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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.

Keywords
Drug administration routes; intradermal injection; intramuscular injection; subcutaneous injection; antibody response; immunisation

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.

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 maximise 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 immunization 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 assessed full text by JLS and CAdP. Discrepancies were resolved by discussion. If JS and CdP 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 ≥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 **Figure 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 [39–41,46–51,54–56,59,60,62,63,65,71,74–76,78–86,88], 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 $1/10^{th}$ of SC dose: Boger et al. [61] compared a dose of 50 to 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 **Figure 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 (**Figure 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%) (**Figure 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 2 doses 1 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 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 **Figure 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 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 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 **Figure 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.

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 **Figure 2h**.

3.7 Measles vaccines

3.7.1 Study characteristics

Six identified 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 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 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 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 neutralization,

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 randomized 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 4,912 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 1949-2000, 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 immunization 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.

4 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, CAPD, HMG, JGD, AG, CS, FS and MPG, contributed to the writing. All authors contributed to and endorsed the final version of the manuscript.

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Conflict of interest

None to declare.

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6 Tables

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 neutralizing antibody titres >1:10
Measles [194]	Seroprotection rate defined as percentage of subjects with post-vaccination measles neutralizing antibody titres ≥120 IU/L
Meningococcal disease [206]	Group C: seroprotection defined as hSBA titre ≥ 4 or SBA titre ≥ 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 neutralizing 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

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

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

		Fractional ID vs IM			Fractional ID vs SC			
Vaccine type	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

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

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

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

8. Figures

Figure 1. Flow chart of study selection

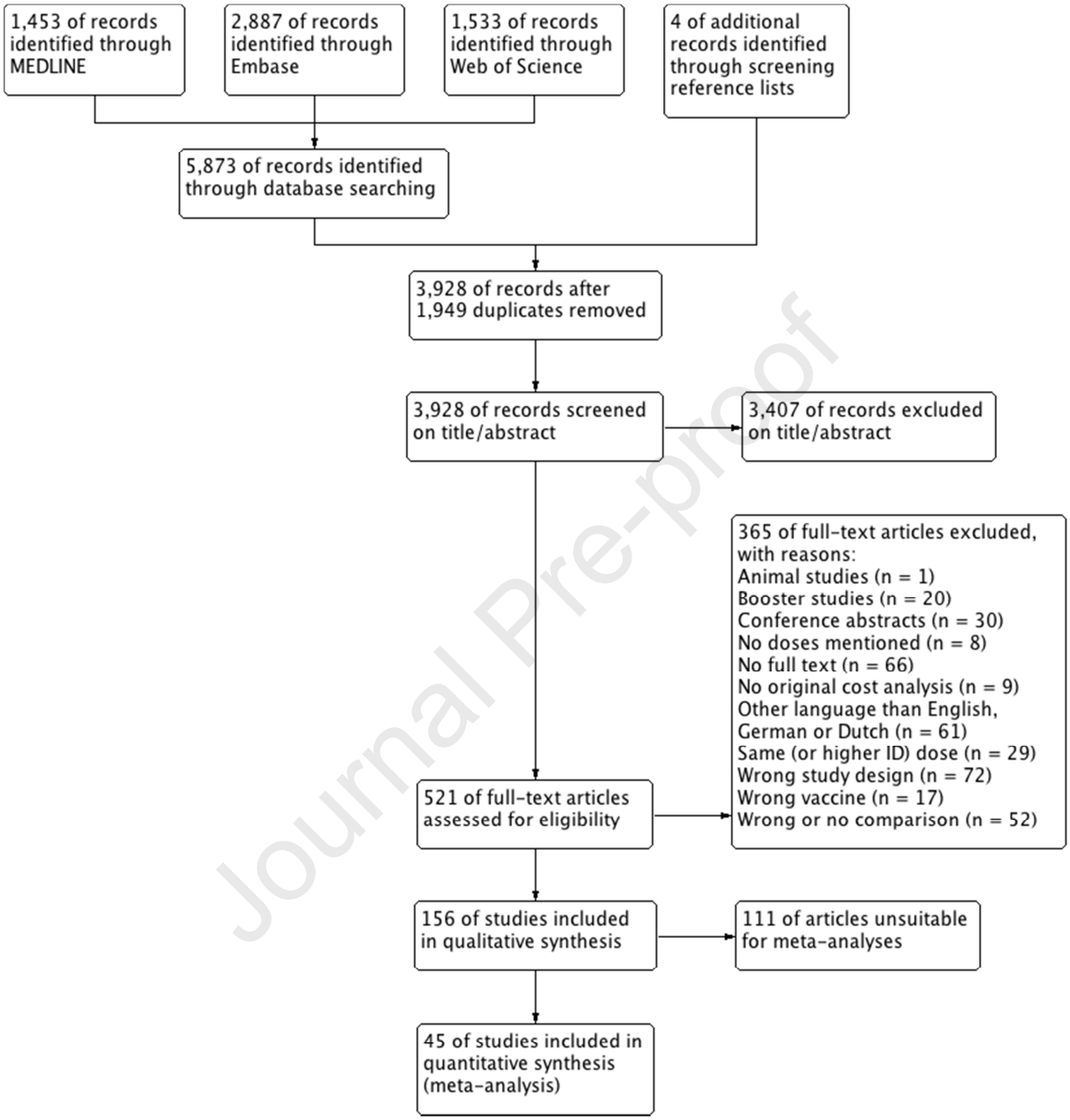


Figure 2a. Forest plots of the risk differences of seroprotection for ID administration of 3 or 4.5 μg compared to IM administration of influenza vaccine in healthy young adults.

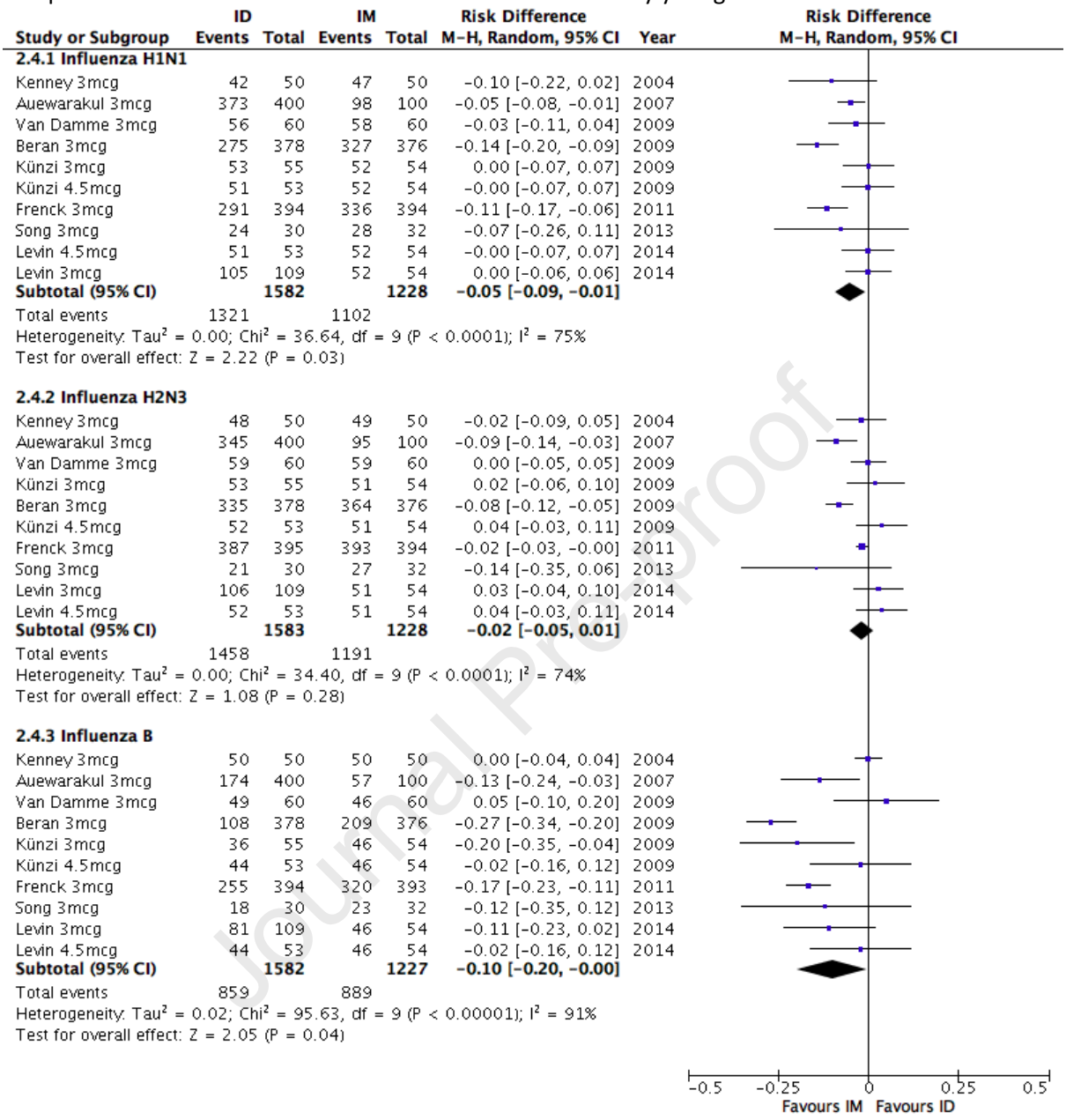


Figure 2b. Forest plots of the risk differences of seroprotection for ID administration of 6 or 7.5 μg compared to IM administration of influenza vaccine in healthy young adults.

Study or Subgroup	ID Events	ID Total	IM Events	IM Total	Risk Difference M-H, Random, 95% CI	Year
2.5.1 Influenza H1N1						
Belshe_a 6mcg	61	61	69	69	0.00 [-0.03, 0.03]	2004
Künzi 6mcg	49	55	52	54	-0.07 [-0.17, 0.02]	2009
Beran 6mcg	267	375	327	376	-0.16 [-0.21, -0.10]	2009
Van Damme 6mcg	56	60	58	60	-0.03 [-0.11, 0.04]	2009
Metanat 6mcg	95	97	94	94	-0.02 [-0.06, 0.01]	2010
Frenck 6mcg	300	392	336	394	-0.09 [-0.14, -0.03]	2011
Song 7.5mcg	27	30	28	32	0.03 [-0.13, 0.18]	2013
Levin 6mcg	49	55	52	54	-0.07 [-0.17, 0.02]	2016
Subtotal (95% CI)		**1125**		**1133**	**-0.06 [-0.12, 0.01]**	
Total events	904		1016			
Heterogeneity: Tau² = 0.01; Chi² = 63.91, df = 7 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 1.74 (P = 0.08)						
2.5.2 Influenza H2N3						
Belshe_a 6mcg	61	61	69	69	0.00 [-0.03, 0.03]	2004
Van Damme 6mcg	58	60	59	60	-0.02 [-0.07, 0.04]	2009
Künzi 6mcg	54	55	51	54	0.04 [-0.03, 0.11]	2009
Beran 6mcg	331	375	364	376	-0.09 [-0.12, -0.05]	2009
Metanat 6mcg	95	97	93	94	-0.01 [-0.05, 0.03]	2010
Frenck 6mcg	391	392	393	394	-0.00 [-0.01, 0.01]	2011
Song 7.5mcg	27	30	27	32	0.06 [-0.11, 0.22]	2013
Levin 6mcg	54	55	51	54	0.04 [-0.03, 0.11]	2016
Subtotal (95% CI)		**1125**		**1133**	**-0.01 [-0.05, 0.04]**	
Total events	1071		1107			
Heterogeneity: Tau² = 0.00; Chi² = 68.96, df = 7 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.5.3 Influenza B						
Belshe_a 6mcg	61	61	69	69	0.00 [-0.03, 0.03]	2004
Künzi 6mcg	40	55	46	54	-0.12 [-0.28, 0.03]	2009
Van Damme 6mcg	51	60	46	60	0.08 [-0.06, 0.22]	2009
Beran 6mcg	123	375	209	376	-0.23 [-0.30, -0.16]	2009
Metanat 6mcg	94	97	91	94	0.00 [-0.05, 0.05]	2010
Frenck 6mcg	294	392	320	393	-0.06 [-0.12, -0.01]	2011
Song 7.5mcg	18	30	23	32	-0.12 [-0.35, 0.12]	2013
Levin 6mcg	40	55	46	54	-0.12 [-0.28, 0.03]	2016
Subtotal (95% CI)		**1125**		**1132**	**-0.07 [-0.16, 0.02]**	
Total events	721		850			
Heterogeneity: Tau² = 0.01; Chi² = 91.52, df = 7 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 1.44 (P = 0.15)						

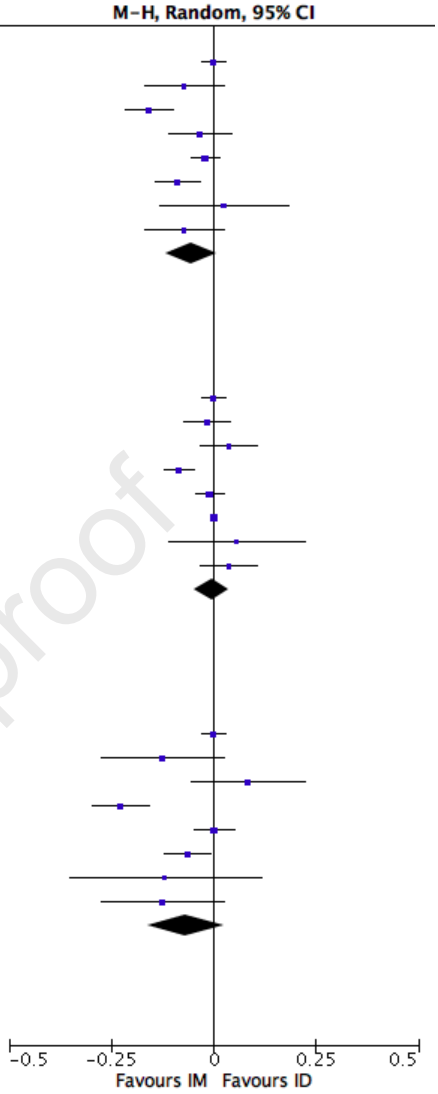


Figure 2c. Forest plots of the risk differences of seroprotection for ID administration of 9 μg compared to IM administration of influenza vaccine in healthy young adults.

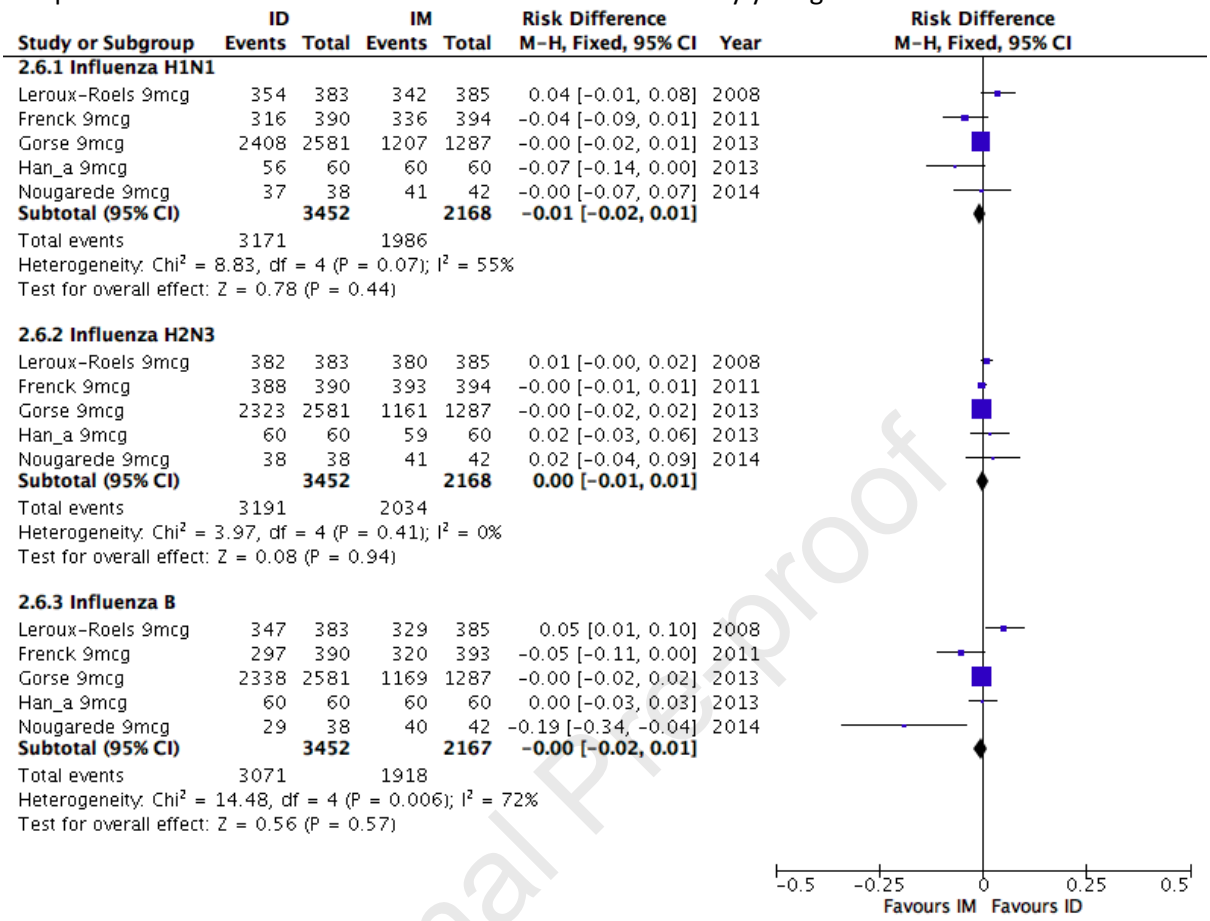


Figure 2d. Forest plots of the risk differences of seroprotection for ID compared to IM administration of influenza vaccine per strain in elderly.

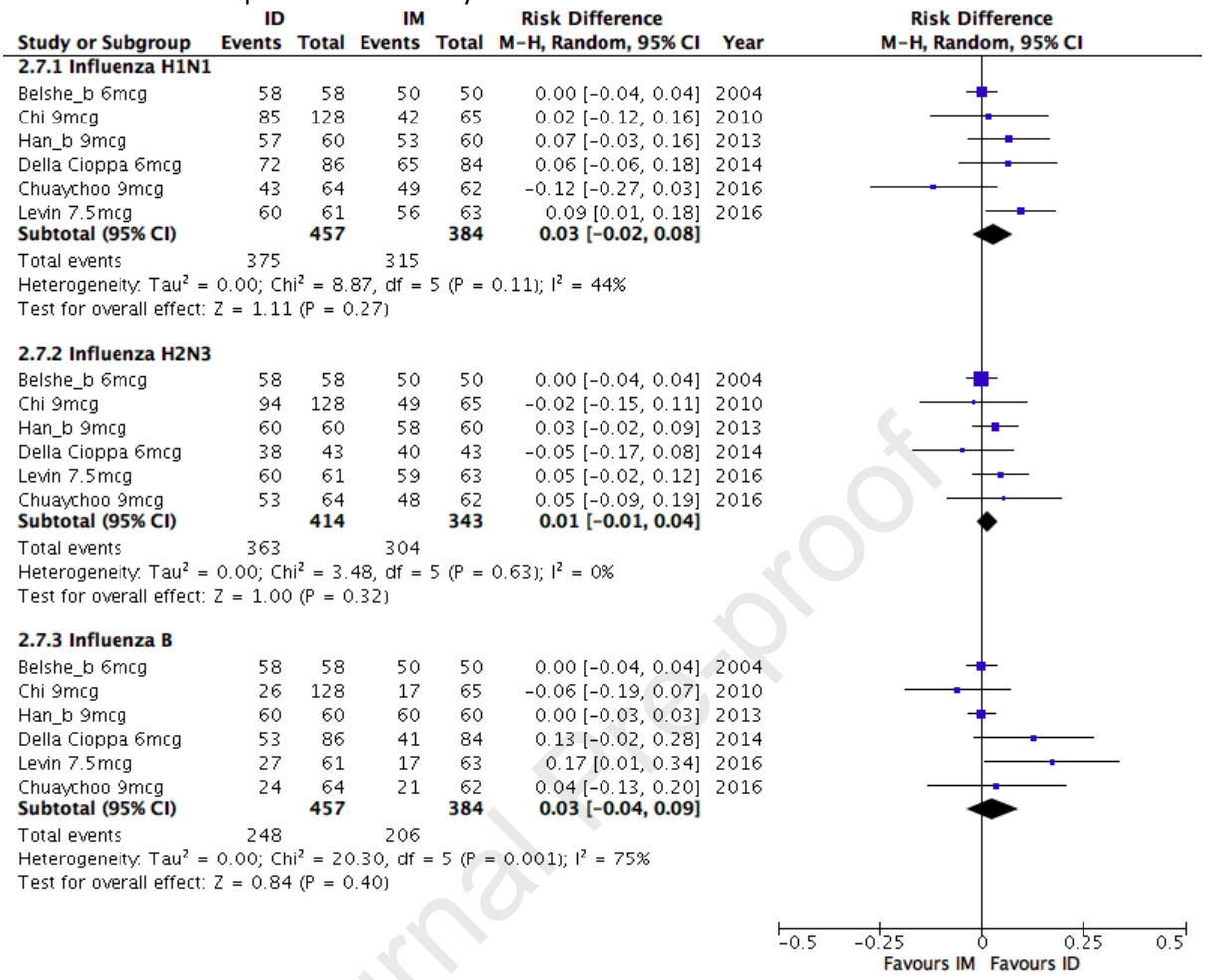


Figure 2e. Forest plots of the risk differences of seroprotection for ID compared to IM administration of influenza vaccine per strain in immunocompromised and chronically ill patients.

