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Intradermal delivery for vaccine dose sparing: Overview of current issues

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ABSTRACT

There is a wide range of methods and technologies aimed at improving human vaccine products and the way they are delivered. Some of these have the potential to increase vaccine effectiveness in specific populations and may furthermore help to increase vaccine access, reduce costs, and ease the logistical burdens of immunization programs, especially in low-resource settings. One strategy under evaluation is the use of intradermal (ID) delivery of vaccines, which has been shown to result in dose sparing with some vaccines. Novel ID delivery devices could enable needle-free and therefore safer and more reliable ID administration than current ID injection methods, facilitating ID delivery and dose sparing with existing or new vaccines. There are promising clinical data with some vaccines that highlight the potential of reduced-dose immunization via the ID route. And more studies are under way. However, a number of clinical and technical research as well as operational challenges exist, including establishing the optimal doses for different vaccines, reformulating to adjust antigen concentration or add preservatives, matching vaccine vial volume to session size, working with vaccine manufacturers to achieve regulatory clearance for ID delivery, and developing ID delivery devices suitable for the varying scenarios of use of different vaccines. These will need to be addressed before the benefits of ID delivery and the impact of novel ID delivery technologies on human health are fully realized.

1. Introduction

Bacillus Calmette–Guérin (BCG) vaccine has been delivered by the intradermal (ID) route for decades. One reason for the interest in delivering a wider range of vaccines by this route is that the dermis and epidermis of the human skin are rich in antigen-presenting cells, such as Langerhans cells and dendritic cells, which play a critical role in the induction of immune responses [1]. Injection of vaccines into the dermis and epidermis delivers antigens closer to these cells than injection into deeper tissues, with the result that smaller doses of antigen might induce an equivalent immune response to the standard dose.

For vaccines where this "dose-sparing" approach is possible, use of a reduced dose can help to increase the availability of vaccines that are in limited supply. In some cases it can also decrease vaccine purchase costs. Use of reduced volumes of vaccine per dose can additionally reduce the space required in the cold chain for storage and distribution of vaccines.

2. Clinical evidence

Findings from clinical studies of ID dose sparing have been summarized in several reviews [2–5]. Promising clinical data supporting dose sparing have been achieved with some but not all vaccines. Notably, dose sparing has been demonstrated for inactivated poliovirus vaccine (IPV) [6,7], yellow fever vaccine [8,9], modified vaccinia Ankara [10], seasonal influenza vaccines, and rabies vaccines [11–16] (Table 1).

In the case of influenza vaccine, ID formulations that contain 9 μg of hemagglutinnin per strain (compared with the standard 15 μg) have now been approved in Europe and by the US Food and Drug Administration [4]. ID regimens employing reduced doses of rabies vaccines for post-exposure prophylaxis are used in Thailand, the Philippines, Sri Lanka and some parts of India [18]. ID regimens for pre- and post-exposure rabies vaccination are approved by the World Health Organization (WHO) [19].

3. Delivery technologies

New devices for easier, more reliable ID delivery are being developed [5,20] that may serve as alternatives to the Mantoux technique and help to promote the implementation of dose-sparing ID vaccination strategies. The range of devices being developed includes adapters for traditional needles and syringes that control the depth and angle of needle penetration, mini-needles, microneedles, and disposable-syringe jet injectors. Although each of the technologies is at a different stage in the product development pipeline, they represent innovative approaches that may ease effective reduced-dose vaccine delivery via the ID route—and some have features that would be particularly applicable for immunization programs

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Table 1
Intradermal delivery of vaccines for dose sparing: status of clinical research and use with specific vaccines [5].

No clinical data	Equivocal or negative data[a]	Positive clinical data[b]	Approved for use via ID delivery
Conjugated polysaccharide vaccines	• Measles • Diphtheria tetanus and pertussis • Tetanus toxoid • Hepatitis B • Non-conjugated polysaccharide vaccines [17]	• IPV [3,6,7,21] • Hepatitis A • Yellow fever [8,9] • Tick-borne encephalitis	• BCG[c] • Rabies [14–16,18,19] • Influenza [4,11–13]

[a] Available data do not show fractional (20 percent volume) doses delivered by the ID route to be equivalent to full doses delivered by the SC/IM route in terms of immunogenicity.
[b] Clinical studies show that fractional (20 percent volume) doses delivered by the ID route can be equivalent to full doses delivered by the SC/IM route in terms of immunogenicity.
[c] Intradermal delivery is the standard route for delivery.

in low-resource settings. Further development and testing are required with all of these devices to determine which ones offer real advantages over ID injection with a needle and syringe, whether they will be cost-effective, and in which settings they can be used.

