If vaccines could be administered without needles and syringes ('sharps'), immunization practice would become safer, more accepted and more suitable for mass use. The author explores the status of technologies that could achieve this aim and the barriers that must be overcome for their implementation.

Can needle-free administration of vaccines become the norm in global immunization?

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Vaccines constitute one of the most cost-effective preventive measures against illness and death from infectious disease. Even as modern biotechnology is generating vaccines against infections that were previously unpreventable, and is improving existing vaccines, other fundamental changes in vaccines and immunization are unfolding on the world scene. Increasingly, the vaccines received by children and adults in industrialized countries are distinct from those given in developing countries, as are their site of manufacture and popular perceptions of vaccine safety (Table 1). In developing countries, infections such as measles (which accounts for ~800,000 deaths annually) and pertussis remain killers, whereas in many industrialized countries, where vaccines have controlled these diseases, there is often greater concern over perceived adverse effects of vaccines than over the diseases themselves. Nevertheless, three fundamental themes remain in common worldwide: first, high immunization coverage of target populations generally must be attained for maximal public health impact; second, most current vaccines are administered parenterally using a needle and syringe; third, there is a broad recognition of the need to find ways to administer vaccines without the use of 'sharps' (that is, needles and syringes).

Why needle-free immunization is desirable

Concerns about the number of injections that must be given to infants and toddlers is driving the development of parenteral combination vaccines. In developed countries, immunization without needles or syringes would increase acceptability (and therefore compliance) and would enhance occupational safety for vaccinators and other health providers. This could be particularly critical in the future should it become necessary to immunize large populations rapidly *en masse* in the face of a pandemic influenza or bioterror emergency.

Needle-free immunization is even more critical for developing countries, where expanded immunization coverage and the addition of new vaccines could prevent millions of childhood deaths. Since the mid-1970s, the World Health Organization's Expanded Programme on Immunization (EPI) has recommended six basic vaccines for infants in developing countries: diphtheria and tetanus toxoids, whole-cell pertussis, bacillus Calmette-Guerin (BCG), and attenuated polio and measles; hepatitis B and *Haemophilus influenzae* type b (Hib) conjugate (where disease burden indicates) were recommended subsequently. Developing countries are also increasingly using mass immunization campaigns to drive measles from communities and to curtail meningococcal epidemics. The Global Alliance for Vaccines and Immunization (GAVI) and its associated Vaccine Fund (which was initially capitalized with $750 million from the Bill and Melinda Gates Foundation and later expanded by other donations to ~$1.2 billion) are addressing the long delay in the introduction of lifesaving vaccines between industrialized versus developing countries.

In developing countries, delivery of immunization would be more efficient and economical if all vaccines were temperature stable, required less than three doses to immunize, and could be administered without needles. However, except for the oral polio vaccine, all EPI vaccines are now given using needle and syringe. This is problematic because in developing countries injection safety is a notorious problem[1,2]: improper practices involving nonsterile needles and syringes (often reused from one person to another) cause abscesses and transmit blood-borne pathogens (such as hepatitis B and C and HIV)[2]. Single-use 'auto-disable syringes' provide a partial solution by preventing reuse, but generate infectious waste that must be properly handled lest it endanger bystanders. Although parenteral vaccination accounts for only a fraction of the needles used by health workers, immunization is held to a higher standard than other uses of needles because it involves healthy individuals.

This commentary reviews technologies for needle-free administration of vaccines across mucosal surfaces or through the skin, and considers their practicality for use in developing countries with current and future vaccines and suitability for low (for example, small health centers) and high workloads (for example, mass campaigns), as well as the practical, logistical and economic barriers to development and deployment.

Vaccines delivered through mucosal surfaces

Among the possible mucosal routes (including oral, nasal, rectal, conjunctival and vaginal) for immunization of humans, oral and nasal are practical for all ages and both genders (Fig. 1)[3]. Specialized microfold (M) cells overlying mucosa-associated lymphoid tissues in the intestine and nose constitute effective portals by which vaccine antigens reach underlying inductive sites for immune responses[4]. Properly formulated, mucosally administered vaccines can stimulate any relevant type of immune response: secretory IgA (S-IgA), serum IgG–neutralizing antibodies (against toxins and viruses) and cell-mediated responses (lymphocyte proliferation, cytokine production and $CD8^+$ cytotoxic lymphocyte activity). Because they elicit S-IgA, mucosal vaccines are attractive for use against pathogens that cause mucosal infection or invade through the mucosa. Some mucosal vaccines, such as Ty21a live oral typhoid vaccine, stimulate long-term protection lasting up to 7 years[5].