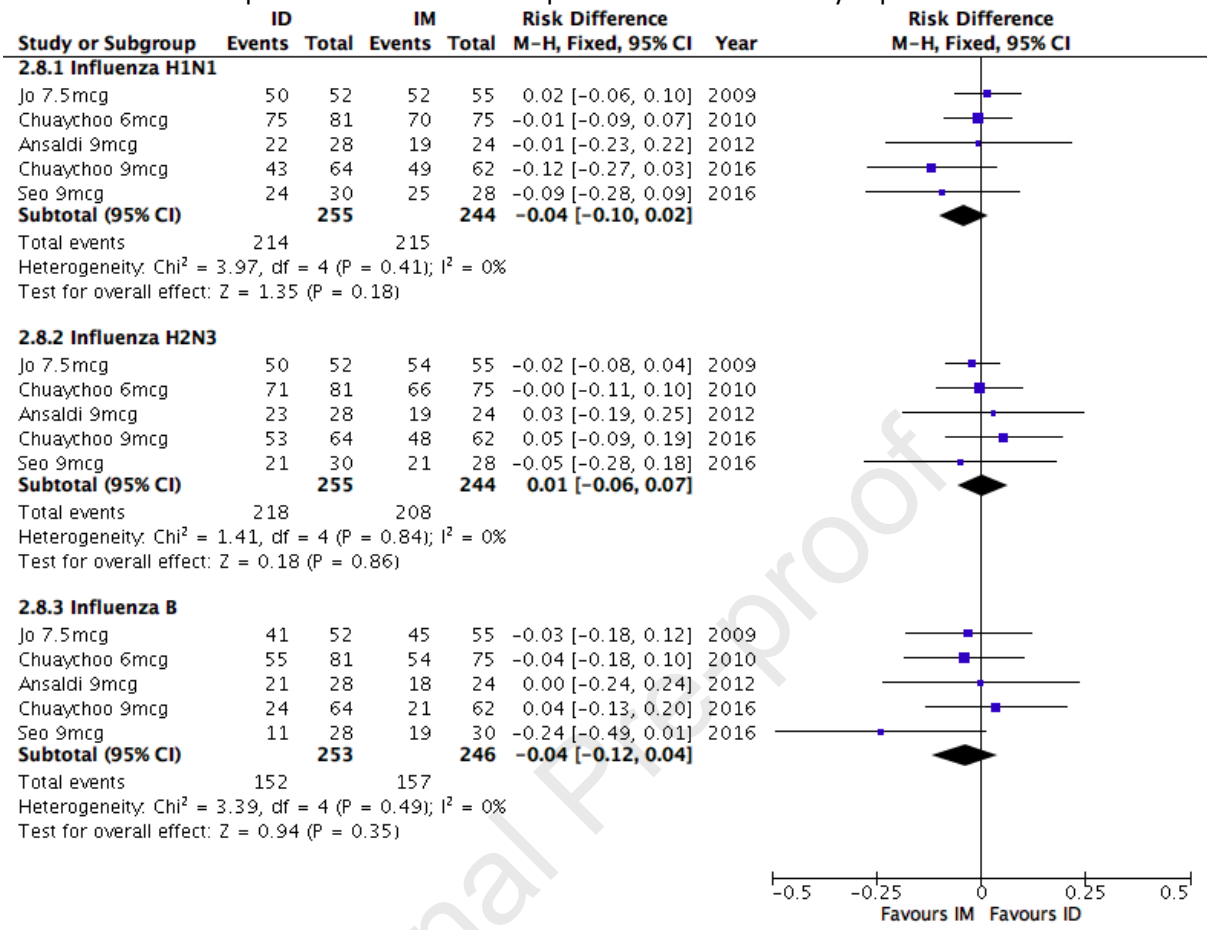


Figure 2f. Forest plots of the risk differences of seroprotection for ID compared to IM administration of HBV vaccines in healthy adults.

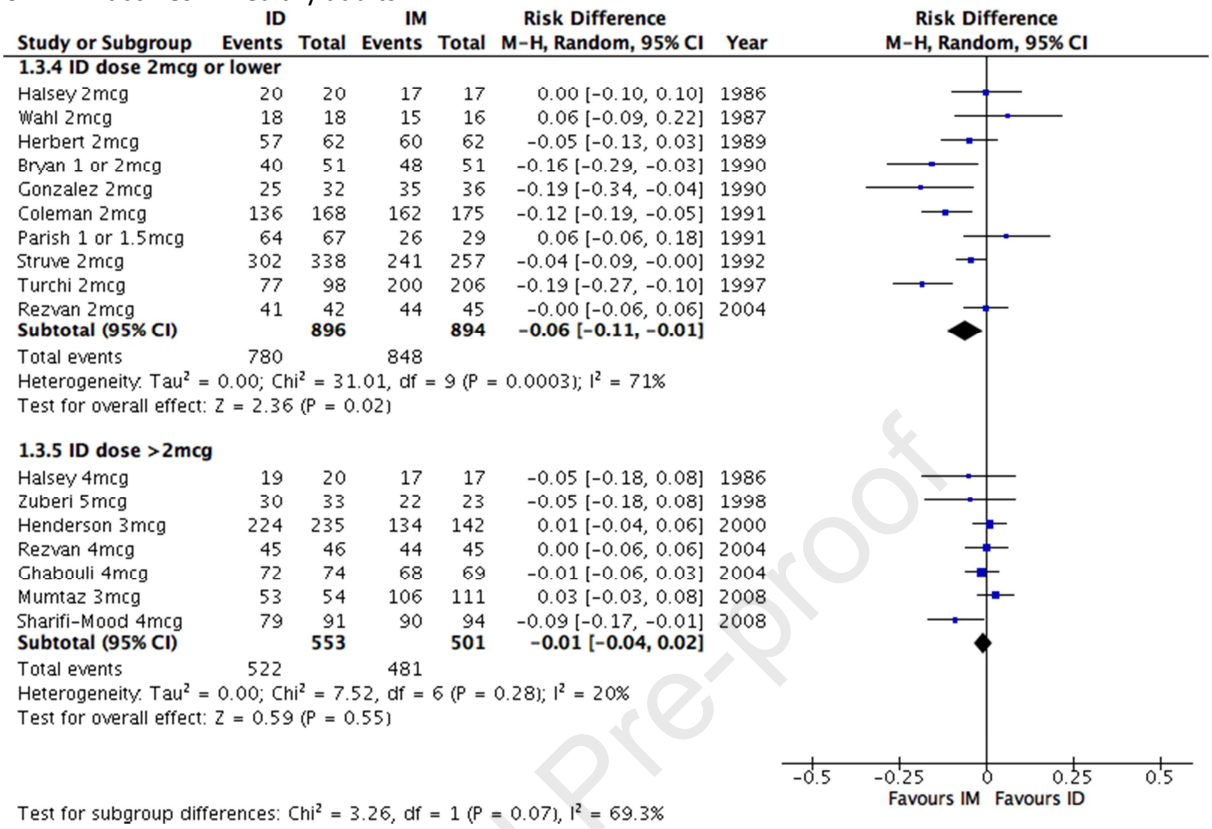


Figure 2g. Forest plots of the risk differences of seroconversion for ID compared to IM administration of pre-exposure rabies vaccines in healthy adults.

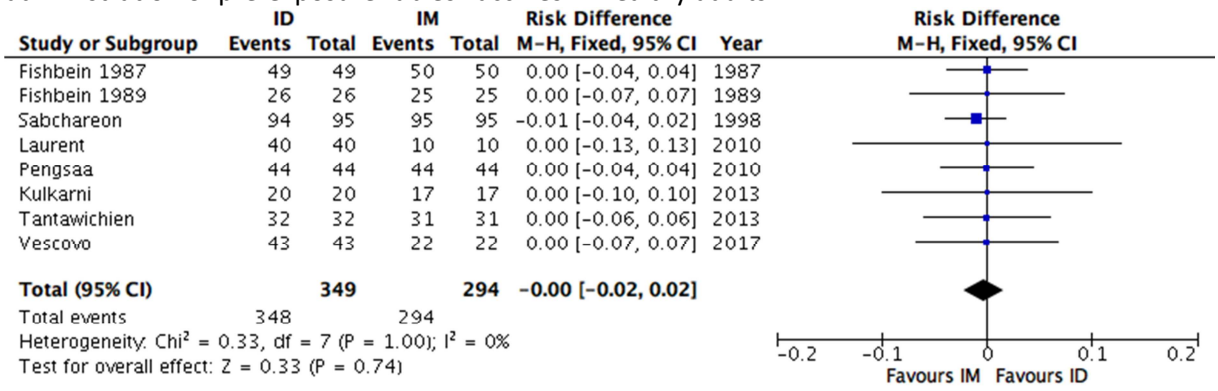
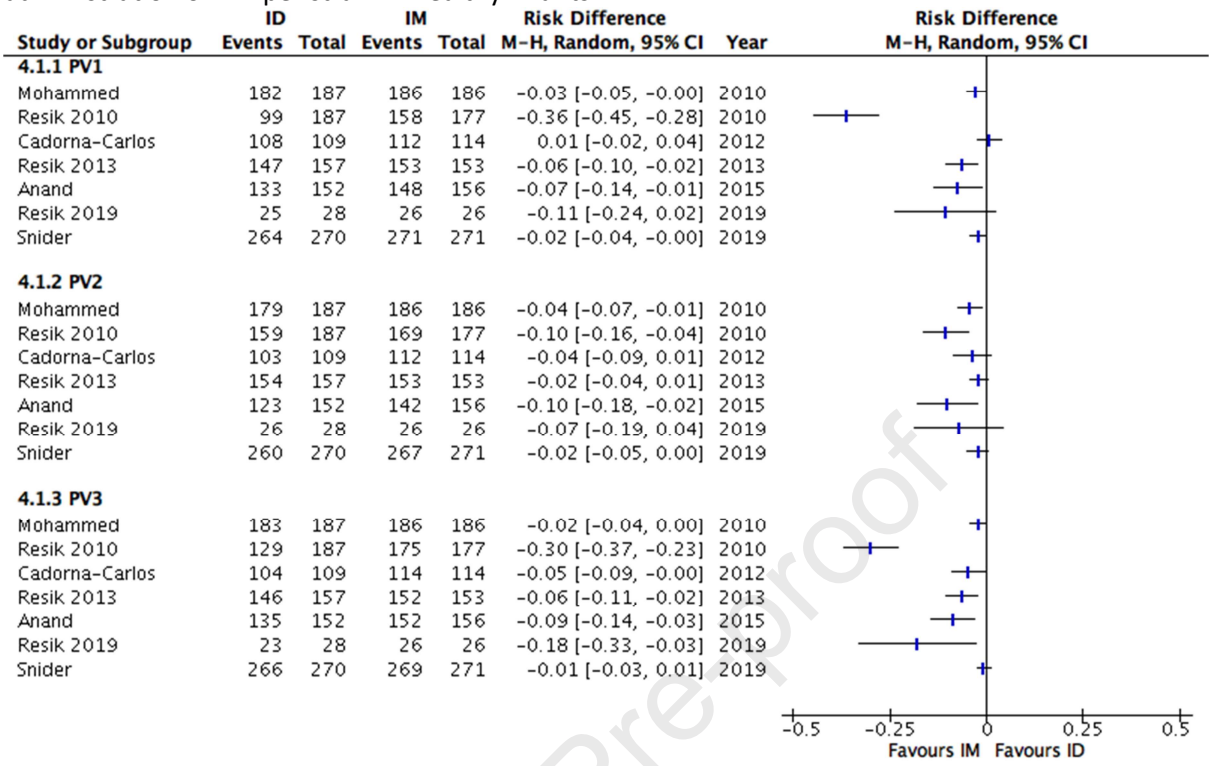


Figure 2h. Forest plots of the risk differences of seroconversion for ID compared to IM administration of IPV per strain in healthy infants.



9. Supplementary Materials

10.

Supplementary Table 1: Search appendix

	Ovid MEDLINE(R) ALL <1946 to November 05, 2019> Search date: 6 November 2019	
#	**Results**	**Hits**
1	Economics/ or exp "costs and cost analysis"/ or exp economics, hospital/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/	276043
2	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or "value for money" or budget$).ab,ti.	780060
3	1 or 2	897877
4	(((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	28537
5	3 not 4	891316
6	(letter or editorial or historical article).pt.	1893154
7	5 not 6	856168
8	exp animals/ not humans/	4640699
9	7 not 8	801941
10	(bmj or "cochrane database of systematic reviews" or "health technology assessment winchester england").jn.	94560
11	9 not 10 [NHS-EED filter Medline adaptation, https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline, consulted 20191031]	795683
12	injections, intradermal/ or injections, intramuscular/ or Injections, Subcutaneous/	66441
13	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c.")).ab,kf,ti.	11003
14	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (intramuscular* or intra muscular* or im or "i.m.")).ab,kf,ti.	27544
15	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (subcutane* or sc or "s.c.")).ab,kf,ti.	50735
16	or/12-15	130533
17	(hav or "hepatitis a" or hbv or "hepatitis b" or influenza or rabies or polio* or yellow fever or measles or tick borne encephalitis or denge or Diphtheria-tetanus-pertussis or "d.t.p." or hpv or humane papilloma* or japanese encephalitis or tetanus or typhoid).ab,hw,kf,ti.	386466
18	and/11,16-17	337

19	limit 18 to yr="2009-current"	149
20	injections, intradermal/	6223
21	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj7 (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c.")).ab,kf,ti.	16040
22	20 or 21 [intradermal route]	19502
23	injections, intramuscular/	30602
24	((vaccin* or dose? or inject* or administr* or route? or regimen?) and (intramuscular* or intra muscular* or im or "i.m.")).ab,kf,ti.	47140
25	23 or 24 [intramuscular route]	63818
26	Injections, Subcutaneous/	32204
27	((vaccin* or dose? or inject* or administr* or route? or regimen?) and (subcutane* or sc or "s.c.")).ab,kf,ti.	111838
28	26 or 27 [subcutaneous route]	127881
29	22 and (25 or 28)	3016
30	animals/ not humans/	4607630
31	(rat or rats or mouse or mice or cattle or nonhuman or veterin*).ab,kf,ti.	2604404
32	29 not (30 or 31)	1357
33	19 or 32	1453
	Ovid Embase Classic+Embase <1947 to 2019 November 05> **Search date: 6 November 2019**	
#	**Results**	**Hits**
1	Health Economics/ or exp Economic Evaluation/ or exp Health Care Cost/ or pharmacoeconomics/	526954
2	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ab,ti.	1065077
3	1 or 2	1289083
4	(letter or editorial or note).pt.	2486777
5	3 not 4	1189170
6	((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	36269
7	5 not 6	1181614
8	animal/ or exp animal experiment/ or nonhuman/	8250938
9	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.	6438867
10	8 or 9	9503422
11	exp human/ or human experiment/	21590482
12	10 not (10 and 11)	7099196
13	7 not 12	1074547
14	(0959-8146 or 1469-493X or 1366-5278).is.	84904
15	1756-1833.en.	30585
16	14 or 15	105495
17	13 not 16	1067610

18	conference abstract.pt.	3624797
19	17 not 18 [NHS-EED filter for Embase]	877287
20	intradermal drug administration/ or intramuscular drug administration/ or subcutaneous drug administration/	181504
21	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c.")).ab,kw,ti.	17267
22	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (intramuscular* or intra muscular* or im or "i.m.")).ab,kw,ti.	40972
23	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj2 (subcutane* or sc or "s.c.")).ab,kw,ti.	77060
24	or/20-23	272408
25	(hav or "hepatitis a" or hbv or "hepatitis b" or influenza or rabies or polio* or yellow fever or measles or tick borne encephalitis or denge or Diphtheria-tetanus-pertussis or "d.t.p." or hpv or humane papilloma* or japanese encephalitis or tetanus or typhoid).ab,hw,kw,ti.	554079
26	and/19,24-25	493
27	limit 26 to yr="2009-current"	154
28	intradermal drug administration/	13786
29	((vaccin* or dose? or inject* or administr* or route? or regimen?) adj7 (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c.")).ab,kw,ti.	24655
30	28 or 29 [intradermal route]	33668
31	intramuscular drug administration/	72739
32	((vaccin* or dose? or inject* or administr* or route? or regimen?) and (intramuscular* or intra muscular* or im or "i.m.")).ab,kw,ti.	72868
33	31 or 32 [intramuscular route]	124670
34	subcutaneous drug administration/	102155
35	((vaccin* or dose? or inject* or administr* or route? or regimen?) and (subcutane* or sc or "s.c.")).ab,kw,ti.	172895
36	34 or 35 [subcutaneous route]	242101
37	30 and (33 or 36)	5031
38	(animal/ or animal experiment/ or animal model/ or nonhuman/ or rat/ or mouse/) not human/	6768020
39	(rat or rats or mouse or mice or cattle or nonhuman or veterin*).ab,kw,ti.	3383667
40	37 not (38 or 39)	2533
41	26 or 40	2887
	Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years Search date: 6 November 2019	
#	**Results**	**Hits**
1	AB=(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or "value for money" or budget$)	1636824

2	TI=(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or "value for money" or budget$)	529617
3	#1 or #2	1920290
4	AB=(((energy or oxygen) NEAR/1 cost) or (metabolic adj cost) or ((energy or oxygen) NEAR/1 expenditure))	41428
5	TI=(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or "value for money" or budget$)	529617
6	#4 OR #5	567298
7	#3 not #6	1372908
8	TS=(letter or editorial or historical article)	316264
9	#7 NOT #8	1360851
10	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c."))	31423
11	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (intramuscular* or intra muscular* or im or "i.m."))	37534
12	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (subcutane* or sc or "s.c."))	92940
13	#10 OR #11 OR #12	154754
14	TS=(hav or "hepatitis a" or hbv or "hepatitis b" or influenza or rabies or polio* or yellow fever or measles or tick borne encephalitis or denge or Diphtheria-tetanus-pertussis or "d.t.p." or hpv or humane papilloma* or japanese encephalitis or tetanus or typhoid)	328749
15	#9 AND #13 AND #14	347
16	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (intracutaneous or intra dermal* or intradermal* or id or ic or "i.c."))	31423
17	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (intramuscular* or intra muscular* or im or "i.m."))	37534
18	TS=((vaccin* or dose or inject* or administr* or route or regimen) and (subcutane* or sc or "s.c."))	92940
19	#16 AND (#17 OR #18)	3621
20	TS=(animal or rat or rats or mouse or mice or cattle or nonhuman or veterin*)	3782761
21	#19 NOT #20	1249
22	#15 OR #21	1533

Supplementary Table 2. The Cochrane Risk-of-Bias tool for assessing quality of randomised clinical trial

Bias domain	Low risk of bias	High risk of bias	Unclear risk of bias
Selection bias	Use of random sequence generator (random number table)	Use of non-random sequence generator e.g. odd or even date of birth	Method of randomisation not described in sufficient detail
	Participants could not foresee route of administration (e.g. use of sealed envelopes)	Participants could possibly foresee route of administration (e.g. open list of random numbers)	Method of randomisation not described in sufficient detail
Performance bias	Use of ID or IM/SC delivered placebo vaccines in both groups, blinding participants and personnel	Participants or personnel were not blinded, or blinded incompletely by no use of placebo vaccines	Blinding not described in sufficient detail
Detection bias	Outcome assessors (e.g. assessor of antibody response) were blinded	Assessors were not blinded	Blinding of assessors not mentioned
Attrition bias	All subjects completed study or reasons for missing outcome data not related to immunisation	Reasons for not completing study related to immunisation (e.g. adverse events)	Not all subjects completed study with no reasons mentioned
Reporting bias	Study protocol available and all of study's prespecified outcomes were reported in prespecified way	Study protocol available, but prespecified outcomes were not all reported in prespecified way	Study protocol was not prospectively registered, and it is unclear if all expected outcomes were prespecified
Other bias	No previously immunised participants included, or proportion of immunised participants equal in both groups Rabies studies: No use of RIG or proportion of participants treated with RIG was equal in both groups	Previously immunised participants included with unequal distribution between groups Rabies studies: Use of RIG with either unmentioned or unequal distribution between groups	Not mentioned if subjects were previously immunised (influenza studies: in the last six months)

Supplementary Table 3: Data extraction of the included studies

Disease	Vaccine	Year	Country	Study design	Population	ID vaccination			Comparator				Outcome (ID vs IM/SC)	Author
						Dose/injection	Scheme	N	Route	Dose/injection	Scheme	N		
DTP[1]														
Diphtheria/ tetanus/pertussis/polio	DTP + IPV	1966	United Kingdom	Prospective cohort study	Infants, 6-12 months	0.1 ml (D: 8.4 Lf; T: 3.0 Lf; P: 5.8 x 10^9 organism, PV I, II, III D units: 60, 0.3, 0.6 resp.)	Week 0, 4, 8	18	IM	0.5 ml (D: 28 Lf; T: 10 Lf; P: 29 x 10^9 organism, PV 1,2,3, D units: 200, 1, 2 resp.)	Week 0, 4, 8	17	GMT 1 month after last dose: Diphtheria antitoxin: 0.31 units/ml vs 0.29 units/ml Tetanus antitoxin: 0.34 units/ml vs 0.52 units/ml; Pertussis agglutinins: 1 in 128 vs 1 in 145 Polio virus neutralizing antibody: PV1: 1 in 857 vs 1 in 1400 PV2: 1 in 270 vs 1 in 430 PV3: 1 in 120 vs 1 in 380 AE: local reaction in all of ID group: induration with erythematous surrounding.	Dick
Diphtheria/ tetanus	Adsorbed and unabsorbed DTP vaccine[2]	1972	Uganda	Prospective cohort study	Infants, 2-12 months	3 x 0.05-0.08 ml	Month 0, 1, 7	109, 28	IM	0.5 ml (D: 10-13 Lf; T: 5-8 Lf)	Month 0, 1, 7	7	Seroprotection rate 1 month after last dose: Diphtheria: 85/105 (81%) (IDads), 16/18 (89%) (IDunads) vs 6/6 (100%) (IMads) Tetanus: 104/109 (95%) (IDads), 22/28 (79%) (IDunads) vs 7/7 (100%) (IMads) AE: small indurated marks, that disappeared within months in ID group.	Stanfield
HAV[3]														
	Inactivated whole-virus HAV vaccine	1994	Switzerland	RCT	Adults	0.1 ml	Week 0, 4, 8	26	IM	1.0 ml	Single visit	18	Seroprotection rate (defined as ≥20 IU/l) 4 weeks after last dose: (23/26) 88% vs 17/18 (94%) AE: No other side-effects than short-lived local tenderness.	Brindle
	Formalin-inactivated whole-virus HAV vaccine	1996	Sweden	Prospective cohort study	Healthcare workers (ID group) and healthy travellers (IM group)	72 EU (0.1 ml)	0, 1, 2, 8 months	28	IM	1440 EU (1.0 ml)	0 and 6-12 months	13	Seroprotection rate (defined as ≥18 IU/l) 1 month after last dose: 96% (ID72), 100% (ID144), 100% (ID216) vs 100% AE: local reaction resembling small slightly itchy mosquito bite was common.	Carlsson
						144 EU (0.1 ml)	0, 1, 2, 8 months	67						
						216 EU (0.15 ml)	0, 1, 6 months	39						
	Virosomal	2009	Germany	Prospective	Healthy	1 x 4.8 IU	Day 0,	30,	IM	24 IU (=0.5	1 visit +	61	Seroprotection rate (defined as ≥20 IU/l) at month 6: 100% (ID1),	Frösner

[1] Primary outcome measure diphtheria: seroprotection rate defined as percentage of subjects with post-vaccination antitoxin level ≥0.1 IU/ml.
Primary outcome measure tetanus: seroprotection rate defined as percentage of subjects with post-vaccination anti-tetanus antibody level of ≥0.01 IU/ml.

