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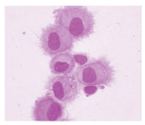

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Ian F. Cook

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REVIEW

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Subcutaneous vaccine administration – an outmoded practice

Ian F. Cook

Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia

ABSTRACT

Subcutaneous vaccine (SC) administration is an outmoded practice which complicates vaccine administration recommendations. Local adverse events following immunization (AEFIs) are a recognized determinant of vaccine hesitancy/refusal which can lead to an increased prevalence of vaccine-preventable disease.

This extensive narrative review provides high-grade evidence that intramuscular (IM) administration of all vaccine types [adjuvanted, live virus and non-adjuvanted (inactivated whole cell, split cell and subunit)] significantly reduces the likelihood of local adverse events. This, combined with moderate grade evidence that IM injection generates significantly greater immune response compared with SC injection, allows a strong recommendation to be made for the IM injection of all vaccines except BCG and Rotavirus.

This will simplify vaccination practice, minimize the inadvertent misadministration of vaccines and potentially improve public trust in vaccination.

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Literature review; outmoded practice; vaccine administration; subcutaneous; intramuscular; local reactogenicity; immunogenicity

Introduction

Vaccination has made, and will continue to make, a very significant contribution to world health.[1] However, adverse events following immunization (AEFTs), including injection site reactions (ISRs), are a significant driver[2,3] of vaccine hesitancy and refusal. The latter has resulted[4] in significantly increased risks of pertussis, varicella and pneumococcal infections in non-vaccinated children compared with vaccinated children.

Consequently, the definition and implementation of best vaccination practice (site, route and technique of injection) in terms of AEFIs (reactogenicity) and immune response (immunogenicity) are mandatory.

The current mantra[5] for vaccination practice has been to administer adjuvanted vaccines by intramuscular injection, live virus vaccines by subcutaneous injection and non-adjuvanted, inactivated whole cell, split and subunit vaccines by either route. This complicated regimen for vaccine administration is due to the unacceptable reactogenicity[6] of subcutaneously administered adjuvanted vaccines.

Evidence-based medicine (EBM) has been championed[7] as a way of improving the quality of patient care through a stepwise process of formulating the clinical questions to be answered, collating and appraising relevant data and defining the optimal response.

The purpose of this review is to use EBM to seek to rationalize the route of administration of vaccines given by SC, IM or either routes. The PICO elements[8] for this review are *P* = human vaccine recipients, I = intramuscular route of injection, C = subcutaneous route of injection and O = reactogenicity and immunogenicity of vaccines.

Methods

Searches were made using Pubmed. Google Scholar, Scopus, Embase, Biological Abstracts, Science Citation index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and Databases of Abstracts of Reviews of Effects (DARE) using the following search terms and their word variants; "vaccines," "administration," "subcutaneous," "intramuscular," "adverse reactions" and "immunogenicity." Manual searches were made from the following journals for the date in parenthesis to January 2020: Acta Paediatrica (1998), Acta Tropica (1980), American Journal of Medicine (1946), American Journal of Public Health (1971), American Journal of Tropical Medicine and Hygiene (1998), Annals of Internal Medicine (1995), Annals of Tropical Pediatrics (1999), Archives of Diseases of Childhood (1926), Bio Drugs (1998), Biologicals (1990), British Medical Journal (1991), Canadian Medical Association Journal (1911), Clinical Infectious Diseases (1999), Clinical and Vaccine Immunology (2006), European Journal of Pediatrics (1997), Infection and Immunity (1970), Journal of Pediatrics and Childhood (1998), Expert Review of Vaccines (2002), Human Vaccines (2005), Human Vaccines & immunotherapeutics (2012), Journal of Pediatrics (1995), Journal of Travel Medicine (1997), Journal of Tropical Pediatrics (1995), Lancet (1990), Medical Journal of Australia (2004), New England Journal of Medicine (1992), Pediatrics (1960), Pediatric Infectious Disease Journal (1995), Pediatrics International (1999), Public Health (1995), Scandinavian Journal of Infectious Disease (1997), Transactions of the Royal Society of Tropical Medicine and Hygiene (1920), Vaccine (1983) and to find additional studies where these were not abstracted.

