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Review

# Fractional dose of intradermal compared to intramuscular and subcutaneous vaccination - A systematic review and meta-analysis

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ABSTRACT

*Background:* Vaccine supply shortages are of global concern. We hypothesise that intradermal (ID) immunisation as an alternative to standard routes might augment vaccine supply utilisation without loss of vaccine immunogenicity and efficacy.

*Methods:* We conducted a systematic review and meta-analysis searching Medline, Embase and Web of Science databases. Studies were included if: licensed, currently available vaccines were used; fractional dose of ID was compared to IM or SC immunisation; primary immunisation schedules were evaluated; immunogenicity, safety data and/or cost were reported. We calculated risk differences (RD). Studies were included in meta-analysis if: a pre-defined immune correlate of protection was assessed; WHO-recommend schedules and antigen doses were used in the control group; the same schedule was applied to both ID and control groups (PROSPERO registration no. CRD42020151725).

*Results:* The primary search yielded 5,873 articles, of which 156 articles were included; covering 12 vaccines. Non-inferiority of immunogenicity with 20–60% of antigen used with ID vaccines was demonstrated for influenza (H1N1: RD -0·01; 95% CI -0·02, 0·01; $I^2 = 55\%$, H2N3: RD 0·00; 95% CI -0·01, 0·01; $I^2 = 0\%$, B: RD -0·00; 95% CI -0·02, 0·01; $I^2 = 72\%$), rabies (RD 0·00; 95% CI -0·02, 0·02; $I^2 = 0\%$), and hepatitis B vaccines (RD -0·01; 95% CI -0·04, 0·02; $I^2 = 20\%$). Clinical trials on the remaining vaccines yielded promising results, but are scarce.

*Conclusions:* There is potential for inoculum/antigen dose-reduction by using ID immunisation as compared to standard routes of administration for some vaccines (e.g. influenza, rabies). When suitable, vaccine trials should include an ID arm.

## 1. Introduction

### 1.1. Background

Episodes of shortages in supplies of established, marketed vaccines occur frequently around the world [1], particularly during epidemics; the challenge of an acute antigen shortage for novel vaccines to come is highlighted by the evolving COVID-19 pandemic. It is expected that by the near future, SARS-CoV-2 vaccines will be successfully developed and marketed, including antigen-based vaccines (e.g. whole virus or subunit vaccines) [2]. However, it is unlikely, that vaccine production plants can be scaled up rapidly enough to immunise the critical proportion of 60–70% of the world's population. Therefore, dose-sparing approaches such as ID vaccination should be considered in mass immunisation. Over the past decades, numerous studies showed that for several vaccines (e.g. hepatitis B [HBV], influenza, rabies) intradermal (ID) immunisation exhibits similar, or even enhanced, immunogenicity, when using a fractional dose only, as compared to intramuscular (IM) or subcutaneous (SC) immunisation. This dose-sparing strategy could increase vaccine supplies and might be cost-saving.

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### 1.2. History of ID immunisation

Discovery of the principle of immunisation is considered to be one of the most important achievements with impact on global health [3]. In 1967, the World Health Organization (WHO) carried out a global immunisation campaign to eradicate smallpox, that was still endemic in Asia and Africa at the end of the 1960s. The bifurcated needle (invented by Dr Benjamin A. Rubin), became the standard instrument for immunisation in the global programme. This bifurcated needle enabled ID administration of the vaccine, allowing the use of a four-times smaller amount of vaccine than with previous techniques [4].

In the 1930s, studies were already performed comparing ID to SC administration using fractional doses of typhoid vaccine and reporting comparable immune response [5,6]. Subsequently, more studies were conducted on various vaccines in ID-fractionated doses in the following decades, including influenza [7–9], measles [10,11], cholera [12,13], rabies [14,15], HBV [16,17] and inactivated polio vaccines (IPV) [18]. Notably for influenza, rabies and HBV vaccines, ID administration and its potential for dose-sparing has been extensively tested. To date, the WHO approved ID administration of rabies vaccine, IPV, and tuberculosis vaccine, using the live attenuated Bacillus Calmette-Guérin (BCG) strain of *Mycobacterium bovis* [19,20]. Since WHO approval, ID rabies immunisation has been introduced at a national level over the last decades by resource-constrained countries such as India, Thailand and the Philippines [21].

### 1.3. Immunology of ID immunisation

The skin consists of three layers from outside to inside: the epidermis, dermis and hypodermis. The dermis comprises two sub-layers: the superficial papillary dermis and the deeper reticular dermis. The papillary dermis (100–300 μm thick), is the target layer for ID immunisation. This layer is rich in antigen-presenting cells (APCs, i.e. dermal dendritic cells [DDCs] and Langerhans cells). DDCs capture antigens deposited in the dermis and migrate to the draining regional lymph nodes, where antigens are presented to T-cells, that will be activated. Soluble antigens migrate to lymph nodes as well, resulting in B-cell activation [22,23]. Due to abundant APCs in the dermis, ID delivery of reduced doses (most often 20% or 30% of the standard amount of antigen) can induce immune responses equivalent to standard doses delivered intramuscularly or subcutaneously [1,24].

### 1.4. Objectives

There has been a large number of clinical trials comparing routes of administration (ID versus IM or SC immunisation). Nevertheless, to date only studies on HBV, influenza or polio have been systematically reviewed [25–31]. To our knowledge, no synoptic systematic review exists to date that compiles and compares all relevant studies conducted on vaccines in reduced ID doses as alternative to IM or SC immunisation.

The aim of this systematic review was to provide an overview of all relevant studies conducted on licensed and currently available vaccines that are used in fractionated ID doses, as an alternative to standard IM or SC administrations. To this end, we address the following questions: Can ID immunisation induce an antibody response equivalent to IM or SC immunisation? Do differences in ID vaccine dose influence antibody response? Can ID immunisation be a safe alternative to IM and SC immunisation? Is ID immunisation cost-saving compared to IM and SC vaccination?

## 2. Methods

For this systematic review and meta-analysis we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [32]. The study protocol was registered in the international prospective register of systematic reviews prior to screening and data extraction (PROSPERO registration no. CRD42020151725).

### 2.1. Literature search and information sources

The search strategy was designed in collaboration with a clinical librarian (JGD). We started with composing a reference set through citation tracking in Google Scholar, screening reference lists of (systematic) reviews and using the 'similar articles' feature in PubMed. A reference set of in total 131 articles was obtained and used to derive the following search concept: ([intradermal] AND [vaccination/administration]) AND (([intramuscular] AND [vaccination/administration]) OR ([subcutaneous] AND [vaccination/administration])). To maximize the yield of articles conducted on cost-effectiveness, an additional search string was used, applying the NHS-EED filter [33] and adding licensed and available vaccines to maximize the sensitivity of the search. This search string for cost-effectiveness was limited to articles published between 2009 and 2019, since recent literature is most relevant to current vaccine policies [34]. For both search strings, a filter was used to exclude animal studies.

A systematic literature search was performed on November 6th in MEDLINE, Embase and Web of Science. The search strategy was adapted for each database to match the controlled vocabulary and search syntax. The details of the search are shown in Supplementary Table 1. All articles in the reference set had to be retrieved by the systematic search strategy in at least one of the databases. Additionally, the NHS-EED database and Academic Search Premier were scoped, but no additional articles matching inclusion criteria were identified.

### 2.2. Eligibility criteria

We included all interventional trials and cohort studies in humans, that compared fractional dose(s) of ID to IM or SC immunisation. We only included studies reporting either immunogenicity, safety and/or original costs outcomes of licensed and currently available vaccines. We excluded case reports, case series, abstracts, animal studies and *in vitro* studies; studies examining booster immunisation only; studies using higher or similar amount of antigen in the ID dose compared to IM or SC; studies in languages other than English, German or Dutch.

If a study evaluated both fractionated doses of ID immunisation, as well as ID immunisation doses equal to IM or SC immunisation, only the results associated with the fractionated ID doses were included. Conversely, when a study evaluated both standard doses of IM or SC immunisation, as well as reduced doses of IM or SC immunisation (equal to ID immunisation), only results regarding the standard dose were included.

If both primary immunisation schedules as booster immunisations were evaluated in a study, only the results associated with the primary immunisation schedule were included. Studies on influenza vaccines, however, were only excluded when previous immunisation of the study population within the previous six months was mentioned; this approach was chosen because of the high number of subjects receiving annual influenza immunisation: by choosing this six-month interval, only the those who were vaccinated for the current influenza season were excluded.

Meta-analyses were conducted for each antigen if more than three of the included studies met all of the following inclusion criteria: assessment of the predefined immune correlate of protection (Table 1); use of WHO-recommend schedules and dose of antigen/inoculum in control group; use of the same schedule in ID group as in control group. No studies were excluded based on study design.

### 2.3. Study selection

After exclusion of duplicates, all identified articles were screened on title and abstract by two independent researchers (JLS and CAdP) using the RAYYAN software tool [35]. Potentially relevant articles were

**Table 1**
Primary outcome measures per vaccine.

| Vaccine | Primary outcome measure |
|---|---|
| Diphtheria [201] | Seroprotection rate defined as percentage of subjects with post-vaccination antitoxin level ≥0.1 IU/ml |
| Hepatitis A [202] | Seroprotection rate defined as percentage of subjects with post-vaccination *anti*-HAV antibodies >10–33 IU/L assessed 4 weeks after completing vaccination series |
| Hepatitis B [191] | Seroprotection rate defined as percentage of subjects with post-vaccination *anti*-HBs antibodies >10 IU/L assessed 1–3 month after completing vaccination series |
| Human papillomavirus [203] | No validated immune correlate of protection available |
| Influenza [204] | Seroprotection rate defined as percentage of subjects with post-vaccination hemagglutinin inhibition (HI) titres ≥1:40 assessed 2–4 weeks after completing vaccination series |
| Japanese encephalitis [205] | Seroconversion rate defined as percentage of subjects with post-vaccination neutralising antibody titres >1:10 |
| Measles [194] | Seroprotection rate defined as percentage of subjects with post-vaccination measles neutralising antibody titres ≥120 IU/L |
| Meningococcal disease [206] | Group C: seroprotection defined as hSBA titre ≥ 4 or SBA titre ≥ 8;<br>Group A, B, W135 and Y: no validated immune correlate of protection available |
| Rabies virus [192] | Seroconversion rate defined as percentage of subjects with post-vaccination rabies virus neutralising antibodies (RVNA) ≥0.5 IU/mL assessed 4 weeks after completing vaccination series |
| Inactivated poliovirus vaccine [193] | Seroconversion rate defined as percentage of subjects achieving ≥4-fold increase in neutralising antibody titres or change from seronegative (<1:8) to positive (≥1:8) assessed 30 days after completing vaccination series |
| Tetanus toxoid [207] | Seroprotection rate defined as percentage of subjects with post-vaccination anti-tetanus antibody level of ≥0.01 IU/ml |
| Varicella zoster [208] | No validated immune correlate of protection available |
| Yellow fever [209] | No validated immune correlate of protection available |

assessed full text by JLS and CAdP. Discrepancies were resolved by discussion. If JLS and CAdP did not agree after discussion, a third author (MPG) was consulted. Reference lists of included studies were reviewed for potentially relevant articles that were missed in the systematic literature search.

### 2.4. Data extraction

Data on the following items were, if noted, extracted: publication year; location of study; study design; disease; vaccine type; age of the population; health status of the population; number of immunised subjects completing study in the ID and IM/SC groups; number and dose of injections in the ID and IM/SC groups; schedule of immunisation in the ID and IM/SC groups; time of assessment of immunogenicity; assessment of immunogenicity by primary outcome measure as defined in Table 1 (or, if not reported, by other outcome measure e.g. geometrical mean titres (GMT)); reported adverse events; incidence of adverse events and costs of ID and IM/SC immunisations.

### 2.5. Quality assessment

To assess the quality of the included articles, different scales were used. The Cochrane Risk-of-Bias tool [36] was used to assess the quality of randomised controlled trials (RCTs). A modified Newcastle Ottawa Scale [37] was used for quality assessment of non-randomised clinical trials and cohort studies.

The Cochrane Risk-of-Bias tool uses a system to assess six different bias domains that can be judged as low, high or unclear risk of bias. Reasons for considering risk of bias as low, high or unclear are mentioned in Supplementary Table 2.

The modified Newcastle Ottawa Scale uses a system in which 'stars' can be assigned for three items: selection, comparability, and outcome. Cohort studies can be assigned a maximum of nine stars if they meet all criteria. First studies were assigned a maximum of four stars if; 1) the study population is truly, or somewhat, representative for the average vaccinated person receiving the specific vaccine (e.g. elderly/immunosuppressed patients for influenza vaccines); 2) the non-exposed cohort is drawn from the same population; 3) injection site is checked for wheal formation after ID immunisation and/or if injection is delivered by a trained nurse or physician; 4) antibody titres and/or adverse events are not present before immunisation. An additional, two stars were assigned if; 1) the study is controlled for age or sex; in case the study was conducted on cost-effectiveness, it was controlled for wastage of vaccine volume; 2) the study is controlled for any additional factor. Finally, three starts were assigned for quality of outcome if; 1) if the assessment of immunogenicity and/or adverse events is blinded; 2) immunogenicity is assessed within the determined time frame (see Table 1) after finishing the primary vaccination schedule; 3) if loss-to-follow-up is unlikely to be caused by immunisation (e.g. adverse events or high costs).

### 2.6. Data synthesis

Risk Differences (RDs) for seroprotection or seroconversion between ID and IM group were calculated in RevMan version 5.3. The term seroprotection refers to a level above a predefined cut-off; seroconversion refers to a change in antibodies from baseline (e.g. >4-fold change) (different for each vaccine, see Table 1). All meta-analyses were carried out using the Mantel-Haenszel method. Statistical heterogeneity was assessed using $I^2$ measure: $I^2$ values above 50% and 75% were predefined as moderate and high heterogeneity, respectively [38]. In case heterogeneity was considered low ($I^2$ <50%), the fixed-effect model was used, and if heterogeneity was considered moderate or high ($I^2 \geq$ 50%), the random-effect model was used. Sub analyses were conducted on the following subgroups, if appropriate: healthy young adults, elderly and immunocompromised patients.

## 3. Results

### 3.1. Selection of studies

The search retrieved a total of 5,873 articles. By reviewing the reference lists of retrieved articles, four additional articles were identified. After removal of duplicates, 3,924 articles remained. All articles were reviewed on title and abstract, and 3,403 articles were excluded. Of the remaining 521 articles, the full text was reviewed. After applying inclusion and exclusion criteria, 156 articles were included in the systematic review, of which 45 articles were included for meta-analyses. The selection of studies is shown in Fig. 1.