[2] Different adjuvants were used in ID and IM vaccine.

[3] Primary outcome measure HAV: seroprotection rate defined as percentage of subjects with post-vaccination anti-HAV antibodies >10-33 IU/L assessed 4 weeks after completing vaccination series.

	HAV vaccine			cohort study	subjects, 18-45 years	2 x 4.8 IU	50, (extra)[4] + booster after 1 year	29		ml)	booster after 1 year		93.1% (ID2) vs 96.7% AE: local induration/swelling and erythema 24.1-37.9% vs 0-3.3%; pain 10% vs 21.3% Systemic: comparable between groups.	
	Virosomal HAV vaccine	2005	Thailand	Prospective cohort study	Healthy children, 8-12 years	0.1 ml	1 visit + booster after 1 year	27	IM	0.25 ml	1 visit + booster after 1 year	50	Seroprotection rate (defined as ≥10 IU/l) 1 month after first dose: 27/27 (100%) vs 50/50 (100%) AE: local overall: 15.2% vs 21.8%; pain/tenderness 9.1% vs 18.2%; induration 0% vs 7.3%; erythema 0% vs 0%; swelling 9.1% vs 9.1% Systemic overall: 21.2% vs 18.2%; fatigue 15.2% vs 12.7%; malaise/irritability 0% vs 7.3%; loss of appetite 3% vs 9.1%; fever 9.1% vs 3.6%	Pancharoen
HBV[5]													
	Recombinant HBV vaccine	2003	Iran	Double-blind RCT	Female school students, mean age 16.1 (ID), 15.6 (IM) years	0.1 ml	Month 0, 1, 6	95	IM	1 ml	Month 0, 1, 6	81	*Seroprotection rate 3 weeks after last dose: 91/95 (95.8%) vs 80/81 (98.8%)*	Afzali
	Recombinant HBV vaccine	1993	Sweden	RCT	Subjects with Down Syndrome, 2-63 years	2 µg	Month 0, 1, 6	42	IM	20 µg	Month 0, 1, 6	41	*Seroprotection rate 6 months after last dose: 12/42(29%) vs 30/41(73%)*	Ahman
	Recombinant HBV vaccine	2006	Iran	RCT	Chronic haemodialysis patients, mean age 45 years	20 µg (=1 ml)	Month 0, 1, 6	11, 11	IM	40 µg (=2 ml)	Month 0, 1, 6	11, 11	*Seroprotection rate 1 month after last dose:* 60% vs 70% With Levamisole: 90% vs 90%	Argani
	Recombinant and plasma-derived HBV vaccine	1990	Pakistan	RCT	Medical students, mean age 19-24 years	1 µg 2 µg	Mont 0, 1, 5	51	IM	10 µg	Mont 0, 1, 5	51	*Seroprotection rate 50 days after last dose:* Seroprotection rate 50 days after last dose: 40/51 (78%) (ID1recomb), 90% (ID2plasmad) vs 48/51 (94%) (IM10recomb) AE: Local (after 3rd dose): erythema 78% vs 6%; induration 66% vs 4%; pruritus 16% vs 6%; pain 10% vs 16%	Bryan
	Recombinant HBV vaccine	2011	Thailand	Open-label RCT	HIV-infected children, with CD4% ≥15% or 200	2 µg	Month 0, 2, 6	41	IM	10 µg	Month 0, 2, 6	39	*Seroprotection rate 1 month after last dose:* 90.2% vs 92.3% AE: Swelling at injection site 29.3-41.5% vs 12.8-18% Pain scores of 1-4 7.2% vs 8.3%	Bunupuradah

[4] Subjects in ID1-group received extra ID dose after day 50 because of GMC was found below 100 mIU/ml at day 29.

[5] Primary outcome measure HBV: seroprotection rate defined as percentage of subjects with post-vaccination anti-HBs antibodies >10 IU/L assessed 1-3 month after completing vaccination series.

					cells/mm3, 1-18 years[6]							Fever 2.4-12.2% vs 5.1-15.4%	
	Recombinant HBV vaccine	1999	Sweden	Prospective cohort study	Healthcare workers, 22-61 years	2 µg	Week 0, 4, 8 or week 0, 2, 6	64, 102	IM	20 µg	Week 0, 4, 8 or week 0, 2, 6	13, 17	*Seroprotection rate 2 weeks after last dose:* *Scheme 0, 4, 8 weeks: 25/64 (39%) vs 9/13 (69%)* *Scheme 0, 2, 6 weeks: 50/102 (49%) vs 14/17 (82%)*	Carlsson
	Recombinant HBV vaccine	2006	Thailand	RCT	Haemodialysis patients, mean age 41 (ID) and 50 (IM) years	2 x 5 µg Cumulative : 70 µg	Week 0, 2, 4, 6, 8, 10, 12	21	IM	2 x 20 µg Cumulative : 120 µg	Month 1, 2, 6	17	*Seroprotection rate at month 7: 19/21 (90%) vs 14/17 (82%)* *AE: ID group experienced erythematous, sometimes indurated macules at injection site, which was acceptable to all patients. No systemic reactions.* *Costs: cost for ID regimen was half of the IM regimen.*	Chanchairujira
	Recombinant HBV vaccine	2000	Canada	RCT	Haemodialysis patients, mean age 52.1 (ID), 45.9 (IM) years	5 µg Cumulative : up to 260µg	Every 2 weeks up to 52 doses	41	IM	2 x 20 µg Cumulative : 160µg	Month 0, 1, 2, 6	42	*Seroprotection rate overall:* 40/41 (97.6%) vs 38/42 (90.5%) Time to seroconversion: 6.1 months vs 4.6 months Dose needed for seroconversion: 57.3 µg vs 127.4 µg AE: no significant side effects.	Charest
	Recombinant HBV vaccine	2004	China	RCT	Patients on continuous ambulatory peritoneal dialysis, mean age 45 (ID), 51 (IM) years	5 µg (=0.25ml) Cumulative dose: 50µg	Every week, 10 doses	27	IM	20 µg (=1 ml) Cumulative dose: 60µg	Month 0, 1, 6	29	Seroprotection rate overall: 22/27 (81.5%) vs 18/29 (62.1%) Time to seroconversion: 5.1 months vs 6.6 months AE: local overall 40/271 (14.8%) vs 2/93 (2%); pruritus 10/271 (3.7%) vs 0/93 (0%) Systemic overall 19/271 (7.0%) vs 2/93 (2.2%); arthralgia 1/271 (0.4%) vs 1/93 (1.1%); general pruritus 2/271 (0.7%) vs 1/93 (1.1%); low grade fever 1/271(0.4%) vs 0/93 (0%); urticaria 8/271 (3.0%) vs 0/93 (0%); headache 2/271 (0.7%) vs 0%; nausea 2/271 (0.7%) vs 0/93 (0%)	Chau
	Plasma-derived HBV vaccine	1994	United States of America	RCT	Healthy, full-term infants, born to HbsAg-negative women	2 µg	0 (birth), 2, 4 months of age	75	IM	2 or 10 µg	0 (birth), 2, 4 months of age	75	Seroprotection rate two months after last dose: 91% vs 100% (IM10) AE: local: induration within 24 h 20-36% vs 7-22%; erythema within 24h 19-32% vs 0-11%; persistent induration 2-9% vs 0%; persistent hyperpigmentation 25-49% vs 0-2% Systemic: significantly lower weight, shorter mean length and smaller head circumference at 6 months in IM group.	Coberly
	Plasma-derived HBV vaccine	1991	United States of America	RCT	Healthcare workers, average age 36.5 years	2 µg	Month 0, 1, 6	168	IM	20 µg	Month 0, 1, 6	175	Seroprotection rate 2 months after last dose: 136/168 (81.0%) vs 162/175 (92.6%) AE: local: physical examination: erythema 7-19% vs 0-1%; induration 1-9% vs 0%; nodule 1-24% vs 0%; pigmentation 8-21% vs 0%; Patient reported: soreness 6-14% vs 12-44%; swelling 2-4% vs 1-5%; erythema 13-16% vs 1-4%; pruritus 19-20% vs 2-5%; lump 17-24% vs 1-3%; skin darkening 5-8% vs 0-1%	Coleman
	Recombinant HBV vaccine	1998	Turkey	RCT	Healthy, full-term infants,	2 µg	Month 0, 1, 6	89, 91	IM	10 µg	Month 0, 1, 6	92, 95	Seroprotection rate 8 weeks after last dose: Infants: 84/89 (94%) vs 90/92 (98%)	Egemen

[6] 53.7% of IM and 4.4% of ID group with history of completing 3 doses of HBV

					born to HbsAg-negative women and preschool children, 3-6 years[7]							Preschool children: 91/91 (100%) vs 93/95 (98%) AE: local: Infants: erythema after 24h: 22-34% vs 5-8%; induration 24h after: 13-16% vs 5-8%; persistent induration 0% vs 0%; hyperpigmentation one month later 26-35% vs 0% Preschool children: erythema after 24h: 11-15% vs 1-5%; induration 24h after: 10-14% vs 3-7%; persistent induration 0-1% vs 0%; hyperpigmentation one month later 20-26% vs 0%	
	Plasma-derived HBV vaccine	1987	Australia	RCT	Healthy healthcare workers, 20-66 years	2 µg	Month 0, 1, 6[8]	19	IM	20 µg	Month 0, 1, 6[9]	19	Non-responders (sample ratio units <2) 1 month after last dose: 14/19 vs 17/19 AE: minor AEs 6 vs 9: IM group mostly local pain or muscle stiffness; ID group mostly immediate local discomfort or erythema without induration.	Frazer
	Recombinant HBV vaccine	2004	Iran	RCT	Healthy students, 17-31 years	4 µg	Month 0, 1, 6	74	IM	20 µg	Month 0, 1, 6	69	Seroprotection rate 1 month after last dose: 72/74 (97.3%) vs 68/69 (98.55%) AE: Local: mild erythema and skin discoloration lasting for few weeks 7/74 (9.5%) in ID group Systemic: no were observed in any of groups.	Ghabouli
	HBV vaccine, type unknown	2004	India	RCT	Infants, born at term	2 µg	6, 10, 14 weeks of age	89	IM	10 µg	6, 10, 14 weeks of age	88	Seroprotection rate 4 weeks after last dose: 92.1% vs 98.8% AE: 4 cases with local erythema in ID group. No AEs in IM group.	Gomber
	Recombinant HBV vaccine	1990	Spain	RCT	Healthcare workers, 20-40 years[10]	2 µg	Month 0, 1, 6 + booster	32	IM	20 µg	Month 0, 1, 6 + booster	36	Seroconversion rate 1 month after 3rd dose: 25/32 (78.1%) vs 35/36 (97.2%) AE: Local overall 84.4% vs 36.1%: pain most common in IM group and induration and swelling in ID group. Systemic overall 6.1% vs 41.7%: headache, asthenia	Gonzalez
	Plasma-derived HBV vaccine	1986	United States of America	RCT	Healthy adults 22-42 years	2 µg 2 x 2µg	*Month 0, 1, 4* *Month 0, 4*	19, 20	IM	20 µg	*Month 0, 1, 4*	17	Seroprotection rate 1 month after last dose: 19/19 (100%) (ID1), 19/20 (95%) (ID2) vs 17/17 (100%) AE: 25% of ID group persistence of induration for 3-12 weeks and small areas of hyperpigmentation 2-12 months post-vaccination. 2 subjects (1 ID, 1 IM) developed fever.	Halsey
	Recombinant HBV vaccine	1991	Japan	Prospective cohort study	Mentally handicapped patients, mean age 28.3 (ID) and 29.1 (IM) years	2 µg (=0.1 ml)	Month 0, 1, 6	51	SC	10 µg (=0.5 mg)	Month 0, 1, 6	44	Seroprotection rate 3 months after last dose: 42/51 (82.3%) vs 38/44 (86.4%) AE: local: pruritus 2/51 (3.9%) vs 0%; induration for 1-2 weeks 17/51 (33.3%); pigmentation 20/51 (39.2%) Costs per person: 34 USD vs 170 USD	Hayashi

[7] Not reported if subjects were previously immunised.

[8] Subjects without antibody response received 2 extra injections of 20 µg at monthly intervals.

[9] Subjects without antibody response received 2 extra injections of 20 µg at monthly intervals.

[10] Not reported if subjects were previously immunised.

	Recombinant HBV vaccine	2000	Canada	RCT + non-randomised clinical trial	Healthcare workers, 1-65 years[11]	3 µg (=0.15ml)	Month 0, 1, 6 + booster	48, 187	IM	20 µg (=1 ml)	Month 0, 1, 6 + booster	43, 99	Seroprotection rate 3 months after 3rd dose: Randomised subjects: 46/48 (96%) vs 42/43 (98%) Non-randomised subjects: 178/187 (95%) vs 92/99 (93%) AE: skin discoloration in 166/370 (45%) of ID group systemic allergic response 2/220 (1 hives, 1 fever, myalgia, skin rash) of IM group	Henderson
	Plasma-derived HBV vaccine	1989	United Kingdom	Prospective cohort study	Healthy students, mean age 22.6 (m), 21.3 (f) years[12]	2 µg	Month 0, 1, 6	62	IM	20 µg	Month 0, 1, 6	62	Seroprotection rate 2 months after last dose: 57/62 (92%) vs 60/62 (96.8%) AE: reactions were mild: 1 ID vaccine with local erythema and pruritus lasting for 2 weeks.	Herbert
	Recombinant HBV vaccine	2006	Turkey	RCT	Haemodialysis patients, 19-70 years	2 µg	Month 0, 2, 3, 4, 5, 6 Cumulative: 12µg	26	IM	20 µg Cumulative: 80 µg	Month 0, 1, 2, 6	30	Seroprotection rate 1 months after last dose: 21/26 (80.8%) vs 25/30 (83.3%)	Karahocagil
	Recombinant HBV vaccine	2001	Iran	RCT	Healthy infants, born at term	2 µg	0 (within first week of life), 1, 6 months	82	IM	10 µg	0 (within first week of life), 1, 6 months	83	Seroprotection rate at 6 months of age (upon 3rd dose): 67/82 (81.7%) vs 77/83 (92.8%) AE: local hyperpigmentation 55% in ID group.	Lankarani
	Recombinant HBV vaccine	2011	France	Open-label, RCT	Adults with HIV-1, 19-74 years	4 µg	Week 0, 4, 8, 24	140	IM	20 or 40 µg	Week 0, 4, 24 Week 0, 4, 8, 24	141, 145	Seroprotection rate 1 months after last dose: 108/140 (77%) vs 91/141 (65%) (IM20x3), 119/145 (82%) (IM40x4) AE: overall: 125/140 (89%) vs 119/140 (87%); Local overall 73/140 (52%) vs 38/140 (27%), 60/144 (42%); including erythema, pain, pruritus, nodule, induration, oedema, discoloration Systemic overall 106/140 (76%) vs 108/140 (77%), 109/144 (76%); including asthenia, headache, fever, myalgia, nausea	Launay
	Recombinant HBV vaccine	1990	Italy	RCT	Mentally handicapped children[13]	5 µg	Week 0, 2, 4, 6	22	IM	20 µg	Month 0, 1, 2	21	Seroprotection rate at 6 months: 21/22 (95.9%) vs 18/21 (85.7%)	Leonardi
	Recombinant HBV vaccine	1998	Italy	RCT	Children with insulin dependent diabetes, 3-17 years and children with	3 µg	At 2, 4, 6, or 8-week intervals	9, 12	IM	10 µg (≤10 years) or 20 µg (>10 years)	Month 0, 1, 6	9, 12	Seroprotection rate 4-5 weeks after last dose: Children with diabetes: 7/9 (78%) vs 9/9 (100%) Normal children: 12/12 (100%) vs 12/12 (100%)	Li Volti

[11] Not reported if subjects were previously immunised.

[12] Not reported if subjects were previously immunised.

[13] Not reported if subjects were previously immunised. All subjects had no evidence of past or current HB infection.

					familiar short stature								
	Recombinant HBV vaccine	2011	Brazil	RCT	Incident haemodialysis patients, mean age 57 (ID), 59 (IM) years	4 µg	Month 0, 1, 2	15	IM	40 µg	Month 0, 1, 2	16	Seroprotection rate: (2/15) 13.3% vs (10/16) 62.5%	Medeiros
	Recombinant HBV vaccine	1996	Germany	RCT	Patients with end stage renal disease	10 µg (= 2 x 0.25 ml)	Month 0, 1, 3, 6	18	IM	40 µg (=2 ml)	Month 0, 1, 3, 6	14	Seroprotection rate 6 weeks after last dose: 11/18 (61%) vs 9/14 (64%) AE: IM: 5 patients experienced dull pain at application site. ID: all patients experienced short burning pain and slightly itching macule at injection site.	Mettang
	Plasma-derived HBV vaccine	1989	United Kingdom	RCT	Patients with congenital coagulation disorders[14]	2 µg	Month 0, 1, 6	8, 14	SC	10 µg (≤10 years) or 20µg (>10 years)	Month 0, 1, 6	8, 17	Seroprotection rate 1 month after last dose: Children (mean age 4 years): 8/8 (100%) vs 8/8 (100%) with all anti-HBs level > 100IU/l) HIV negative adults (median age 30 years): 14/14 (100%) vs 17/17 (100%) AE: no adverse events in any of the participants.	Miller
	Plasma-derived HBV vaccine	1989	United Kingdom	Prospective cohort study	Patients with β-thalassaemia or sickle cell disease, 1.2-25.4 years	2 µg (0.1 ml)	Month 0, 1, 6	16	IM	10-20 µg (0.5-1 ml)	Month 0, 1, 6	16	Seroprotection rate 1 months after last dose: 16/16 (100%) vs 16/16 (100%)	Mok
	Recombinant HBV vaccine	2008	Pakistan	Prospective cohort study	Healthcare workers, 20-50 years	3 µg	Month 0, 1, 6	54	IM	10 or 20 µg	Month 0, 1, (6)	55, 56, 60	Seroprotection rate 8 weeks after last dose: 53/54 (98.14%) vs 53/55 (96.36%) (3IM20), 53/56 (94.64%) (3IM10), 57/60 (95%) (2IM20)	Mumtaz
	Recombinant HBV vaccine	1991	United States of America	RCT	Medical students and hospital employees, 21-58 years	1 or 1.5 µg	Month 0, 1, 6	36, 31	IM	10 µg	Month 0, 1, 6	29	Seroprotection rate 2 months after last dose: In all groups > 90% 34/36 (94%) (ID1), 30/31 (97%) (ID1.5) vs ≈ 88% AE: IM group: 18% reported local soreness; ID group: 80% reported small areas of local induration and/or discoloration. All lesion faded over time. (numbers with ≈ in front were obtained from graphic and are therefore an approximation)	Parish
	Plasma-derived HBV vaccine	1985	United States of America	Double blinded RCT	Healthy healthcare workers, < 45 years	2 µg (=0.1 ml)	Month 0, 1, 6	25	IM	20 µg (=1 ml)	Month 0, 1, 6	25	Seroconversion (defined as (P/N ratio) of ≥ 2.1) 24/25 (96%) vs 25/25 (100%) AE: Sore arm 0 vs 9-14; local skin reaction 2-18 vs 0	Redfield
	Recombinant HBV vaccine	2004	Iran	RCT	Healthcare workers, 21-	2 µg 4 µg	Month 0, 1, 6	42, 46	IM	20 µg or 20 µg + 2	Month 0, 1, 6	45	Seroprotection rate 3 months after last dose: 41/42 (97.6%) (ID2), 45/46 (97.8%) (ID4) vs 44/45 (97.7%)	Rezvan

[14] Not reported if subjects were previously immunised.

