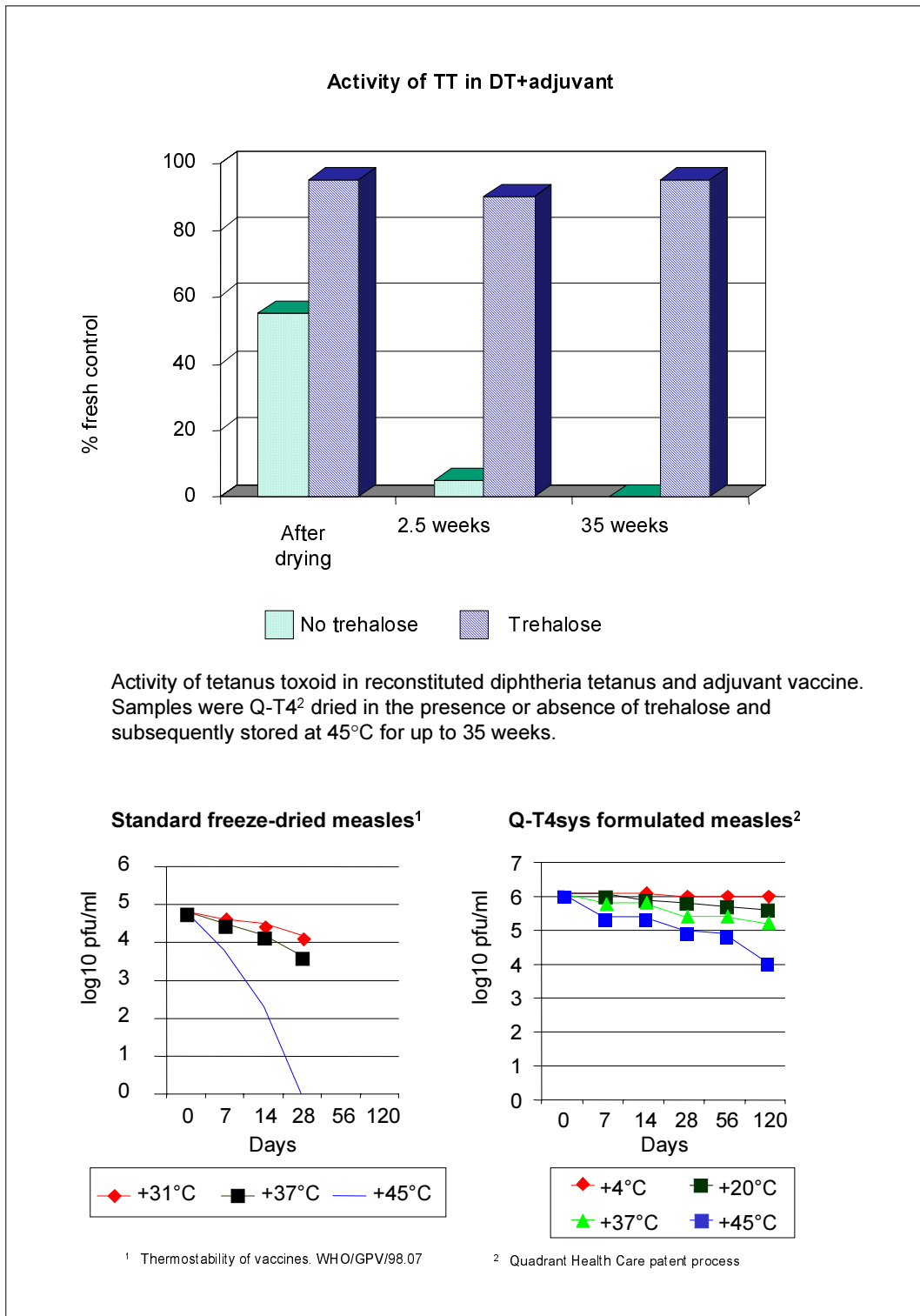
### **Needle-free systems for dried vaccines**

Two parenteral systems have been proposed for the delivery of sugar-glass dried vaccines. The first requires the vaccine to be spray-dried in the form of a fine powder (1-3 microns), suspended in a non-aqueous liquid, and injected through needles or under pressure as a liquid jet stream. The second, named PowderJect™, is designed to deliver powder and could inject particles of sugar-dried vaccine measuring approximately 40 microns in diameter at 850 metres per second directly into the epidermis. In this case, the vaccine would be stored between two diaphragms in a removable or integral capsule within the injector body. Both systems require research and development, but PowderJect™ has already reached the market with anaesthetic products and has been successfully tested with vaccines.

