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Technologies to Improve Immunisation Safety

C. John Clements, Maria Teresa Aguado and *Luis Jódar*

Department of Vaccines & Biologicals, Health Technology and Pharmaceuticals Cluster, World Health Organization, Geneva, Switzerland

Abstract

Ever since a vaccine was first used against smallpox, adverse events following immunisation have been reported. Adverse reactions may be caused by a fault in vaccine production, idiosyncratic responses or unsafe handling and vaccine administration practices. Technological advances that promise to bypass many of the dangers currently associated with vaccine administration are described. Plans for the next decade and beyond include developing injection-free systems for vaccine delivery that overcome the limitations of current immunisation programmes and help prevent programmatic mistakes. Also under development are new parenteral administration devices such as the auto-disable syringe and the mono-dose prefilled device, and mucosal and transcutaneous immunisation systems. Training needs to be at the forefront of efforts to limit human error. Above all, there must be a willingness to respond to new climates and new technologies in order to ensure safe immunisation of children globally.

Vaccination is widely recognised as one of the most efficient and least costly tools available in public health. An analysis of health interventions published in the 1993 World Bank Report on World Development[1] showed that basic childhood vaccination was the most cost-effective health intervention in terms of averted disease burden and economic savings for low- and middle-income countries.

Even a cursory glance is sufficient to grasp the tremendous progress that has been achieved in preventing infectious diseases through vaccination. In 1974, when the Expanded Programme of Immunisation (EPI) was launched by the World Health Organization (WHO), only 5% of the world's children were immunised against the initial six target diseases; tuberculosis, diphtheria, tetanus, whooping cough, polio and measles.[2] However, the launch of vaccination on a national scale increased vaccine coverage to almost 80% by 1990, with an estimated 3 million childhood deaths being prevented each year and at least 750 000 fewer disabled children, worldwide.[2] Today, over 100 million children are immunised annually throughout the world. It is estimated that 1.2 billion vaccine injections are performed every year, and the number of antigens routinely administered is increasing rapidly.[3] It is anticipated that most of the new vaccines that will be available by the year 2005 will be administered by injection, and the number of immunisation-related injections will have increased further.

Vaccines are extremely safe; safer than acquiring the wild disease by many orders of magnitude. However, the situation is somewhat different when it comes to safety related to the administration of vaccines. In the developing world, the general population continues to be at risk of acquiring bloodborne diseases as a result of administering vaccines in an unsafe manner. The WHO has estimated that

about 50% of the curative injections of vaccines and one-third of the childhood vaccine injections are delivered in an unsafe manner.[2] Such unsafe delivery of vaccines by injection clearly has the potential to lead to the transmission of blood-borne diseases such as viral hepatitis B and C and HIV/AIDS.[4-6] Several studies have identified unsafe administration of vaccines by injection as a major risk factor in outbreaks of blood-borne infectious diseases.[7-9] Although many of the currently available vaccines used in immunisation programmes have not changed over decades, the public perception regarding their safety has shifted.[10] Paradoxically, as many of the old scourges such as poliomyelitis, diphtheria and tetanus have almost disappeared as a consequence of successful immunisation programmes, the general public has become increasingly concerned about the risks associated with vaccines. Vaccines are administered to healthy individuals, most of them infants and young children, and therefore require the practice of high standards of safety. Furthermore, since vaccination is such a common and memorable event, it is easy to surmise (for the most part, incorrectly) a causal relationship between vaccination and the onset of an illness. Reasonable as well as outrageous claims have been made against both the old and the newly-introduced vaccines.

Against this backdrop, safety related to immunisation (i.e. developing new safer technologies to administer vaccines, ensuring and monitoring the safety of all aspects of immunisation including vaccine quality, storage and handling and the process of vaccine administration) has become imperative. This article discusses the current situation and the potential for future improvements in the safety of immunisation.

1. Causes of Adverse Events

Adverse reactions associated with immunisations, may be caused by a fault in vaccine production, by an idiosyncratic response of an individual to an intrinsic property of the vaccine, or by an error in vaccine handling or administration.