					35 years					µg ID			
	Recombinant HBV vaccine	2005	Iran	RCT	Haemodialysis patients, mean age 52.7 (ID), 53.6 (IM) years	20 µg (=2 x 0.5 ml)	Month 0, 1, 4	35	IM	40 µg (=1 ml)	Month 0, 1, 4	27	Seroprotection rate 3 months after last dose: 19/35 (54.3%) vs 15/27 (55.6%) AE: local pain and skin irritation in ID group.	Roozbeh
	Recombinant HBV vaccine	2008	Iran	RCT	Medical and nursing students, 18-23 years	4 µg	Month 0, 1, 6	91	IM	20 µg	Month 0, 1, 6	94	Seroprotection rate 1 month after last dose: 79/91 (87%) vs 90/94 (96%)	Sharifi-Mood
	Recombinant HBV vaccine	1992	Sweden	Prospective cohort study	Healthcare workers, median age 33 (ID), 37 (IM) years	2 µg	Month 0, 1, 6	338	IM	20 µg	Month 0, 1, 6	257	Seroprotection rate 1 month after last dose: 302/338 (89%) vs 241/257 (94%) AE: local: overall 137/293 vs 44/241; reaction (nodule, swelling, pruritus, discoloration, pain) 134/293 vs 34/241; extension of local symptoms to arm or shoulder 1/293 vs 10/241; paraesthesia distally to injection site 2/293 vs 0/241 Systemic: 28/293 vs 28/241 fever 5/293 vs 7/241; headache 18/293 vs 7/241; arthralgia 1/293 vs 2/241; generalized pruritus 3/293 vs 1/241; flush 1/293 vs 0/241; vesicular stomatitis 1/293 vs 0/241	Struve
	Recombinant HBV vaccine	2014	Iran	RCT	Haemodialysis patients, 16-64 years	2 x 2 µg	Month 0, 1, 2, 6	25	IM	2 x 20 µg	Month 0, 1, 2, 6	25	Seroprotection rate 1 month after last dose: 17/25 (68%) vs 17/25 (68%) AE: 3/25 of ID group complaint of pain and erythema at injection site 24 hours post-vaccination. No complaints in IM group. No fever in week post-vaccination in both groups.	Tavanaee Sani
	Recombinant HBV vaccine	1997	Brazil	RCT	Healthy medical and nurse students, 17-28 years	2 µg	Month 0, 1, 6	92	IM	20 µg 10 µg	Month 0, 1, 6	114, 98	Seroprotection rate 1-3 months after last dose: 77/98 (78.6%) vs 113/114 (99.1%) (IM20), 87/92 (94.6%) (IM10) AE: local adverse reactions (pruritus, erythema, swelling, hyperpigmentation) 62.3% vs 2.7%; pain 8.4% vs 3.5% Systemic: low grade fever 2.4% vs 1.1%;	Turchi
	Plasma-derived HBV vaccine	1987	Sweden	Prospective cohort study	Medical students and healthcare workers, 20-42 years	2 µg	Month 0, 1, 6	18	IM	20 µg	Month 0, 1, 6	16	Seroprotection rate 1 month after last dose: 18/18 vs 15/16 AE: local (n of injections): discoloration 23/63 (37%) vs 0/48; pruritus 11/63 (17%) vs 0/48; nodule formation 8/63 (13%) vs 0/48	Wahl
	Plasma-derived HBV vaccine	1991	Gambia	RCT	Children, 0-4 years[15]	2 µg	Month 0, 2, 4	66	IM	20 µg 10 µg 20 µg + 2 µg ID	Month 0, 2, 4, (9)	74, 233	Peak anti-Hbs concentration ≥ 10 IU/l 2 months after last dose: 51/65 vs 74/74 (3IM20), 226/233 (4IM10) Breakthrough infection: 5/53 vs 5/66 (3IM20), 17/169(4IM10) Long-term effects described in Whittle, 1995[16]	Whittle

[15] 37.5% of children in Manduar and 72.5% in Keneba were previously immunised with HBV vaccines.

	Recombinant HBV vaccine	1990	Sweden	RCT	Healthcare workers, 21-50 years	2 µg	Month 0, 1, 6	38	IM	10 µg	Month 0, 1, 6	37	Seroprotection rate at month 6: 20/38 (53%) vs 36/37 (97%) Seroprotection rate 6 months after last dose: 21/38 (55%) vs 36/37 (97%) AE: Local overall: 41% (IDnonresponders), 83% (IDresponders) vs 15% Long-term effects described in Wistrom, 1995[17]	Wiström
	Recombinant HBV vaccine	1997	Japan	RCT	Medical and nurse students, 18-22 years	2 or 4 µg Cumulative : 6-12 µg	Week 0, (1), (2), 4, (6), (25)	19, 29, 28, 25, 23, 23	IM	10 µg Cumulative : 30 µg	Month 0, 1, 6	26	Seropositivity (anti-HBs >2 IU/l) 1 month after last dose: 92-100% vs 100% ID group: local: pruritus 17%; pain 3% Systemic: general fatigue 8%, fever 2%	Yamashiki
	Recombinant HBV vaccine	1998	Pakistan	RCT	Healthcare workers, mean age 30 (ID), 28 (IM) years [18]	5 µg	Month 0, 1, 6	36	IM	20 µg	Month 0, 1, 6	25	Seroprotection rate 1 months after last dose: 30/33 (90.9%) vs 22/23 (95.7%)	Zuberi
HPV[19]														
	Bivalent HPV 16/18 vaccine and quadrivalent HPV 6/11/16/18 vaccine	2013	Hong Kong	RCT	Sexually naïve women, 18-26 years	0.1 ml	Month 0, 2, 6	Bivalent: 5, 5 Quadrivalent: 5, 6	IM	0.5 ml 0.1 ml	Month 0, 2, 6	Bivalent: 5, 5 Quadrivalent: 6, 5	Seroconversion rate (titre≥1:320) at day 35: HPV 16: Bivalent: 5/5 (IDNS), 4/4 (IDPJ) vs 4/5 (IM0.5); Quadrivalent: 3/4 (IDNS), 6/6 (IDPJ) vs 4/6 (IM0.5) HPV 18: Bivalent: 4/5 (IDNS), 3/4 (IDPJ) vs 4/5 (IM0.5); Quadrivalent: 1/4 (IDNS), 3/6 (IDPJ) vs 2/6 (IM0.5) Day 95: 100% seroconversion in all subjects AE: local: pain 13/19 vs 16/21; erythema 18/19 vs 5/21; skin peeling 5/19 vs 0/21; swelling 15/19 vs 3/21; firmness 10/19 vs 2/21; pruritus 17/19 vs 2/21; bruising 0/19 vs 2/21; discoloration 11/19 vs 3/21; taking medication for site reaction 1/19 vs 0/21 Systemic: nausea 0/19 vs 1/21; vomiting 2/19 vs 1/21; diarrhoea 2/19 vs 0/21; runny nose 4/19 vs 4/21; cough 0/19 vs 4/21; dizziness 1/19 vs 4/21; feeling unwell 4/19 vs 3/21; tiredness 6/19 vs 8/21; myalgia 2/19 vs 6/21; headache 2/19 vs 4/21; taking medication for AE: 9/19 vs 11/21	Nelson
Influenza[20]														

[16] Whittle, H. C., Pilkington, J., Maine, N., Mendy, M., Fortuin, M., Hall, A., ... & Howard, C. (1995). Long-term efficacy of continuing hepatitis B vaccination in infancy in two Gambian villages. The Lancet, 345(8957), 1089-1092.

[17] Wiström, J. (1995). Intramuscular vs intradermal hepatitis B vaccination: a 6-year follow-up. *Jama*, *273*(23), 1835-1836.

[18] Not reported if subjects were previously immunised.

[19] Primary outcome measure HPV not available.

[20] Primary outcome measure influenza: seroprotection rate defined as percentage of subjects with post-vaccination hemagglutinin inhibition (HI) titres ≥1:40 assessed 2-4 weeks after completing vaccination series.

	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2012	Italy	RCT	HIV-infected adults, < 60 years	9 µg HA/strain	Single visit	28	IM	15 µg HA/strain	Single visit	24	Seroprotection rate 1 month post-vaccination: A(H1N1): 79% vs 80% A(H3N2): 82% vs 80% B 75% vs 76% AE: Local: over 64% vs 19%; pruritus 29% vs 4%; erythema 46% vs 8%; swelling 43% vs 12%; induration 46% vs 4% Systemic: fever 7% vs 15%; headache 19% vs 4%; shivering 21% vs 12%	Ansaldi
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2015	Japan	RCT	Healthy, 20-64 and ≥65 years	6, 9, 15 µg HA/strain	Single visit or day 0, 21	50 each	SC	15 µg HA/strain	Single visit or day 0, 21	50 each	Seroprotection rate 21 days after 1st dose: Adults 20-64 years: A(H1N1): 94.0% (ID6), 96.0% (ID9) vs 96.0% (SC15), 98.0% (2SC15) A(H3N2): 94.0% (ID6), 98.0% (ID9) vs 92.0% (SC15), 100.0% (2SC15) B :76.0% (ID6), 68.0% (ID9) vs 68.0% (SC15), 78.0% (2SC15) Adults > 60 years: A(H1N1): 92.0% (ID6), 96.0% (ID9) vs 96.0% (SC15), 90.0% (2SC15) A(H3N2): 100.0% (ID6), 98.0% (ID9) vs 96.0% (SC15), 94.0% (2SC15) B: 62.0% (ID6),66.0% (ID9) vs 40.0% (SC15), 30.0% (2SC15) AE: Local overall 93-95% vs 69-76%; erythema 92-93% vs 58-66%; swelling 50-59% vs 36-49%; pruritus 33-45% vs 31-47%; warmth 21-30% vs 26-32%; pain 17-18% vs 32-37%; induration 9-14% vs 9-14%; ecchymosis 1-4% vs 4-6% Systemic overall 18-22% vs 15-26%; malaise 9-15% vs 14-19%; headache 10-13% vs 4-10%; shivering 1-6% vs 2-6%; fever 0-1% vs 0-1%; rash 0% vs 0%	Arakane
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2007	Thailand	RCT	Healthy, 20-50 years	3 µg HA/strain	Single visit	400	IM	15 µg HA/strain	Single visit	100	Seroprotection rate 28 days post-vaccination: A(H1N1): 93.3% vs 98.0% A(H3N2): 86.3% vs 95.0% B: 43.5% vs 57% AE: Local: erythema 92.2% vs 2.0%; induration 68.4% vs 4.0%; skin temperature 51.1% vs 28.0%; local pruritus 49.4% vs 6.0%; pain 35.1% vs 44.0% Systemic: generalized pruritus 15.8% vs 5.0%; malaise 13.0% vs 24.0%; myalgia 18.0% vs 30.0%; chills 4.3% vs 7.0%; fever 4.5% vs 6.0%; nausea/vomiting 2.8% vs 4.0%; rash 1.5% vs 1.0%; arthralgia 9.8% vs 10.0%	Auewarakul
	Trivalent influenza vaccine: H1N1, H3N2, Influenza B[21]	2004	United States of America	Open-label RCT	Healthy adults 18-60 years and elderly > 60 years[22]	6 µg HA/strain	Single visit	61, 58	IM	15 µg HA/strain	Single visit	69, 50	Seroprotection rate 21-28 days post-vaccination: Adults 18-60 years: A(H1N1): 61/61 (100%) vs 69/69 (100%) A(H3N2): 61/61 (100%) vs 69/69 (100%) B: 61/61 (100%) vs 69/69 (100%)	Belshe

[21] ID and IM vaccine differ in brand, adjuvants used (ID vaccine no gelatine) and in B strain: B/Johannesburg 5/99 vs B/Victoria/504/2000.

												Adults > 60 years: A(H1N1): 58/58 (100%) vs 50/50 (100%) A(H3N2): 58/58 (100%) vs 50/50 (100%) B: 58/58 (100%) vs 50/50 (100%) AE: adults 18-60 years Pain 45% vs 67%; induration 75% vs 6%; erythema 88% vs 6%; swelling 52% vs 9% Adults > 60 years Pain 19% vs 16%; induration 67% vs 4%; erythema 78% vs 8%; swelling 39% vs 4%	
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2007	United States of America	Open-label RCT	Healthy adults, 18-49 years	3, 6, 9 µg HA/strain	Single visit	31, 31, 30	IM	3, 6, 9, 15 µg HA/strain	Single visit	31, 31, 32, 31	Seroconversion rate 28 days post-vaccination: A(H1N1): 17% (ID3), 18% (ID6), 15% (ID9) vs 21% (IM15) A(H3N2): 20% (ID3), 22% (ID6), 21% (ID9) vs 29% (IM15) B: 16% (ID3), 19% (ID6), 17% (ID9) vs 21% (IM15) AE (Day 0): local reactions (pain, erythema and swelling): 26/30 (ID3), 30/30 (ID6), 30/30 (ID9) vs 12/31 (IM)	Belshe
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2009	Belgium, Czech Republic, Lithuania	Dose-ranging RCT	Healthy adults, 18-57 years	3 or 6 µg HA/strain	Single visit	378, 375	IM	15 µg HA/strain	Single visit	376	Seroprotection rate 21 days post-vaccination: A(H1N1): 275/378 (72.7%) (ID3), 267/375 (71.3%) (ID6) vs 327/376 (87.1%) A(H3N2): 335/378 (88.5%) (ID3), 331/375 (88.2%) (ID6) vs 364/376 (96.9%) B: 108/378 (28.5%) (ID3), 123/375 (32.9%) (ID6) vs 209/376 (55.7%) AE: ≥1 EMEA reaction: 38/384 (9.9%), 39/383 (10.2%) vs 50/382 (13.1%); Local: induration 0%, 0% vs 1/382 (0.3%); ecchymosis 2/384 (0.5%), 1/383 (0.3%) vs 7/382 (1.8%); Systemic: fever 4/384 (1.0%), 5/383 (1.3%) vs 6/382 (1.6%); malaise 12/384 (3.1%), 17/383 (4.4%) vs 19/382 (5.0%); shivering 26/384 (6.8%), 26/383 (6.8%) vs 21/382 (5.5%)	Beran
	Monovalent influenza vaccine: Asian strain	1957	United States of America	Prospective cohort study	Hospitalised patients ≥ 70 years	50 CCA	Single visit	22	SC	550 CCA	Single visit	22	Seroprotection rate 4 weeks post-vaccination: 8/22 (36%) vs 20/22 (91%)	Boger
	Polyvalent influenza vaccine: Japan 170/62, MD 1/59, PR8, Ann Arbor 1/57	1966	United States of America	Prospective cohort study	Employees at electric company[23]	0.1 ml	Single visit	47	SC	1.0 ml	Single visit	48	Seroconversion rate 1 month post-vaccination: A2: 6/47 (12%) vs 8/48 (17%) B: 3/47 (6%) vs 6/48 (13%) AE: any type of reaction 20% vs 30%; losing one or more days form work 0% vs 2.5%	Brown

[22] Not mentioned if subjects were immunised in the last six months.

[23] Not mentioned if subjects were immunised in the last six months.

	Monovalent whole-virus influenza vaccine: A/New Jersey/26	1977	United States of America	RCT	Medical students, staff and family members 18-53 years[24]	40 CCA ID + 200 CCA IM	Day 0 (ID), 30 (IM)	11	IM	200 CCA	Day 0, (30)	10	Seroconversion rate (defined as fourfold rise or HI titre ≥1:20) 30 days after first dose: 18-24 years: 42% vs 69% ≥25 years: 54% vs 67% AE: local: pain, tenderness 34-38% vs 37-38%; erythema, induration 91-92% vs 4-8%	Brown
	Monovalent influenza vaccine: A/Japan/305/57	1959	United States of America	Prospective cohort study	Inhabitants of a home for the aged	20, 40 CCA	Week 0, 2	12, 75	SC	100, 200 CCA	Week 0, 2	19, 34	Mean titre two weeks after 1st dose: 20.16 (ID20), 13.57 (ID40) vs 11.52 (SC100), 15.36 (SC200)	Bruyn
	Bivalent influenza vaccine: PR8, Lee	1949	United States of America	Prospective cohort study	Health department employees	0.1 ml	Single visit	34	SC	1.0 ml	Single visit	31	Mean fold rise 14-16 days post-vaccination: PR8: 4.8 vs 4.4 Lee: 3.3 vs 2.8 Mean titre 14-16 days pre and post-vaccination:	Bruyn
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2010	United States of America	Open-label RCT	Healthy elderly, ≥ 65 years[25]	9 µg or 2 x 4.5 µg HA/strain	Single visit + booster	63, 65	IM	9, 15 µg HA/strain	Single visit + booster	65, 64	Seroprotection rate 4 weeks after 1st dose: A(H1N1): 42/63 (68.9%) (ID9), 43/65 (67.2%) (2ID) vs 42/65 (65.6%) (IM15) A(H3N2): 46/63 (75.4%) (ID9), 48/65 (75.0%) (2ID) vs 49/65 (76.66%) (IM15) B: 10/63 (16.5%) (ID9), 16/65 (25.0%) (2ID) vs 17/65 (26.6%) (IM15) AE (grade 2/3): Local: erythema 4.8-6.2% vs 0%; swelling 3.2-4.6% vs 0%; pain 0% vs 0%; pruritus 0-3.1% vs 0%; arm motion limitation 0% vs 0% Systemic: fever 0-1.5% vs 0; chills 0-1.5% vs 1.6%; fatigue 0-9.2% vs 3.1%; body pain 3.2-6.2% vs 1.6%; headache 0-7.7% vs 0%; nausea 0% vs 1.6%	Chi
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2009	Hong Kong	RCT	Healthy infants, 2-3 months	3 µg HA/strain	0, 1 month	61	IM	7.5 µg HA/strain	0, 1 month	62	Mean fold rise 21 days post-vaccination: A(H1N1): 1.21 vs 1.13 A(H3N2): 1.26 vs 1.26 B: 1.15 vs 1.07 AE: induration 6.5% vs 3.2%; erythema 12.1% vs 3.2%; ecchymosis 0.8% vs 0% Systemic: malaise 33.1% vs 31.5%; shivering 0% vs 2.4%; fever 3.2% vs 2.4%; irritable 11.3% vs 7.3%; decrease appetite 8.1% vs 4.0%	Chiu
	Trivalent purified surface	2007	Hong Kong	Open-label RCT	Hospitalised children, 3–18 years[26]	3 µg HA/strain	Single visit	56	IM	15 µg HA/strain	Single visit	56	Seroprotection rate 21 days post-vaccination: A(H1N1): 55/56 (98%) vs 55/56 (98%) A(H3N2): 56/56 (100%) vs 56/56 (100%)	Chiu

[24] Not mentioned if subjects were immunised in the last six months.