Oral vaccines. Oral polio vaccine sets the standard for ease of administration to individuals of any age. The overall experience with licensed oral vaccines, including Ty21a (ref. 5), live cholera vaccine strain CVD 103-HgR (ref. 6) and nonliving cholera vaccines[7,8], has been positive, although some problems have appeared. In the United States, post-licensure sur-

Table 1 Diverging immunization realities

	Industrialized countries	Developing countries
Infant combination vaccines	Acellular pertussis-based	Whole-cell pertussis-based
Measles vaccine	Trivalent MMR	Monovalent measles
Polio vaccine	Inactivated parenteral	Live oral
BCG	Uncommon	Routine
Varicella, pneumococcal conjugate	Increasingly common	Not introduced yet
Immunization schedule extends to year 2 of life	Routine	Uncommon
Source of vaccine	Industrialized country manufacturers	Mostly developing country manufacturers
Use of multidose vials	Minority of vaccine used	Majority of vaccine used
Public perception	Concerns over vaccine safety	Fear of disease

In contrast to the situation summarized here, as recently as the mid-1980s there was little difference in the array of vaccines given to infants in the industrialized and developing world. In addition, a notable proportion of vaccines procured by UNICEF for developing countries were from manufacturers in industrialized countries (mainly European). BCG, bacillus Calmette-Guerin; MMR, measles-mumps-rubella.

veillance detected an uncommon association between tetravalent reassortant rhesus rotavirus vaccine and intestinal intussusception[9], resulting in its withdrawal from the market. New rotavirus, and perhaps other oral infant vaccines, must address the risk of intussusception through large clinical trials before licensure. It has also been observed that some live oral vaccines are less immunogenic in individuals in developing countries than in industrialized states[10–12]. Contributing influences include small-bowel bacterial overgrowth[13], intestinal helminths[14] and competing enteric viruses.

Unfortunately, there is little clinical experience with platform technologies that might allow existing EPI vaccines to be administered orally or allow development of alternative oral EPI vaccines[3]. These include bacterial and viral live vectors expressing foreign antigens, DNA vaccines administered directly or by means of bacterial vectors[15], transgenic plant 'edible vaccines', and various nonliving antigen delivery systems including liposomes, proteosomes and polylactide/polyglycolide microspheres. Clinical trials with these technologies have yielded mixed results[16–18], some of which are promising[16,17].

Nasal vaccines. Live, cold-adapted trivalent influenza vaccine, administered by a single-use spray device that painlessly delivers vaccine to the nasal mucosa (Fig. 1), is under consideration for licensure by the US Food and Drug Administration (FDA), on the basis of its safety, immunogenicity and efficacy[19,20].

Researchers are seeking well-tolerated adjuvants to enhance immunological responses to nonliving vaccines administered through mucosal surfaces. Cholera toxin (CT) and heat-labile enterotoxin (LT) of enterotoxigenic *Escherichia coli* are powerful adjuvants that enhance local S-IgA and serum antibody responses to coadministered soluble or particulate antigens. Although they are unacceptable as human oral adjuvants, in that as little as 5.0 μg causes severe diarrhea[21], they have been explored for nasal use. LT adjuvant was incorporated in a nasal, nonliving influenza vaccine used in Europe[22]. Disappointingly, however, postlicensure surveillance identified a possible association with cases of Bell's palsy, leading to withdrawal of the vaccine from the market. To increase safety, mutant LT and CT molecules have been modified to reduce toxicity but retain adjuvanticity for antigens coadministered intranasally[23,24]. Safety concerns remain, because in some species ganglioside-binding properties of mutant LT and CT allow uptake by nasal olfactory nerve fibers and retrograde transport to the olfactory lobes of the brain[25]. Because it is not known whether this occurs in humans and what consequences might result, clinical trials using mutant toxins intranasally must proceed with due caution and watch carefully for adverse effects.