### 3.2. Study characteristics

Of the 156 included studies, 109 were RCTs and 47 were cohort studies, of which 45 were prospective and two were retrospective cohort studies. Both retrospective cohort studies were conducted on cost-effectiveness. Most of the studies (122) compared ID immunisation to IM immunisation. Thirty-two studies compared ID immunisation to SC immunisation, and two studies compared ID immunisation to both. The majority of studies was conducted on influenza (n = 5 1) [39–89], HBV (n = 43) [17,90–131] and rabies (n = 37) [14,15,132–166] vaccines. The remaining studies were conducted on IPV [167–173], measles [10,174–178], hepatitis A (HAV) [179–182], diphtheria-tetanus-pertussis (DTP) [183,184], Japanese encephalitis (JE) [185,186], human papillomavirus (HPV) [187], meningococcal disease [188], varicella zoster [189] and yellow fever [190] vaccines. The sections below summarise study characteristics and outcomes of the individual vaccines. Details on

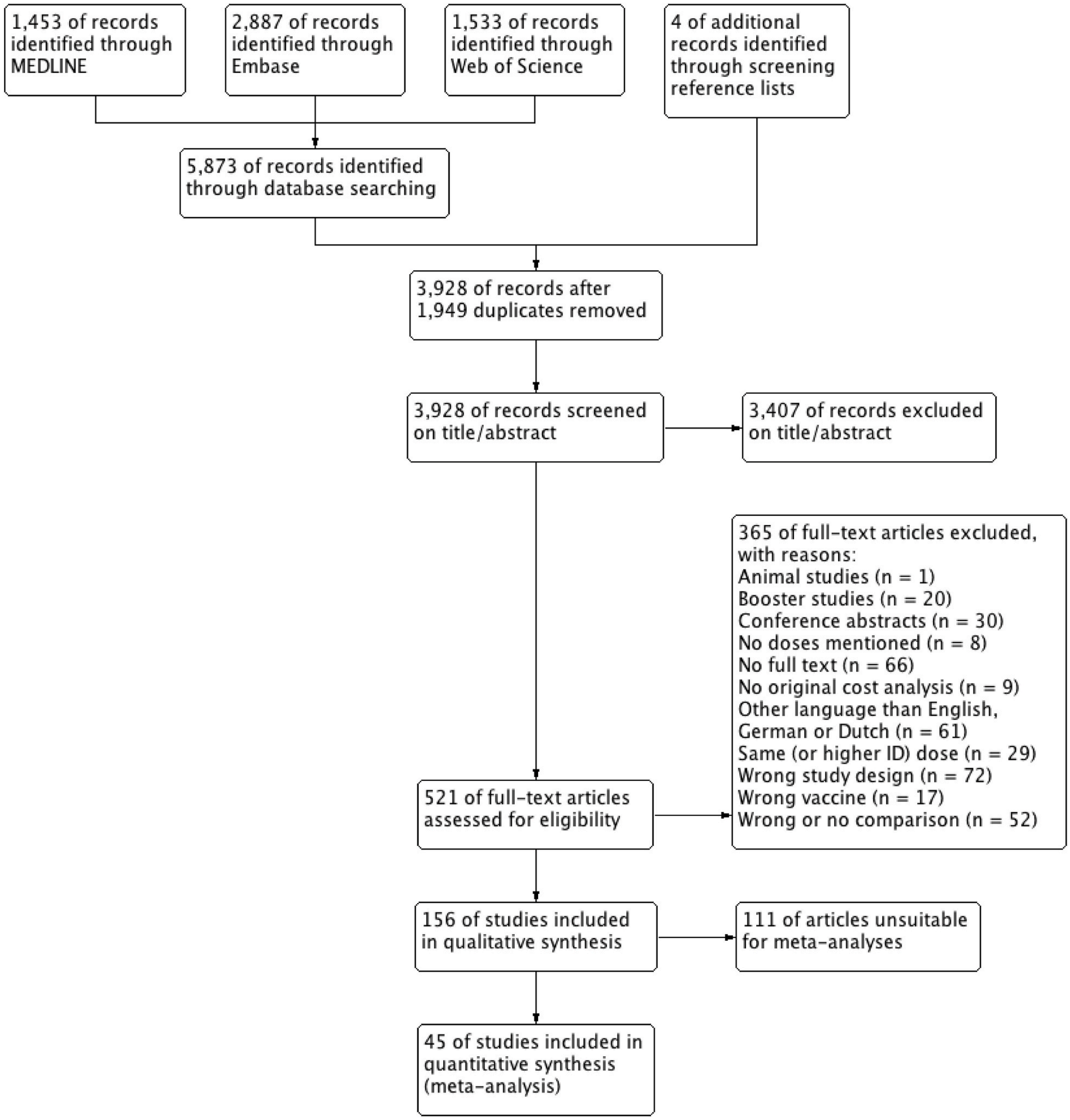


**Fig. 1.** Flow chart of study selection.

the study characteristics and outcomes of the identified studies are shown in Supplementary Table 3.

### 3.3. Influenza vaccines

#### 3.3.1. Study design and patient characteristics

Among the included studies (n = 51) [39–89], 19 studies compared ID immunisation to SC immunisation of which all, except one [87], were historic studies (1949–1981) [42,44,45,52,53,57,58,61,64,66–70,72,73,77,89]. Studies comparing IM immunisation with ID (n = 32) immunisation were conducted more recently and were all published after 2003 [39–41,46–51,54–56,59,60,62,63,65,71,74–76,78–86,88], with the exception of Brown et al. [43] published in 1977. Study populations of the identified studies on influenza vaccines consisted of healthy adults, elderly, children (0–18 years), chronically ill and immunocompromised patients, or combinations of these groups. Many (n = 19) studies did not report whether participants were immunised in the last six months with influenza vaccine [42,43,48,51,57,59,62,64,66,68,69,71,75,81,82,84,86,88,89].

#### 3.3.2. Vaccination

All included trials studied inactivated influenza vaccines (IIVs). Types of IIVs used were mostly sub-virion vaccines (including both split and purified surface antigen vaccines) [39–41,46–51,54,56,59,60,62,65,71,74–76,78–80,82,83,85–87], and in several studies whole virus vaccines [64,77,89]. A large amount of studies did not report the type of IIV (n = 18) [42,44,45,52,53,55,57,58,61,66–70,72,73,81,88]. Studies were predominantly performed on trivalent influenza vaccines [39–41,46–51,54–56,58–60,63–65,71,72,74–76,78–80,82–88,136], but also on monovalent [43,45,52,53,57,61,67,70,89], bivalent [44,77] or polyvalent influenza vaccines [42,66,68,69,73]. The primary immunisation schedule mainly consisted of a single dose [39–51,54–65,68,69,71–73, 75–88]. In six studies [52,53,66,70,74,89], a two-dose regimen was used for both ID and IM or SC immunisation, administering the second dose within a two-to-four-week interval. The study by Tauraso et al. [67] was the only study to use a three-dose regimen. Studies administering vaccine intramuscularly mostly used the standard dose of 15 μg of hemagglutinin (HA) per strain and an ID dose varying between 3 and 9 μg HA per strain. Studies in which the vaccine was administered subcutaneously were, as aforementioned, mainly older studies, expressing dose of antigen in chick cell-agglutinating (CCA) units. Doses used for ID administrations varied between 10 and 80 CCA units and for SC administrations between 100 and 550 CCA units.

#### 3.3.3. Study outcomes

In the majority of studies, immunogenicity was the primary endpoint investigated, and safety was often the secondary endpoint. Three studies [54,69,73] were solely conducted on safety, and none of the studies evaluated cost-effectiveness. Studies mostly used hemagglutinin inhibition (HI) assays to assess the levels of strain-specific antibodies and used seroprotection (Table 1) as the primary outcome measure. The number of studies or study subgroups (53 in total) that reported either inferior, similar or superior seroprotection rates (or equivalent outcome measures, if seroprotection rates were not mentioned) after ID immunisation compared to IM or SC immunisation are shown in Table 2a. In all studies and study subgroups comparing ID and IM immunisation similar antibody responses were reported. In studies and study subgroups comparing ID to SC immunisation similar (n = 2), or higher (n = 1) antibody responses were reported for ID, except in two studies with elderly individuals, reporting inferior antibody responses in the ID group [61,66]. Both studies used a fractional ID dose of about 1/10th of SC dose: Boger et al. [61] compared a dose of 50–550 CCA units and Saslaw et al. [66] compared 10 or 20 CCA units per strain to 100 and 200 CCA units per strain.

#### 3.3.4. Meta-analyses

In total, 22 RCTs on trivalent influenza vaccines met eligibility criteria for meta-analyses [39,41,46–51,55,56,59,60,62,63,65,76,78–80,82,85,88]. Meta-analyses were performed separately for healthy young adults (18–64 years), elderly (>60 years), and immunocompromised and chronically ill patients. Forest plots of studies on healthy young adults stratified per ID dose are shown in Fig. 2a–c. The seroprotection rates for H1N1, H2N3 and B strain induced by an ID dose of 6, 7.5 and 9 μg of HA per strain were all comparable to those elicited by IM immunisation of the standard dose of 15 μg. In recipients of an ID dose of 3 or 4.5 μg, the seroprotection rates were significantly lower for the H1N1 strain (RD 0.05; 95% CI -0.09, −0.01; $I^2 = 75\%$) and B strain (RD 0.10; 95% CI -0.20, −0.00; $I^2 = 91\%$). Similarly, the seroprotection rates in elderly after ID immunisation were equivalent to IM immunisation for each strain (Fig. 2d). The overall RD was 0.03 (95% CI -0.02, 0.08; $I^2 = 44\%$) for H1N1, 0.01 (95% CI -0.01, 0.04; $I^2 = 0\%$) for H2N3 and 0.03 (95% CI -0.04, 0.09; $I^2 = 75\%$) for influenza B viruses. Also in immunocompromised and chronically ill patients, seroprotection rates of ID recipients did not significantly differ from IM recipients (H1N1: RD -0.04; 95% CI -0.10, 0.02; H2N3: RD 0.01; 95% CI -0.06, 0.07; B: RD -0.04; 95% CI -0.12, 0.04; $I^2 = 0\%$) (Fig. 2e).

#### 3.3.5. Safety

In almost all studies, local adverse events at the injection site were more common after ID (31–100%) than after IM immunisation (13–60%). Common local reactions after ID immunisation were erythema (12–93%), pruritus (27–49%), swelling (15–98%), and induration (90-75%). Incidence of systemic adverse events were overall similar in the ID group (7–48%) and the IM group (6–49%). Frequently reported systemic adverse events were malaise, fever, headache and shivering. Local reactions were also more common after ID immunisation when compared to SC immunisation, while systemic reactions were comparable [77,87].

### 3.4. Hepatitis B vaccines

#### 3.4.1. Study design and patient characteristics

Forty-three identified studies [17,90–131] were conducted on HBV vaccines. Forty-one studies compared ID delivery to IM immunisation and just two studies [105,115] compared ID to SC delivery. The identified studies were conducted in healthy adults (n = 21) (predominantly healthcare workers and medical students) [17,90,93,95,99,100,102,103,106,107,117–120,122,123,125,126,128–131], haemodialysis patients (n = 9) [92,96–98,108,113,114,121,124], chronically ill patients (including HIV, coagulation disorders, sickle cell disease or β-thalassaemia) (n = 4) [110,112,115,116], and children (0–18 years) n = 10) [90,91,94,101,104,105,109,111,112,127]. The vast majority of studies mentioned participants having no history of immunisation with HBV or having negative HBsAg, *anti*-HBs and *anti*-HBc, which rendered previous immunisation unlikely.

#### 3.4.2. Vaccination

Both plasma-derived and recombinant HBV vaccines were included in this review. Most studies used the WHO-recommended [191] three-dose schedule, administering the first two doses one month apart and the third dose 1–12 months later (n = 28) [17,90–93,100–103,105–107,109,113,115–123,125,126,128,130,131]. Seven studies used a different ID regimen, administering vaccine either every week [98], every two weeks [96,97,111,112,129], or monthly [108]. ID and IM doses typically used were 1–2 μg and 10–20 μg, respectively. Studies performed on haemodialysis patients used higher doses (ID: up to 20 μg; IM: to 40 μg) [92,96–98,108,113,114,121,124].

#### 3.4.3. Outcomes of studies

All studies reported immunogenicity as their primary outcome; 29 studies reported safety as secondary outcome [17,93,94,96–107,109,110,114,115,118,119,121,123–126,128,129,131], and two studies [96,105] mentioned costs. The majority of studies (n = 38) reported seroprotection rates (Table 1) [17,90–101,103–118,120–126,128,130]. The number of studies or study subgroups (44 in total) that reported either inferior, similar or superior seroprotection rates (or equivalent outcome measures, if seroprotection rates were not mentioned) after ID immunisation compared to IM or SC immunisation are shown in Table 2b. The immunogenicity outcomes varied between studies. Although the majority of studies/study subgroups (n = 29) reported similar antibody responses after ID compared to IM/SC immunisation [17,90,92,94,96–99,101,103,105–108,110–112,114–121,124,126,129,130], a

**Table 2a**
Summary of outcomes of studies/study subgroups on immunogenicity of influenza vaccines.

| | Fractional ID vs IM | | | Fractional ID vs SC | | | |
|---|---|---|---|---|---|---|---|
| Study population | ID inferior | Similar | ID superior | ID inferior | Similar | ID superior | Total |
| Healthy adults | 0 | 16 | 0 | 0 | 10 | 0 | 26 |
| Elderly | 0 | 5 | 0 | 2 | 4 | 1 | 12 |
| Children | 0 | 3 | 0 | 0 | 2 | 0 | 5 |
| Chronically ill and immuno-compromised | 0 | 9 | 0 | 0 | 1 | 0 | 10 |
| Total | 0 | 33 | 0 | 2 | 17 | 1 | 53 |

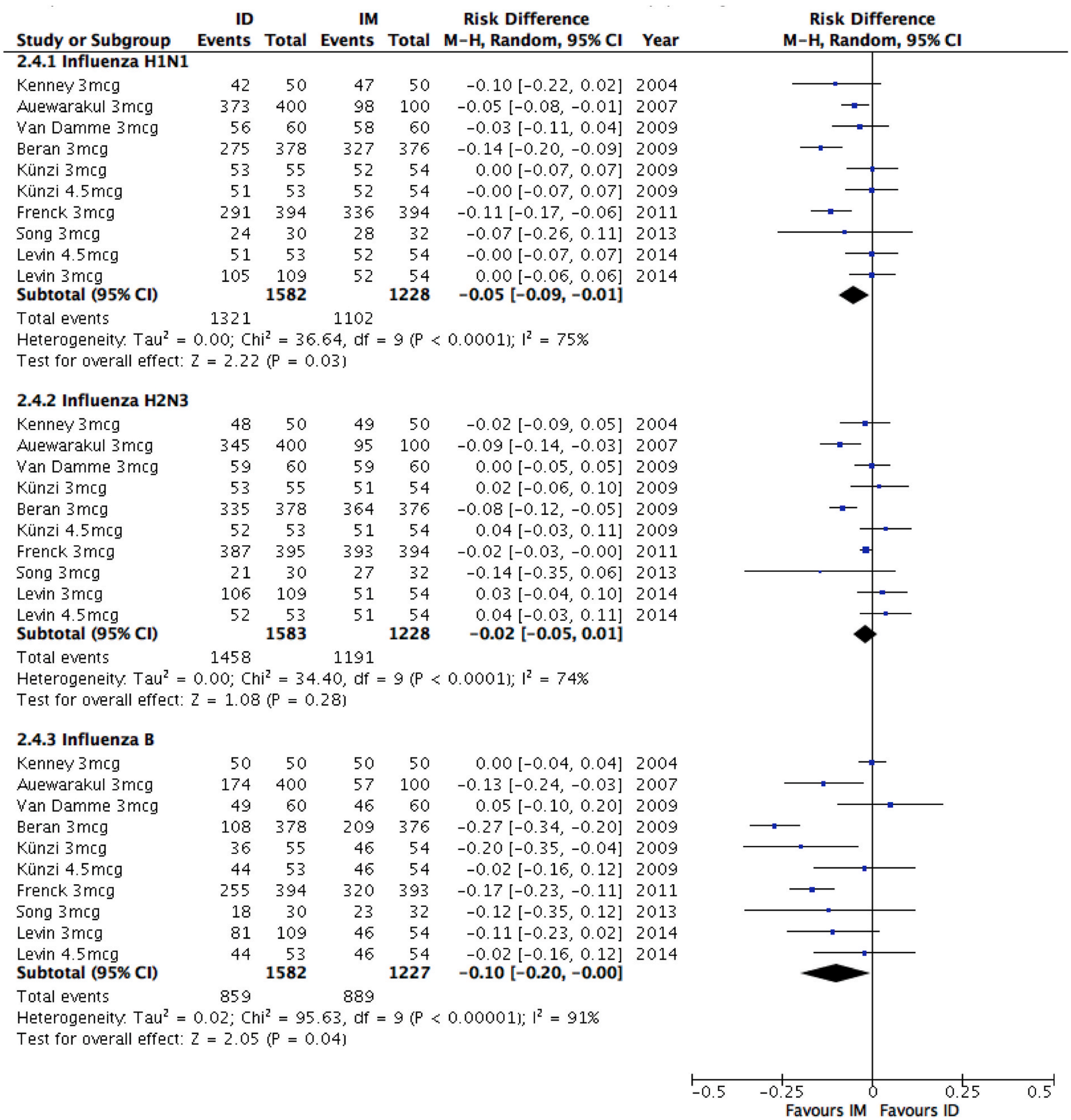


**Fig. 2a.** Forest plots of the risk differences of seroprotection for ID administration of 3 or 4.5 μg compared to IM administration of influenza vaccine in healthy young adults.

considerable number of studies found inferior antibody responses in the ID group compared to IM (n = 15) [91,93,95,100,102,104,109,112,113,122,123,125,127,128,131]. Nine out of ten studies on haemodialysis patients showed potential for dose-sparing with ID immunisation [92,96–98,113,114,121,124]. However, as aforementioned, this study population received higher antigen doses. Of note, the only study conducted on haemodialysis patients showing an inferior antibody response [114], was also the only study in this population using a lower ID dose (4 μg).