[25] Majority of subjects received influenza vaccine in the previous year. Not mentioned if subjects were immunised in the last six months.

	antigen influenza vaccine: H1N1, H3N2, Influenza B											B: 54/56 (96%) vs 52/56 (93%) AE (during 1st 3 days post-vaccination): Local: induration 25% vs 5.4%; erythema 57.1% vs 3.6%; ecchymosis 5.4% vs 0%; pruritus 5.4% vs 0%; pain 1.8% vs 5.4% Systemic: malaise 26.8% vs 23.2%; shivering 3.6% vs 5.4%; fever 5.4% vs 7.1%; headache 3.6% vs 1.8%; cough 3.6% vs 3.6%; hoarseness of voice 0% vs 1.8%; myalgia 1.8% vs 0%	
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2016	Thailand	Open-label, RCT	COPD patients, ≥65 years	2 x 4.5 µg HA/strain	Single visit	64	IM	15 µg HA/strain	Single visit	62	Seroprotection rate 1 month post-vaccination: A(H1N1): 67.2% vs 79.0% A(H3N2): 82.8% vs 77.4% B: 37.5% vs 33.9% AE: Local: erythema 67/67 (100%) vs 34/67 (50.7%); pruritus 18/67 (26.9%) vs 1/67 (1.5%); swelling 66/67 (98.5%) vs 11/67 (16.4%); ecchymosis 16/67 (23.9%) vs 2/67 (3.05) Systemic: fever 0% vs 2/67 (3.0%); myalgia 1/67 (1.5%) vs 4/67 (6.0%); headache 0% vs 3/67 (4.5%)	Chuaychoo
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2010	Thailand	RCT	COPD patients, 36-91 years	2 x 3 µg HA/strain	Single visit	81	IM	15 µg HA/strain	Single visit	75	Seroprotection rate 4 weeks post-vaccination: A(H1N1): 92.6% vs 93.3% A(H3N2): 87.7% vs 88.0% B: 67.9% vs 72.0%	Chuaychoo
	Monovalent influenza vaccine: Asian strain	1969	Canada	RCT	Healthcare workers	60 CCA	Single visit	64	SC	60 CCA (=0.1 ml) 300 CCA (=1.0 ml)	Single visit	91, 85, 77	Seroconversion rate 1 month post-vaccination: A2/Aus/57 37/64 (57.8%) vs 50/85 (58.8%), 31/77 (40.2%)	Davies
	Trivalent subunit influenza vaccine: H1N1, H3N2, Influenza B	2014	Germany, Poland and Belgium	RCT	Elderly, ≥60 years	A(H1N1); 6 µg A(H3N2): 6 or 12µg B: 6 µg	Single visit	43, 43	IM	A(H1N1); 15 µg A(H3N2):15 or 30 µg B: 15 µg	Single visit	43, 41	Seroprotection rate 22 days post-vaccination: A(H1N1): 72/86 (84%) (ID6) vs 65/84 (77%) (IM15) A(H3N2): 38/43 (88%) (ID6), 39/43 (90%) (ID12) vs 40/43 (93%) (IM15), 33/41 (80%) (IM30) B: 53/86 (61%) (ID6) vs 41/84 (49%) (IM15) AE: local overall 96-100% vs 44-45%; most common erythema, induration, swelling and pain Systemic overall 28-40% vs 30-36%; most common headache, arthralgia, fatigue, myalgia	Della Cioppa
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B[27]	2011	Italy	RCT	Healthy children aged ≥3 years[28]	9 µg and 15 µg HA /strain	Single visit	38 and 37	IM	15 µg HA/strain	Single visit	37	Seroprotection rate 1 month days post-vaccination: A(H1N1): 35/38 (92.1%) (ID9) vs 32/37 (86.5%) A(H3N2): 37/38 (97.4%) (ID9) vs 35/37 (94.6%) B: 21/38 (55.3%) (ID9) vs 12/37 (32.4%) AE: Local overall 12/38 (31.6%) vs 5/37 (13.5%); including erythema, swelling/induration, pain	Esposito

[26] All children between 3-9 years received previous immunisation. Not mentioned if subjects were immunised in the last six months.

[27] ID and IM vaccine differ in brand and IM vaccine is virosome-adjuvanted and ID vaccine not.

												Systemic overall 16/38 (42.1%) vs 14/37 (37.8%); including fever, rhinitis, irritability, sleepiness, changed eating habits, vomiting, diarrhoea	
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B B	2011	United States of America	RCT	Healthy, 18–64 years	3 µg, 6 µg and 9 µg HA/strain	Single visit	400, 399 and 394	IM	15 µg HA/strain	Single visit	398	Seroprotection rate 21 days post-vaccination: A(H1N1): 291/394 (74%) (ID3), 300/392 (77%) (ID6), 316/390 (81%) (ID9) vs 336/394 (85%) A(H3N2): 387/395 (98%) (ID3), 391/392 (99.7%) (ID6), 388/390 (99.5%) (ID9) vs 393/394 (99.7%) B: 255/394 (65%) (ID3), 294/392 (75%) (ID6), 297/390 (76%) (ID9) vs 320/393 (81%) AE: local: erythema 73%, 73%, 74% vs 3%; swelling 15%, 22%, 27% vs 1.3% Systemic: headache 27%, 28%, 31% vs 25% Mean pain score (0-100): 21.52, 17.19, 17.31 vs 10.52.	Frenck
	Trivalent subunit influenza vaccine: H1N1, H3N2, Influenza B	2009	Netherlands	RCT	Immunocompromised patients and healthy adults[29]	3 µg HA/strain	Single visit	98	IM	15 µg HA/strain	Single visit	99	Seroprotection rate 28 days post-vaccination: A(H1N1): healthy ≈ 80% vs 83% immunocompromised: ≈25-75% vs 50-83% A(H3N2): healthy ≈ 97% vs 100% immunocompromised: 67-83% vs 55-83% B: healthy ≈ 85% vs 92% immunocompromised ≈ 33-72% vs 50-82% (numbers with ≈ in front were obtained from graphic and are therefore an approximation) AE: overall healthy: 89% vs 18% immunocompromised: 25-58% vs 11-48%	Gelinck
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2013	United States of America	Open-label RCT	Healthy, 18–64 years	9 µg HA/strain	Single visit	2581	IM	15 µg HA/strain	Single visit	1287	Seroprotection rate 21-28 days post-vaccination: A(H1N1): 93.3% vs 93.8% A(H3N2): 90.0% vs 90.2% B: 90.6% vs 90.8% AE: Local overall 89.2% vs 60.2%; ecchymosis 9.3% vs 6.2%; erythema 76.4% vs 13.2%; induration 58.4% vs 10.0%; pain 51.0% vs 53.7%; pruritus 46.9% vs 9.3%; swelling 56.8% vs 8.4% Systemic overall 48.3% vs 49.2%; fever 3.9% vs 2.6%; headache 31.2% vs 30.3%; malaise 23.3% vs 22.2%; myalgia 26.5% vs 30.8%; shivering 7.3% vs 6.2%	Gorse
	Trivalent split-virion influenza vaccine:	2013	Korea	RCT	Adults 18-59 years, ≥ 60 years	9 µg HA/strain	Single visit	60, 60	IM	15 µg HA/strain	Single visit	60, 60	Seroprotection rate 21 days post-vaccination: 18-59 years A(H1N1): ≈93% vs 100% A(H3N2): 100% vs ≈98%	Han

[28] All subjects had received seasonal influenza vaccination the previous year. Not mentioned if subjects were immunised in the last six months.

[29] 25-61% of subjects were previously immunised with a higher frequency in ID group. Not mentioned if subjects were immunised in the last six months.

	H1N1, H3N2, Influenza B[30]											B: 100% vs 100% ≥ 60 years: A(H1N1): ≈95% vs 88% A(H3N2): 100% vs ≈97% B: 100% vs 100% (numbers with ≈ in front were obtained from graphic and are therefore an approximation) AE: Local: induration 0/60 (0%) vs 0/60 (0%); ecchymosis 2/60 (3.3%) vs 2/60 (3.3%) Systemic: pyrexia 0/60 (0%) vs 0/60 (0%); malaise 14/60 (23.3%) vs 14/60 (23.3%); shivering 11/60 (18.3%) vs 7/60 (11.7%)	
	Bivalent whole-virus influenza vaccine: A/ New Jersey/76, A/Victoria/75	1979	Canada	RCT	Patients with chronic pulmonary diseases, 17-82 years[31]	40 CCA	Single visit	70	SC	200 CCA	Single visit	70	Seroprotection rate 4 weeks post-vaccination: A/New Jersey/76 53/70: (76%) vs 62/70 (89%) A/Victoria/75: 58/70 (83%) vs 56/70 (80%) AE: Local (pain or swelling) 26% vs 12% Systemic 14% vs 12%	Herbert
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B[32]	2012	Hong Kong	Open-label RCT	Elderly and chronically ill adults ≥ 21 years[33]	3 or 9 µg HA/strain	Single visit	63, 68, 65	IM	15 µg HA/strain	Single visit	66	Seroprotection rate 21 days post-vaccination: A(H1N1): 57/63 (90.5%) (ID3MJ), 59/68 (86.8%) (ID9MJ), 53/65 (81.5%) (ID9BDS) vs 47/66 (71.2%) A(H3N2): 57/63 (90.5%) (ID3MJ), 62/68 (91.2%) (ID9MJ), 60/65 (92.3%) (ID9DBS) vs 61/66 (92.4%) B: 53/63 (84.1%) (ID3MJ), 55/68 (80.9%) (ID9MJ), 53/65 (81.5%) (ID9BDS) vs 44/66 (66.7%) AE: local (grade 2 or 3): erythema 13/63, 14/68, 5/65 vs 0/66; swelling 0/63, 2.68, 1/65 vs 0/66; induration 0/63, 0/68, 0/65 vs 0/66; ecchymosis 0/63, 0/68, 0/65 vs 0/66; pain 0/63, 0/68, 0/65 vs 0//6 Systemic: 0/63, 2/68, 0/65 vs 0/66; headache 6/63, 4/68, 8/65 vs 5/66; malaise 13/63, 12/68, 13/65 vs 6/66; myalgia 9/63, 11/68, 10/65 vs 4/66; arthralgia 8/63, 5/68, 7/65 vs 4/66; severe AEs 0/63, 0/68, 0/65 vs 0/66	Hung
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2009	Korea	RCT	Patients with carcinoma, 19-64 years	7.5 µg HA/strain	Single visit	52	IM	15 µg HA/strain	Single visit	55	Seroprotection rate 4-6 weeks post-vaccination: A(H1N1): 96.1% vs 94.5% A(H3N2): 96.1% vs 98.1% B: 78.8% vs 81.8% AE: local: erythema 7/52 (13%) vs 0; swelling 10/52 (19.2%) vs 3/55 (5.5%); pain 0 vs 2/55	Jo

[30] Brand of ID vaccine differed from IM vaccine

[31] Part of the subjects had been previously immunised with no significant differences in frequencies between groups. Subjects had not been previously immunised with A/ New Jersey/76 or A/Victoria/75.

[32] Brand of ID vaccine differed from IM vaccine.

[33] 16.4% of subjects received H1N1 vaccine in the previous year with no significant differences in frequencies between groups. Not mentioned if subjects were immunised in the last six months.

												Systemic (fever or myalgia) 1/52 (1.9%) vs 2/55 (3.6%)	
	Trivalent purified surface antigen influenza vaccine: H1N1, H3N2, Influenza B	2004	Belgium	RCT	Healthy, 18-40 years[34]	3 µg HA/strain	Single visit	50	IM	15 µg HA/strain	Single visit	50	Seroprotection rate 21 days post-vaccination: A(H1N1): 84% vs 94% A(H3N2): 96% vs 98% B: 100% vs 100% AE: Local: erythema 96% vs 8%; pruritus 42% vs 4%; swelling 84% vs 10%; induration 34% vs 8% Systemic: no significant differences in systemic AEs.	Kenney
	Influenza vaccine, type unknown	2006	United States of America	RCT	HIV positive patients[35]	0.1 ml	Single visit	43	IM	0.5 ml	Single visit	26	Percentage of responders (>1-fold change in titre): 18/43 (42%) vs 9/26 (35%) AE: local erythema in ID group.	Khanlou
	Trivalent purified surface antigen influenza vaccine: H1N1, H3N2, Influenza B	2009	Switzerland	RCT	Healthy, 18–60 years	3 µg, 4.5 µg and 6 µg HA/strain	Single visit	55, 53, 55	IM	15 µg HA/strain	Single visit	54	Seroprotection rate 3 weeks post-vaccination: A(H1N1): 53/55 (96.4%) (ID3), 51/53 (96.2%) (ID4.5), 49/55 (89.1%) (ID6) vs 52/54 (96.3%) A(H3N2): 53/55 (96.4%) (ID3), 52/53 (98.1%) (ID4.5), 54/55 (98.2%) (ID6) vs 51/54 (94.4%) B: 36/55 (65.5%) (ID3), 44/53 (83.0%) (ID4.5), 40/55 (72.7%) (ID6) vs 46/54 (85.2%) AE: Local overall 69.6%, 73.2%, 78.6% vs 50%; more common in IM group: pain, ecchymosis. More common in ID group: erythema and induration. Systemic overall 23.2-33.9% vs 21.4%; most common were headache, pruritus and diarrhoea.	Künzi
	Trivalent whole-virus influenza vaccine: H1N1, H3N2, Influenza B	1981	Canada	Prospective cohort study	Ambulatory geriatric population[36]	1/5 of dose	Single visit	34	SC	7 µg HA/strain	Single visit	29	Seroprotection rate 2 weeks post-vaccination: A(H1N1): 30/34 (88%) vs 26/29 (90%) A(H3N2): 17/34 (50%) vs 11/29 (38%) B: 21/34 (62%) vs 18/29 (62%)	Lawee
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2008	Belgium/ Germany /Switzerland	RCT	Healthy, 18–57 years	9 µg HA/strain	Single visit	383	IM	15 µg HA/strain	Single visit	385	Seroprotection rate 21 days post-vaccination: A(H1N1): 92.4% vs 88.8% A(H3N2): 99.7% vs 98.7% B: 90.6% vs 85.5% AE: ≥ 1 EMEA reaction 15.6% vs 19%; induration 0.2% vs 0.0%; ecchymosis 1.5% vs 2.3%; fever 1.5% vs 0.8%; malaise 11.6% vs 14.4%; shivering 6.0% vs 7.4%	Leroux-Roels
	Trivalent split-virion and surface	2016	Belgium/ Germany	Open-label, RCT	Healthy elderly, ≥65 years	7.5 and 15 µg HA/strain	Single visit	61, 61, 60	IM	15 and 45 µg HA/strain	Single visit	63, 62, 63	Seroprotection rate 22 days post-vaccination: A(H1N1): 60/61 (98.4%) (IDinflexal7.5) vs 56/63 (88.9%) (IMinflexal15)	Levin

[34] Significant higher frequency of subjects receiving influenza vaccination in past 3 years in ID group. Not mentioned if subjects were immunised in the last six months.

[35] Not mentioned if subjects were immunised in the last six months.

[36] Not mentioned if subjects were immunised in the last six months.

	purified antigen influenza vaccine: H1N1, H3N2, Influenza B[37]											A(H3N2): 60/61 (98.4%) (IDinflexal7.5) vs 59/63 (93.7%) (IMinflexal15) B: 27/61 (44.3%) (IDinflexal7.5) vs 17/63 (27%) (IMinflexal15) AE: local overall 56/61 (91.8%) vs 29/62 (46.0%); erythema 54/61 (88.5%) vs 19/63 (30.2%); ecchymosis 0 vs 4/63 (6.3%); induration 34/61 (55.7%) vs 12/63 (19.0%); pain 15/61 (24.6%) vs 21/63 (33.3%) Systemic overall 5/61 (8.2%) vs 8/63 (12.7%); shivering 2/61 (3.3%) vs 4/63 (6.3%); malaise 2/61 (3.3%) vs 7/63 (11.1%); fever 3/61 (4.9%) vs 0/63 (0%)	
	Trivalent purified surface antigen influenza vaccine: H1N1, H3N2, Influenza B	2014	Switzerland	RCT	Healthy adults[38]	3, 4.5, 6 µg HA/strain	Single visit	55, 54, 53, 55	IM	15 µg HA/strain	Single visit	54	Seroprotection rate 21 days post-vaccination: A(H1N1): 53/55 (96.4%) (ID3), 52/54 (96.3%) (ID3MJ), 51/53 (96.2%) (ID4.5), 49/55 (89.1%) (ID6) vs 52/54 (96.3%) A(H3N2): 53/55 (96.4%) (ID3), 53/54 (98.1%) (ID3MJ), 52/53 (98.1%) (ID4.5), 54/55 (98.2%) (ID6) vs 51/54 (94.4%) B: 36/55 (65.5%) (ID3), 45/54 (83.3%) (ID3MJ), 44/53 (83.0%) (ID4.5), 40/55 (72.7%) (ID6) vs 46/54 (85.2%) AE: local: pain 10.9% (ID3MJ) vs 38.9%; induration 50.9% (ID3MJ) vs 16.7%; erythema more common in ID group. Systemic: no significant differences between groups.	Levin
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B[39]	2011	Canada/Switzerland	RCT	Lung transplant recipients, mean age 51.1 (ID) and 50.5 (IM) years	2 x 3 µg HA/strain	Single visit	41	IM	15 µg HA/strain	Single visit	43	Seroprotection rate (HAI titre of ≥ 1:32) 4 weeks post-vaccination: A(H1N1): 16/41 (39%) vs 12/43 (28%) A(H3N2): 34/41 (83%) vs 42/43 (98%) B: 12/41 (29%) vs 25/43 (58%) Efficacy: subjects developing influenza 2/41 (4.8%) vs 0; 1 subject influenza A(H3N2) 125 days, and 1 subject influenza A(H1N1) 116 days post-vaccination AE: local overall 17/41 (41%) vs 11/44 (25%); erythema 12/41 vs 5/44; pruritus 3/41 vs 0/41; induration 6/41 vs 5/41; tenderness 7/41 vs 9/41 Systemic: overall 3/41 (7%) vs 7/41 (16%); fever 0 vs 0; nausea 2/41 vs 1/42; fatigue 3/41 vs 4/41	Manuel
	Monovalent influenza vaccine: A/Aichi2/68	1971	Hong Kong	Prospective cohort study	Adults, 25-39 years (ID group) and mentally retarded children (SC group)	160 CCA	0, 4 weeks	14	SC	800 CCA	0, 4 weeks	77	Seroconversion rate 4 weeks after 1st vaccination: 12/14 (86%) vs 66/80 (86%) Seroprotection rate 4-6 weeks after 2nd vaccination: 12/14 (86%) vs 75/75 (100%)	Marks
	Monovalent	1958	United	Prospective	Healthcare	20 CCA	0, 1 week	95,	SC	20 CCA	Single	67,	Seroprotection rate 3 weeks after first vaccination (2 different	McCarrol

[37] Three different vaccine brands were used: Inflexal V, Fluad and Intanza.

[38] Not mentioned if subjects were immunised in the last six months.

[39] Two different vaccine brands were used: Fluviral and Mutagrip.

	influenza vaccine: Asian strain		States of America	cohort study	workers, 18-65 years	40 CCA		46		40 CCA 200 CCA	visit or 0, 1 week	50, 41, 39	titration methods used): 1st: 44.0% (2ID0.1), 89.0% (2ID0.2) vs 71.0% (2SC0.5), 53% (SC1) 2nd: 61.0% (2ID0.1), 76.0% (2ID0.2) vs 91.0% (2SC0.5), 86.0% (SC1)	I
	Trivalent split-virion and subunit influenza vaccine: H1N1, H3N2, Influenza B[40]	2017	Netherlands	Prospective cohort study	Healthcare workers, < 60 years	9 µg HA/strain	Single visit	1081	IM	15 µg HA/strain	Single visit	393	AE overall: 609/1081 (56%) vs 103/393 (26%) Local overall 570/1081 (53%) vs 90/393 (23%); AE in subjects that experienced local AE's: pain 453/570 (79%) vs 79/90 (88%); swelling 516/570 (91%) vs 70/90 (78%); erythema 520/570 (91%) vs 63/90 (70%); warm feeling 461/570 (81%) vs 66/90 (73%); pruritus 492/570 (86%) vs 63/90 (70%); subcutaneous haemorrhage 372/570 (65%) vs 55/90 (61%) Systemic 129/1081 (12%) vs 23/393 (6%); AE in subjects that experienced systemic AE's: headache 73/128 (57%) vs 15/23 (65%); fatigue 86/128 (67%) vs 19/23 (82%); myalgia 80/128 (63%) vs 19/23 (82%); joint pain 62/128 (48%) vs 14/23 (61%); flu-like symptoms 96/128 (75%) vs 20/23 (87%); lymphadenopathy 61/128 (48%) vs 14/23 (61%) Preference for route of administration: directly after vaccination 41.7% (ID) vs 17.6% (IM) vs 40.7% (no preference) Following year: 39.6% (ID) vs 30.3% (IM) vs 30.1% (no preference)	Meijer
	Trivalent influenza vaccine: H1N1, H3N2, Influenza B	2010	Iran	RCT	Healthcare workers, 22-50 years	6 µg HA/strain	Single visit	97	IM	15 µg HA/strain	Single visit	94	Seroprotection rate 21-28 days post-vaccination: A(H1N1): 97.9% vs 100% A(H3N2): 97.9% vs 98.9% B: 96.9% vs 96.8% AE: local: pain 2.1% vs 1.1%; erythema 8.2% vs 0%; induration 6.2% vs 0%; pruritus 1% vs 0% Systemic: headache 6.2% vs 9.6%; fever 4.1% vs 2.1%; myalgia 4.1% vs 3.2%; coryza 4.1% vs 3.2%	Metanat
	Monovalent whole virus and subunit influenza vaccine: A/USSR/92/77	1979	United Kingdom	RCT	Healthy volunteers 12-25 years and ≥26 years[41]	3, 9 µg HA and 2, 6, 7 µg HA	0, 4 weeks	Total 207	SC	5, 9, 16, 32, 47, 94 µg HA and 7, 10, 18, 21, 60, 66 µg HA	0, 4 weeks	Total 535	Seroprotection rate 4 weeks after 1st dose: Whole virus vaccine: 12-25 years: 44% (ID3), 47% (ID4) vs 47-95% (SC16-94) ≥26 years: 93% (ID3), 85% (ID9) vs 92-100% (SC16-94) Aqueous subunit vaccine: 12-25 years: 41% (ID2), 32% (ID6) vs 24-63% (SC10-60) ≥26 years CTAB: 80% (ID2), 91% (ID6) vs 92-100% (SC21-60); Triton: 97% (ID2), 97% (ID7) vs 93-100% (SC18-66) Seroprotection rate 4 weeks after 2nd dose: Whole virus vaccine: 12-25 years: 61% (ID3), 70% (ID9) vs 94-100% (SC16-94) Aqueous subunit vaccine:	Nicholson

[40] Different vaccine brands were used in ID (Intanza=split-virion) and IM group (Influvac=subunit, Vaxigrip=split-virion).

[41] Not mentioned if subjects were immunised in the last six months.