CONTACT Ian F. Cook drifcook@bigpond.com; University of Newcastle, Callaghan, NSW 2308, Australia

Bibliographies of all relevant articles were searched for additional studies. All route comparative studies were included for analysis except those involving patients with chronic cutaneous, subcutaneous and muscular disorders and non-English language studies unless the full article was available for translation.

Results

Fifty-eight studies, which satisfied the inclusion criteria, were retrieved by the searches (51 by literature search, 7 by a manual search of appropriate Journals). They were divided into two study design groups, randomized trials and observational studies, as recommended in the GRADE guidelines.[9] The former has the potential to provide moderate to high-grade evidence whilst the latter could only give very low to low-grade evidence.

Local reactogenicity data were recorded as warmth, pain, redness and swelling. These and immunogenicity data were collated into vaccine groups; adjuvanted vaccines, live virus vaccines and non-adjuvanted vaccines (inactivated whole cell, split cell and subunit). These are presented as Tables 1–3 respectively.

Thirty studies[10–39] comparing intramuscular with subcutaneous administration of adjuvanted vaccines are presented in alphabetical order in Table 1 (6 anthrax[10–15], 1 botulinum toxoid,[16] 9 diphtheria and tetanus toxoid containing vaccines,[17–25] 4 hepatitis,[26–29] 7 hepatitis, [30–36] 1 herpes zoster,[37] 1 influenza[38] and 1 tick-borne encephalitis[39]). These studies could be subdivided into two groups; one with 21 randomized trials and the other with 7 observational studies and 2 randomized trials with unacceptable biases.

The 21 randomized trials being; 6 anthrax[10–15], 1 botulinum toxoid,[16] 5 diphtheria toxoid containing vaccines,[17,19-22] 3 hepatitis, [27–29] 3 hepatitis, [32,34,35] with 1 each of herpes zoster,[37] influenza[38] and tick-borne encephalitis[39] vaccines. There were 7 observational studies. These were 4 diphtheria/tetanus toxoid containing vaccines[18,23-25] and 3 hepatitis B vaccines.[30,33,36]

Two studies were excluded from the randomized trial group due to unacceptable biases. In the study, Ragni et al.[26] with hepatitis A vaccine, patients with hemophilia were given SC injection and compared with non-hemophilic siblings given IM injection. Whilst in the study by Probst et al.[31] with hepatitis B vaccine IM injection was given into the deltoid muscle and SC injection was given into the volar surface of the forearm.

Five studies[20–24] with diphtheria/tetanus toxoid were included where the vaccines were given with a 16 mm compared with 25 mm long needle as the former was considered to give SC injection and the latter to give IM injection.

In the 21 randomized trials, local reactogenicity data were provided in 20 studies. In 18 studies,[10–17,19–22,28,29,34,37-39] SC injection gave significantly greater rates of reaction than IM injection. In two other studies,[27,35] SC gave greater rates of reaction than IM injection but this did not reach statistical significance. Subcutaneous nodules were significantly more frequent for SC compared with IM injection for anthrax vaccine[10–15], botulinum toxoid vaccine[16] and a combination diphtheria toxoid vaccine.[17] In an observational study[18] with diphtheria toxoid containing vaccines, sterile abscess formation was significantly greater for SC compared with IM injection.

Pain immediately after injection (assessed with a pain analogue scale) was reported[11] to be significantly less for a 4 IM regimen of anthrax vaccine compared with a 4 SC regimen. Mark et al.[19] reported a similar trend but this did not reach statistical significance.

Immunogenicity data were recorded in 19 of the randomized trials.[10–12,14–17,19,20,22,27-29,32,34,35,37-39] Immunogenicity was greater for IM compared with SC injection in six studies[27,32,34,35,37,38] being significantly greater in the studies by Kishino et al.[34] (hepatitis B vaccine) and Ikeno et al.[38] (first dose of an influenza vaccine). In the remaining 13 studies[10–12,14–17,19,20,22,28,29,39], the immune response was comparable for IM and SC injection.