When incrimminating a vaccine for an adverse event, poor vaccine quality is uppermost in the minds of the public. In reality, the stringent controls imposed on vaccine manufactures ensure a very high standard of production, making it extremely unusual to identify production errors as a cause of adverse reactions related to vaccination.[2]

Vaccines compare favourably with other pharmaceutical agents in terms of the incidence of adverse reactions.[11,12] It is an established fact that a very small number of individuals are harmed by immunisation [e.g. vaccine-associated paralytic poliomyelitis; anaphylaxis induced by varicella, measles/ mumps/rubella (MMR) or hepatitis B vaccines; encephalitis following measles vaccination].[13,14] Considerable efforts have been made to assemble the available data on vaccine-associated adverse events.[13,15] However, our knowledge about causality and pathogenesis is still fairly limited.

The area where positive steps can most readily be taken to reduce the incidence of advere events involves programme errors. Several examples of programmatic errors that can potentially cause adverse events are listed below.

1.1 Inappropriate handling of vaccines

Nonsterile procedures during reconstitution or inadequate storage, and the use of reconstituted vaccine over several vaccination sessions are likely to result in the administration of contaminated vaccine. Bacillus Calmette-Guerin (BCG) vaccine has no preservative and measles and yellow fever vaccines contain only a limited amount of antibacterial. A rapid multiplication of pathogens could therefore occur, particularly when reconstituted vaccine is allowed to warm or is kept overnight. Contamination of reconstituted measles vaccine with *Staphylococcus aureus* has been documented in a number of countries with disastrous results.[16-18]

Injection of inappropriate substances is another potential source of adverse events. Dangerous medications packed in vials or ampoules that resemble vaccines or their diluents have been used by mistake to reconstitute vaccines. There have been reports of inadvertent administration of muscle re-

laxants such as pancuronium bromide or succinylcholine or administration of insulin, resulting in deaths in infants.[18]

The use of improper techniques during the administration of vaccines can lead to infections. BCG lymphadenitis has been reported following immunisation with the BCG vaccine.[19-21] Paralysis has been documented following administration of vaccines too close to the sciatic nerve.

1.2 Unsafe Administration Practices

Syringes and multi-dose vials constitute the main elements in the delivery system involving immunisation procedures in developing countries, accounting for 80% of the vaccines administered globally. The WHO estimates that, worldwide, around one-third of the vaccine injections are administered in an unsafe manner.[3] Sterilisation methods are not always appropriately followed, and the reuse of syringes and needles is fairly common in developing countries because of inadequate supply, significant resale value and a cultural resistance to waste.[8] Accidental needle-stick injury has also become a major public health problem, as shown by studies in industrialised countries where as many as 75% of health workers under report needle-stick injuries.[22] In developing countries, the conditions of work are also arguably more difficult. For example, over half of the injections for immunisation are provided with sterilisable syringes and needles that must be handled and cleaned individually before sterilisation. Accidental needle-stick injury can also occur as a result of failure to dispose of equipment safely. In developing countries, discarded vaccine needles can be found on the ground in the vicinity of many hospitals and health centres.

2. Development and Introduction of Safer Technologies

A number of adverse events associated with immunisation can be greatly reduced or avoided if current vaccine administration techniques can be simplified and improved. Designing systems that are simpler and less prone to adverse events, regardless of the human factor, are therefore very attractive solutions. The current biotechnological revolution, together with increased knowledge about immune responses, is allowing the construction of new delivery systems and technologies that may revolutionise immunisation programmes in the coming decade.

2.1 Parenteral Administration of Vaccines

2.1.1 Needle-Containing Injection Devices and Technologies

It is anticipated that future delivery systems will:

- protect the integrity and sterility of the vaccine dose until the moment of administration
- minimise the risk of needle-stick injury through use of non-reusable devices
- guarantee the availability of sterile injection devices with each vaccine dose
- simplify distribution, eliminate vaccine wastage and minimise the volume of contaminated material to be disposed of
- increase thermostability.