												12-25 year: 65% (ID2), 40% (ID6) vs 33-82% (SC21-6)	
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B[42]	2014	France	Open-label RCT	Healthy, 18-40 years	9 µg HA/strain	Single visit	38	IM	15 µg HA/strain	Single visit	42	Seroprotection rate 21 days post-vaccination: A(H1N1): ≈98% vs ≈98% A(H3N2): 100% vs ≈98% B: ≈75% vs ≈95% (numbers with ≈ in front were obtained from graphic and are therefore an approximation)	Nougarede
	Trivalent influenza vaccine: A/England, B/Berkeley or B/Vic, B/HK[43]	1974	United Kingdom	Prospective cohort study	Boarding schoolboys and girls	60, 15, 15 IU of A/Eng, B/Berk, B/HK, resp. or A/Eng, BVic, B/HK, resp.	Single visit	50	SC	400, 100, 100 IU of A/Eng, BVic, B/HK, resp.	Single visit	37	Seroconversion rate 3 weeks post-vaccination: A/Eng/42/72: 12/50 (24%) vs 14/37 (38%) A/Eng/1/68: 10/50 (20%) vs 10/37 (27%) B/HK/5/72: 7/50 (14%) vs 8/37 (22%)	Payler
	Monovalent influenza vaccine: A2/Aichi/2/68	1970	United States of America	Prospective cohort study	Female nurse students 17-22 years[44]	80 CCA	Single visit	34	SC	400 CCA	Single visit	71	Seroconversion rate 4-5 weeks days post-vaccination: 27/34 (79%) vs 63/71 (89%) AE: local reactions (induration, erythema and soreness of at least 4 hr) 7/35 (20%) vs 15/80 (19%)	Phillips
	Polyvalent Influenza vaccine: PR8 type A, Asian/57, Asian/62, Ann Arbor 1/57, Great Lakes 1739/54, Maryland B	1964	United States of America	Prospective cohort study	Members of domiciliary units of Veterans Hospital, 50-80 years[45]	10 CCA	Single visit	60	SC	25, 50, 100 CCA	Single visit	62, 59, 56	Seroprotection rate 4 weeks post-vaccination: PR8 type A: 85.0% vs 91.9% (SC0.25), 91.5% (SC0.5), 87.5% (SC1.0) Asian/57: 70.0% vs 87.1% (SC0.25), 86.4% (SC0.5), 78.6% (SC1.0) Asian/62: 56.7% vs 66.1% (SC0.25), 89.8% (SC0.5), 91.1% (SC1.0) Ann Arbor 1/57: 68.3% vs 69.4% (SC0.25), 83.1% (SC0.5), 73.2% (SC1.0) Great Lakes 17: 39/54 85.0% vs 87.1% (SC0.25), 93.2% (SC0.5), 89.3% (SC1.0) Maryland B: 78.3% vs 77.4% (SC0.25), 84.7% (SC0.5), 87.5% (SC1.0)	Saslaw
	Trivalent influenza vaccine: H1N1, H3N2, Influenza B	1967	United States of America	Prospective cohort study	Medical students	10 CCA/ strain 20 CCA	Single visit	47, 47	SC	100 CCA/strain 200 CCA	Single visit	40, 41	Seroconversion rate 4 weeks post-vaccination: 1963-64 vaccine (Asian/57, Asian/62): 38.3% vs 40.0% 1964-65 vaccine (Asian/62): 45.7% vs 38.5%	Saslaw
	Polyvalent influenza	1963	United States of	Prospective cohort	Members of domiciliary	10, 20, 10, 10 CCA IU	Month 0, 3	269	SC	100, 200, 100, 100	Month 0, 3	293	Seroprotection rate 3 months after 1st vaccination: PR8: 176/269 (65.4%) vs 210/293 (71.7%)	Saslaw same

[42] Different vaccine brands were compared for ID (Intanza) and IM (Vaxigrip) group.

[43] Different vaccine brands with different strains were compared for ID (Admune (B/Vic strain) or Influvac (B/Berkely)) and IM (Admune (B/BVic strain)).

[44] Not mentioned if subjects were immunised in the last six months.

[45] Subjects were previously immunised with influenza vaccine 1 and 2 years before and participated in Saslaw '63. Not mentioned if subjects were immunised in the last six months.

	vaccine: PR8, Asian, Ann Arbor1/57, Great Lakes		America	study	units of Veterans Hospital, 50-80 years[46]					CCA IU			Asian: 166/269 (61.7%) vs 231/293 (78.9%) Ann Arbor: 143/269 (53.2%) vs 232/293 (79.2%) Great Lakes: 165/269 (61.3%) vs 215/293 (73.4%) Seroprotection rate 5 weeks after 2nd vaccination: PR8: 67.1% vs 74.5% Asian: 59.% vs 79.8% Ann Arbor: 1/57 58.9% vs 84.0% Great Lakes: 65.8% vs 78.7%	study as Slutzker '63, but presenting immunogenicity results
	Trivalent split-virion and subunit influenza vaccine: H1N1, H3N2, Influenza B[47]	2016	Korea	Open-label RCT	HIV infected adults,18-60 years[48]	9, 15 µg HA/strain	Single visit	30 and 28	IM	15 µg HA/strain	Single visit	28	Seroprotection rate 1 month post-vaccination: A(H1N1): 24/30 (80.0%) (ID9) vs 25/28 (89.3%) A(H3N2): 21/30 (70.0%) (ID9) vs 21/28 (75.0%) B: 11/28 (36.7%) vs 19/30 (67.9%) AE: tenderness, erythema and muscle aches more common in ID groups. No difference of incidence of systemic AE between groups.	Seo
	Polyvalent influenza vaccine: PR8, Asian, Ann Arbor1/57, Great Lakes	1963	United States of America	Prospective cohort study	Members of domiciliary units of Veterans Hospital, 50-80 years[49]	10, 20, 10, 10 CCA IU	Month 0, 3	269	SC	100, 200, 100, 100 CCA IU	Month 0, 3	293	AE: no reaction 214/293 (73.0%) vs 227/314 (72.1%) Painful arms 8% vs 18%; swollen arms 4% vs 5%; erythema 9% vs 4%;	Slutzker, same study as Saslaw '63, but presenting safety results
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2013	Korea	RCT	Healthy, 18-30 years[50]	3, 7.5 µg HA/strain	Single visit	30, 30	IM	15 µg HA/strain	Single visit	32	Seroprotection rate 1 month post-vaccination: A(H1N1): 80.0% (ID3), 90.0% (ID7.5) vs 87.5% A(H3N2): 70.0% (ID3), 90.0% (ID7.5) vs 84.4% B: 60.0% (ID3), 60.0% (ID7.5) vs 71.9%	Song
	Monovalent influenza vaccine: A/Aichi/2/68	1969	United States of America	Prospective cohort study	Resident patients in a home for the aged	65 CCA	Week 0, 2 or 4	26, 25	SC	65 CCA, 160 CCA, 320 CCA	Week 0, (2 or 4)	Total 211	Seroconversion rate 2 weeks after initial vaccination: A2/Aichi2/68: 18/26 (69%) (ID2w), 23/25 (92%) (ID4w) vs 12/25 (48%) (160SC2w), 20/28 (71%) (160SC4w), 16/24 (67%) (320SC2w), 18/26 (69%) (320SC4w) Seroconversion rate 4 weeks after initial vaccination: A2/Aichi2/68: 22/26 (85%) (ID2w), 20/25 (80%) (ID4w) vs 17/25 (68%) (160SC2w), 19/28 (68%) (160SC4w), 19/24 (79%) (320SC2w), 17/26 (65%) (320SC4w)	Tauraso

[46] 49.1% of subjects were previously immunised. Not mentioned if subjects were immunised in the last six months.

[47] Different vaccine brands were compared for ID (IDflu9mg) and IM (Agrippal) group.

[48] Not mentioned if subjects were immunised in the last six months.

[49] 49.1% of subjects were previously immunised. Not mentioned if subjects were immunised in the last six months.

[50] Not mentioned if subjects were immunised in the last six months.

												Seroconversion rate 6 weeks after initial vaccination: A2/Aichi2/68: 22/26 (85%) (ID2w), 21/25 (84%) (ID4w) vs 21/25 (84%) (160SC2w), 19/28 (68%) (160SC4w), 17/24 (71%) (320SC2w), 20/26 (77%) (320SC4w)	
	Trivalent split-virion influenza vaccine: H1N1, H3N2, Influenza B	2009	Belgium	RCT	Healthy, 18–40 years	3, 6 µg HA/strain	Single visit	60, 60	IM	15 µg HA/strain	Single visit	60	Seroprotection rate 21 days post-vaccination: A(H1N1): 93% (ID3), 93% (ID6) vs 97% A(H3N2): 98% (ID3), 97% (ID6) vs 98% B: 82% (ID3), 85% (ID6) vs 76% AE: Local: pain 34/60 (56.6%) (ID3), 41/60 (68.3%) (ID6) vs 42/60 (70%); erythema 60/60 (100%) (ID3), 60/60 (100%) (ID6) vs 15/60 (25%); swelling 60/60 (100%) (ID3), 60/60 (100%) (ID6) vs 7/60 (11.7%); induration 53/60 (88.3%) (ID3), 55/60 (91.7%) (ID6) vs 11/60 (18.3%); ecchymosis 2/60 (3.3%) (ID3), 1/60 (1.7%) (ID6) vs 1/60 (1.7) Systemic: headache 38.3% (ID3), 30.0% (ID6) vs 28.3%; malaise 25.0% (ID3), 8.3% (ID6) vs 18.3%; myalgia 15.0% (ID3), 3.3% (ID6) vs 16.7%	Van Damme
	Polyvalent influenza vaccine: Swine, PR8, AA, Taiwan, Lee, Md	1972	Czechoslovakia	Prospective cohort study	Children 3-6 years, secondary school students 16-17 years	20 CCA, 20 CCA, 10 CCA, 30 CCA, 10 CCA, 30 CCA	Single visit	32, 43	SC	100 CCA, 100 CCA, 200 CCA, 150 CCA, 50 CCA, 150 CCA	Single visit	33, 42	AE (48-hour post-vaccination): children 3-6 years erythema 11/32 (34%) vs 10/33 (30%); fever 0 vs 0. Children 16-17 years: erythema 13/43 (30%) vs 5/42 (12%); fever 0/42 vs 1/43 (2%)	Zavadova
Japanese encephalitis[51]													
	Mouse brain-derived inactivated JE vaccine	1993	Thailand	RCT	Healthy adults, partly immune	1 x 0.1 ml 2 x 0.1 ml 3 x 0.1 ml	1 visit	54, 58, 53	SC	1.0 ml	Single visit	56	Seroconversion rate 90 days post-vaccination: Subjects non-immune before vaccination: 11/27 (41%) (ID1), 23/40 (58%) (ID2), 15/29 (52%) (ID3) vs 18/33 (55%) Subjects immune before vaccination: 18/27 (67%) (ID1), 15/18 (83%) (ID2), 24/24 (100%) (ID3) vs 21/23 (91%)	Intralawan
	Mouse brain-derived inactivated JE vaccine	2006	Australia	Open-Label RCT	Healthy Australian soldiers	1 x 0.1 ml 2 x 0.1 ml	Week 0, 1, 4	68, 75	SC	1.0 ml	Week 0, 1, 4	61	Seroconversion 2 weeks after last dose: 1st battalion: 24/68 (37%) (1ID), 54/75 (72%) (2ID) vs 46/61 (75%) Pooled results of 1st and 2nd battalion: 237/347 (68.3%) (2ID) vs 46/61 (75%) AE: any: 37/243 (15.2%), 45/249 (18.1%) vs 47/213 (22.1%); arm pain 0-5%, 0-4% vs 7-14%	Kitchener
Measles[52]													
	Live attenuated	1968	United States of	Prospective cohort	Children, 5 years	200 $TCID_{50}$ (=0.1 ml)	1 visit	90	SC	1000 $TCID_{50}$ (=0.5 ml)	Single visit	98, 92	HI titres ≥1:10 3 weeks post-vaccination: 43/90 (47.8%) vs 83/98 (84.7%) (SC0.5)	Calafiore

[51] Primary outcome measure Japanese encephalitis: seroconversion rate defined as percentage of subjects with post-vaccination neutralizing antibody titres >1:10.

[52] Primary outcome measurement measles: seroprotection rate defined as percentage of subjects with post-vaccination measles neutralizing antibody titres ≥120 IU/L.

	measles vaccine: Schwarz strain		America	study						200 $TCID_{50}$ (=0.1 ml)			
	Live attenuated measles vaccine	1983	Kenya	Prospective cohort study	Children, 9-23 months	0.1 ml	1 visit	21	SC	0.5 ml	Single visit	23	Seroprotection rate (HI titres ≥1:24) 4 weeks post-vaccination: 19/21 (90.5%) vs 17/23 (73.9%) GMT: 51.3 vs 36.6	Kok
	Live attenuated measles vaccine: Schwarz and Beckenham 31 strain	1967	Hong Kong	RCT	Healthy children, 9-24 months	200 $TCID_{50}$ (=0.1 ml) 178 $TCID_{50}$ (=0.1 ml)	1 visit	91, 96	IM	1000 $TCID_{50}$ (=0.5 ml) 890 $TCID_{50}$ (=0.5 ml)	Single visit	369, 354	Seroconversion rate (definition not mentioned) 1 month post-vaccination: Neutralization test: Schwarz: 74.72% vs 98.37% Beckenham: 86.45% vs 96.51% HI test: Schwarz: 73.63% vs 96.15% Beckenham: 83.87% vs 95.40% AE: overall S: 68.13% vs 68.83% B: 73.96% vs 82.20%; fever S: 42.86% vs 35.23%, B: 33.33% vs 27.97%; rash S: 0% vs 1.36%, B: 0% vs 0%; conjunctivitis S: 0% vs 0.81%, B: 0% vs 0%; Koplik's spots S: 0% vs 0%, B: 1.04% vs 0.28%	Hong Kong Measles Vaccine Committee
	Live attenuated measles vaccine: Beckenham 31 strain	1971	Uganda	Prospective cohort study	Children, ≤ 6 years	100 $TCID_{50}$ (0.05 ml)	1 visit	52	IM	200 $TCID_{50}$ (=0.5 ml) or 100 $TCID_{50}$ (=0.5 ml)	Single visit	22	Seroconversion (HI) rate (definition not mentioned) 1 month post-vaccination: 7/52 (14%) vs 16/22 (72.7%) (IM200)	Stanfield
	Live attenuated measles vaccine: Edmonston-Zagreb strain	1984	Gambia	Prospective cohort study	Infants, 4-6 weeks[53]	2 x 0.1 ml (= total 11400 PFU)	1 visit	21	SC	0.5 ml (=39800 PFU)	Single visit	21	Mean titre 16 weeks post-vaccination: HI test: after 6 weeks: 7.5 vs 7.4, after 16-24 weeks: 6.6 vs 6.8 Neutralization test: after 6 weeks: 7.5 vs 8.3; after 16-24 weeks: 1.3 vs 2.1 Efficacy: during follow-up of 12-17 months no child has had measles AE: ID group 3 children with low-grade fever.	Whittle
	Measles vaccine, type unknown	1980	Zaire (nowadays Democratic Republic of Congo)	Prospective cohort study	Children, without previous measles disease	2 x 0.1 ml	1 visit	34	SC	0.5 ml	Single visit	30	Seroconversion rate (defined as 10-fold increase of HI antibody levels) after 1 month: 18/34 (53%) vs 24/30 (80%)	Wood
Meningococcal disease[54]														

[53] Part of the children had previously had measles disease and therefore already had antibody tires prior to immunisation.

[54] Primary outcome measure meningococcal vaccine: Group C: seroprotection defined as hSBA titre ≥ 4 or SBA titre ≥ 8. Group A, B, W135 and Y: no primary outcome measure available.

	Group A + C meningococcal polysaccharide	1984	Gambia	Prospective cohort study	Schoolboys, 8-9 years[55]	10 µg 10 µg + tetanus toxoid	1 visit	25, 25 (+tetanus toxoid)	SC	50 µg 10 µg	1 visit	25, 25	HI antibody titres pre- and 4 weeks post-vaccination: Group A: 4.0 and 5.1 (ID), 3.9 and 5.7 (IDTT) vs 4.3 and 7.6 (SC50) Group C: 2.4 and 4.6 (ID), 2.0 and 4.9 (IDTT) vs 2.1 and 5.6 (SC50)	Hassanking
Polio[56]													
	Trivalent IPV	2015	Bangladesh	Open-label RCT	Healthy infants	0.1 ml	6 and 14 weeks of age + OPV week 18	152	IM	0.5 ml	6 and 14 weeks of age + OPV week 18	156	Seroconversion rate 1 month after 2nd dose: PV1: 133/152 (87.5%) vs 148/156 (94.9%) PV2: 123/152 (80.9%) vs 142/156 (91%) PV3: 135/152 (88.8%) vs 152/156 (97.4%) AE: no AEs attributed to vaccines.	Anand
	Trivalent IPV	2012	The Philippines	Open-label RCT	Healthy infants	8, 1.6, 6.4 D antigen units (type 1, 2, 3, resp.) = 0.1 ml	6, 10, 14 weeks of age + booster 15-18 months	109	IM	40, 8, 32 D antigen units (type 1, 2, 3, resp.) =0.5 ml	6, 10, 14 weeks of age + booster 15-18 months	114	Seroconversion rate 1 month after 3rd dose: PV1: 108/109 (99.1%) vs 112/114 (98.2%) PV2: 103/109 (94.5%) vs 112/114 (98.2%) PV3: 104/109 (95.4%) vs 114/114 (100%) AE: Local: tenderness 60.2% vs 50.4%; erythema 69.5% vs 29.1%; swelling 21.2% vs 9.4% Systemic: fever 5.9% vs 10.3%; vomiting 15.3% vs 21.4%; crying abnormal 33.9% vs 30.8%; drowsiness 37.3% vs 35.0%; appetite loss 16.1% vs 19.7%; irritability 49.2% vs 43.6%	Cadorna-Carlos
	Trivalent IPV	2010	Oman	RCT	Healthy infants	0.1 ml	2, 4, 6 months of age + OPV 7 months	187	IM	40, 8, 32 D antigen units (type 1, 2, 3, resp.) =0.5 ml	2, 4, 6 months of age + OPV 7 months	186	Seroconversion rate 1 month after 3rd dose: PV1: 182/187 (97.3%) vs 186/186 (100%) PV2: 179/187 (95.7%) vs 186/186 (100%) PV3: 183/187 (97.9%) vs 186/186 (100%) AE: serious adverse events (all requiring hospitalization) 18 vs 24; most common were diarrhoea and upper respiratory infection. Parents preference: 172/185 (93.0%) preferred ID vs 8/185 (4.3%) preferred IM vs 5/185 (2.7%) no preference	Mohammed
	Trivalent IPV	2019	Cuba	Randomised non-inferiority trial	Healthy infants	0.1 ml	4 and 8 months of age	28	IM	0.1 ml 0.2 ml 0.5 ml	4, 8 months of age	80, 78, 26	Seroconversion rate 1 month after 2nd dose: PV1 25/28 (89%) vs 100% PV2: 26/28 (93%) vs 100% PV3: 23/28 (82%) vs 100% AE: no serious adverse events occurred.	Resik
	Trivalent IPV	2010	Cuba	RCT	Healthy infants	0.1 ml	6, 10, 14 weeks of age	187	IM	40, 8, 32 D antigen units (type 1, 2, 3,	6, 10, 14 weeks of age	177	Seroconversion rate 1 month after 3rd dose: PV1: 99/187 (52.9%) vs 158/177 (89.3%) PV2: 159/187 (85.0%) vs 169/177 (95.5%) PV3: 129/187 (69.0%) vs 175/177 (98.8%)	Resik

[55] Not mentioned if subjects were previously immunised. High pre-immunisation titre probably because of two recent epidemics of group A meningococcal disease.