### 3.4.4. *Meta-analyses*

Fifteen studies on HBV vaccines were included in the meta-analyses [17,93,100,103,106,107,117,118,120,122,123,125,126,130,131]. Both RCTs and prospective cohort studies were included, since the CI of the overall RD of both RCTs and prospective cohort studies entirely overlapped with the CI of the overall RD of RCTs only. Forest plots of studies on healthy adults stratified per ID dose are shown in Fig. 2f. Seroprotection rates were significantly lower after ID immunisation with a dose of 1–2 μg compared to IM immunisation with the standard dose of 10 or 20 μg (RD -0.07; 95% CI -0.12, −0.02; $I^2 = 72\%$). However, when an ID dose >2 μg was used, seroprotection rates were found equivalent to those of IM vaccines (RD -0.01; 95% CI -0.04, 0.02; $I^2 = 20\%$).

### 3.4.5. *Safety and costs*

In all studies, local adverse events were more common after ID immunisation (15–84%) than after IM immunisation (2–36%). Local reactions after ID immunisation consisted of erythema, pruritus and induration lasting up to 12 weeks, and a small area of discoloration lasting up to 12 months [17]. Systemic adverse events included fever, asthenia, headache, arthralgia and myalgia and were preponderantly similar in both groups. Chanchairujira et al. [96] mentioned costs for ID regimens being half of that for IM regimens, considering that the total ID

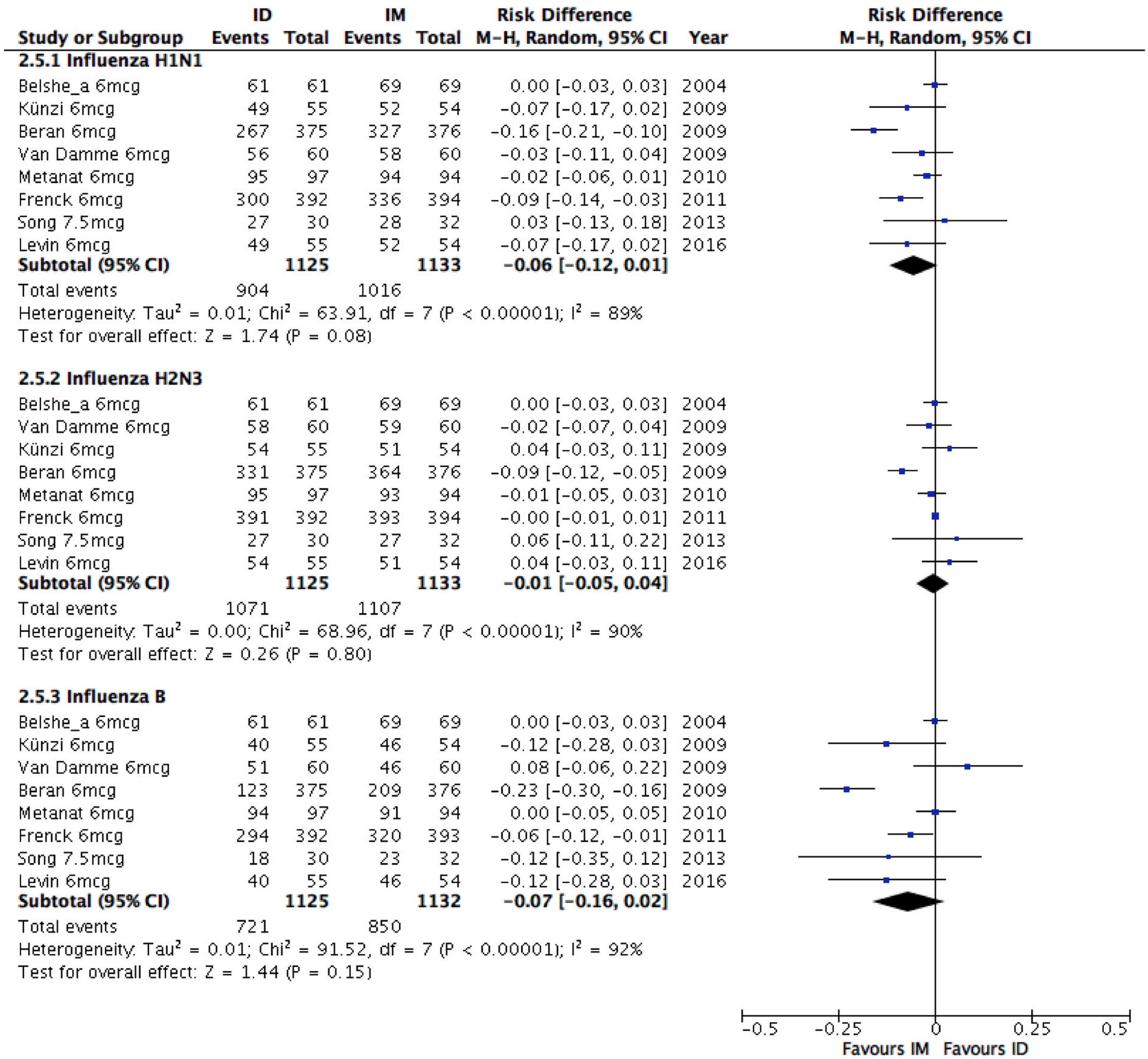


**Fig. 2b.** Forest plots of the risk differences of seroprotection for ID administration of 6 or 7.5 μg compared to IM administration of influenza vaccine in healthy young adults.

dose used was only 44% of IM dose. Hayashi et al. [105] reported a total cost of 34 USD for three vaccinations by the ID route compared with 170 USD for the SC regimen.

## 3.5. Rabies vaccines

### 3.5.1. Study characteristics

A total of 37 studies were conducted on rabies vaccines [14,15,132–166]. Since we only considered licensed and available vaccines in this review, only human diploid cell vaccines (HDCV), purified Vero cell rabies vaccines (PVRV) and purified chick embryo cell vaccines (PCECV) were included.

### 3.5.2. Pre-exposure prophylaxis

Participants of pre-exposure prophylaxis (PrEP) studies were immune naïve predominantly healthy adults. Twenty-two PrEP studies compared ID to IM immunisation [14,136,138–140,143–147,149–151,153–155,157,158,161–163,166]; two studies [132,141] compared ID to SC immunisation, and one study [15] compared ID with both IM and SC immunisation. ID doses consisted of either one injection of 0.1 ml or, in eight studies [143–146,160,164–166], of multiple injections of 0.1 ml. IM doses consisted of 0.5 or 1 ml, and SC doses of 0.25, 1 or 2 ml, respectively. Sixteen studies used the WHO-recommend regimen for both ID and IM immunisation, administering vaccines on day 0, 7 and 21 or 28 [15,136,138–140,143,147,150,151,153,155,157,158,161,163,166].

### 3.5.3. Post-exposure prophylaxis

Eleven studies assessing post-exposure prophylaxis (PEP) compared ID to IM immunisation [133–135,137,142,148,152,156,159,160,164]; and one study [165] compared ID to both IM and SC immunisation. Eight studies [133,137,142,148,152,156,159,160] used the Essen regimen (days 0, 3, 7, 14 and 28) for IM immunisations, of which seven studies [133,137,148,152,156,159,160] used the Updated Thai Red Cross regimen (0.1 ml at two sites on days 0, 3, 7 and 28) for ID immunisations. Six studies [133,134,156,160,164,165] were conducted on immunogenicity; and three studies [134,135,142] reported efficacy. Safety was assessed in eight studies [133–135,142,156,160,164,165] and the compliance rate of completing the schedule in two studies [152,159]. Four studies [135,137,148,152] investigated costs of the different PEP regimens.

### 3.5.4. Outcome of studies

Most studies investigating immunogenicity reported seroconversion

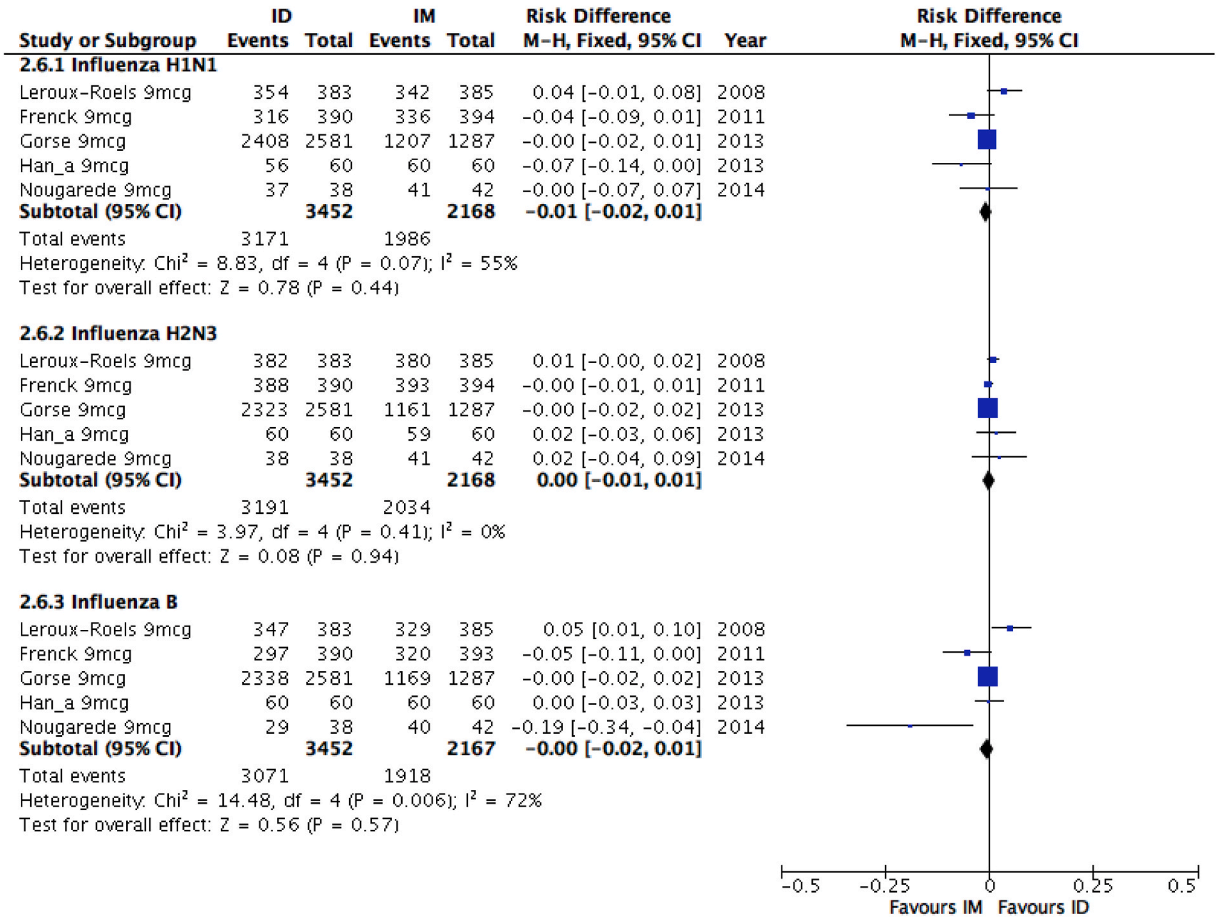


**Fig. 2c.** Forest plots of the risk differences of seroprotection for ID administration of 9 μg compared to IM administration of influenza vaccine in healthy young adults.

rates (n = 21) (Table 1) [133,134,136,139,140,143–147,149,150,155,156,158,160–164,166]. Mostly *in vitro* virus-neutralisation assays, as advised by the WHO [192], were used to assess Rabies virus neutralising antibodies (RVNAs). A few, mostly older studies [142,153,155,162] used the old mouse neutralisation test (MNT). One study [141] used Enzyme-Linked Immuno Sorbent Assay (ELISA) to assess immunogenicity. The number of studies or study subgroups (35 in total) that reported either inferior, similar or superior seroconversion rates (or equivalent outcome measures, if seroconversion rates were not mentioned) after ID immunisation compared to IM or SC immunisation are shown in Table 2c. In the majority of studies or study subgroups (n = 30), antibody responses after ID immunisation were non-inferior to IM or SC immunisation [14,15,133–136,139–141,143–147,149–151,153,155–158,160–166]. Although GMTs were often lower after ID immunisation, adequate titres of RVNAs of ≥0.5 IU/mL were achieved in 17/21 studies [133,134,139,140,144,145,147,149,150,155,156,160–164,166]. All three studies investigating efficacy of PEP yielded no deaths after both regimens [134,135,142].

### 3.5.5. *Meta-analyses*

Only 8 out of 37 studies met the eligibility criteria for meta-analysis; all were RCTs conducted on pre-exposure rabies vaccines in healthy adults [139,140,147,150,155,158,161,163]. The forest plot is shown in Fig. 2g. In most studies seroconversion rates were 100% for both ID and IM recipients; the overall RD was therefore 0.00 (95% CI -0.12, −0.02 $I^2$ = $0^{\%}$).

### 3.5.6. *Safety and costs*

Similar to influenza and HBV vaccines, local reactions (e.g. erythema, pruritus, swelling, and axillar lymphadenopathy) were more common after ID than after IM or SC administration of rabies vaccines. Systemic reactions did not differ between groups and included primarily asthenia, headache, myalgia and dizziness. Both Shankaraiah et al. [159] and Mankeswar et al. [152] found significantly higher compliance rates with completing rabies vaccine schedules if an ID regimen was used, as compared to IM regimens (77–84% vs. 40–60%, respectively). Financial considerations were reported most frequently as the major constraint for not completing the schedule [159]. Dhaduk et al. [137] calculated costs by measuring utilized volumes of regimens and found costs to be almost five times lower with the ID Updated Thai Red Cross regimen than with the IM Essen regimen. Three studies [135,148,152] reported costs of ID regimens being two to three times lower than IM regimens, although two of them [135,152] did not control for waste of vaccine volume or ID application devices.

## 3.6. *Inactivated poliovirus vaccines*

### 3.6.1. *Study characteristics*

Seven studies [167–173] on IPV were identified, all comparing ID to IM immunisation. All studies on IPV were conducted on healthy infants with trivalent IPV. In all studies, a dose of 0.5 ml in the IM group was used, containing 40, 8, 32 D antigen units of types 1, 2, and 3 poliovirus, respectively; and 20% of this dose was used in the ID group. In three of the studies [167,170,171], two doses were used in both groups. In three studies [168,169,172] a schedule of three doses was used in both groups. Snider et al. [173] compared three ID doses to two IM doses.

