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

Jenny L. Schnyder, Cornelis A. De Pijper, Hannah M. Garcia Garrido, Joost G. Daams, Abraham Goorhuis, Cornelis Stijnis, Frieder Schaumburg, Martin P. Grobusch

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.

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; I² = 55%, H2N3: RD 0.00; 95% CI -0.01, 0.01; I² = 0%, B: RD -0.00; 95% CI -0.02, 0.01; I² = 72%), rabies (RD 0.00; 95% CI -0.02, 0.02; I² = 0%), and hepatitis B vaccines (RD -0.01; 95% CI -0.04, 0.02; I² = 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.
1.2. 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], poliomyelitis [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 synaptic 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 CAeP) 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 \( \geq 0.1 \) 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 \( \geq 1:40 \) 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 \( \geq 120 \) IU/L |
| Meningococcal disease [206]  | Group C: seroprotection defined as hSBA titre \( \geq 4 \) or SBA titre \( \geq 8 \); 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) \( \geq 0.5 \) IU/mL assessed 4 weeks after completing vaccination series |
| Inactivated poliovirus vaccine [193] | Seroconversion rate defined as percentage of subjects achieving \( \geq 4 \)-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 \( \geq 0.01 \) 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/immuno-suppressed 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 stars 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 \( n = 51 \) [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
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 [39–41,46–51,54,56,59,60,62,63,65,71,74–76,78–80,82,83,85–87], 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 [39–41,46–51,54,56,58–60,63–65,72,74–76,78–80,82–88,136], 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,
Summary of outcomes of studies/study subgroups on immunogenicity of influenza vaccines.

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 doses of 15 and 150 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; I² = 75%) and B strain (RD 0.10; 95% CI -0.20, -0.00; I² = 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; I² = 44%) for H1N1, 0.01 (95% CI -0.01, 0.04; I² = 0%) for H2N3 and 0.03 (95% CI -0.04, 0.09; I² = 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; I² = 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-thalassemia) (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 [96,97,111,122,129], or monthly [106]. 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],

| Table 2a | Summary of outcomes of studies/study subgroups on immunogenicity of influenza vaccines. |
|----------|----------------------------------------------------------|
| Study population | Fractional ID vs IM | Fractional ID vs SC |
| | 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 |
A 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, 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, 98, 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; I² = 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; I² = 20%).

#### 3.4.5. Safety and costs

In all studies, local adverse events were more common after ID (15–84%) than after IM (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...
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 [14,163–165,168–170], eight studies [143–146,164–165] 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 [143–146,164–165], of multiple injections of 0.1 ml. IM doses consisted of 0.5 or 1 ml, and SC doses of 0.25, 0.5 or 1 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 [15,133,138–140,143,147,150,151,153,155,157,158,161,163,166].

3.5.3. Post-exposure prophylaxis

Eleven studies assessing post-exposure prophylaxis (PEP) compared ID to IM immunisation [133–137,142,148,152,156,159,160,164]; 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 14) 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 [133–135,142,148,152,156,159,160] 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...
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 2. 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 [133,134,139,140,143–147,149–150,155,156,160–164,166]. 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 I² = 0%).

3.5.6. Safety and costs

Similar to influenza and HBV vaccines, local reactions (e.g. erythema, pruritus, swelling, and axillary 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.
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/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
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.
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 2c
Summary of outcomes of studies/study subgroups on immunogenicity of rabies vaccines.

| Vaccine       | Fractional ID vs IM | Fractional ID vs SC |
|---------------|---------------------|---------------------|
|               | 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. 2f. Forest plots of the risk differences of seroprotection for ID compared to IM administration of HBV vaccines in healthy adults.

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

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

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

**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 and 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 fractional-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 vac-
cines, the question whether differences in ID vaccine dosing would in-
fluence the antibody response could not be answered due to insufficient
data. More studies 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 measur-
able 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 compre-
hensible 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 inves-
tigating 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 heteroge-
neity, 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 litera-
ture 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 in-
jection [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 un-
derway against a number of widely neglected (tropical) infectious dis-
orders 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 there-
fore 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 viruses by the use of ID administration. Clinical trials on the
remaining vaccines (HAV, DTP, HPV, JE, meningococcal, VZV and yel-
low 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

MGP 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 MGP. JLS, CAdP, HMG, JGD, AG, CS, FS, and MGP contributed to the writing. All authors contributed to and endorsed the final version of the manuscript.

Declaration of competing interest

None to declare.

Acknowledgements

We thank Mariska M. Leeflang for her help with the methodology of meta-analyses.

Appendix A. Supplementary data

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

Funding

None.

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