Safer intranasal adjuvants are needed. An intriguing one is CTA1-DD, which links the enzymatically active subunit A of CT to an Ig receptor-binding peptide[26], thereby targeting the immune system's B cells[26]. Theoretically, adjuvants like CTA1-DD could be coadministered intranasally with existing diphtheria-pertussis-tetanus (DTP), hepatitis B (HBV) and Hib conjugate vaccines. The effectiveness of these promising nasal vaccination strategies must be documented in infants in developing countries, in whom upper respiratory infections and nasal discharge are highly prevalent.

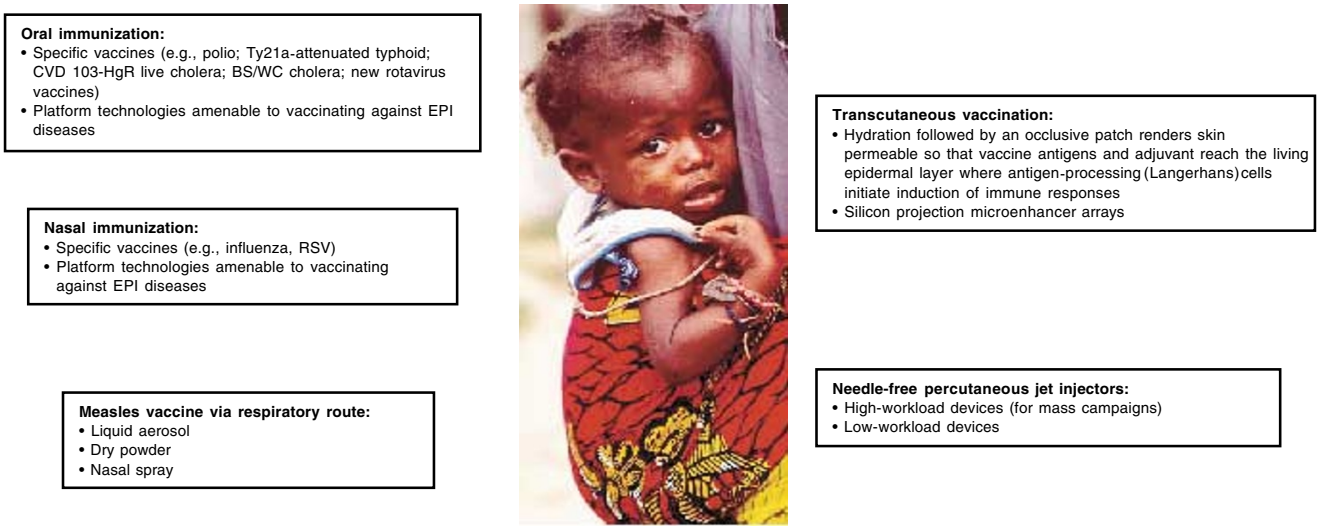

Fig. 1 Promising needle-free vaccination technologies and strategies.

Table 2 Needle-free vaccine technologies versus needle and syringe

Needle-free strategy	Ease of use for health worker	Use with existing 'off-the-shelf' vaccines	Suitability for low workloads[a]	Suitability for mass immunization campaigns	Generates dangerous infectious waste	Remaining clinical development hurdles	Production and supply issues	Financial barrier[b]
Oral								
Adjuvant	5+	Yes	5+	5+	No	4+	3+	3+
Platform technologies[c]	5+	No	5+	5+	No	4+	4+	4+
Nasal and aerosol								
Adjuvant	4+	Yes	5+	4+	No	4+	3+	3+
Platform technologies[c]	4+	No	4+	4+	No	4+	4+	4+
Aerosol measles	3+	Yes	2+	4+	No	3+	3+[d]	2+
Transcutaneous								
Simple patch	3+	Yes	4+	3+	No	4+	3+	3+
Specially formulated patch	4+	No	5+	4+	No	4+	4+	4+
Jet injectors								
Experimental multiple-use nozzle	2+	Yes	2+	5+	No	5+	4+	4+
Single-use nozzle	3+	Yes	4+	3+	No	2+ (or none)	3+	4+
Single-use nozzle with 'universal' cartridge	3+	Yes	4+	4+	No	3+	4+	5+
Current 'sharps' technology								
Auto-disable needle and syringe	3+	Yes	4+	3+	Yes	None	2+	1+

[a]Small health centers and outreach programs. [b]Includes the estimated costs of clinical development leading to licensure, process development, large-scale production and widespread implementation of a needle-free technology to administer current or alternative EPI vaccines against currently targeted diseases. [c]For example, DNA vaccines, live vectors, microspheres, proteosomes, liposomes, transgenic plants. [d] Related to developing a suitable rapid, robust portable aerosol device.