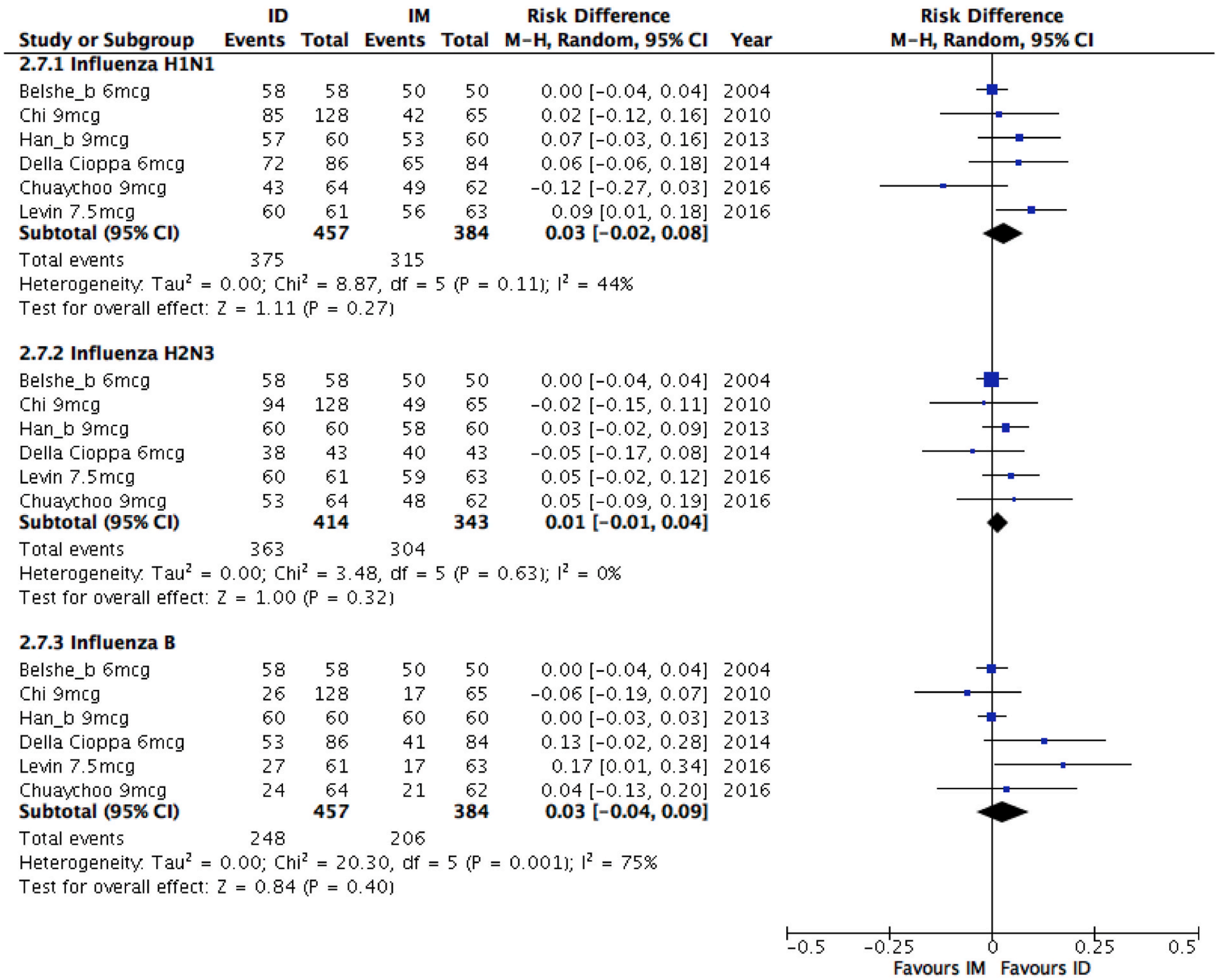


**Fig. 2d.** Forest plots of the risk differences of seroprotection for ID compared to IM administration of influenza vaccine per strain in elderly.

#### 3.6.2. Outcomes

All studies assessed both immunogenicity and safety of IPV. None of the studies analysed costs. All studies used neutralisation assays to assess antibody responses, and used seroconversion rates as a clinical endpoint. Since all studies were conducted on infants in the first few months of life, most infants would still have circulating maternal IgG antibodies [193]. Therefore, in infants with maternal antibodies, seroconversion was defined as a ≥4-fold increase in neutralising antibodies with an adjustment for decay of maternal antibodies, assuming a 28-day half-life of maternal antibodies. In infants with no maternal antibodies, seroconversion was defined as the switch from seronegative to seropositive (Table 1). The number of studies that reported either inferior, similar or superior seroprotection rates (or equivalent outcome measures, if seroprotection rates were not mentioned) after ID immunisation compared to IM or SC immunisation are shown in Table 2d. Seroconversion rates were significantly lower after ID immunisation in three out of seven studies [167,171,172]. The incidence of local reactions at injection site was higher with ID route [168,171,172].

#### 3.6.3. Meta-analyses

On account of the variation in immunisation schedules, studies were considered unsuitable for meta-analyses. However, since all studies reported on the same immune correlate of protection and were conducted on a similar population, forest plots were prepared, though without pooling the data. Forest plots are shown in Fig. 2h.

### 3.7. Measles vaccines

#### 3.7.1. Study characteristics

Six studies [10,174–178] were conducted on measles vaccines. All of them were published before 1985. Four studies [174,175,177,178] compared ID to SC immunisation, and two studies [10,176] compared ID to IM immunisation. All studies were conducted in young children, at a maximum age of 6 years [176]. Most studies included solely children without previous measles infection or vaccination [10,174–176,178]. Five studies used the live attenuated measles vaccine [10,174–177] and one study [178] did not mention vaccine type. The following strains were used: Schwarz [10,174], Beckenham 31 [10,176] and Edmonston-Zagreb [177]. All studies administered a single dose, using an ID dose containing 20–50% of the SC dose.

#### 3.7.2. Outcomes

All studies applied the HI assays to assess antibody response, a test that is no longer commonly used. Only two studies [10,177] used, besides HI assay, the WHO-recommend plaque reduction neutralisation assay [194]. Of note, none of the studies used the predefined outcome measure of seroprotection (Table 1). Instead, all kinds of different outcome measures with different cut-offs to assess immunogenicity were applied. The number of studies that found antibody response after ID immunisation either inferior, similar or superior to IM or SC immunisation are shown in Table 2e. Most studies found an inferior antibody response of ID immunisation versus IM/SC [10,174,176,178]. Only two studies [175,177] suggested similar antibody responses. The study conducted by the Hong Kong Measles Vaccine Committee [10] assessed

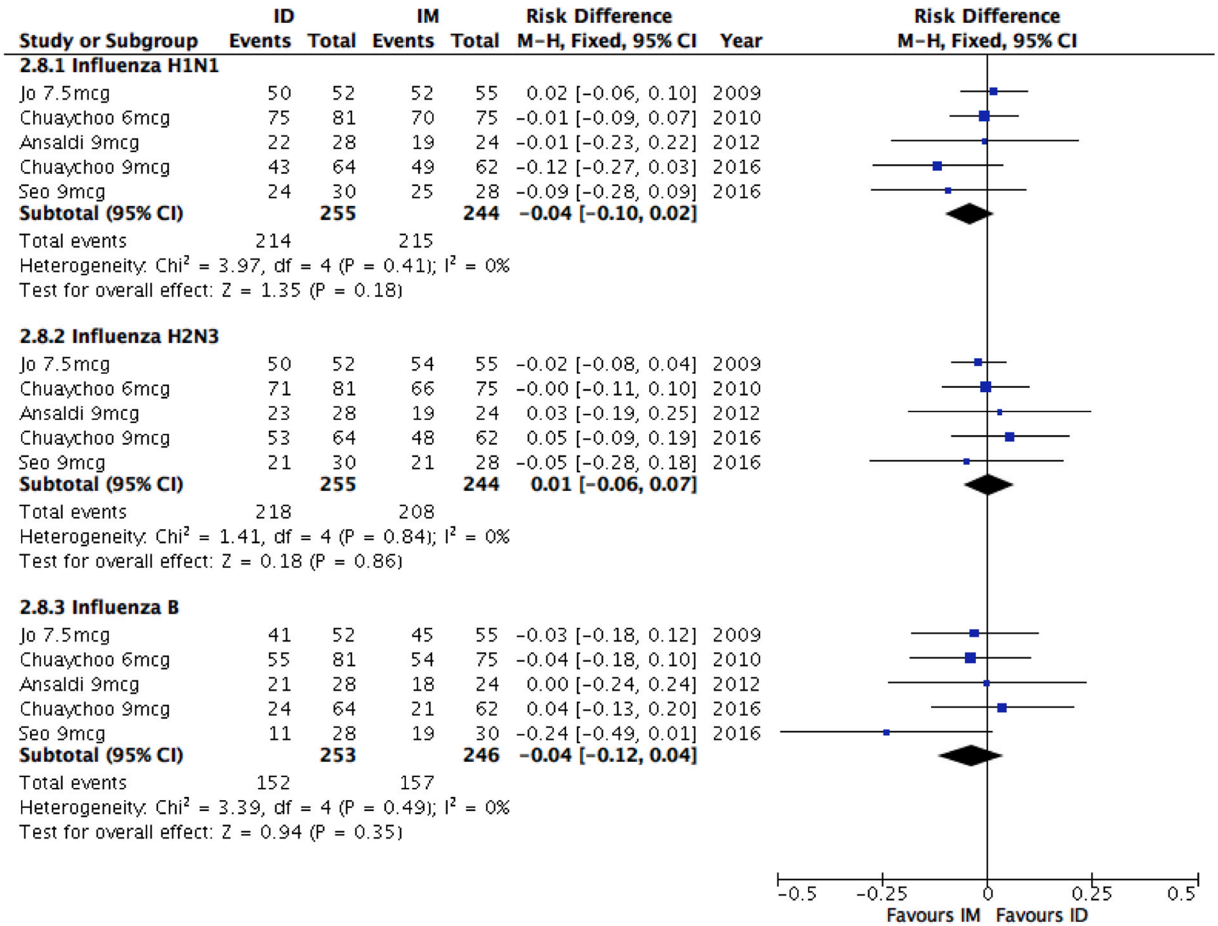


**Fig. 2e.** Forest plots of the risk differences of seroprotection for ID compared to IM administration of influenza vaccine per strain in immunocompromised and chronically ill patients.

**Table 2b**
Summary of outcomes of studies/study subgroups on immunogenicity of hepatitis B vaccines.

| Vaccine type | | Fractional ID vs IM | | | Fractional ID vs SC | | | |
|---|---|---|---|---|---|---|---|---|
| | Study population | ID inferior | Similar | ID superior | ID inferior | Similar | ID superior | Total |
| Recombinant HBV vaccine | Healthy adults | 6 | 7 | 0 | 0 | 0 | 0 | 13 |
| | Haemodialysis patients | 1 | 8 | 0 | 0 | 0 | 0 | 9 |
| | Children | 2 | 5 | 0 | 0 | 1 | 0 | 8 |
| | Chronically ill | 1 | 1 | 0 | 0 | 1 | 0 | 3 |
| Plasma-derived HBV vaccine | Healthy adults | 3 | 5 | 0 | 0 | 0 | 0 | 8 |
| | Children | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Sickle cell disease or β-thalassaemia | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Unknown vaccine type | Infants | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| | Total | 15 | 27 | 0 | 0 | 2 | 0 | 44 |

safety and reported the following adverse effects: fever, rash, conjunctivitis, Koplik's spots and convulsions. Complication rates after ID and SC administrations were similar.

### *3.8. Hepatitis A vaccines*

#### *3.8.1. Study characteristics*

Four studies [179–182] compared ID to IM immunisation with HAV vaccines. Three studies were conducted in healthy adults, and one study [182] in children. None of the study participants had received previous HAV immunisation. Two studies used inactivated whole-virus HAV vaccines [179,180], and two studies [181,182] used virosomal HAV vaccines. Regimens used varied between studies, administering 1–4 doses ID and 1–2 doses IM, at time intervals ranging from 1 up to 12 months. ID doses used were 0.1 or 0.15 ml; and IM doses ranged from 0.25 ml to 1 ml.

#### *3.8.2. Outcomes*

In all studies, seroprotection served as clinical endpoint. Different cut-offs for seroprotection were applied; all in a range within 10–20 IU/ml. Each study used an immunoassay to assess *anti*-HAV antibodies. The number of studies reporting inferior, similar or superior seroprotection rates after ID compared to IM or SC immunisation are shown in Table 2f. Only Brindle et al. [179] suggested lower seroprotection rates after ID immunisation. In this study three ID doses of 0.1 ml delivered at 4-week intervals were compared to a single IM dose of 1 ml. After the third dose, 23/26 of participants in the ID group and 17/18 of participants in the IM group achieved seroprotection.

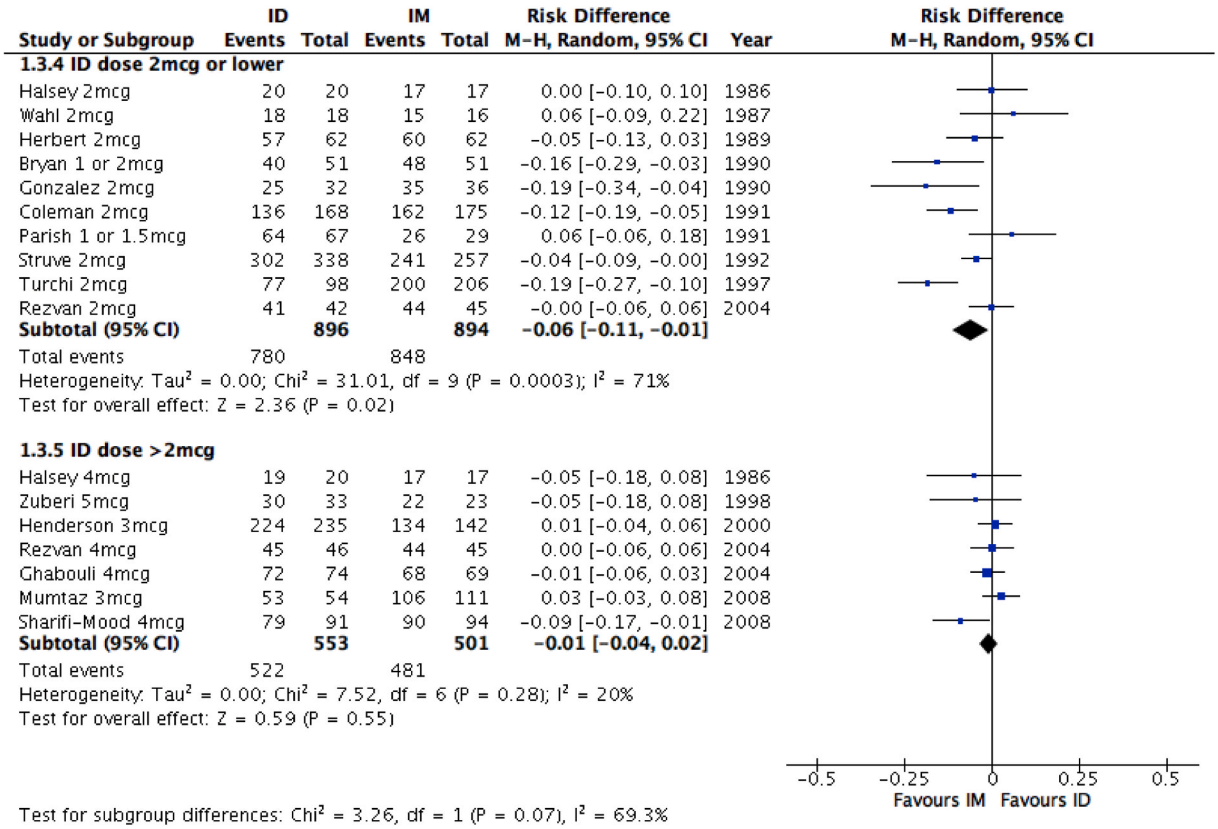


**Fig. 2f.** Forest plots of the risk differences of seroprotection for ID compared to IM administration of HBV vaccines in healthy adults.

**Table 2c**
Summary of outcomes of studies/study subgroups on immunogenicity of rabies vaccines.

| | | Fractional ID vs IM | | | Fractional ID vs SC | | | |
|---|---|---|---|---|---|---|---|---|
| | Vaccine | ID inferior | Similar | ID superior | ID inferior | Similar | ID superior | Total |
| PrEP | HDCV | 2 | 6 | 0 | 1 | 2 | 0 | 11 |
| | PVRV | 0 | 11 | 0 | 0 | 0 | 0 | 11 |
| | PCECV | 1 | 5 | 0 | 0 | 0 | 0 | 6 |
| PEP | HDCV | 1 | 0 | 0 | 0 | 1 | 0 | 2 |
| | PVRV | 0 | 3 | 0 | 0 | 0 | 0 | 3 |
| | PCECV | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| | Total | 4 | 27 | 0 | 1 | 3 | 0 | 35 |

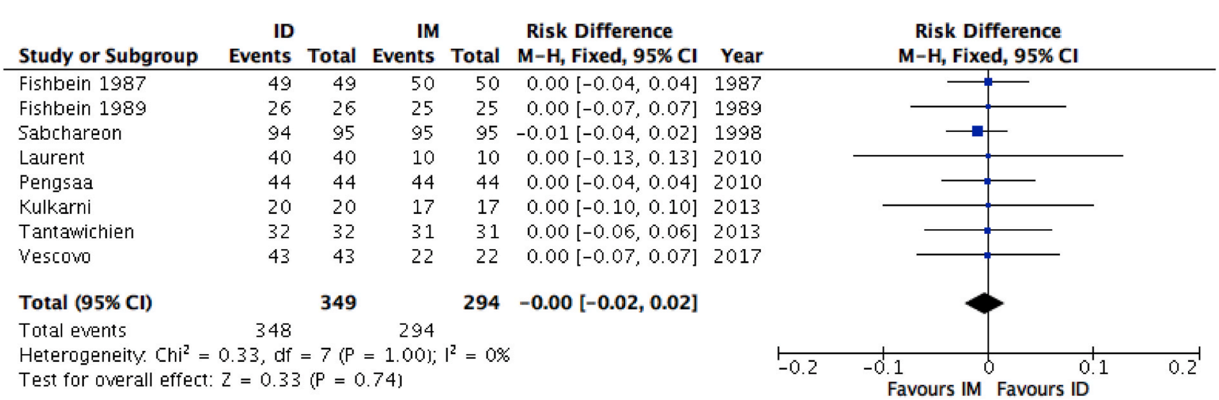


**Fig. 2g.** Forest plots of the risk differences of seroconversion for ID compared to IM administration of pre-exposure rabies vaccines in healthy adults.