The preferred syringe for mass immunisation campaigns is currently the auto-disable (A-D) syringe.[23] This syringe has been tested both in the laboratory and the field,[24] and has been shown to be easier to use and is preferred by health workers. Overall, the A-D syringe contributes to decreased blood-borne pathogen transmission between patients by preventing reuse and resale, both of which are common practices in developing countries. In a field trial in Indonesia, the SoloShot A-D syringe delivered more precise and consistent vaccine doses and 15% more doses per vial than disposable syringes.[25] However, A-D syringes do not eliminate the hazards of sharp waste in the environment. Furthermore, they are still more expensive than other types of syringes, although costs are being reduced through transfer of technology and market forces.[26]

The potential for safer injection practices increases with the use of mono-dose, prefilled vaccine presentations integrated with the injection device. This technology eliminates the risks of cross-contamination and guarantees the integrity of the

vaccine up to the moment of use. Prefilled, monodose injection devices have been available in the US and Europe for almost 20 years. However, the vaccine in these devices is stored in glass ampoules that are often more expensive than the vaccine itself. A few years ago, the Program for Appropriate Technology in Health (PATH) developed a plastic pouch holding a single dose of drug or vaccine linked directly to a hypodermic needle and designed to self destruct after use. The device was field tested in Bolivia where traditional birth attendants were trained to administer tetanus toxoid vaccine during outreach activities. In Indonesia, midwives used the same device during home visits to immunise newborns with hepatitis B vaccine and to immunise their mothers with tetanus toxoid vaccine. These studies reported high user preference attributed to ease of use and speed of injection, as well as economic benefits such as reduced wastage and simplified logistics.[27-29]

Fewer doses means less opportunity for mishap. Today, the development of combination vaccines is proceeding rapidly with the creation of new formulations containing an array of antigens. Combination vaccines can not only reduce the number of injections, needles and syringes, but can also reduce the need for transport, storage, paperwork, training and in some cases, reduce the number of visits needed. Among the first combinations formulated were the diphtheria/tetanus/pertussis (DTP) vaccine, followed by the multi-strain Salk polio vaccine and the MMR vaccines. All major vaccine manufacturers are currently working, either alone or through strategic alliances, towards developing different variations of multivalent vaccines. They are doing this by adding antigens such as inactivated polio virus, conjugated *Haemophilus influenzae* type b polysaccharide and hepatitis B surface antigen to the DTP vaccine either in its whole cell or acellular pertussis formulations.[30] However, the decision to introduce a particular combined vaccine in a given country is influenced not only by epidemiological desirability and technical feasibility, but also by cost effectiveness, the country's infrastructure capacity to add a new antigen, the affordability of the multivalent product compared to the separated components and the implications for local producers. A selection of combination vaccines of highest priority is needed, as well as a careful assessment of the potential demand for these combination vaccines and an indication of how accurate these demand estimates are.[31,32]

For many years now, the scientific community has been striving to develop vaccines capable of conferring a strong immune response, thereby eliminating the need for booster doses. A single dose of antigen could be delivered and released in a predetermined way, mimicking conventional vaccines that would require multiple doses. This 'single' dose vaccine would go a long way in solving the problem of high vaccine drop out rates among hard-to-reach populations living in remote areas of the developing world. So far, research has centred largely on the development of a single-dose tetanus toxoid vaccine embedded in tiny polymer beads known as microspheres. Following administration of the vaccine, the microspheres release tetanus toxoid at a rate determined by the size and chemical composition of the surrounding capsule. There is every expectation that controlled-release vaccines manufactured using microspheres will prove both safe and effective for the delivery of tetanus toxoid as well as other antigens, new adjuvants and cytokines.[33-35]

The delivery systems described above contain a hypodermic needle and therefore the possibility of transmission of blood-borne pathogens as a result of accidental needle-stick injury can not be avoided. In contrast, needle-free devices will eliminate both accidental needle-stick transmission of pathogens between patients and health workers, as well as the risk of accidents in the community related to improper disposal of hypodermic needles.

2.1.2 Needle-Free Injection Devices

Multi-dose injection systems such as jet guns draw vaccine from multi-dose vials of vaccine and can administer sequential injections rapidly. They have been available for a number of years and have no risk of accidental needle-stick injury, with no sharp waste burden and the lowest cost per dose delivered. However, current multi-dose jet injectors have

been shown to have an inherent risk of blood-borne pathogen transmission.[36] The WHO presently advises against the use of such multi-dose needle-free injectors on more than one patient and is supporting the development and evaluation of modified jet injectors that avoid blood contamination.