### **The properties and potentials of sugar-glass vaccines:**

- thermostable;
- demonstrated with recombinant, bacterial, viral vaccines;
- inert (non-hygroscopic);
- rapidly soluble;
- inert (non-reactive);
- potential for combination;
- controlled particle size;
- may be foamed, spray-dried, air-dried, vacuum-dried, milled or extruded;
- drying processes which are generally faster than freeze-drying and do not require refrigeration;
- this could influence the speed, capacity and cost of vaccine production.

**Fig. 9. Comparative heat stability of measles vaccine in alternative drying systems**



### 3.5.3 Prospects

Vaccine manufacturers have been reluctant to exploit the sugar-glass drying technology because there is no market for stabilized vaccine products in the industrialized countries and the commitment of clients in the developing world is uncertain. This reluctance is unlikely to be overcome by a single decision or a single expression of commitment. Nevertheless, WHO launched the “Sugar Project” on 1 January 2000 in accordance with the strategy outlined in Fig. 12.

Fig. 10. Autoreconstitution device

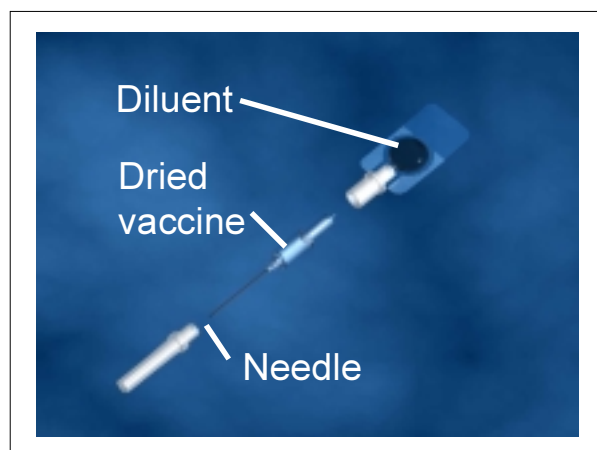
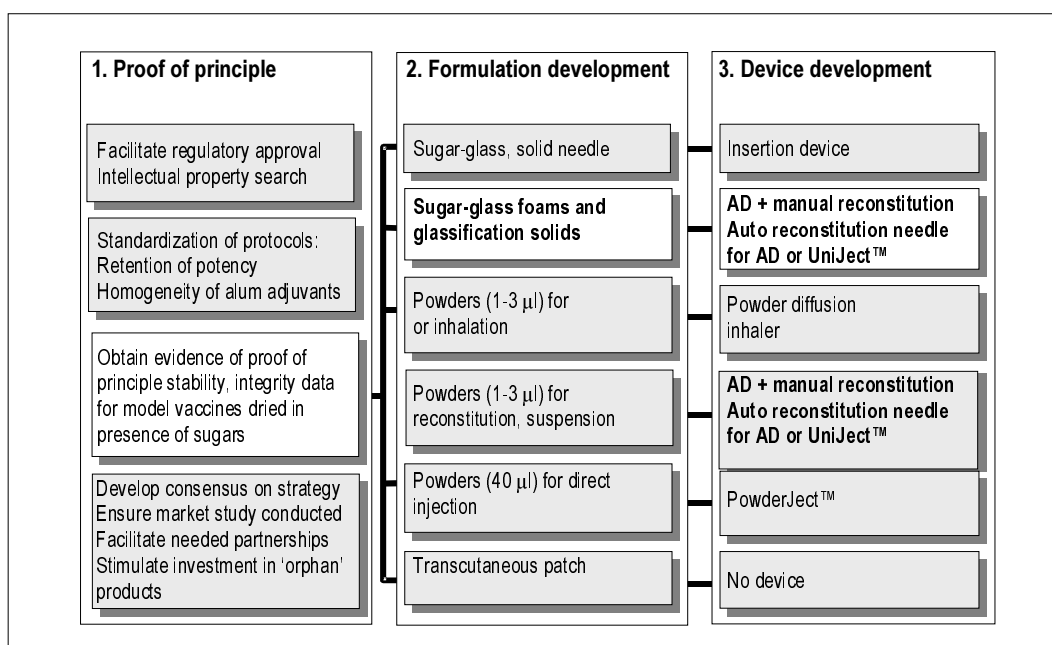