Frösner et al. [181] reported local adverse events such as induration and erythema to be more common in the ID group, while the number of participants reporting systemic adverse events (mostly headache) was comparable between groups. Pancharoen et al. [182], on the other hand, found no participants exhibiting erythema and induration after ID immunisation. Systemic adverse events reported were fatigue, malaise

**Table 2d**
Summary of outcomes of studies on immunogenicity of IPV.

| | Fractional ID vs IM | | | |
|---|---|---|---|---|
| Scheme | ID inferior | Similar | ID superior | Total |
| 2 doses | 2 | 1 | 0 | 3 |
| 3 doses | 1 | 2 | 0 | 3 |
| 3 doses ID vs 2 doses IM | 0 | 1 | 0 | 1 |
| | 3 | 4 | 0 | 7 |

and fever, and were comparable in frequency and severity in both groups.

### 3.9. Other vaccines

The remaining studies comparing ID to IM or SC delivery of vaccine were conducted on DTP [183,184], HPV [187], JE [185,186], meningococcal disease [188], varicella zoster [189] and yellow fever [190] vaccines. The summary of outcomes on immunogenicity of these vaccines is shown in Table 2g. Study characteristics and results of each vaccine are further described in the paragraphs below.

#### 3.9.1. Diphtheria-tetanus-pertussis vaccine

Two studies compared ID to IM immunisation with DTP vaccines [183,184]. Both of them were performed in infants. The first study was conducted on both DTP vaccine and IPV (four antigens) [183]; in the ID group, a one-third dose was used compared to the IM group dose. There were no significant differences in GMTs of antibodies to the diphtheria, tetanus, and pertussis components. GMTs of all three polio types were higher in the IM group. The second study, conducted by Stanfield et al. [184], compared IM alum-adsorbed vaccines to ID alum-adsorbed and non-adsorbed vaccines. Seroprotection rates of both diphtheria and tetanus were similar in both groups. Antibody response to pertussis was not measured. Both studies reported induration of the injection site in the ID group, that disappeared within months. No other adverse events were reported.

#### 3.9.2. Human papillomavirus vaccine

Nelson et al. [187] compared ID delivery of HPV vaccine to standard IM delivery. Sexually naïve women with HPV 16 or HPV 18 neutralising antibodies below 1:80 were included. Both, bivalent HPV 16/18 vaccine, and quadrivalent HPV 6/11/16/18 vaccines were used; with the IM group receiving a full dose and the ID group a reduced (20%) dose. Seroconversion, defined as a neutralising antibody titre ≥1:320, was

**Table 2e**
Summary of outcomes of studies on immunogenicity of measles vaccines.

| Fractional ID vs IM | | | Fractional ID vs SC | | | |
|---|---|---|---|---|---|---|
| ID inferior | Similar | ID superior | ID inferior | Similar | ID superior | Total |
| 2 | 0 | 0 | 2 | 2 | 0 | 6 |

**Table 2f**
Summary of outcomes of studies on immunogenicity of HAV vaccines.

| Fractional ID vs IM | | | |
|---|---|---|---|
| ID inferior | Similar | ID superior | Total |
| 1 | 3 | 0 | 4 |

**Table 2g**
Summary of outcomes of studies on immunogenicity of other vaccines.

| | Fractional ID vs IM/SC | | | |
|---|---|---|---|---|
| Vaccine | ID inferior | Similar | ID superior | Total |
| DTP | 0 | 2 | 0 | 2 |
| HPV | 0 | 1 | 0 | 1 |
| Japanese encephalitis | 0 | 2 | 0 | 2 |
| Meningococcal disease | 1 | 0 | 0 | 1 |
| Varicella zoster | 0 | 1 | 0 | 1 |
| Yellow fever | 0 | 1 | 0 | 1 |

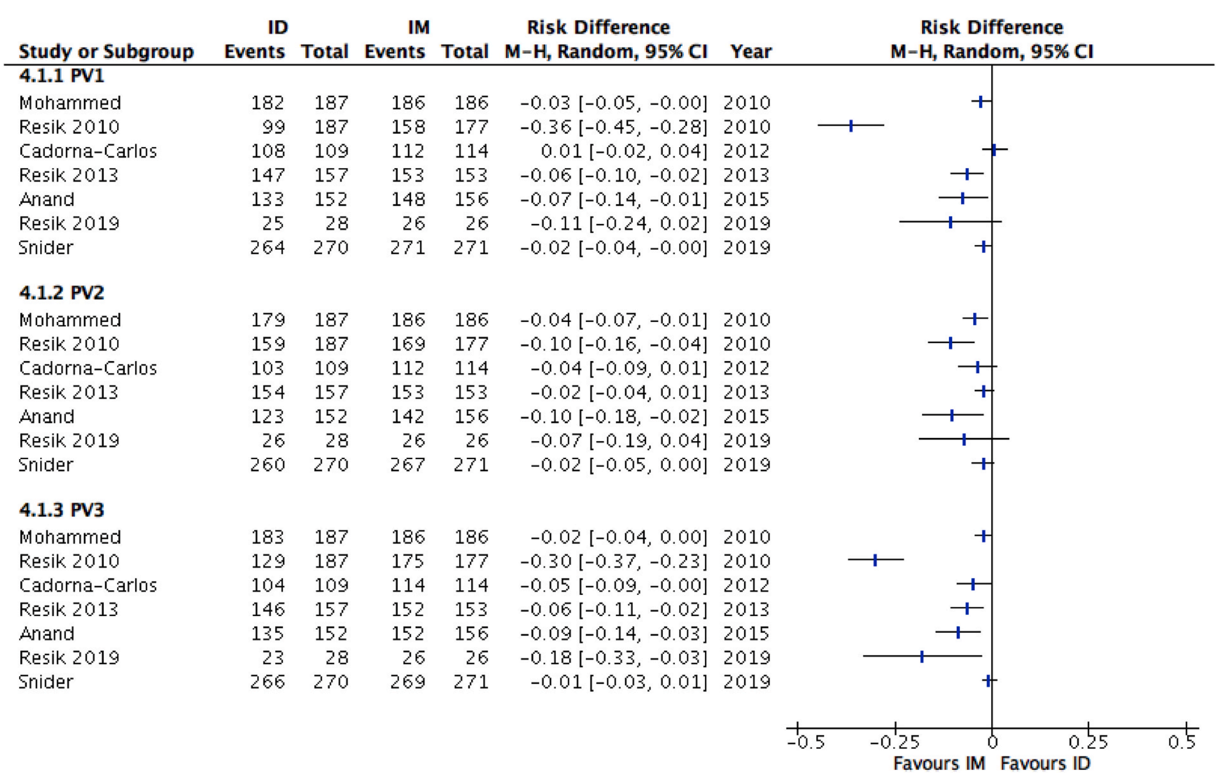


**Fig. 2h.** Forest plots of the risk differences of seroconversion for ID compared to IM administration of IPV per strain in healthy infants.

achieved in both groups after a 3-dose course. Local adverse events (erythema, swelling, firmness, itch and discoloration) were more common in the ID group. There were no differences in systemic adverse events between groups.

*3.9.3. Japanese encephalitis vaccine*

The two studies [185,186] conducted on JE vaccines both compared ID to SC immunisation. Both studies used mouse brain-derived inactivated JE vaccine and were conducted in healthy adults. The first study [185] was conducted amongst Australian soldiers, of which some already had antibodies prior to immunisation. This study compared ID injections of 0.1 ml, at one, two and three sites at a single visit, to a 1.0 ml IM dose. With the two and three-site ID injections, a similar seroconversion rate was achieved as with IM immunisation. Kitchener et al. [186] also compared one and two site ID injections to IM immunisation, yielding similar results: one site ID injection showed lower seroconversion rates, while two-site ID and IM immunisation seroconversion rates were similar. Adverse events were comparable between groups, except for arm pain, which was more common after IM immunisation.

*3.9.4. Meningococcal vaccine*

The only study on meningococcal vaccine [188] compared ID immunisation to SC immunisation. Gambian schoolboys received group A and C meningococcal polysaccharide vaccine. The ID and IM groups received 10 μg and 50 μg of vaccine, respectively. In this study, the antibody response of ID immunisation was inferior to IM immunisation. Safety was not assessed.

*3.9.5. Varicella zoster vaccine*

The study of Beals et al. [189] was conducted on the immunogenicity and safety of a live attenuated herpes zoster vaccine (Zostavax), comparing ID with SC immunisation. The study was conducted in healthy adults aged ≥50 with a history of a primary varicella infection (chickenpox), and without previous herpes zoster immunisation. The study showed an equivalent antibody response of a reduced ID dose to the standard SC dose. Injection site erythema, swelling and induration were more common in the ID group.

*3.9.6. Yellow fever vaccine*

Roukens et al. [190] performed a study comparing fractional ID dose of yellow fever vaccine to the standard SC dose. With a reduced 20% ID dose, seroprotection, defined as 80% virus neutralisation, was achieved in all study participants. Erythema, swelling and itching at injection site were more common in the ID group, while pain was more common in the SC group.

*3.10. Quality of studies*

The included studies were critically appraised. The methodological quality varied between individual studies, but could overall be considered as not ideal. Only a minority of the RCTs fully described methods of randomisation [17,40,41,71,75,79,84,90,91,98,99,101,110,121,133,138,147,164,173,187,190]. Blinding of outcome assessors was mentioned in a marginal proportion of RCTs [45,71,74,77,83,90,93,103,106,119], and blinding of participants and personnel by the use of placebo vaccines, in only one RCT [119]. Risk of attrition bias due to nature, amount or handling of incomplete outcome data was, however, considered low in the majority (n = 65) of RCTs [17,39–41,45,47,49,51,55,56,59,60,62,63,71,75,77–79,82,83,85,86,88,90–92,94,96–99,101,102,108–111,113,114,119–122,124,131,138,142,144,147,149,150,156,158,160,161,163,166,168,169,171,173,187,189,190]. Furthermore, selective outcome reporting was considered unclear in most RCTs, mostly due to the absence of prospectively registered study protocols. At last, bias caused by previous immunisation or the use of rabies immunoglobulins (RIG), only occurred in a minority of the RCTs.

The vast majority of cohort studies was considered of fair or low quality, mainly due to a lack of certainty of vaccine being exclusively delivered to the dermis (e.g. no inspection for wheal formation) n = 40 [14,42,44,52–54,57,58,61,66–70,72,73,95,107,117,132,135,137,141,145,151–153,159,162,174–178,180–184,188], and a lack of blinding of outcome assessors. Results of the critical appraisal of the included randomised clinical trials and cohort studies are shown in Supplementary Table 4.

## 4. Discussion

This systematic review demonstrates a potential for reducing dose, and therefore reducing costs, by using ID immunisation as compared to standard routes of administration for at least certain vaccines as a safe alternative. This dose-sparing potential has clearly been shown for influenza and rabies vaccines, for ID doses above 2 μg for HBV vaccines, and is doubtful for IPV and measles vaccines. Clinical trials on the remaining vaccines (HAV, DTP, HPV, JE, meningococcal disease, VZV and yellow fever vaccines) were scarce, but in most cases promising.

*4.1. Interpretation*

*4.1.1. Immunogenicity*

The results of the identified trials on influenza vaccines suggest there is no substantial difference in the immunogenicity of a fractional dose as low as 20% of ID immunisation and the standard IM dose in the following populations: healthy adults, elderly, immunocompromised patients and children. These findings are consistent with previous systematic reviews and meta-analyses, focusing on the immunogenicity of influenza vaccines in immunocompetent adults, elderly and immunocompromised patients [25–27]. For rabies vaccines, antibody responses after fractional ID immunisation (10–20%) were equivalent to IM or SC immunisation in 29 of 33 studies. However, a recent meta-analysis on booster vaccines including 4912 subjects revealed lower antibody levels after primary ID compared to IM immunisation [195]; it must be pointed out, however, that this review evaluated antibody responses 1–2 years after primary immunisation schedules (pre-booster); while in our review, we focused on assessment of immunogenicity 4 weeks after primary immunisation. Because booster responses were preserved after previous ID vaccination, the question is whether this difference is clinically relevant, because booster vaccinations are always indicated after animal associated injuries with risk of exposure to rabies virus.

Studies on HBV vaccines, typically delivering an ID dose of 10–20% of the standard dose, showed variable results. Our meta-analysis of 15 studies on healthy adults found ID doses of 1–2 μg to be inferior to IM immunisation; by contrast, ID doses >2 μg, were equally effective. A meta-analysis by Sangaré et al. of five clinical trials [196] on immunocompetent populations, demonstrated that ID HBV immunisation was slightly (14%) less likely to achieve seroprotection than IM immunisation. However, the meta-analysis was not stratified for ID dose used. In studies amongst haemodialysis patients seroprotection rates with higher dose fractional-ID immunisation were mostly equivalent to IM immunisation. A similar pattern of results was obtained by two studies that were conducted in patients with chronic kidney disease and haemodialysis patients, respectively [29,30]. The authors concluded that ID HBV vaccines, despite a lower vaccine dose, induce superior seroprotection rates as compared to IM route at completion of the vaccination schedule. This could imply that fractioned-ID doses of HBV vaccine are more beneficial in haemodialysis patients than in other populations. However, these stronger antibody responses could also simply be caused by the higher ID-doses used in studies amongst haemodialysis patients.

Only four out of seven IPV trials and two of six measles trials demonstrated equivalent antibody responses with fractioned-ID immunisation as with conventional delivery, which questions the dose-sparing potential of IPV and measles vaccines. However, it is important to note that all measles trials were published before 1985, using older generation devices for ID delivery of the vaccine, which are presumed less reliable. Moreover, measles is now only administered as measles-mumps-rubella (MMR) and polio is typically combined with DTP, HBV and *Haemophilus influenzae* type b (Hib) in most countries, which could affect immunogenicity. Clinical trials on the remaining vaccines (HAV, DTP, HPV, JE, meningococcal, VZV and yellow fever vaccines) were scarce, but in most cases promising; 10 of 12 clinical trials showed equivalent antibody responses with reduced-dose ID immunisation compared to conventional routes of administration. For all those vaccines, the question whether differences in ID vaccine dosing would influence the antobody response could not be answered due to insufficient data. Morestudies are required to estimate the extent of the dose-sparing potential of these vaccines.

#### 4.1.2. Safety

Overall, local reactions at the injection site were more common after ID immunisation compared to conventional delivery. These local adverse events included erythema, pruritus, swelling, induration, and, discoloration lasting up to several months. Systemic adverse events, such as asthenia, fever, headache and myalgia, were at large comparable in frequency and severity in both groups. Moreover, ID delivery of vaccines may become safer, as needle-free devices are being developed, leading to a reduction of needle-stick injuries [197].

#### 4.1.3. Costs

Only studies on HBV and rabies vaccines reported costs. Costs of ID regimens of HBV vaccines were half of those of IM regimens and 1/5th of that of SC regimens [96,105]. However, the authors did not report how costs were calculated. Costs of ID rabies regimens varied, but were considerably lower than IM regimens in all studies, reducing costs 2- to 5-fold [135,137,148,152]. Of note, compliance rates were higher when ID regimens were used with financial consideration being the major motive [152,159].