While eliminating the risks associated with accidental needle-stick injury, liquid needle-free injectors deliver solutions that are less stable than powders and are usually vulnerable to freezing. Injection of liquids can also break the skin causing a wound. For these reasons the WHO is supporting the development and introduction of needle free, injectable, sugar-based dry power vaccines.

Air-drying in the presence of certain sugars such as the di-saccharide trehalose or its derivatives, produce a powder that is chemically inert, unaffected by ambient humidity and with a particle size and rate of dissolution in aqueous liquid that can be controlled accurately. Sugar-based dry powders may also allow the vaccine to be presented in the same form and in the same volume in which it will be usually administered. Besides, bio-compatible sugar glass may not only serve to stabilise the vaccine antigens but also control the rate of antigen release according to the composition of the glass. Release is triggered by contact with water or body fluids. This induces surface erosion of the glass, so that the active component remains embedded in the protective matrix of the glass and will only come into contact with body fluids at the moment of release. If the sugar-glass controlled-release strategy proves to be effective, the outlook for this technology as a fundamental component for drug and vaccine development will be most appealing.[37,38] Already, sugar-based dry powder vaccines are being tested in animals and occasionally in humans. A few companies are currently focusing on the development of injection devices to deliver these vaccines. The most advanced, PowderJect™, is designed to deliver powder and could inject particles of sugar-dried vaccine directly into the epidermis and has already been tested in human volunteers.[39,40]

Presently, vaccines are required to be stored and transported under refrigeration, although some vaccines are relatively heat stable. For this purpose, a global cold chain system has been established that has increased the cost of immunisation by around 14%. This figure will rise if new mono-dose vaccine products are to remain in the cold chain. Vaccine vial monitors (VVMs) presently enable health workers and managers to monitor the heat exposure of individual vials and react appropriately to weaknesses in the cold chain. This also opens up the possibility of vaccines being used in difficult circumstances well beyond the reach of conventional ice-lined vaccine carriers and refrigerators. But VVMs do not go as far as allowing for the elimination of the cold chain all together. Vaccine preparations based upon sugar-based dry powder technology, now under development, would be completely heat stable. This could have a dramatic impact on vaccination programmes in the developing world. New, multivalent vaccines stabilised with sugar-based or other heat-stabilising technology would allow for storage at temperate or tropical room temperatures for the entire shelf life of the product. If all vaccines could be stabilised, refrigerated equipment and their associated maintenance would no longer be needed, saving approximately $US200 million globally each year.[37,38]

2.2 Mucosal Immunisation

As an alternative to needle-free parenteral administration of vaccines, mucosal vaccination either by nasal or oral routes offers obvious advantages in terms of safety. It eliminates the risks of infection (person-to-person, person-to-health worker and environmental), is generally more readily accepted than injectable vaccines and offers large logistic advantages for immunisation programmes, as attested by the polio eradication initiative.[41]

The mucosal cells, in the digestive, respiratory or reproductive systems, are constantly exposed to antigens of microbial, environmental or food origin and require an effective defence system for immunological protection. The mucosal immune system extends over 400m^2 in humans and the cellular mass exceeds the total number of lymphoid cells found in the bone marrow, thymus, spleen and

lymph nodes combined. Immune cells stimulated at one mucosal surface disseminate protection to other mucosal surfaces, thus providing the potential for vaccines to be used for a broad spectrum of infectious disease.[42]

Successful experience with the oral trivalent attenuated Sabin poliovirus vaccine, the major driver in the global polio eradication effort, has triggered research into oral vaccine formulations. There have been a few successes such as the Ty21 a live oral typhoid vaccine, CVD 103-HgR live oral cholera vaccine, B-subunit inactivated *Vibrio cholerae* 01 combination oral vaccine, and the trivalent cold-adapted live intranasal influenza vaccine.[43-45] There have also been some drawbacks, notably, studies suggesting a link between the oral tetravalent human rhesus reassortant rotavirus vaccine and intussusception, resulting in this oral vaccine being no longer recommended for infant use by the US Advisory Committee on Immunisation Practices (ACIP).[46]