Aerosol measles vaccine. Mass immunization campaigns in Latin America and pilot campaigns in southern Africa with parenteral measles vaccine have decreased measles incidence and mortality. Nevertheless, such campaigns would be simpler and safer if measles vaccine could be administered without needles and by aerosol (creating small particles that reach the lung), which is known to be immunogenic and efficacious[27,28]. Whereas early aerosol measles vaccine devices had limitations in rapidity of use, portability or robustness, there are now under evaluation devices that are both simpler and more compact.

Vaccines delivered through the skin without needle and syringe

Jet injectors. Jet injectors are needle-free instruments that propel liquid (live or nonliving) vaccine through a minute orifice under high pressure percutaneously to the dermis, subcutaneous tissue or muscle (Fig. 1). They induce immune responses comparable to vaccine injected by needle and syringe, albeit accompanied by somewhat higher rates of local reactions. From the 1950s through the 1980s, multiple-use nozzle jet injectors were widely used in mass immunizations against such diseases as smallpox, measles and yellow fever in less developed countries[29]. Multiple (up to 50)-dose vials allowed these devices to vaccinate 600–1000 individuals per hour using the same dose chamber (replenished automatically from the multiple-dose vial after each injection), fluid path and nozzle on consecutive individuals. In the mid-1980s it was recognized that multiple-use nozzle jet injectors could, albeit rarely, transmit blood-borne infections such as hepatitis B (ref. 30). The global emergence of HIV led to their discontinuation.

The 2001 anthrax emergency in the United States has prompted public health authorities to consider how they might conduct mass immunization campaigns if confronted by a bioterror event. This threat has kindled interest in new high-workload devices such as a multiple-use nozzle jet injector that incorporates a disposable cap to reduce the risk of splashback of blood or serum onto the nozzle after injection and injectors that use disposable cartridges that self-disable after use. Should clinical trials document their safety, these instruments could be used in developing countries in mass campaigns against, for example, measles and meningitis.

For administering vaccines in lower-workload situations, there are also available single-dose jet injectors that use disposable cartridges and nozzles for each individual to avoid cross-contamination[31]. Some (such as the Biojector 2000) are presently used to vaccinate in physicians' offices and clinics in industrialized countries to overcome aversion to needles and to avoid needle-stick injuries[31,32]. These devices are not yet affordable for developing countries. One limitation of these instruments is that the vaccine must be transferred from its vial into the cartridge using a needle or special adaptor, a potential complication in developing-country settings[33]. Although this intermediate step is advantageous for reconstituting lyophilized vaccines, it could be avoided if manufacturers prefilled vac-

cines directly into universal standard single-dose cartridges that could fit a variety of injectors. One experimental system, the Imule cartridge[34], which inserted into a hand-wound spring-powered injector (Mini-Imojet)[34], produced encouraging results in adults and infants in industrialized and developing countries[34]. Needle-free devices have also successfully delivered DNA vaccines in clinical trials[35].

Transcutaneous administration of vaccines. Recognition that skin is a highly competent immunological organ replete with dendritic antigen-presenting (Langerhans) cells has led to attempts at 'transcutaneous immunization' (Fig. 1). Hydration followed by application of an adhesive patch makes skin permeable so that vaccine antigens and adjuvant can reach the living epidermis, where Langerhans cells are attracted, take up antigen and initiate induction of immune responses[36]. Results of preliminary clinical trials in which patches with *E. coli* antigen and LT were applied to the skin of healthy adults were encouraging[37]. More practical dry-patch formulations impregnated with various antigens and adjuvant are being prepared for clinical trials. This highly flexible technology holds much potential.