#### 4.1.4. General considerations

A factor not featuring prominently in most studies is the discussion of potential obstacles to ID vaccine administration. Those are mainly technical rather than cultural issues; a certain degree of reservation might be encountered by vaccinators with regard to the level of accuracy of vaccine application (corresponding to the level of optimal antigen deposition within the dermal target layer). These concerns seem to be unsubstantiated as the production of a defined wheal is easily measurable and controllable, and that the proper ID vaccination route can be trained very effectively and time-efficiently also with the assistance of specific ID-application devices [1].

### 4.2. Strengths and limitations of this review

In this systematic literature review we provided a unique comprehensible overview of all relevant studies conducted on licensed and currently available vaccines that are used against a range of infectious diseases in fractionated ID doses as an alternative to standard IM or SC delivery. A total of 156 clinical trials have been reviewed, conducted on vaccines against 12 different diseases. A comparable report from the Program for Appropriate Technology in Health (PATH) and the WHO was published in 2009 [24]. They performed a literature survey investigating ID delivery of several different vaccines, including studies on both primary immunisation schedules and booster schedules, without restrictions on ID dose used, which is very valuable in its own way. However, the aim of our review was to investigate the dose-sparing potential of ID vaccines, and it was therefore decided to only include studies using fractioned ID doses. Additionally, to minimise heterogeneity, only studies that evaluated primary immunisation schedules were included. Furthermore, our review differentiates from the report from PATH and WHO by the systematic methodology used to review literature and the meta-analysis.

There are, that notwithstanding, several limitations to this approach. First, we excluded all studies comparing same amounts of antigen delivered by ID and IM or SC routes. However, it is possible that dose-sparing is not a phenomenon unique to ID immunisation, and that a level of dose-sparing could be achieved with fractioned IM and SC doses as well [24]. Second, historical studies were included as well; roughly half of the identified studies were published between 1949 and 2000, although more reliable novel devices for ID delivery have only been developed in the past two decades [198]. Moreover, novel needle-free devices, such as the nowadays widely used Biojector® 2000, appear to induce a better antibody response than the conventional needle injections [51,199]. Therefore, historical studies could possibly have underestimated the ability of ID delivered vaccines to achieve adequate antibody responses. Third, we were unable to retrieve all of the full texts of potentially relevant articles. This could partly be due to the fact that many of the potentially relevant articles were published more than 40 years ago. As all articles with missing full text were excluded, there may be a selective inclusion bias based on availability of full text.

Last, this research focused mainly on short term immunogenicity based on seroprotection and seroconversion rates. Several studies, however, showed lower peak GMTs in ID groups [138,151,153,154,161,162], which may lead to a significantly shorter duration of protection. For some vaccines, such as influenza, or in outbreak settings this is not really a limitation. In contrast, when long term protection is required, for example against measles in a national immunisation program, this becomes an important issue.

### 4.3. Implications for research and practice

Notably for influenza and rabies vaccines, the dose-sparing capacity of ID delivery has been clearly established. Some countries, such as India and Thailand, have already approved ID rabies immunisation [21]. However, more resource-constrained countries as well as high income countries need to start considering the introduction of ID regimens to lower costs and possibly enhance vaccine compliance. With regard to influenza vaccines, both a trivalent and quadrivalent formulation of an ID vaccine, Fluzone® (Sanofi Pasteur), were recently FDA approved [200]. Physicians should be informed about ID influenza vaccines and their potential benefits, so they can be implemented on a larger scale. Although studies on HAV, DTP, HPV, JE, VZV and yellow fever vaccines were scarce, their results were promising. Further studies are warranted to clarify if ID applications of these vaccines could actually replace conventional routes of administration. Additionally, more research investigating long term immunogenicity of fractionated ID doses, as well as dose-sparing potential of IM and SC immunisation is needed, as it is uncertain if dose-sparing is a phenomenon unique to ID immunisation; a systematic review is warranted to compile and compare the literature comparing identical amounts of antigen delivered by ID and IM or SC routes.

Early-stage vaccine development trajectories, as for example underway against a number of widely neglected (tropical) infectious diseases including chikungunya and Lassa fever, should include ID regimen trials. Policy-makers in both low- and high-income settings should be encouraged to start considering the introduction of ID regimens to lower costs and possibly enhance vaccine compliance.

## 5. Conclusions

Compared to standard routes of administration, ID immunisation has a potential to reduce the inoculum and hence antigen dose, and therefore reduce costs for some vaccines (i.e. influenza and rabies vaccines). The potential for ID HBV vaccine to induce an antibody response equivalent to IM immunisation was illustrated for doses down to 3 μg. It remains uncertain, if the dose can be reduced for inactivated polio and measles vaccines by the use of ID administration. Clinical trials on the remaining vaccines (HAV, DTP, HPV, JE, meningococcal, VZV and yellow fever vaccines) were scarce, but yielded promising results; thus, more studies are required to estimate the dose-sparing potential of these vaccines. The safety profile of ID vaccines was at large similar to IM and SC vaccines, although minor local adverse events, such as erythema and pruritus, were more common after ID delivery. The potential to move to ID administration of carefully selected antigens carries an enormous potential to expand the benefit of vaccination against certain infectious agents on a considerable scale, specifically in global emergency situations as we are confronted with at the moment with SARS-CoV-2.

## Author contributions

MPG and FS conceived the project. JGD designed the search strategy. CAdP and JLS selected the included papers. JLS extracted the data, reviewed the selected papers and drafted the manuscript, supported by senior review author MPG. JLS, CAdPdP, HMG, JGD, AG, CS, FS, and MPG contributed to the writing. All authors contributed to and endorsed the final version of the manuscript.

## Declaration of competing interest

None to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2020.101868.

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## References

[1] Schaumburg F, De Pijper CA, Grobusch MP. Intradermal travel vaccinations-when less means more. Trav Med Infect Dis 2019;28:3–5. https://doi.org/10.1016/j.tmaid.2019.03.007.
[2] Chen W-H, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Reports 2020:1–4. https://doi.org/10.1007/s40475-020-00201-6.
[3] Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc B Biol Sci 2014;369:20130433.
[4] Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication, vol. 6. Geneva, Switzerland: WHO; 1988.
[5] Tuft L, Yagle EM, Rogers S. Comparative study of the antibody response after various methods of administration of mixed typhoid vaccine: with particular reference to the intradermal and oral methods. J Infect Dis 1932;50:98–110.
[6] Perry RM. Comparison of typhoid" O" and" H" agglutinin responses following intracutaneous and subcutaneous inoculation of typhoid, paratyphoid A and B vaccine. Am J Hyg 1937;26:388–93.
[7] Van Gelder DW, Greenspan FS, Dufresne NE. Influenza vaccination; comparison of intracutaneous and subcutaneous methods. U S Nav Med Bull 1947;47:197–206.
[8] Bruyn HB, Meiklejohn G, Brainerd H. Influenza vaccine. A study of serologic responses and incidence of reactions following subcutaneous and intradermal inoculation. Am J Dis Child 1949;77:149–62.
[9] Appleby JC, Himmelweit F, Stuart-Harris CH. Immunization with influenza virus A vaccines. Comparison of intradermal and subcutaneous routes. Lancet 1951;1:1384–7.
[10] Committee HKMV. Comparative trial of live attenuated measles vaccine in Hong Kong by intramuscular and intradermal injection. Bull World Health Organ 1967;36:375–84.
[11] Burland WL. Measles vaccination by the intradermal route. Postgrad Med 1969;45:323–6.
[12] McBean AM, Agle AN, Compaore P, Foster SO, McCormack WM. Comparison of intradermal and subcutaneous routes of cholera vaccine administration. Lancet 1972;1:527–9.
[13] Vella EE. Cholera vaccination: subcutaneous or intradermal administration? Lancet 1972;1:796–7.
[14] Aoki FY, Tyrrell DA, Hill LE. Immunogenicity and acceptability of a human diploid-cell culture rabies vaccine in volunteers. Lancet 1975;1:660–2.
[15] Bernard KW, Roberts MA, Summer J. Human diploid cell rabies vaccine. Effectiveness of immunization with small intradermal or subcutaneous doses. J Am Med Assoc 1982;247:1138–42.
[16] Zoulek G, Lorbeer B, Jilg W, Deinhardt F. Evaluation of a reduced dose of hepatitis B vaccine administered intradermally. J Med Virol 1984;14:27–32.
[17] Halsey NA, Reppert EJ, Margolis HS. Intradermal hepatitis B vaccination in an abbreviated schedule. Vaccine 1986;4:228–32.
[18] Samuel BU, Cherian T, Sridharan G, Mukundan P, John TJ. Immune response to intradermally injected inactivated poliovirus vaccine. Lancet Glob Health 1991;338:343–4.
[19] World Health Organization. WHO expert consultation on rabies, vol. 931; 2005.
[20] World Health Organization. Polio vaccines: WHO position paper–March, 2016. Wkly Epidemiol Rec 2016;91:145–68.
[21] Gongal G, Sampath G. Introduction of intradermal rabies vaccination–A paradigm shift in improving post-exposure prophylaxis in Asia. Vaccine 2019;37:A94–8.
[22] Lambert PH, Laurent P. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? Vaccine 2008;26:3197–208.
[23] Nicolas J-F, Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. Expert Rev Vaccines 2008;7:1201–14.
[24] World Health Organization and Programme for Appropriate Technology in Health (Path). Intradermal delivery of vaccines: a review of the literature and the potential for development for use in low-and middle-income countries. Geneva, Switzerland: WHO; 2009.
[25] Marra F, Young F, Richardson K, Marra CA. A meta-analysis of intradermal versus intramuscular influenza vaccines: immunogenicity and adverse events. Influ Other Respir Viruses 2013;7:584–603.
[26] Pileggi C, Mascaro V, Bianco A, Nobile CG, Pavia M. Immunogenicity and safety of intradermal influenza vaccine in the elderly: a meta-analysis of randomized controlled trials. Drugs Aging 2015;32:857–69.
[27] Pileggi C, Lotito F, Bianco A, Nobile CG, Pavia M. Immunogenicity and safety of intradermal influenza vaccine in immunocompromized patients: a meta-analysis of randomized controlled trials. BMC Infect Dis 2015;15:427.
[28] Chen W, Gluud C. Vaccines for preventing hepatitis B in health-care workers. Cochrane Database Syst Rev 2005:CD000100.
[29] Fabrizi F, Dixit V, Magnini M, Elli A, Martin P. Meta-analysis: intradermal vs. intramuscular vaccination against hepatitis B virus in patients with chronic kidney disease. Aliment Pharmacol Ther 2006;24:497–506.
[30] Fabrizi F, Dixit V, Messa P, Martin P. Intradermal vs intramuscular vaccine against hepatitis B infection in dialysis patients: a meta-analysis of randomized trials. J Viral Hepat 2011;18:730–7.
[31] Anand A, Molodecky NA, Pallansch MA, Sutter RW. Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: a novel dose sparing immunization schedule. Vaccine 2017;35:2993–8.
[32] Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA group. The PRISMA group (2009). Preferred reporting items for systematic reviews and MetaAnalyses: the PRISMA statement. PLoS Med 2009;6:1000097.
[33] Centre for Reviews and Dissemination. CRD database: search strategies. https://www.crd.york.ac.uk/crdweb/searchstrategies.asp 2019.
[34] Ozawa S, Mirelman A, Stack ML, Walker DG, Levine OS. Cost-effectiveness and economic benefits of vaccines in low-and middle-income countries: a systematic review. Vaccine 2012;31:96–108.
[35] Ouzzani Mourad, Hammady Hossam, Fedorowicz Zbys, Rayyan AE. A web and mobile app for systematic reviews. Syst Rev 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.
[36] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011;343:d5928.
[37] Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hosp Res Inst; 2000.
[38] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.
[39] Auewarakul P, Kositanont U, Sornsathapornkul P, Tothong P, Kanyok R, Thongcharoen P. Antibody responses after dose-sparing intradermal influenza vaccination. Vaccine 2007;25:659–63.
[40] Belshe RB, Newman FK, Wilkins K, Graham IL, Babusis E, Ewell M, et al. Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. Vaccine 2007;25:6755–63.
[41] Beran J, Ambrozaitis A, Laiskonis A, Mickuviene N, Bacart P, Calozet Y, et al. Intradermal influenza vaccination of healthy adults using a new microinjection system: a 3-year randomised controlled safety and immunogenicity trial. BMC Med 2009;7:13.
[42] Brown AJ. Evaluation of an influenza immunization program. Arch Environ Health 1966;12:597–9.
[43] Brown H, Kasel JA, Freeman DM, Moise LD, Grose NP, Couch RB. The immunizing effect of influenza A/New Jersey/76 (Hsw1N1) virus vaccine administered intradermally and intramuscularly to adults. J Infect Dis 1977;136:S466–71.
[44] Bruyn HB, Meiklejohn G, Brainerd HD. Influenza vaccination; a comparison of antibody response obtained by various methods of administration. J Immunol 1949;62:1–11.
[45] Davies JW, Simon WR. Antibody response to influenza immunization by jet injection. Canad 1969;104–8.