New delivery systems are now being developed for the administration of nonliving and living antigens (proteosomes, cytokines) to mucosal surfaces.[47,48] Polymeric micro- and nano-particles, which allow encapsulation of antigens inside a polymeric matrix thus protecting them against enzymatic and hydrolytic degradation, could potentially be used for mucosal vaccine delivery of peptide antigens.[49,50] The application of recombinant DNA technology has also allowed the construction of recombinant strains that may prove useful as either vaccines or vectors to deliver antigens. Furthermore, DNA vaccine plasmids have been successfully administered in animal models via mucosal surfaces using nonliving delivery systems and live vectors.[51,52]

Finally, the potential impact of oral vaccines could be even greater with the advent of transgenic plants. These plants act as vehicles for the expression of antigens which can then be administered as edible vaccines. Subunit vaccines produced in plants against viruses (Norwalk, hepatitis B) or bacteria [Enterotoxigenic *Escherichia coli* (ETEC), cholera] have been shown to induce strong immune responses in animals. Encouraging results have also been shown in a phase I 'proof of principle' clinical trial, where 90% of individuals who were fed small amounts of transgenic potato expressing heat labile enterotoxin B (LT B) subunit developed significant increases in serum immunoglobulin G (IgG) LT antitoxin.[53,54]

Purified recombinant and synthetic peptide vaccine candidates have proved to be weakly immunogenic. The availability of improved adjuvants suitable for clinical use is therefore improtant. Such adjuvants enhance the immunogenic properties of weakly immunogenic vaccines and display different profiles of activity to achieve either a humoral or cell-mediated immune response. New adjuvants for mucosal delivery are now at an exciting stage of development with many candidates undergoing clinical trials (e.g. emulsion-based adjuvant formulations, saponins and immune stimulating complexes (ISCOMS), monophosphoryl lipid A derivatives, non-ionic block copolymers, etc.).[55]

2.3 Transcutaneous Immunisation

Transcutaneous immunisation (TCI) which involves delivery of antigens by topical application to intact skin, may have profound implications for immunisation programmes because of their safety and immunological merits. From a safety point of view, TCI is a simple, needle-free vaccine delivery system with the potential to eliminate risks associated with injection devices. The feasibility of TCI is based on the potential role of the skin as a potent immunological site. Penetration of the skin through hydration is a key factor in targeting Langerhan's cells which are potent antigen-presenting cells found in the superficial layers of the skin. Langerhan's cells are abundant in the skin (25% of surface area) and are highly phagocytic, inducing co-stimulatory molecules and cytokines. Preclinical studies have shown that TCI is able to induce priming and secondary humoral immune responses, without signs of local or systemic toxicity.[56,57]

3. Conclusion

Vaccines prevent disability and death from infectious diseases and are regarded as one of the

most cost-effective interventions within the public health armamentarium. However, it is also recognised that not all vaccines are completely safe or protective in every vaccinated individual. Since vaccines were firstly used against smallpox, adverse events following immunisation have been reported, some due to the vaccine itself and others due to the method of vaccine administration. Many of the undesirable effects associated with vaccination are preventable through the advent of new technology.

Immunisation will expand dramatically in the next century, as the number of vaccines administered increases and as mass control efforts get under way. With few exceptions, most vaccines are administered as part of routine childhood immunisation programmes. It is anticipated that the majority of new vaccines that will be available by the year 2005 will be injectable and the number of vaccine-related injections will increase further. Those allegations regarding vaccine-related adverse effects that are not rapidly and effectively dealt with may undermine confidence in a vaccine and ultimately, may have dramatic consequences for immunisation coverage and disease incidence.

It is becoming increasingly apparent that changes are needed to transform today's immunisation delivery system into a one that is more equitable, efficient and safe. The 21st century brings reformed health systems that better integrate preventive and curative services, new multi-valent vaccines and technologies for safer administration and simpler distribution. As this article has attempted to show, there is for the first time, the possibility of a vaccine delivery system that does not require refrigeration, is closely integrated with the delivery of drugs, utilises safe, pre-filled injection devices containing single doses of thermostable vaccines, and processes waste at the point of use without harm to the environment. However, only the shared and sustained commitment to this vision will ensure safe immunisation for all the world's children.

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Correspondence and offprints: Dr *John Clements*, Department of Vaccines & Biologicals, Health Technology and Pharmaceuticals Cluster, The World Health Organisation, 1211 Geneva 27, Switzerland.