In preclinical studies, DNA vaccines have been administered transcutaneously using various techniques, including an instrument bearing arrays of micron-scale silicon projections (microenhancer arrays or MEAs) that breach the stratum corneum, allowing vaccine to reach the epidermis and to elicit strong immune responses[38]. These promising results are prompting clinical trials.

Feasibility, opportunity and barriers

New oral (for example, rotavirus, *Shigella,* typhoid) and intranasal (for example, respiratory syncytial virus (RSV), parainfluenza) and perhaps also transcutaneous vaccines against specific diseases will surely become licensed during this decade. But what is the likelihood that needle-free vaccination can completely replace the routine vaccines that are currently administered with needles, particularly in developing countries? Accelerated development and implementation of needle-free vaccination technologies are impeded by three formidable barriers: (i) insufficient clinical data, (ii) financial ramifications and (iii) global diversity in immunization practices. It is improbable that alternative EPI vaccines based on platform technologies such as live vectors and DNA vaccines would garner investment to complete clinical development and create manufacturing capacity. This is because the path to licensure of new vaccines, which is based on demonstrating their safety, efficacy and consistency of manufacture, is expensive, time-consuming and very risky. The result is that few succeed[39] (Table 2). It is more likely that investment in platform technologies will be attracted to support the development of vaccines against previously unpreventable infections[39].

Obtaining regulatory approval to administer existing vaccines by alternative routes should be faster and cheaper, particularly when immunological correlates of protection exist. Thus, aerosol or intranasal administration of measles vaccine (either alone, with rubella or as trivalent measles-mumps-rubella) might attract investment, as might the switching of administration routes of existing parenteral EPI vaccines to intranasal or transcutaneous (Table 2). Nevertheless, the hurdle faced by generic strategies to document safety and immunogenicity equivalence must not be underestimated.

Arguably, the greatest likelihood of biological success for non-needle delivery of existing (and future) parenteral vaccines could be by improved jet injectors. In industrialized countries, preparations to immunize populations *en masse* against pandemic influenza and bioterror threats, as well as cultural aversion to needles, are driving interest in jet injectors. However, products geared to populations in the industrialized world will probably be too expensive for developing world needs. If jet injectors do come into wide use, it will further accentuate the divergence in the realities of immunization in the industrialized versus the developing world (Table 1).

Regulatory agencies in industrialized countries set extremely high standards with respect to vaccine safety, often with far-reaching consequences. Following FDA recommendations that thimerosal, which contains ethyl mercury and is used in vaccine production as a bacteriostatic preservative in multidose vials (as well as for other purposes), be removed because of concerns about possible risk of mercury exposure for immunized infants[40], US and European manufacturers are moving to produce, exclusively, single-dose vials.

For the foreseeable future, vaccine manufacturers in developing countries will continue to produce multidose vials containing thimerosal, because a switch to single-dose presentation will require large investments to alter production lines and would increase cost per dose and volume to be handled by the cold chain (refrigerators and transport containers that control temperature thereby protecting live vaccine from high temperature and protein vaccine from freezing) (Table 1). On the positive side, single doses diminish vaccine wastage, a critical concern for expensive vaccines and settings (for example, outreach) where wastage is high. Given the major changes in production already underway, some may contend this is a propitious moment for manufacturers in industrialized and developing countries alike to consider filling their vaccines into consensus single-dose universal cartridges that could be administered by means of an array of commissioned single-use-nozzle, auto-destruct needle-free injectors. Because such cartridges can be markedly smaller than single-dose vaccine vials, cold-chain storage requirements would be less. In reality, the enormous investment needed to modify production lines globally and to provide jet injectors is likely to be prohibitive in comparison with the benefits gained. Moreover, such a change could not proceed unless agreed to by all stakeholders, including countries, manufacturers and international agencies.

This author's long-term enthusiasm for investigating ways to immunize without needles remains unabated, and biotechnology continues to expand the options. Nevertheless, economic constraints, logistical and safety concerns, and diverging immunization practices make it unlikely that in the foreseeable future needle-free vaccination can completely replace the use of needles worldwide. Yet optimism is still warranted for the vision that, in the more distant future, all vaccines will be administered without needles and syringes.

Note: The opinions expressed in this commentary are personal views of the author and do not represent institutional or agency endorsements.

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