[46] Frenck Jr RW, Belshe R, Brady RC, Winokur PL, Campbell JD, Treanor J, et al. Comparison of the immunogenicity and safety of a split-virion, inactivated, trivalent influenza vaccine (Fluzone) administered by intradermal and intramuscular route in healthy adults. Vaccine 2011;29:5666–74.
[47] Gorse GJ, Falsey AR, Fling JA, Poling TL, Strout CB, Tsang PH. Intradermally-administered influenza virus vaccine is safe and immunogenic in healthy adults 18-64 years of age. Vaccine 2013;31:2358–65.
[48] Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. N Engl J Med 2004;351:2295–301.
[49] Künzi JM, Seiberling MK, Herzog C, et al. Immunogenicity and safety of low dose virosomal adjuvanted influenza vaccine administered intradermally compared to intramuscular full dose administration. Vaccine 2009;27(27):3561–7.
[50] Leroux-Roels I. Seasonal influenza vaccine delivered by intradermal microinjection: a randomised controlled safety and immunogenicity trial in adults. Vaccine 2008;26:6614–9.
[51] Levin Y, Kochba E, Kenney R. Clinical evaluation of a novel microneedle device for intradermal delivery of an influenza vaccine: are all delivery methods the same? Vaccine 2014;32:4249–52.
[52] Marks MI, Eller JJ. Intradermal influenza immunization. Experience with Hong Kong vaccine. Am Rev Respir Dis 1971;103:579–81.
[53] McCarroll JR, Kilbourne ED. Imunization with asia-atrain influenza vaccine. Equivalence of the subcutaneous and intrasermal routes. N Engl J Med 1958;259: 315–20.
[54] Meijer WJ, Wensing AMJ, Bos AA, Kuiphuis JCF, Hagelen EMM, Wilschut JC, et al. Influenza vaccination in healthcare workers; comparison of side effects and preferred route of administration of intradermal versus intramuscular administration. Vaccine 2017;35:1517–23.
[55] Metanat M, Salehi M, Sharifi-Mood B, Safai MR. Serum antibody responses after intradermal injection of influenza vaccine. Int J Virol 2010;6:41–4.
[56] Nougarede N, Bisceglia H, Rozieres A, Goujon C, Boudet F, Laurent P, et al. Nine mug intradermal influenza vaccine and 15 mug intramuscular influenza vaccine induce similar cellular and humoral immune responses in adults. Hum Vaccines Immunother 2014;10:2713–20.
[57] Phillips CA, Forsyth BR, Christmas WA, Gump DW, Whorton EB, Rogers I, et al. Purified influenza vaccine: clinical and serologic responses to varying doses and different routes of immunization. J Infect Dis 1970;122:26–32.
[58] Saslaw S, Carlisle HN, Perkins RL. Effect of dosage and influenza vaccine content on antibody response in medical students. Am J Med Sci 1967;253:710–7.
[59] Song JY, Cheong HJ, Noh JY, Yang TU, Seo YB, Hong KW, et al. Long-term immunogenicity of the influenza vaccine at reduced intradermal and full intramuscular doses among healthy young adults. Clin Exp Vaccine Res 2013;2: 115–9.
[60] Van Damme P, Oosterhuis-Kafeja F, Van der Wielen M, Almagor Y, Sharon O, Levin Y. Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. Vaccine 2009;27:454–9.
[61] Boger WP, Liu OC. [Subcutaneous and intradermal vaccination with Asian influenza vaccine]. J Am Med Assoc 1957;165:1687–9.
[62] Chi RC, Rock MT, Neuzil KM. Immunogenicity and safety of intradermal influenza vaccination in healthy older adults. Clin Infect Dis 2010;50:1331–8.
[63] Della Cioppa G, Nicolay U, Lindert K, Leroux-Roels G, Clement F, Castellino F, et al. A dose-ranging study in older adults to compare the safety and immunogenicity profiles of MF59-adjuvanted and non-adjuvanted seasonal influenza vaccines following intradermal and intramuscular administration. Hum Vaccines Immunother 2014;10:1701–10.
[64] Lawee D, Steele D, Gutman M, Demanuele F. Efficacy of influenza inoculation: intradermal versus subcutaneous route. Can Fam Physician 1981;27:411–4.
[65] Levin E, Shukarev G, Rusch S, et al. A phase 1, open-label, randomized study to compare the immunogenicity and safety of different administration routes and doses of virosomal influenza vaccine in elderly. Vaccine 2016;34(44):5262–72.
[66] Saslaw S, Carlisle HN, Slutzker B. Antibody response to polyvalent influenza virus vaccine administered intradermally or subcutaneously in an aged population. Am J Med Sci 1963;245:387–98.
[67] Tauraso NM, Gleckman R, Pedreira FA, Sabbaj J, Yahwak R, Madoff MA. Effect of dosage and route of inoculation upon antigenicity of inactivated influenza virus vaccine (Hong Kong strain) in man. Bull World Health Organ 1969;41:507–16.
[68] Saslaw S, Carlisle HN. Effect of dosage on antibody response to polyvalent influenza virus vaccine in an aged population. Am J Med Sci 1964;248:273–84.
[69] Slutzker B, Simon W, Saslaw S. Reactions to polyvalent influenza virus vaccine in an aged population. Am J Med Sci 1963;246:62–4.
[70] Bruyn HB, Lennette EH. Immunological evaluation of monovalent influenza vaccine in adults and in children. AMA Arch Intern Med 1959;103:914–23.
[71] Esposito S, Daleno C, Picciolli I, Tagliaferri L, Scala A, Prunotto G, et al. Immunogenicity and safety of intradermal influenza vaccine in children. Vaccine 2011;29:7606–10.
[72] Payler DK, Skirrow MB. Letter: intradermal influenza vaccination. Br Med J 1974; 2:727.
[73] Zavadova H, Adam E, Vonka V, Domorazkova E, Kratochvilova M, Burian V, et al. Clinical reactivity and immunogenicity of hemagglutinin influenza vaccine. II. Clinical reactions, hemagglutination-inhibitiong and strain and type-specific complement-fixing antibody responses in infants. Arch Gesamte Virusforsch 1972;36:53–61.
[74] Chiu SS, Chan KH, Tu W, Lau YL, Peiris JS. Immunogenicity and safety of intradermal versus intramuscular route of influenza immunization in infants less than 6 months of age: a randomized controlled trial. Vaccine 2009;27:4834–9.
[75] Chiu SS, Peiris JS, Chan KH, Wong WH, Lau YL. Immunogenicity and safety of intradermal influenza immunization at a reduced dose in healthy children. Pediatrics 2007;119:1076–82. https://doi.org/10.1007/s40475-020-00201-6.
[76] Chuaychoo B, Wongsurakiat P, Nana A, Kositanont U, Maranetra KN. The immunogenicity of intradermal influenza vaccination in COPD patients. Vaccine 2010;28:4045–51.
[77] Herbert FA, Larke RP, Markstad EL. Comparison of responses to influenza A/New Jersey/76-A/Victoria/75 virus vaccine administered intradermally or subcutaneously to adults with chronic respiratory disease. J Infect Dis 1979;140: 234–8.
[78] Jo YM, Song JY, Hwang IS, Lee J, Oh SC, Kim JS, et al. Dose sparing strategy with intradermal influenza vaccination in patients with solid cancer. J Med Virol 2009; 81:722–7.
[79] Chuaychoo B, Kositanont U, Rittayamai N, Niyomthong P, Songserm T, Maranetra KN, et al. The immunogenicity of the intradermal injection of seasonal trivalent influenza vaccine containing influenza A(H1N1)pdm09 in COPD patients soon after a pandemic. Hum Vaccines Immunother 2016;12:1728–37.
[80] Ansaldi F, Valle L, de Florentiis D, Parodi V, Murdaca G, Bruzzone B, et al. Phase 4 randomized trial of intradermal low-antigen-content inactivated influenza vaccine versus standard-dose intramuscular vaccine in HIV-1-infected adults. Hum Vaccines Immunother 2012;8:1048–52.
[81] Khanlou H, Sanchez S, Babaie M, Chien C, Hamwi G, Ricaurte JC, et al. The safety and efficacy of dose-sparing intradermal administration of influenza vaccine in human immunodeficiency virus-positive patients. Arch Intern Med 2006;166: 1417.
[82] Seo YB, Lee J, Song JY, Choi HJ, Cheong HJ, Kim WJ. Safety and immunogenicity of influenza vaccine among HIV-infected adults: conventional vaccine vs. intradermal vaccine. Hum Vaccines Immunother 2016;12:478–84.
[83] Manuel O, Humar A, Berutto C, Ely L, Giulieri S, Lien D, et al. Low-dose intradermal versus intramuscular trivalent inactivated seasonal influenza vaccine in lung transplant recipients. J Heart Lung Transplant 2011;30:679–84.
[84] Gelinck LB, van den Bemt BJ, Marijt WA, van der Bijl AE, Visser LG, Cats HA, et al. Intradermal influenza vaccination in immunocompromized patients is immunogenic and feasible. Vaccine 2009;27:2469–74.
[85] Han SH, Woo JH, Weber F, Kim WJ, Peck KR, Kim SI, et al. Immunogenicity and safety of Intanza/IDflu intradermal influenza vaccine in South Korean adults : a multicenter, randomized trial. Hum Vaccines Immunother 2013;9. 1971–7.
[86] Hung IF, Levin Y, To KK, Chan KH, Zhang AJ, Li P, et al. Dose sparing intradermal trivalent influenza (2010/2011) vaccination overcomes reduced immunogenicity of the 2009 H1N1 strain. Vaccine 2012;30:6427–35.
[87] Arakane R, Nakatani H, Fujisaki E, Takahama A, Ishida K, Yoshiike M, et al. Immunogenicity and safety of the new intradermal influenza vaccine in adults and elderly: a randomized phase 1/2 clinical trial. Vaccine 2015;33:6340–50.
[88] Belshe RB, Newman FK, Cannon J, Duane C, Treanor J, Van Hoecke C, et al. Serum antibody responses after intradermal vaccination against influenza. N Engl J Med 2004;351:2286–94.
[89] Nicholson KG, Tyrrell DAJ, Harrison P. Clinical studies of monovalent inactivated whole virus and subunit A/USSR/77 (H1N1) vaccine: serological responses and clinical reactions. J Biol Stand 1979;7:123–36.
[90] Afzali H, Vali GR, Khalifeh-Soltani A. Comparative effect of intradermal and intramuscular injections of hepatitis B vaccine. Arch Iran Med 2003;6:9–12.
[91] Ahman L, Back E, Bensch K, Olcen P. Non-efficacy of low-dose intradermal vaccination against hepatitis B in Down's syndrome. Scand J Infect Dis 1993;25: 16–23.
[92] Argani H, Akhtarishojaie E. Levamizole enhances immune responsiveness to intra-dermal and intra-muscular hepatitis B vaccination in chronic hemodialysis patients. J Immune Base Ther Vaccine 2006;4:3.
[93] Bryan JP, Sjogren M, Iqbal M, Khattak AR, Nabi S, Ahmed A, et al. Comparative trial of low-dose, intradermal, recombinant- and plasma-derived hepatitis B vaccines. J Infect Dis 1990;162:789–93.
[94] Bunupuradah T, Ananworanich J, Pancharoen C, Petoumenos K, Prasitsuebsai W, Wongngam W, et al. Randomized study of intradermal compared to intramuscular hepatitis B vaccination in HIV-infected children without severe immunosuppression. Vaccine 2011;29:2962–7.
[95] Carlsson T, Struve J, Sonnerborg A, Weiland O. The anti-HBs response after 2 different accelerated intradermal and intramuscular schemes for hepatitis B vaccination. Scand J Infect Dis 1999;31:93–5.
[96] Chanchairujira T, Chantaphakul N, Thanwandee T, Ong-Ajyooth L. Efficacy of intradermal hepatitis B vaccination compared to intramuscular vaccination in hemodialysis patients. J Med Assoc Thail 2006;89:S33–40.
[97] Charest AF, McDougall J, Goldstein MB. A randomized comparison of intradermal and intramuscular vaccination against hepatitis B virus in incident chronic hemodialysis patients. Am J Kidney Dis 2000;36:976–82.
[98] Chau KF, Cheng YL, Tsang DN, Choi KS, Wong KM, Chak WL, et al. Efficacy and side effects of intradermal hepatitis B vaccination in CAPD patients: a comparison with the intramuscular vaccination. Am J Kidney Dis 2004;43:910–7.
[99] Coberly JS, Townsend T, Repke J, Fields H, Margolis H, Halsey NA. Suboptimal response following intradermal hepatitis B vaccine in infants. Vaccine 1994;12: 984–7.
[100] Coleman FE, Serovich J, Hadler SC, et al. Intradermal hepatitis B vaccination in a large hospital employee population. Vaccine 1991;9(10):723–7.
[101] Egemen A, Aksit S, Kurugol Z, Erensoy S, Bilgic A, Akilli M. Low-dose intradermal versus intramuscular administration of recombinant hepatitis B vaccine: a comparison of immunogenicity in infants and preschool children. Vaccine 1998; 16:1511–5.

[102] Frazer IH, Jones B, Dimitrakakis M, Mackay IR. Intramuscular versus low-dose intradermal hepatitis B vaccine. Assessment by humoral and cellular immune response to hepatitis B surface antigen. Med J Aust 1987;146:242–5.
[103] Ghabouli MJ, Sabouri AH, Shoeibi N, Bajestan SN, Baradaran H. High seroprotection rate induced by intradermal administration of a recombinant hepatitis B vaccine in young healthy adults: comparison with standard intramuscular vaccination. Eur J Epidemiol 2004;19:871–5.
[104] Gomber S, Sharma R, Ramachandran VG. Immunogenicity of low dose intradermal hepatitis B vaccine and its comparison with standard dose intramuscular vaccination. Indian Pediatr 2004;41:922–6.
[105] Hayashi J, Nakashima K, Noguchi A, Morofuji M, Kashiwagi S. Cost effectiveness of intradermal vs. subcutaneous hepatitis B vaccination for the mentally handicapped. J Infect 1991;23:39–45.
[106] Henderson EA, Louie TJ, Ramotar K, Ledgerwood D, Hope KM, Kennedy A. Comparison of higher-dose intradermal hepatitis B vaccination to standard intramuscular vaccination of healthcare workers. Infect Control Hosp Epidemiol 2000;21:264–9.
[107] Herbert M, Butler AV, Roome AP, Caul EO. Comparison of intradermal and intramuscular hepatitis B vaccination in university students. Vaccine 1989;7:395–6.
[108] Karahocagil MK, Buzgan T, Irmak H, Karsen H, Akdeniz H, Akman N. Comparison of intramuscular and intradermal applications of hepatitis B vaccine in hemodialysis patients. Ren Fail 2006;28:561–5.
[109] Lankarani KB, Taghavi AR, Agah S, Karimi A. Comparison of intradermal and intramuscular administration of hepatitis B vaccine in neonates. Indian J Gastroenterol 2001;20:94–6.
[110] Launay O, Van Der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA, J Am Med Assoc 2011;305:1432–40.
[111] Leonardi S, Musumeci S, Sciacca A, Greco D, Romano C. Reliability of intradermal vaccination against hepatitis B for accelerated prophylaxis. Pediatr Infect Dis J 1990;9:520.
[112] Li Volti S, Caruso-Nicoletti M, Biazzo F, Sciacca A, Mandara G, Mancuso M, et al. Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus. Arch Dis Child 1998;78:54–7.
[113] Medeiros RH, Figueiredo AE, Poli-de-Figueiredo CE, d'Avila DO, de los Santos CA. Low response to intradermal hepatitis B vaccination in incident hemodialysis patients. J Bras Nefrol 2011;33:45–9.
[114] Mettang T, Schenk U, Thomas S, Machleidt C, Kiefer T, Fischer FP, et al. Low-dose intradermal versus intramuscular hepatitis B vaccination in patients with end-stage renal failure. A preliminary study. Nephron 1996;72:192–6.
[115] Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PB. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. J Med Virol 1989;28:96–100.
[116] Mok Q, Underhill G, Wonke B, Aldouri M, Kelsey M, Jefferies D. Intradermal hepatitis B vaccine in thalassaemia and sickle cell disease. Arch Dis Child 1989;64:535–40.
[117] Mumtaz B, Siddiq M. Immunogenicity and economic evaluation of different recombinant hepatitis-B vaccines in different dosages, schedules, and routes of administration. Pakistan J Med Sci 2008;24:833–7.
[118] Parish DC, Muecke HW, Joiner TA, Pope WT, Hadler SC. Immunogenicity of low-dose intradermal recombinant DNA hepatitis B vaccine. South Med J 1991;84:426–30.
[119] Redfield RR, Innis BL, McNair Scott R. Clinical evaluation of low-dose intradermally administered hepatitis B virus vaccine. A cost reduction strategy. J Am Med Assoc 1985;254:3203–6.
[120] Rezvan H, Fayaz-Vasseghi M. Low-dose hepatitis B vaccination with recombinant vaccine in Iranian health care workers. Arch Iran Med 2004;7:178–81.
[121] Roozbeh J, Moini M, Lankarani KB, Sagheb MM, Shahpoori S, Bastani B. Low dose intradermal versus high dose intramuscular hepatitis B vaccination in patients on chronic hemodialysis. Am Soc Artif Intern Organs J 2005;51:242–5.
[122] Sharifi-Mood B, Izadi S, Salehi M, Qaedi H. Comparison of immunogenicity of low-dose intradermal hepatitis B vaccine with the standard-dose intramuscular vaccination in young healthy Iranian adults. Hepat Mon 2008;8:111–4.
[123] Struve J, Aronsson B, Frenning B, Granath F, von Sydow M, Weiland O. Intramuscular versus intradermal administration of a recombinant hepatitis B vaccine: a comparison of response rates and analysis of factors influencing the antibody response. Scand J Infect Dis 1992;24:423–9.
[124] Tavanaee Sani A, Naghibi M, Esmaeili H, Mahmoudi M, Mohammadi K. Comparision of low dose intradermal vaccination against hepatitis b with routine dose interamuscular vaccination in end-stage renal disease patients. Can J Infect Dis Med Microbiol 2012;23:39B.
[125] Turchi MD, Martelli CM, Ferraz ML, Silva AE, Cardoso D, das D, Martelli P, et al. Immunogenicity of low-dose intramuscular and intradermal vaccination with recombinant hepatitis B vaccine. Rev Inst Med Trop Sao Paulo 1997;39:15–9.
[126] Wahl M, Hermodsson S. Intradermal, subcutaneous or intramuscular administration of hepatitis B vaccine: side effects and antibody response. Scand J Infect Dis 1987;19:617–21.
[127] Whittle HC, Inskip H, Hall AJ, Mendy M, Downes R, Hoare S. Vaccination against hepatitis B and protection against chronic viral carriage in the Gambia. Lancet 1991;337:747–50.
[128] Wistrom J, Settergren B, Gustafsson A, Juto P, Norrby RS. Intradermal vs intramuscular hepatitis B vaccinations. J Am Med Assoc 1990;264:181–2.
[129] Yamashiki M, Kosaka Y, Nishimura A. An effective intradermal hepatitis B vaccination. Vaccine 1997;15:1618–23.
[130] Zuberi BF, Rajput MR, Muzaffar L, Jatoi N, Shaikh WM. Efficacy of low dose intradermal hepatitis B vaccination schedule. JPMA - J Pakistan Med Assoc 1998;48:377–8.
[131] Gonzalez ML, Usandizaga M, Alomar P, Salva F, Martin Erroz FMJ, Lardinois R. Intradermal and intramuscular route for vaccination against hepatitis B. Vaccine 1990;8:402–5.
[132] Ajjan N, Soulebot JP, Triau R, Biron G. Intradermal immunization with rabies vaccine. Inactivated Wistar strain cultivated in human diploid cells. J Am Med Assoc 1980;244:2528–31.
[133] Bose A, Munshi R, Tripathy RM, Madhusudana SN, Harish BR, Thaker S, et al. A randomized non-inferiority clinical study to assess post-exposure prophylaxis by a new purified vero cell rabies vaccine (Rabivax-S) administered by intramuscular and intradermal routes. Vaccine 2016;34:4820–6.
[134] Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S, et al. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull World Health Organ 2000;78:693–8.
[135] Chutivongse S, Supich C, Wilde H. Acceptability and efficacy of purified vero-cell rabies vaccine in Thai children exposed to rabies. Asia Pac J Publ Health 1988;2:179–84.
[136] Cunha RS, da Silva ADR, Batista AM, Chaves LB, Barata RB. Equivalence between pre-exposure schemes for human rabies and evaluation of the need for serological monitoring. Rev Saude Publica 2010;44:548–54.
[137] Dhaduk KM, Unadkat SV, Katharotiya PR, Mer AR, Chaudhary MC, Prajapati MM. Case profile, volume analysis, and dropout rate of antirabies vaccination regimens among animal bite victims in Gujarat. Indian J Publ Health 2016;60:268–72.
[138] Dreesen DW, Fishbein DB, Kemp DT, Brown J. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine 1989;7:397–400.
[139] Fishbein DB, Dreesen DW, Holmes DF, Pacer RE, Ley AB, Yager PA, et al. Human diploid cell rabies vaccine purified by zonal centrifugation: a controlled study of antibody response and side effects following primary and booster pre-exposure immunizations. Vaccine 1989;7:437–42.
[140] Fishbein DB, Pacer RE, Holmes DF. Rabies preexposure prophylaxis with human diploid cell rabies vaccine: a dose-response study. J Infect Dis 1987;156:50–5.
[141] Grandien M, Fridell E, Kindmark CO. Intradermal immunization with reduced doses of human diploid cell strain rabies vaccine: evaluation of antibody response by ELISA and mixed hemadsorption test. Scand J Infect Dis 1985;17:173–8.
[142] Jaiiaroensup W, Lang J, Thipkong P, Wimalaratne O, Samranwataya P, Saikasem A, et al. Safety and efficacy of purified Vero cell rabies vaccine given intramuscularly and intradermally. (Results of a prospective randomized trial). Vaccine 1998;16:1559–62.
[143] Jaijaroensup S, Khawplod PWL. Immunogenicity of rabies postexposure booster injections in subjects who had previously received intradermal preexposure vaccination. J Trav Med 1999;6:234–7.
[144] Jonker EFF, Visser LG. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study. J Trav Med 2017;24:1.
[145] Khawplod P, Jaijaroensup W, Sawangvaree A, Prakongsri S, Wilde H. One clinic visit for pre-exposure rabies vaccination (a preliminary one year study). Vaccine 2012;30:2918–20.
[146] Khawplod P, Wilde H, Benjavongkulchai M, Sriaroon C, Chomchey P. Immunogenicity study of abbreviated rabies preexposure vaccination schedules. J Trav Med 2007;14:173–6.
[147] Kulkarni A, D'costa PM, Bavdekar AR, et al. Safety and immunogenicity of a new purified vero cell rabies vaccine (PVRV) administered by intramuscular and intradermal routes in healthy volunteers. Vaccine 2013;31(24):2719–22.
[148] Kundu BK, Meshram GG, Bhargava S, Meena O. Cost savings of using updated Thai red Cross intradermal regimen in a high-throughput anti-rabies clinic in New Delhi, India. Trav Med Infect Dis 2019;4:22.
[149] Lang J, Hoa DQ, Gioi NV, Tho LT, Vien NC, Rouyrre N, et al. Immunogenicity and safety of low-dose intradermal rabies vaccination given during an Expanded Programme on Immunization session in Viet Nam: results of a comparative randomized trial. Trans R Soc Trop Med Hyg 1999;93:208–13.
[150] Laurent PE, Bourhy H, Fantino M, Alchas P, Mikszta JA. Safety and efficacy of novel dermal and epidermal microneedle delivery systems for rabies vaccination in healthy adults. Vaccine 2010;28:5850–6.
[151] Lemon SM, Miller RN, Pang LW, Prier RE, Bernard KW. Failure to achieve predicted antibody responses with intradermal and intramuscular human diploid cell rabies vaccine. Lancet 1984;1:1098–100.
[152] Mankeshwar R, Silvanus V, Akarte S. Evaluation of intradermal vaccination at the anti rabies vaccination OPD. Nepal Med Coll J NMCJ 2014;15:228–30.
[153] Nicholson KG, Farrow PR, Bijok U, Barth R. Pre-exposure studies with purified chick embryo cell culture rabies vaccine and human diploid cell vaccine: serological and clinical responses in man. Vaccine 1987;5:208–10.
[154] Nicholson KG, Turner GS, Aoki FY. Immunization with a human diploid cell strain of rabies virus vaccine: two-year results. J Infect Dis 1978;137:783–8.
[155] Pengsaa K, Limkittikul K, Sabchareon A, Ariyasriwatana C, Chanthavanich P, Attanath P, et al. A three-year clinical study on immunogenicity, safety, and booster response of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12- to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine. Pediatr Infect Dis J 2009;28:335–7.