4. Cost estimates

Cost analyses of ID delivery of several vaccines have been published [21–24] indicating that dose sparing can be cost saving.

Preliminary cost modeling of different strategies to increase the affordability of routine immunization of inactivated poliovirus vaccine [21] found that compared with the intramuscular delivery of a "full-dose" with a traditional needle and syringe, reduced-dose ID delivery could result in cost savings of about 75 percent per dose. Modeling of costs associated with post-exposure rabies vaccination has also suggested that 70 percent savings in the cost of death averted could be achieved [24].

In practice, however, while the cost savings might be real, they may not be so significant. A study of the actual costs associated with post-exposure rabies vaccination of 428 patients showed that delivery of 1/5 doses resulted in 15–38 percent savings to the clinic depending on the setting (dog-bite center or health clinic) [23]. Additional cost analyses will be necessary to evaluate the overall cost impact of ID delivery for specific vaccines, ID delivery devices, and use scenarios.

5. Challenges moving forward

Several research and operational challenges will need to be addressed before any of the potential benefits of (dose sparing) ID vaccine delivery can be realized. These include the following topic areas.

5.1. Clinical effectiveness

The immunological advantage of ID delivery varies between vaccines. It cannot be assumed that reduced-dose ID delivery will be safe and effective for all vaccines or populations. The optimum dose for target populations will need to be established in high-quality clinical trials, and the effectiveness of reduced-dose immunization will need to be monitored after introduction to confirm that long-lasting immunity is induced (as has been shown with rabies vaccine [25]).

In cases where dose sparing is achieved, it might not be with doses as low as 10–20 percent of the standard dose, as found in large-scale trials with seasonal influenza vaccines wherein the approved ID formulation contains 60 percent of the antigen content of the standard intramuscular (IM) dose [4].

5.2. Requirements for reformulation

Typical ID injections of vaccine are 0.1 ml (or 0.05 ml); therefore, for pragmatic reasons ID doses of 20 percent of a standard 0.5-ml dose or 10 percent of a 1.0-ml dose have been used in the past. If these are shown to be equivalent to the standard dose in terms of immunogenicity, it is possible that the vaccine could be used for ID injection without need for reformulation, although preservatives might need to be added to adhere to WHO prequalification requirements [26]. If more antigen per volume is necessary, then adjustments in vaccine concentration will be required for successful delivery to be achieved in a smaller volume [27].

5.3. Vaccine presentations and immunization session size

Matching the number of doses per vial with the session size will be a priority for immunization programs that seek to advance dose-sparing strategies to minimize wastage and also reduce supply, storage, and disposal costs [28]. In the case of rabies, the savings that might be obtained by using ID regimens are dependent on clinic throughput, but even clinics with low throughput (approximately 10 new patients per month) could reduce vial usage by 25 percent [24]. To maximize cost savings, presentations with few doses per vial (e.g., a single 0.5-ml dose becoming five 0.1-ml doses) should be used for ID regimens. Use of presentations with small numbers of doses per vial could also reduce the possible impact of septum "coring" (caused by the repeated piercing of vial septum with a vial adapter or standard needle) which can lead to contamination of the vial contents.

5.4. Regulatory and commercial issues

ID delivery of reduced doses of existing vaccines that are intended for subcutaneous or intramuscular injection could be delivered on an "off-label" basis (as has been done with rabies vaccines). However, regulatory approvals and label changes (by vaccine manufacturers) are required for the official "on-label" use of fractional doses. The degree of clinical evidence required to obtain a label change for a new depth of delivery must be determined on a vaccine- and delivery device-specific basis but might be similar to the requirements for approval of a new vaccine. As a result, non-inferiority studies may need to be advanced. There will also be a need to demonstrate immunogenicity in all the relevant population groups that receive the vaccine. It is likely that the longevity of the immune response will also need to be evaluated. Collaboration between the vaccine manufacturer and device developer will be needed for the clinical trials required to support the use of a new dose of vaccine via a changed route and using a new device. As stated above, reformulation to incorporate preservatives might also be required to convert a preservative-free, single-dose presentation for multiple ID dose use. Reformulation work and clinical evaluations will have an impact on the potential economic benefit of changing to the ID route for delivery.

New vaccines in development may therefore be better candidates for ID delivery. Unless there are strong incentives to do otherwise, vaccine manufacturers are likely to continue to use