[56] Primary outcome measure IPV in infants: seroconversion defined as the change from seronegative (<1:8) to positive (≥1:8), or a four-fold rise in antibody titres after vaccination, adjusted for maternal antibody decay, assessed 30 days after completing vaccination series

									resp.) =0.5 ml			AE: local: erythema 1-13% vs 0-4%; induration 1.6-2.6% vs 0-1%; pain 0-0.5% vs 0-0.5% Systemic: fever 0-0.5% vs 0-1%	
	Trivalent IPV	2013	Cuba	RCT	Healthy infants	0.1 ml	4 and 8 months of age	157	IM	40, 8, 32 D antigen units (type 1, 2, 3, resp.) =0.5 ml	4 and 8 months of age	153	Seroconversion rate 1 month after last dose: PV1: 93.6% (147/157) vs 100% (153/153) PV2: 98.1% (154/157) vs 100% (153/153) PV3: 93.0% (146/157) vs 99.3% (152/153) AE: local: erythema 23.6-30.0% vs 1.3-2.0%; induration 7-8.9% vs 0.7-1.3%; infiltration (combination of erythema, induration, pain) 0-0.6% vs 0%; Systemic: fever: 0.6-1.3% vs 0-1.3%	Resik
	Trivalent IPV	2019	Bangladesh	Open-label RCT	Healthy infants	0.1 ml	6, 14, 22 weeks of age	270	IM (+ ID)	40, 8, 32 D antigen units (type 1, 2, 3, resp.) =0.5 ml	14, 22 weeks of age or 14 + 22 (ID) weeks or 6 + 22 (ID) weeks	271	Seroconversion rate 1 month after last dose: PV1: 98% (264/270) vs 100% (271/271) (IM) PV2: 96% (260/270) vs 99% (267/271) (IM) PV3: 99% (266/270) vs 99% (269/271) (IM) AE: none were attributed to use of vaccines.	Snider
Rabies[57]													
	Human diploid cell rabies vaccine	1980	France	Prospective cohort study	Veterinary students, 19-29 years	0.1 ml, 2 x 0.05ml, 0.1 ml + 1.0 ml SC	0, 4 weeks + booster after 1 year	28, 30, 22	SC	1 ml	0, 4 weeks + booster after 1 year	25	Mean VNA titres 4 weeks after 2nd dose: 5.32 IU/ml (1ID) and 4.74 IU/ml (2ID) vs 7.8 IU/ml AE: Local reactions: 0/58 vs 2/30 Axillar lymphadenopathy 1/58 vs 1/30	Ajjan
	Human diploid cell vaccine	1975	United Kingdom	Prospective cohort study	Healthy, 18-60 years	0.1 ml	0 and 4 weeks	19	IM	1 ml	0 and 4 weeks	16	Mean VNA titres 4 weeks after 2nd dose: 6.87 IU/ml vs 7.18 IU/ml Antibody titre >1.7 IU/ml: 19/19 vs 16/16 AE: Local: erythema 74-79% vs 0%; pruritus 33-43% vs 0%; swelling 33-57% vs 0% Systemic: Feeling ill 2-6/19 vs 1-2/15; headache 3-4/19 vs 1-4/15; abdominal pain 1/19 vs 0/15; wheezing 0/19 vs 1/15	Aoki
	Human diploid cell vaccine	1982	United States of America	RCT	Veterinary students and staff, 19-59 years	0.1 ml	Day 0, 7 and 28	26, 28	IM and SC	1 ml IM 0.1 ml SC 0.25 ml SC	Day 0, 7 and 28	18, 28	Seroprotection (defined as > 0.16 IU) 3 weeks after last dose: 100% in all groups. GMT 3 weeks after last dose: 7.44 IU/ml (IDNS), 3.05 IU/ml (IDJI) vs 12.87 IU/ml (IM) and 6.47 IU/ml (SC0.25) Local: 93.3% (s) and 66.7% (j.i.) vs 89.5% (IM) and 64.3% (SC) AE: local overall 93.3%, 66.7% vs 89.5%, 64.3%; lymphadenopathy 6.7%, 6.7% vs 15.8%, 7.1% Systemic: lymphadenopathy 0%, 0% vs 5.3%, 3.6%; headache	Bernard

[57] Primary outcome measure rabies vaccine: seroconversion rate defined as percentage of subjects with post-vaccination rabies virus neutralizing antibodies (RVNA) ≥0.5 IU/mL assessed 4 weeks after completing vaccination series.

												10%, 3.3% vs 5.3%, 9%; malaise 6.7%, 3.3% vs 5.3%, 7.1%; fever 6.7%, 0% vs 5.3%, 0%; myalgia 3.3%, 3.3% vs 5.3%, 3.6%; arthralgia 0%, 3.3% vs 5.3%, 0%; nausea 10%, 3.3% vs 0%, 0%; pruritus 3.3%, 0% vs 0%, 0%; urticaria 3.3%, 0% vs 0%, 0%; breathlessness, wheezing 3.3%, 0% vs 0%, 0%; diarrhoea 3.3%, 0% vs 0%, 0%; dizziness 0%, 0% vs 0%, 3.6%	
	Purified Vero cell rabies vaccine and purified chick embryo cell rabies vaccine	2016	India	Open-label RCT	Patients after possible rabies exposure, 5-77 years[58]	2 x 0.1 ml	PEP: Day 0, 3, 7 and 28	27, 27	IM	1 ml	Day 0, 3, 7, 14 and 28	27, 27, 31, 29	Seroconversion rate 14 days after last dose: Category II exposure: 27/27 (100%) (ID-PVRV) vs 27/27 (100%) (IM-PVRV) Category III exposure: 27/27 (100%) (ID-PVRV) vs 27/27 (100%) (IM-PVRV) AE: Local: category II: pain 31.0% vs 66.7%; erythema 44.8% vs 10.0%; oedema 34.5% vs 6.7%; pruritus 34.5% vs 6.7%. Category III: pain 12.5% vs 43.3%; erythema 3.1% vs 0%; oedema 3.1% vs 3.3%; pruritus 5.3% vs 3.3% Systemic: frequency of events was not statistically different across groups; most of events were mild. Most common: asthenia, headache, myalgia, dizziness.	Bose
	Purified chick embryo cell vaccine and purified Vero cell rabies vaccine	2000	Thailand	RCT	Patients after possible rabies exposure[59]	2 x 0.1 ml (dose 1-3) 1 x 0.1 ml (dose 4-5)	PEP: Day 0, 3, 7, 30 and 90 days	59	IM	1 ml	Day 0, 3, 7, 14, 30 and 90	37	Seroconversion rate on day 14: 59/59 (ID-PCECV) vs 35/37 (IM-PCECV) GMT on day 14: 28.5 IU/ml (ID-PCECV) vs 12.3 IU/ml (IM-PCECV) Efficacy: no deaths in any of the groups. AE: 48% vs 33%. Most common: erythema, pain and/or swelling at site of injection, and fever.	Briggs
	Purified Vero cell rabies vaccine	1988	Thailand	Prospective cohort study	Children <15 years, after possible rabies exposure[60]	2 x 0.1 ml (dose 1-3) 1 x 0.1 ml (dose 4-5)	PEP: Day 0, 3, 7, 30 and 90 days	99	IM	0.5 ml	Day 0, 3, 7, 14, 30 and 90	467	Efficacy: no deaths in any of the groups. AE: Local: lymphadenopathy 10/99 vs 5/467; pain 2/99 vs 8/467; pruritus 7/99 vs 4/467; erythema 1/99 vs 3/467; swelling 1/99 vs 1/467; rash 2/99 vs 1/467; nodule 2/99 vs 0/467 Systemic: fever 3/99 vs 18/467; influenza-like 2/99 vs 15/467; headache 0/99 vs 2/467; asthenia 0/99 vs 10/467 Costs: 18 vs USD 45	Chutivongse
	Purified Vero cell rabies vaccine	2010	Brazil	RCT	Professionals at risk of rabies exposure, ≥ 18 years	0.1 ml	Day 0, 7 and 28	65	IM	0.5 ml	Day 0, 7 and 28	62	Seroconversion rate 10 days after last dose: 96.9% vs 100% AE after first injection (n of subjects): local: erythema 2 vs 1; stiffening 0 vs 1; pain 3 vs 4 Systemic: headache 1 vs 2; nausea 2 vs 1	Cunha
	Rabies vaccine, type unknown	2016	India	Follow-up study	Animal bite victims presenting to anti-rabies	2 x 0.1 ml	PEP: Day 0, 3, 7 and 28	14750 (2013)	IM	1 ml	Day 0, 3, 7, 14 and 28	1631	Costs of vaccine/victim/visit in INR: 63.9 (2013 ID) and 63.0 (2014 ID) vs 300 (2014 IM) Volume utilized/person/visit: 0.213 ml (2013 ID) and 0.210 ml (2014 ID) vs 1.00 ml 2014 IM)	Dhaduk

[58] Patients with Category III exposure all received HRIG 20 IU/kg.

[59] Some of the patients were also treated with HRIG; they were randomly assigned to both study groups.

[60] 47 children (8.3%) with severe exposures received RIG.

					vaccine clinics			and 17066 (2014)					
	Purified chicken embryo cell vaccine and Human diploid cell vaccine	1989	United States of America	RCT	Volunteers, 21-37 years	0.1 ml	Day 0, 7 and 28 + booster after 1 year	19, 20	IM	1 ml	Day 0, 7 and 28 + booster after 1 year	19, 20	GMT 22 days after 3rd dose: PCECV: 316 vs 619 (reciprocal titres) HDCV: 103 vs 231 (reciprocal titres) All subjects had RVNA titres of ≥ 1:11 AE: local reactions occurred in around 45% of subjects were not statistically different across groups. Systemic reactions were less common and did not statistically different across groups. Most common: malaise, headache and dizziness.	Dreesen
	(Conventional and purified) human diploid cell vaccine	1989	United States of America	RCT	Veterinary students and employees	0.1 ml	Day 0, 7 and 28 + booster after 2 years	26, 23	IM	1 ml	Day 0, 7 and 28 + booster after 2 years	25, 25	Seroconversion rate 21 days after 3rd dose: Conventional HDCV: 100% vs 100% Purified HDCV: 100% vs 100% AE: Local overall 85% (conv), 91% (pur) vs 60% (conv), 84% (pur); erythema 69% (conv), 83% (pur) vs 32% (conv), 44% (pur); pain 35% (conv), 30% (pur) vs 60% (conv), 90% (pur); swelling 31% (conv), 57% (pur) vs 16% (conv), 32% (pur); pruritus 54% (conv), 73% (pur) vs 4% (conv), 12% (pur); lymphadenopathy 4% (conv), 0% (pur) vs 16% (conv), 4% (pur); Systemic overall 15% (conv), 22% (pur) vs 32% (conv), 36% (pur); pruritus 4% (conv), 0% (pur) vs 4% (conv), 0% (pur); fever 0% (conv), 0% (pur) vs 4% (conv), 12% (pur); myalgia 4% (conv), 9% (pur) vs 20% (conv), 20% (pur); joint pain 0% (conv), 13% (pur) vs 4% (conv), 8% (pur); lymphadenopathy 12% (conv), 0% (pur) vs 0% (conv), 0% (pur); malaise 0% (conv), 0% (pur) vs 8% (conv), 8% (pur); headache 4% (conv), 0% (pur) vs 8% (conv), 16% (pur); dizziness 4% (conv), 0% (pur) vs 4% (conv), 0% (pur); nausea 0% (conv), 4% (pur) vs 4% (conv), 4% (pur); vomiting 0% (conv), 0% (pur) vs 4% (conv), 4% (pur); abdominal pain 0% (conv), 0% (pur) vs 8% (conv), 0% (pur); urticaria 0% (conv), 0% (pur) vs 0% (conv), 0% (pur);	Fishbein
	Human diploid cell rabies vaccine	1987	United States of America	RCT	Veterinary students	0.1 ml (10, 3 or 1% of standard dose)	Day 0, 7 and 28	28, 26, 22	IM	1 ml 0.1 ml (10 or 3% of standard dose)	Day 0, 7 and 28	26, 29, 23	Seroconversion rate 21 days after last dose: 26/26 (100%) (ID-10%) vs 25/25 (100%) (IM100%)	Fishbein
	Human diploid cell vaccine	1985	Sweden	Prospective cohort study	Healthy medical students and laboratory staff	0.1 ml	Day 0 and 30 + booster after 1 year	14	SC	1 ml	Day 0 and 30	14	Seropositivity (by ELISA, cut off 0.2, corresponding to 0.5 IU/ml) 1 month after 2nd dose: 14/14 vs 14/14 Rabies antibody titres: 30: 1.9 EU/mL vs 3.0 EU/mL AE: no systemic reactions were observed.	Grandien

	Purified Vero cell rabies vaccine	1998	Thailand	RCT	Patients after possible rabies exposure[61]	2 x 0.1 ml (dose 1-3) 1 x 0.1 ml (dose 4-5)	PEP: Day 0, 3, 7, 28 and 90	299	IM	0.5 ml	Day 0, 3, 7, 14 and 28	299	AE: local overall 120/299 vs 71/299; oedema 1/299 vs 1/299; pustule 2/299 vs 0/299; erythema 26/299 vs 1/299; induration 8/299 vs 0/299; pain 8/299 vs 0/299; pruritus 107/299 vs 8/299 Systemic overall 36/299 vs 41/299; asthenia 6/299 vs 4/299; fever 20/299 vs 8/299; headache 3/299 vs 3/299; influenza-like symptoms 2/299 vs 14/299; lymphadenopathy 1/299 vs 1/299; malaise 6/299 vs 5/299; myalgia 0/299 vs 0/299; nausea 0/299 vs 0/299; mild oedema of extremity 2/299 vs 1/299; joint and back pain 1/299 vs 2/299; generalized pruritus 0/299 vs 3/299; rash 0/299 vs 2/299; somnolence 0/299 vs 4/299; dizziness 4/299 vs 9/299 Efficacy: no deaths in any of the groups.	Jaiiaroensup
					Veterinary and nursing students	0.1 ml	Day 0, 7 and 28	300	IM	0.5 ml	Day 0, 7 and 28	300	AE: local overall 80/300 vs 58/300; including oedema pustule erythema induration pain; pruritus Systemic overall 40/300 vs 40/300; including asthenia, fever, headache, influenza-like symptoms, lymphadenopathy, malaise, myalgia, nausea, mild oedema of extremity, joint and back pain, generalized pruritus, rash, somnolence, dizziness	
	Purified chicken embryo cell vaccine	1999	Thailand	RCT	Veterinary students, mean age 19.0-20.0	1 x 0.1 ml 2 x 0.1 ml	0,7 and 28 days + booster one year later	52, 51	IM	1 ml	0,7 and 28 days + booster one year later	28	Seroconversion rate 62 days after 3rd dose: 22/52 (42%) (ID1), 49/51 (96%) vs 26/26 (100%)	Jaijaroensup
	Purified Vero cell rabies vaccine	2017	Netherlands	Dose finding RCT	Healthy volunteers, 18-65 years	1 x 0.1 ml (=0.6IU) 2 x 0.1 ml 3 x 0.1 ml	Single visit + 2 booster 1 year later	10, 5, 5	IM	0.5 ml (=3.2IU)	Single visit + 2 boosters 1 year later	10	Seroconversion rate 1 month after first dose: 9/10 (1ID), 5/5 (2ID), 5/5 (3ID) vs 9/10 AE: local: erythema 4/10, 3/5, 4/5 vs 0/10 Systemic: myalgia 2/10, 2/5, 1/5 vs 3/10; headache 3/10, 2/5, 0/5 vs 3/10; fatigue 1/10, 1/10, 1/10 vs 3/10	Jonker
	Purified chicken embryo cell vaccine	2012	Thailand	Prospective cohort study	Veterinary students and staff, 18-45 years	1 x 0.1 ml 2x 0.1 ml	Day 0, (7, 21) + 1 or 2 boosters after 1 year	36,39	IM	1 ml	Day 0 + 1 or 2 boosters after 1 year	33	Seroconversion rate 35 days after 1st dose: PVRV: 36/36 (100%) (3ID1), 30/39 (77%) (1ID2) vs 32/33 (97%)	Khawplod
	Purified Vero cell rabies vaccine and purified chicken embryo cell vaccine	2007	Thailand	RCT	Healthy volunteers, 8-40 years	2 x 0.1 ml	Day 0, 7 and 28, day 0, 3 and 7 or one visit	16, 16, 13	IM	1 ml	0, 3 and 7 days	20	Seroconversion rate after 1 year: 13/16 (ID0,7,28), 5/16 (ID0,3,7), 5/13 (ID0) vs 16/20 AE: minor pruritus and erythema at injection sites, no other AEs.	Khawplod
	Purified Vero cell rabies	2013	India	Open-label RCT	Healthy adults 18-50	0.1 ml	Day 0, 7 and 21	20	IM	1 or 0.5 ml	Day 0, 7 and 21	17, 17	Seroconversion rate 21 days after last dose: 20/20 (100%) vs 17/17 (100%)	Kulkarni

[61] Subjects with WHO category III exposures received either HRIG (50) or ERIG (155).

	vaccine				years							AE: local: pain 3/20 (15%) vs 4/20 (20%); erythema 3/20 (15%) vs 1/20 (5%); oedema 2/20 (10%) vs 0/20 (0%); pruritus 4/20 (20%) vs 0/20 (0%); induration 2/20 (10%) vs 0/20 (0%) Systemic: fever 2/20 (10%) vs 1/20 (5%); shivering 2/20 (10%) vs 1/20 (5%); faintness 0/20 (0%) vs 2/20 (10%); asthenia 2/20 (10%) vs 1/20 (5%); headache 5/20 (25%) vs 3/20 (15%); dizziness 0/20 (0%) vs 0/20 (0%); arthralgia 4/20 (20%) vs 4/20 (20%); myalgia 3/20 (15%) vs 3/20 (15%); nausea 1/20 (5%) vs 1/20 (5%); abdominal pain 0/20 (0%) vs 0/20 (0%)	
	Purified Vero cell rabies vaccine[62]	2019	India	Retrospective cohort study	Patients with history of animal bite	2 x 0.1 ml	PEP: Day 0, 3, 7 and 28	16,904	IM	1 ml	Day 0, 3, 7, 14 and 28	12,619	Costs per patient: 3.87 USD (2012) vs 12.27 USD (2010) Estimated as per 2018 rates: 2.40 USD vs 5.60 USD	Kundu
	Purified Vero cell rabies vaccine	1999	Vietnam	Open RCT	Healthy infants, 2-5 months	0.1 ml	2, 3 and 4 months of age	117	IM	0.5 ml	2 and 4 months of age	118	Seroconversion rate 1 month after last dose: 116/116 (100%) vs 117/117 (100%) AE[63]: local overall: 6% vs 0.8-3.4%; including erythema, pruritus Systemic overall 7.7-35% vs 11.9-40.7%; including insomnia, irritability, fever, unusual crying	Lang
	Purified Vero cell rabies vaccine	2010	France	Open-label RCT	Healthy adults 18-50 years	0.12 ml	Day 0, 7 and 21	10, 10, 10, 10	IM	0.5 ml	Day 0, 7 and 21	10	Seroconversion rate 28 days after last dose: 10/10 (N1mm), 10/10 (N2mm), 10/10 (N1.5mm), 10/10 (N3mm) vs 10/10 AE: minor local pain was common in IM group, not in ID group.	Laurent
	Human diploid cell rabies vaccine	1984	United States of America	Prospective cohort study	Special Forces soldiers	0.1 ml	Day 0, 7 and 28	85	IM	1 ml	Day 0, 7 and 28	9	GMT 3 weeks post-vaccination: 1.76 IU/ml vs 2.53 IU/ml ID: >0.45 IU/ml: 66/85 (78%) IM: ≥0.6 IU/ml: 9/9 (100%)	Lemon
	Purified chicken embryo cell rabies vaccine	2014	India	Retrospective cohort study	Patients after possible rabies exposure	2 x 0.1 ml	PEP: Day 0, 3, 7 and 28	1460	IM	1 ml	Day 0, 3, 7, 14, 28	1075	Compliance rate for completing schedule: 84.2% (1230/1460) vs 40% (432/1075) Vaccine cost: Rs. 280,600 (measured) vs between Rs. 782,230 to 501,630 (estimated)	Mankeshwar
	Purified chicken embryo cell vaccine and human diploid cell rabies vaccine	1987	United Kingdom	Prospective cohort study	Healthy students, 18-24 years	0.1 ml	Day 0, 7, 21 or day 0, 28, 56	11-15 each	IM	1 ml	Day 0, 7, 21 or day 0, 28, 56	11-15 each	GMT 3 weeks after 3rd dose: 6.1 IU/ml (PCECVID7,21), 12.0 IU/ml (PCECVID28,56) vs 8.4 IU/ml (PCECVIM7,21), 14.1 IU/ml (PCECVIM28,56), 13.7 IU/ml (IMHDCV7,21, 19.3 IU/ml (IMHDCV28,56) AE: local: pain 11% vs22.5%; erythema 71% vs 2%; swelling 35% vs 5%; pruritus 12.5% vs 2% Systemic: urticarial skin rashes 2 cases vs 2 cases	Nicholson
	Human diploid cell rabies vaccine	1978	United Kingdom	RCT	Volunteers potentially at risk of rabies exposure, 29-61 years	0.1 ml	Day 0, 28 and 56 + booster after 1 or 2 year	39	IM	1 ml	Day 0, 28 and 56 + booster after 1 or 2 year	38	GMT 1 month after 3rd dose: 10.3 IU/ml vs 17.5 IU/ml All subjects had RVNAs of ≥0.5 IU/mL. AE: local: erythema 91% vs 14%; pruritus/burning/stinging/pain 38% vs 17%; nodes 11% vs 8%	Nicholson

[62] Different brands compared: ChengDa (IM) vs Abhayrab (ID).