Fig. 11. Strategy of the “Sugar Project”



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## Licensed sugar-glass dried vaccine products

The most advanced path towards thermostable vaccines is indicated in bold in Fig. 12. This path represents a priority for the partners involved because it offers the best chance for early progress and could establish a prevalent vaccine delivery technology during the next 10 years. Since 1999, WHO has been collaborating with PATH in this course of development. Funding comes from the HealthTech Programme, which is supported by USAID, and from the Bill and Melinda Gates Children's Vaccine Program. The project will proceed in the following four steps, each developing a licensed product.

- First, a demonstration that measles vaccine can be more economically and rapidly produced than the current freeze-dried vaccine by using these drying methods.<sup>11</sup> These factors are critical to global measles control and elimination.
- Second, a demonstration that measles vaccine can also be sugar-dried and presented in a prefilled, monodose injection device that automatically reconstitutes the dried vaccine during the process of injection. This product has the potential to raise routine coverage with measles vaccine and to assure safety.
- Third, the development of a sugar-glass dried multivalent vaccine in an autoreconstitution monodose prefilled needle and the demonstration of shelf-life at tropical room temperature.
- Fourth, the development of a sugar-glass dried multivalent vaccine in a cartridge, to be used either as a powder for direct powder injection or as a non-aqueous suspension for liquid needle-free injection.

## Sugar-glass needle

Possibly the most radical and ambitious solution to needle-free parenteral delivery of sugar-glass dried vaccine is the concept of the sugar needle. This concept, as yet only superficially tested, suggests that it is possible to fabricate a sugar glass as a solid needle so that the vaccine itself is the needle. Once inserted the needle quickly dissolves, leaving only the packaging and the insertion device behind. The concept remains both controversial and tentative. It is claimed that solid sectors of the needle may be dedicated to different antigens and that the engineering of the needle surface may permit dissolution in the body at controllable rates.

A related concept is that of a **hypodermic needle constructed from a biodegradable material**, possibly even a sugar, which would achieve the safety advantages of needle-free injection with a simpler, more conventional technology. The realization of this concept is not yet on the horizon but should be pursued so that the safety of needle-based injection systems can be maximized.

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<sup>11</sup> The Sugar Project Working Group, which met in Geneva in March 1999, noted that alternative air- or vacuum-drying processes that create a sugar-glass foam are three times quicker than freeze-drying although they can be conducted without refrigeration in the same equipment. The resulting dried vaccine product reconstitutes several times faster than freeze-dried vaccine and is at least four times more heat-stable.

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## 4. Timetable and milestones

Each technology passes through the phases of research and development, product launch, market development and post-market monitoring.



Activity	00	01	02	03	04	05	06	07	08	09	10
<b>1. Safer multidose vaccine delivery</b>											
• AD syringes and safety boxes only for mass immunization											
• AD or sterilizable syringes and safety boxes for routine; <b>no</b> disposable syringes											
• Only AD syringes for routine, unless sterilization monitored											Unlikely that multidose vials will still be used.
• Needle-free manual reconstitution devices											
• Reintroduction of multidose, reusable needle-free injectors for campaigns											
• Thermoprocessing											
• Needle destructors											
• Small-scale incinerators											
<b>2. Monodose prefilled injection devices</b>											
• Tetanus toxoid and monovalent hepatitis B vaccine in monodose prefilled devices											
• Liquid pentavalent vaccine in monodose prefilled devices											
• Development of monodose needle-free injectors for all immunizations											
<b>3. Thermostable vaccines distributed with drugs</b>											
• Development and introduction of a sugar-glass multidose measles vaccine											
• Sugar-glass measles vaccine in autoreconstitution monodose prefilled needle											
• Sugar-glass multivalent vaccine in autoreconstitution monodose prefilled needle											
• Sugar-glass multivalent vaccine in monodose needle-free injectors											

**Key:**  Research and development  Product introduction  Market development  Post-market monitoring