[156] Phanuphak P, Khawplod P, Sirivichayakul S, Siriprasomsub W, Ubol S, Thaweepathomwat M. Humoral and cell-mediated immune responses to various economical regimens of purified Vero cell rabies vaccine. Asian Pac J Allergy Immunol 1987;5:33–7.
[157] Recuenco S, Warnock E, Osinubi MOV, Rupprecht CE. A single center, open label study of intradermal administration of an inactivated purified chick embryo cell culture rabies virus vaccine in adults. Vaccine 2017;35:4315–20.
[158] Sabchareon A, Chantavanich P, Pasuralertsakul S, Pojjaroen-Anant C, Prarinyanupharb V, Attanath P, et al. Persistence of antibodies in children after intradermal or intramuscular administration of preexposure primary and booster immunizations with purified Vero cell rabies vaccine. Pediatr Infect Dis J 1998; 17:1001–7.
[159] Shankaraiah RH, Rajashekar RA, Veena V, Hanumanthaiah AN. Compliance to anti-rabies vaccination in post-exposure prophylaxis. Indian J Publ Health 2015; 59:58–60.
[160] Sudarshan MK, Madhusudana SN, Mahendra BJ, Ashwath Narayana DH, Ananda Giri MS, Popova O, et al. Evaluation of a new five-injection, two-site,intradermal schedule for purified chick embryo cell rabies vaccine: a randomized, open-label, active-controlled trial in healthy adult volunteers in India. Curr Ther Res Clin Exp 2005;66:323–34.
[161] Tantawichien T, Sibunruang S, Angsanakul J, Limsuwan K, Khumvilai S. Safety and immunogenicity of new chromatographicallypurified Vero cell rabies vaccine (CPRV) for human use in pre- and post-exposure rabies. Int J Antimicrob Agents 2013;42:S158.
[162] Turner GS, Nicholson KG, Tyrrell DA, Aoki FY. Evaluation of a human diploid cell strain rabies vaccine: final report of a three year study of pre-exposure immunization. J Hyg 1982;89:101–10.
[163] Vescovo P, Rettby N, Ramaniraka N, Liberman J, Hart K, Cachemaille A, et al. Safety, tolerability and efficacy of intradermal rabies immunization with DebioJectTM. Vaccine 2017;35:1782–8.
[164] Warrell MJ, Riddell A, Yu LM, Phipps J, Diggle L, Bourhy H, et al. A simplified 4-site economical intradermal post-exposure rabies vaccine regimen: a randomised controlled comparison with standard methods. PLoS Neglected Trop Dis 2008;2: e224.
[165] Warrell MJ, Warrell DA, Suntharasamai P, Viravan C, Sinhaseni A, Udomsakdi D, et al. An economical regimen of human diploid cell strain anti-rabies vaccine for post-exposure prophylaxis. Lancet 1983;2:301–4.
[166] Wongsaroj P, Udomchaisakul P, Tepsumethanon S, Khawplod P, Tantawichien T. Rabies neutralizing antibody after 2 intradermal doses on days 0 and 21 for pre-exposure prophylaxis. Vaccine 2013;31:1748–51.
[167] Anand A, Zaman K, Estivariz CF, Yunus M, Gary HE, Weldon WC, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: a randomized controlled trial. Vaccine 2015;33:6816–22.
[168] Cadorna-Carlos J, Vidor E, Bonnet MC. Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines. Int J Infect Dis 2012;16:e110–6.
[169] Mohammed AJ, AlAwaidy S, Bawikar S, Kurup PJ, Elamir E, Shaban MM, et al. Fractional doses of inactivated poliovirus vaccine in Oman. N Engl J Med 2010; 362:2351–9.
[170] Resik S, Mach O, Tejeda A, Jeyaseelan V, Fonseca M, Diaz M, et al. Immunogenicity of intramuscular fractional dose of inactivated poliovirus vaccine. J Infect Dis 2019;26:26.
[171] Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemani N, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013;368: 416–24.
[172] Resik S, Tejeda A, Lago PM, Diaz M, Carmenates A, Sarmiento L, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. J Infect Dis 2010;201:1344–52.
[173] Snider CJ, Zaman K, Estivariz CF, Yunus M, Weldon WC, Wannemuehler KA, et al. Immunogenicity of full and fractional dose of inactivated poliovirus vaccine for use in routine immunisation and outbreak response: an open-label, randomised controlled trial. Lancet 2019;393:2624–34.
[174] Calafiore DC, Nader PR, Lepow ML, Nankervis GA, Casey H, Warren RJ. Attenuated measles virus vaccine dosage study–Cleveland, Ohio. Am J Epidemiol 1966;87:247–53. 1968.
[175] Kok PW, Kenya PR, Ensering H. Measles immunization with further attenuated heat-stable measles vaccine using five different methods of administration. Trans R Soc Trop Med Hyg 1983;77:171–6.
[176] Stanfield JP, Bracken PM. Measles vaccination: studies in methods and cost reduction in developing countries. Trans R Soc Trop Med Hyg 1971;65:620–8.
[177] Whittle HC, Rowland MG, Mann GF, Lamb WH, Lewis RA. Immunisation of 4-6 month old Gambian infants with Edmonston-Zagreb measles vaccine. Lancet 1984;2:834–7.
[178] Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire–when and how? Trans R Soc Trop Med Hyg 1980;74:381–2.
[179] Brindle RJ, Morris CA, Berger R, Kurtz JB. Inadequate response to intradermal hepatitis A vaccine. Vaccine 1994;12:483–4.
[180] Carlsson U, Brudin L, Eliasson I, Hansson BG. Hepatitis A vaccination by intracutaneous low dose administration: a less expensive alternative. Scand J Infect Dis 1996;28:435–8.
[181] Frosner G, Steffen R, Herzog C. Virosomal hepatitis a vaccine: comparing intradermal and subcutaneous with intramuscular administration. J Trav Med 2009;16:413–9.
[182] Pancharoen C, Mekmullica J, Thisyakorn U, Kasempimolporn S, Wilde H, Herzog C. Reduced-dose intradermal vaccination against hepatitis A with an aluminum-free vaccine is immunogenic and can lower costs. Clin Infect Dis 2005; 41:1537–40.
[183] Dick G. Combined vaccines. Can J Public Health 1966;57:435–46.
[184] Stanfield J, Waddell KGD. Diphtheria-tetanus-pertussis immunization by intradermal jet injection. Br Med J 1972;2:197–9.
[185] Intralawan P, Paupunwatana S. Immunogenicity of low dose Japanese encephalitis vaccine (BIKEN) administered by the intradermal route: preliminary data. Asian Pac J Allergy Immunol 1993;11:79–83.
[186] Kitchener S, Nasveld P, Brennan L, Ward D. Comparative safety and efficacy of subcutaneous and intradermal administration of inactivated Japanese encephalitis vaccine during predeployment preparations in the Australian defence force. Mil Med 2006;171:1190–5.
[187] Nelson EA, Lam HS, Choi KC, Ho WC, Fung LW, Cheng FW, et al. A pilot randomized study to assess immunogenicity, reactogenicity, safety and tolerability of two human papillomavirus vaccines administered intramuscularly and intradermally to females aged 18-26 years. Vaccine 2013;31:3452–60.
[188] Hassanking M, Greenwood BM, Wall RA, Williams K. Meningococcal vaccine – intradermal versus subcutaneous. Lancet 1984;1:790.
[189] Beals CR, Railkar RA, Schaeffer AK, Levin Y, Kochba E, Meyer BK, et al. Immune response and reactogenicity of intradermal administration versus subcutaneous administration of varicella-zoster virus vaccine: an exploratory, randomised, partly blinded trial. Lancet Infect Dis 2016;16:915–22.
[190] Roukens AH, Vossen AC, Bredenbeek PJ, van Dissel JT, Visser LG. Intradermally administered yellow fever vaccine at reduced dose induces a protective immune response: a randomized controlled non-inferiority trial. PloS One 2008;3. e1993.
[191] World Health Organization. The immunological basis for immunization series. Module 22: hepatitis B. Geneva, Switzerland: WHO; 2012.
[192] World Health Organization. The immunological basis for immunization series. Module 17: Rabies. Geneva, Switzerland: WHO; 2017.
[193] World Health Organization. The immunological basis for immunization series. Module 6: Poliomyelitis. Geneva, Switzerland: WHO; 1993.
[194] World Health Organization. The immunological basis for immunization series. Module 7: measles Update 2009. Geneva, Switzerland: WHO; 2009.
[195] Langedijk AC, De Pijper CA, Spijker R, Holman R, Grobusch MP, Stijnis C. Rabies antibody response after booster immunization: a systematic review and meta-analysis. Clin Infect Dis 2018;67:1932–47.
[196] Sangare L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. Vaccine 2009;27:1777–86.
[197] Hickling JK, Jones KR, Friede M, Zehrung D, Chen D, Kristensen D. Intradermal delivery of vaccines: potential benefits and current challenges. Bull World Health Organ 2011;89:221–6.
[198] Weniger BG, Papania MJ. Alternative vaccine delivery methods. Vaccines. fifth ed. Amsterdam Elsevier; 2008. p. 1357–92.
[199] Resik S, Tejeda A, Mach O, Fonseca M, Diaz M, Alemany N, et al. Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: a randomized controlled trial in Cuba. Vaccine 2015;33:307–13.
[200] Pasteur Sanofi. Sanofi Pasteur announces FDA approval of Fluzone® intradermal quadrivalent (influenza vaccine) for adults. http://www.news.sanofi.us/2014-12-12-Sanofi-Pasteur-Announces-FDA-Approval-of-Fluzone-R-Intradermal-Quadrivalent-Influenza-Vaccine-for-Adults 2014.
[201] World Health Organization. The immunological basis for immunization series. Module 2: diphtheria Update 2009. Geneva, Switzerland: WHO; 2009.
[202] World Health Organization. The immunological basis for immunization series. Module 18: hepatitis A. Geneva, Switzerland: WHO; 2019.
[203] World Health Organization. The immunological basis for immunization series. Module 19: human papillomavirus infection. Geneva, Switzerland: WHO; 2011.
[204] World Health Organization. The immunological basis for immunization series. Module 23: influenza vaccines. Geneva, Switzerland: WHO; 2017.
[205] World Health Organization. The immunological basis for immunization series. Module 13: Japanese encephalitis. Geneva, Switzerland: WHO; 2010.
[206] World Health Organization. The immunological basis for immunization series: module 15: meningococcal disease. Geneva, Switzerland: WHO; 2010.
[207] World Health Organization. The immunological basis for immunization series. Module 3: tetanus Update 2018. Geneva, Switzerland: WHO; 2018.
[208] World Health Organization. The immunological basis for immunization series. Module 10: varicella-zoster virus. Geneva, Switzerland: WHO; 2008.
[209] World Health Organization. The immunological basis for immunization series. Module 8: yellow fever. Geneva, Switzerland: WHO; 1993.