[63] Subjects received DTP-IPV simultaneously with rabies vaccines.

												systemic: fever/chills 3% vs 3%; malaise/aching 10% vs 2%; pruritus/rash 0% vs 2%; breathlessness/wheezing 2% vs 2%; gastrointestinal symptoms 8% vs 3%; headache 5% vs 6%; dizziness 1% vs 1%	
	Purified chicken embryo cell rabies vaccine	2009	Thailand	Open-label RCT	Healthy children, 12-18 months	0.1 ml	Day 0, (7), 28 + booster 1 year later	44, 44	IM	1 ml 0.5 ml	Day 0, 7, 28 + booster 1 year later	44, 45	Seroconversion rate 3 weeks after 3rd dose: 100% (ID2), 100% (ID3) vs 100% (IM1), IM0.5	Pengsaa
	Purified Vero cell rabies vaccine	1987	Thailand	RCT	Patients after low-risk exposure to rabies, 14-58 years	1 x 0.1 ml 2 x 0.1 ml 4 x 0.1 ml	PEP: Day 0, 3, 7, 28 On 28 1-site for all groups	14, 15, 14	IM	0.5 ml	Day 0, 3, 7, 14, 28	15	Seroconversion rate 1 week after last dose: 14/14 (ID1), 15/15 (ID2), 14/14 (ID4) vs 15/15 GMT 1 weeks after last dose: 4.96 IU/ml (ID1), 4.69 IU/ml (ID2), 10.73 IU/ml (ID4) vs 8.99 IU/ml AE (n of subjects): local: inflammatory reaction 1/14, 3/15, 3/14 vs 0/15; pruritus 7/14, 7/15, 9/14 vs 0/15; Systemic: febrile reaction 1/14, 1/15, 0/14 vs 3/15; lymphadenopathy 3/14, 3/15, 4/14 vs 1/15; headache 1/14, 2/15, 1/14 vs 1/15; malaise 0/14, 2/15, 2/14 vs 4/15; weakness 0/14, 2/15, 2/14 vs 2/15; dizziness 0/14, 0/15, 1/14 vs 1/15; nausea 0/14, 1/15, 0/14 vs 0/15	Phanuph ak
	Purified chicken embryo cell rabies vaccine	2017	United States of America	Non-blinded, prospective cohort study	Healthy adults, 20-60 years	0.1 ml (=0.25 IU)	Day 0 ,7, 21	30	IM	1 ml (=2.5 IU)	Day 0 ,7, 21	29	Seroconversion rate (defined as ≥0.1 IU/ml) 14 days after last dose: 30/30 (100%) vs 29/29 (100%) AE: local: erythema 75.8% vs 15.2%; tenderness 6.1% vs 57.6%; induration 64.5% vs 6.1%; pain 0% vs 45.5% Systemic: fever 9.1% vs 6.1%; fatigue 12.1% vs 21.2%; headache 27.3% vs 15.2%	Recuenco
	Purified Vero cell rabies vaccine	1998	Thailand	Open-label RCT	Healthy schoolchildren, 5-13 years	0.1 ml	Day 0 ,7, 28 + booster 1 year later	95	IM	0.5 ml	Day 0 ,7, 28 + booster 1 year later	95	Seroconversion rate 28 days after 3rd dose 98.9% vs 100% AE (day 28): local: pain 1% vs 0%; induration 40% vs 1%; pruritus 26% vs 0%; lymphadenopathy 22% vs 10% Systemic: fever 0% vs 0%; headache 0% vs 1%; rash 0% vs 0%	Sabchare on
	Rabies vaccine, type unknown	2015	India	Prospective cohort study	Patients after possible rabies exposure	2 x 0.1 ml	PEP: Day 0, 3, 7 and 28	521	IM	Unknown	Day 0, 3, 7, 14, and 28	215	Compliance rate for completing schedule: 401/521 (77%) vs 129/215 (60%) Major constraints: loss of wages 39/90 vs 26/54; forgotten dates 16/90 vs 9/54; cost incurred 13/90 vs 7/54; interference with working hours/school timings 10/90 vs 6/54; distance from the hospital 12/90 vs 6/54	Shankara iah
	Purified chicken embryo cell rabies vaccine	2005	India	Open-label RCT	Healthy, ≥ 18 years	2 x 0.1 ml (=0.943 IU)	PEP: Day 0, 3, 7, 14, and 28	45	IM	1 ml (=9.43 IU)	Day 0, 3, 7, 14, and 28	46	Seroconversion rate 62 days after last dose: 45/45 (100%) vs 46/46 (100%) AE (n of injections): local: pain 2/225 (0.9%) vs 10/230 (4.3%); pruritus 5/225 (2.2%) vs 0/230 (0%) Systemic: none	Sudarsha n
	(Chromatographically) purified Vero cell rabies	2013	Thailand	RCT	Healthy volunteers, 18-23 years	0.1 ml	Day 0, 7, 28 + 2 boosters after 1	32	IM	0.5 ml	Day 0, 7, 28 + 2 boosters after 1	31, 31	Seroconversion rate 2 weeks after 3rd dose: 100% (CPRV) vs 100% (CPRV), 100% (PVRV); GMT: 5.02 IU/ml (CPRV) vs 14.23 IU/ml (CPRV), 11.49 IU/ml (PVRV)	Tantawic hien

	vaccine						year				year		
	Human diploid cell rabies vaccine	1982	United Kingdom	Prospective cohort study	Volunteers potentially at risk of rabies exposure, 16-68 years	0.1 ml	Day 0, 28 and 56 + booster after 6, 12 or 24 months	36	IM	1 ml	Day 0, 28 and 56 + booster after 6, 12 or 24 months	37	Seroconversion rate 1 month after 3rd dose: 36/36 (100%) vs 37/37 (100%) GMT 1 month after 3rd dose: 10.4 IU/ml vs 18.7 IU/ml	Turner
	Purified Vero cell rabies vaccine	2017	Switzerland	RCT	Healthy, 18-50 years	0.1 ml	Day 0, 7, 28	21, 22	IM	0.5 ml	Day 0, 7, 28	21	Seroconversion rate 28 days after last dose: 21/21 (100%) (IDM), 22/22 (100%) (IDDJ) vs 22/22 (100%) AE: DebioJect less pain at needle insertion than Mantoux and IM route. No significant difference in other AEs.	Vescovo
	Purified Vero cell rabies vaccine	2008	United Kingdom	RCT	Healthy volunteers, 18-51 years	4 x 0.1 ml (dose 1) 2 x 0.1 ml (dose 2) 1 x 0.1 ml (dose 3-4) Total 0.9 ml	PEP: Day 0, 7, 28, 90	55	IM	0.5 ml Total 2.5 ml	Day 0, 3, 7, 14, 28, 90	56	Seroconversion rate on day 90: 55/55 (100%) (ID4), 56/56 (100%) (ID8), 58/58 (100%) (ID2) vs 56/56 (100%) AE: local: erythema 96.4%, 96.7%, 93.1% vs 25.0%; swelling 76.4%, 80.0%, 79.3% vs 14.3%; hardness 74.6%, 73.3%, 65.5% vs 16.1%; tenderness/pain 70.9%, 58.3%, 70.7% vs 55.4%; pruritus 47.3%, 48.3%, 48.3% vs 3.6%; lymphadenopathy 9.1%, 25.0%, 13.8% vs 0% Systemic (n of symptoms reported that are possibly/probably related to vaccine): shivery 7, 5, 4 vs 3; vomited 2, 0, 0 vs 0; muscular/joint 11, 13, 7 vs 4; headache 25, 23, 21 vs 9; diarrhoea 5, 2, 1 vs 0; rash 4, 4, 2 vs 1	Warrell
						8 x 0.05 ml (dose 1) 4x 0.1 ml (dose 2) 1x 0.1 ml (dose 3-4) Total 0.8 ml	PEP: Day 0, 7, 28, 90	58					
						2 x 0.1 ml (dose 1-3) 1 x 0.1 ml (3-4) Total 0.8 ml	PEP: Day 0, 3, 7, 28, 90	58					
	Human diploid cell rabies vaccine	1983	Thailand	RCT	Healthy volunteers, 14-67 years	8 x 0.1 ml, 4 x 0.1 ml	PEP: Day 0, 14, (91)	10 each	IM	1 ml	Day 0, 3, 7, 14, 28, (91)	10, 7,10, 11	IM group significant higher GMTs than ID group. SC group significant similar GMTs as ID group. AE (n of subjects): ID 8-site, 1-site vs IM 1-site, 2-site Local: pruritus 13/16 (ID8), 4/16 (ID1) vs 2/16 (IM1), 0/7 (IM2); pain 2/16 (ID8), 2/16 (ID1) vs 13/16 (IM1), 4/7 (IM2); erythema 12/16 (ID8), 4/16 (ID1) vs 1/16 (IM1) vs 0/7 (IM2); induration 5/15 (ID8), 6/16 (ID1) vs 1/16 (IM1), 0/7 (IM2); lymphadenopathy 12/16 (ID8), 5/16 (ID1) vs 4/16 (IM1), 4/7 (IM2) Systemic: fever 1/16 (ID8), 3/16 (ID1) vs 3/16 (IM1), 2/7 (IM2); headache 2/16 (ID8), 4/16 (ID1) vs 8/16 (IM1), 1/7 (IM2); weakness 2/16 (ID8), 0/16 (ID1) vs 1/16 (IM1), 0/7 (IM2)	Warrell
						1x 0.1 ml	PEP: Day 0, 3, 7, 14, 28, (91)		IM	2 x 1 ml, 1 x 1 ml	Day 0, 3, 14 and 91			
									SC	0.1 ml + 0.98 mg aluminium hydroxide	Day 0, 3, 7, 14, 28, (91)			
									SC	2 ml	14 consecutive days,			

											day 21, 28, 91			
	Purified Vero cell rabies vaccine	2013	Thailand	RCT	Healthy, 18-24 years	2 x 0.1 ml	Day 0, 21 + 2 boosters 1 year later	39	IM	0.5 ml (=4.8 IU)	Day 0, 7, 21 + 2 boosters 1 year later	16	Seroconversion rate 14 days after last dose: 39/39 (100%) vs 16/16 (100%) AE: local: pain 0-2.6% vs 6.3-37.5%; pruritus 7.7-23.1% vs 0-6.3%; erythema 15.4-43.6% vs 0%; Systemic: fever 0-2.6% vs 0-18.8%; dose day 21: 0% vs 0%	Wongsaroj
Varicella Zoster[64]														
	Live, attenuated varicella-zoster virus	2016	United States of America	RCT	Healthy adults, ≥ 50 years, with history of varicella	2 x 0.15 ml (full dose[65]) 1 x 0.1 ml (1/3, 1/10 or 1/27 of dose)	Single visit	34, 35, 34, 34	SC	0.65 ml 0.22 ml	Single visit	52, 34	gpELISA GMT 6 weeks postvaccination: 441 (ID1/3), 483 (ID1/10), 319 (ID1/27) vs 327 (SC0.65), 310 (SC0.22) GMFR 6 weeks postvaccination: 2.58 (ID1/3), 2.22 (ID1/10), 1.64 (ID1/27) vs 1.74 (SC0.65), 1.64 (SC0.22) AE: local overall: 79%, 63%, 56%, 56% vs 52%, 21% vs 13% (placebo); erythema 77%, 60%, 47%, 53% vs 31, 15% vs 10% (placebo); pain 24%, 26%, 15%, 18% vs 29%, 12% vs 0% (placebo); swelling 38%, 23%, 18%, 21% vs 25%, 12% vs 5% (placebo); induration 35%, 34%, 32%, 30% vs 10%, 6% vs 3% (placebo); pruritus 12%, 12%, 3%, 3% vs 2%, 6% vs 0% (placebo); haematoma anaesthesia, rash, scab 6%, 3%, 0%, 0% vs 6%, 0% vs 0% (placebo)	Beals
Yellow fever[66]														
	Live attenuated yellow fever 17D vaccine	2008	Netherlands	RCT	Healthy, ≥18 years	0.1 ml	Single visit	77	SC	0.5 ml	Single visit	78	Seroprotection rate 4 weeks post-vaccination: 77/77 (100%) vs 78/78 (100%) AE: local: erythema 82% vs 32%; swelling 68% vs 12%; pain 8% vs 19% Systemic: myalgia 16% vs 22%; fever 5% vs 10% Long-term effects described in Roukens, 2018[67]	Roukens

Abbreviations: DTP= diphtheria-tetanus-polio, HAV= hepatitis A virus, HBV= hepatitis B virus, HPV= human papillomavirus, ID= intradermal, IM= intramuscular, SC= subcutaneous, N=needle, NS= needle/syringe, JI= jet-injector, PJ= PharmaJet, MJ= MicronJet600TM, BDS = BD SoluviaTM device, CCA= chick cell-agglutinating, TCID= Tissue culture infective doses, GMT= geometric mean titre, AE= adverse events, SAE= serious adverse events, EMEA= European Medicines Evaluation Agency, RCT= randomized clinical trial

[64] Primary outcome measure HPV not available.

[65] 2 x 0. 15ml dose contained same amount of antigen as SC 0.65 ml dose.

[66] Primary outcome measure yellow fever: *seroprotection rate defined as percentage of subjects with post-vaccination* 80% virus neutralisation

[67] Roukens, A. H., van Halem, K., de Visser, A. W., & Visser, L. G. (2018). Long-term protection after fractional-dose yellow fever vaccination: follow-up study of a randomized, controlled, noninferiority trial. *Annals of internal medicine*, *169*(11), 761-765.

Supplementary Table 4: Critical appraisal of the included studies

Table 4a. Results critical appraisal randomised clinical trials.

Studies	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Selective reporting	Other sources of bias
Influenza vaccines							
Ansaldi 2012	Unclear	Unclear	High	High	Unclear	Unclear	Low
Arakane 2015	Low	Unclear	Unclear	Unclear	High	Low	Low
Auewarakul 2007	Low	Unclear	High	High	Low	Unclear	Low
Belshe 2004	Low	Unclear	High	High	Low	Unclear	Unclear
Belshe 2007	Low	Low	High	High	Low	Unclear	Low
Beran 2009	Low	Low	High	High	Low	Low	Low
Brown 1977	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Chi 2010	Low	Unclear	High	High	Low	Low	Low
Chiu 2009	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
Chiu 2007	Low	Low	High	High	Low	Unclear	Low
Chuaychoo 2016	Low	Low	High	Unclear	Low	Unclear	Low
Chuaychoo 2010	Low	Unclear	High	High	Unclear	Unclear	Low
Davies 1969	Low	Unclear	High	Low	Low	Unclear	Low
Della Cioppa 2014	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Esposito 2011	Low	Low	High	Low	Low	Unclear	Low
Frenck 2011	Unclear	Unclear	High	High	Unclear	Unclear	Low
Gelinck 2009	Low	Low	Unclear	Unclear	Unclear	Unclear	High
Gorse 2013	Unclear	Unclear	High	High	Low	Low	Low
Han 2013	Unclear	Unclear	High	High	Low	Low	Low
Herbert 1979	Low	Unclear	High	Low	Low	Unclear	Low
Hung 2012	Low	Unclear	High	High	Low	Low	Low
Jo 2009	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Kenney 2004	Low	Unclear	High	High	Unclear	Unclear	High
Khanlou 2006	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kunzi 2009	Low	Unclear	High	High	Low	Unclear	Low
Leroux-Roels 2008	Low	Unclear	High	High	High	Low	Low
Levin 2016	Low	Unclear	High	High	Unclear	Unclear	Low
Levin 2014	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Manuel 2011	Low	Unclear	Unclear	Low	Low	High	Low
Metanat 2010	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Nicholson 1979	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Nougarede 2014	Low	Unclear	High	High	Low	High	Low
Seo 2016	Low	Unclear	High	High	Low	Unclear	Unclear
Song 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Van Damme	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low

2009							
Hepatitis B vaccines							
Afzali 2003	Low	Low	High	Low	Low	Unclear	Low
Ahman 1993	Low	Low	Unclear	Unclear	Low	Unclear	Low
Argani 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Bryan 1990	Unclear	Low	High	Low	Unclear	Unclear	Low
Bunupuradah 2011	Unclear	Unclear	High	High	Low	Unclear	Low
Chanchairujira 2006	Unclear	Unclear	High	High	Low	Unclear	Low
Charest 2000	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Chau 2004	Low	Low	Unclear	Unclear	Low	Unclear	Low
Coberly 1994	Low	Low	Unclear	Unclear	Low	Unclear	Low
Coleman 1991	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low
Egemen 1998	Low	Low	High	Unclear	Low	Unclear	Low
Frazer 1987	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Ghabouli 2004	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
Gomber 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Gonzalez 1990	Unclear	Unclear	High	High	Low	Unclear	Low
Halsey 1986	Low	Low	Unclear	Unclear	Low	Unclear	Low
Henderson 2000	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Karahocagil 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Launay 2011	Low	Low	High	High	Low	High	Low
Lankarani 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Leonardi 1990	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Li Volti 1998	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Medeiros 2011	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Mettang 1996	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Miller 1989	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Parish 1991	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low
Redfield 1985	Low	Unclear	Low	Low	Low	Unclear	Low
Rezvan 2004	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Roozbeh 2005	Low	Low	Unclear	Unclear	Low	Unclear	Low
Sharifi-Mood 2008	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Tavanaee Sani 2014	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Turchi 1997	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Whittle 1991	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wistrom 1990	Unclear	Unclear	High	High	High	Unclear	Low
Yamashiki 1997	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Zuberi 1998	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Rabies vaccines							
Bernard 1982	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Bose 2016	Low	Low	High	High	Unclear	Low	Low
Briggs 2000	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low

Cunha 2010	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Dreesen 1989	Low	Low	Unclear	Unclear	Unclear	Unclear	Low
Fishbein 1989	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Fishbein 1987	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Jaiiaroensup 1998	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Jaiiaroensup 1999	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Jonker 2017	Low	Unclear	High	High	Low	Unclear	Low
Khawplod 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Kulkarni 2013	Low	Low	High	High	Low	Low	Low
Lang 1999	Low	Unclear	High	High	Low	Unclear	Low
Laurent 2010	Unclear	Unclear	High	High	Low	Unclear	Low
Nicholson 1978	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Pengsaa 2009	Unclear	Unclear	High	High	Unclear	Low	Low
Phanuphak 1987	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Sabchareon 1998	Unclear	Unclear	High	High	Low	Unclear	Low
Sudarshan 2005	Low	Unclear	High	High	Low	Unclear	Low
Tantawichien 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Vescovo 2017	Low	Unclear	High	High	Low	Unclear	Low
Warrell 2008	Low	Low	Unclear	Unclear	High	Unclear	Low
Warrell 1983	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wongsaroj 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Inactivated poliovirus vaccines							
Anand 2015	Low	Unclear	High	High	Unclear	Low	Low
Cadorna-Carlos 2012	Unclear	Unclear	High	High	Low	Low	Low
Mohammed 2010	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Resik 2010	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low
Resik 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Resik 2013	Unclear	Low	Unclear	Unclear	Low	Unclear	Low
Snider 2019	Low	Low	High	High	Low	Unclear	Low
Measles vaccines							
Hong Kong Measles Vaccine Committee 1967	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Hepatitis B vaccines							
Brindle 1994	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Other vaccines							
Nelson 2013	Low	Low	High	High	Low	High	Low

Intralawan 1993	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Kitchener 2006	High	Unclear	High	High	Unclear	Unclear	Low
Beals 2016	Low	Unclear	High	High	Low	Low	Low
Roukens 2008	Low	Low	Unclear	Unclear	Low	High	Low

Table 4b. Results critical appraisal prospective cohort studies.

Study	Representativeness cases	Selection controls	Ascertainment of exposure	Outcome not present at start	Comparability	Assess-ment of outcome	Time follow-up	Adequacy follow-up	Total
Influenza vaccines									
Boger 1957	★	★	-	-	-	-	★	★	3
Brown 1966	★	★	-	★	-	-	★	-	4
Bruyn 1959	★	★	-	-	-	-	-	★	4
Bruyn 1949	-	★	-	-	-	-	★	★	4
Lawee 1981	★	★	★	-	-	-	★	-	4
Marks 1971	-	-	-	★	-	-	★	-	2
McCarroll 1958	-	★	-	-	-	-	★	★	3
Meijer 2017	★	★	-	-	★	-	★	-	3
Payler 1974	-	★	-	★	★	-	★	★	4
Phillips 1970	★	★	-	★	-	-	★	-	4
Saslaw 1964	★	★	-	-	-	-	★	★	4
Saslaw 1967	-	★	-	★	-	-	★	★	4
Saslaw 1963	★	★	-	-	-	-	★	-	3
Slutzker 1963	★	★	-	-	-	-	★	-	3
Tauraso 1969	★	★	-	★	-	-	★	-	4
Zavadova 1972	-	★	-	-	-	-	★	-	2
Hepatitis B vaccines									
Carlsson 1999	★	★	-	★	-	-	-	★	4
Hayashi	-	★	★	★	★	-	★	-	4

1991									
Herbert 1989	★	★	-	-	★★	-	★	-	3
Mok 1989	-	★	★	★	★★	-	★	★	5
Mumtaz 2008	★	★	-	★	★★	-	★	-	4
Struve 1992	★	-	★	★	-	-	★	-	4
Wahl 1987	★	-	★	★	-	-	★	-	4
Rabies vaccines									
Ajjan 1980	★	★	-	-	-	-	★	-	3
Aoki 1975	★	★	-	★	-	-	★	-	4
Chutivongse 1988	★	-	-	-	-	-	★	★	3
Dhaduk 2016	★	★	-	-	★	-	★	-	4
Grandien 1985	★	-	-	★	-	-	★	★	4
Khawplod 2012	★	★	-	★	-	-	★	-	4
Kundu 2019	★	★	★	-	★★	-	★	★	6
Lemon 1984	★	★	-	★	-	-	★	-	4
Mankeshwar 2014	★	★	-	-	★	-	★	★	5
Nicholson 1987	★	★	-	★	-	-	★	-	4
Recuenco 2017	-	-	★	★	-	-	★	-	3
Shankaraiah 2015	★	★	-	-	-	-	★	★	4
Turner 1982	★	★	-	★	-	-	★	-	4
Measles vaccines									
Calafiore 1968	★	★	-	★	-	-	★	★	5
Kok 1983	★	★	-	-	-	-	★	-	3
Stanfield 1971	★	★	-	★	-	-	★	-	4
Whittle 1984	★	-	-	★	-	-	★	★	4
Wood 1980	★	★	-	★	-	-	★	-	4
Hepatitis A vaccines									
Carlsson 1996	-	-	-	★	-	-	★	-	2
Frösner	-	★	-	★	★★	-	-	★	3

2009									
Pancharoen 2005	★	★	-	★	★	-	★	★	5
Other vaccines									
Stanfield 1972	★	★	-	★	-	-	★	-	4
Dick 1966	-	-	-	-	-	-	★	-	1
Hassanking 1984	★	★	-	★	-	-	★	★	5