Seventeen studies comparing IM with SC administration of live virus vaccines are presented in alphabetical order in Table 2 (1 cytomegalovirus,[40] 1 herpes zoster,[41] 3 human Immunodeficiency virus,[42–44] 5 measles-mumps-rubella,[45–49] 1 Rift Valley fever,[50] 4 vaccinia,[51–54] 1 varicella[55] and 1 yellow fever[56]). Fifteen of the 17 studies were randomized trials.[40–45,47-55]

In 13 studies[40-44,47–53,55] out of the15 studies where reactogenicity data were provided, SC injection gave significantly greater rates of local reaction than IM injection. In the study by Lafeber et al.,[45] pain immediately after injection was greater with SC compared with IM injection but this did not reach statistical significance. Two subcutaneous nodules were observed following SC injection of one HIV vaccine[44] but not with IM injection.

IM and SC immunogenicity data were comparable in 15 randomized trials.[40–45,47-55] Immunogenicity was greater for IM compared with SC injection in one study.[54] In this study by Seaman et al.[54] immunogenicity was greater for IM compared with SC injection but this did not reach statistical significance.

Eleven studies comparing IM with SC administration of non-adjuvanted, inactivated (whole cell, split cell and subunit) vaccines are presented in alphabetical order in Table 3 (1 Hemophilus influenzae type b,[57] 6 influenza,[58–63] 1 leptospirosis,[64] 2 meningococcal,[65,66] 1 pneumococcal[67]).

Nine of the 11 studies were randomized trials.[58–65,67] In 8[58–60,62-65,67] of the 9 studies where reactogenicity data were provided, SC injection was associated with significantly greater rates of reaction than IM injection. In seven of the nine randomized trials where immunogenicity data were provided,[58–61,64,65,67] IM gave comparable results with SC injection in four studies.[61,64,65,67] In three studies,[58–60] antibody response was significantly greater for IM compared with SC injection for influenza A.

Discussion

This extensive narrative review provided high-grade evidence[9] that intramuscular (IM) injection significantly reduced the likelihood of local reactogenicity compared with subcutaneous (SC) injection. High-grade evidence was drawn from studies with all vaccine types (adjuvanted n = 18, live virus n = 13, non-adjuvanted inactivated (whole cell, split and subunit) n = 8).

The greater rates of reactogenicity were also seen for vaccines recommended[5] to be given by SC injection (quadrivalent

Table 1. Adjuvanted vaccines and intramuscular compared with subcutaneous administration – reactogenicity and immunogenicity.

Author	Study design	Patients	Intervention	Outcome
Wright et al[10]	Multi-center, randomized, double-blind, phase IV study.	Healthy US adults 18–61 y old n = 1564	Anthrax toxoid (AVA) vaccine administered according to 7 different protocols.	**Reactogenicity** IM < SC odds ratio for warmth, tenderness, erythema, induration, subcutaneous nodules. **Immunogenicity** IM not inferior to SC at 9 weeks post vaccination.
Marano et al[11]	Multi-center, randomized, double blind, phase IV study.	Healthy US adults. 18–64 y old n = 1005	Anthrax toxoid (AVA) vaccine administered according to 7 different protocols.	**Reactogenicity** IM < SC odds ratio for warmth, tenderness, erythema, induration, subcutaneous nodules and pain immediately after injection. **Immunogenicity** IM not inferior to SC administration.
Pittman et al[12] and Pittman[13]	Single-center, randomized, double-blind study.	Healthy US adults 18–61 y old n = 173	Anthrax toxoid (AVA) vaccine administered according to 7 different protocols.	**Reactogenicity** SC > IM odds ratio and $p < .05$ for warmth, tenderness, erythema, induration and subcutaneous nodule. **Immunogenicity** IM and SC comparable response[12] and no data.[13]
Campbell et al[14]	Single-center, randomized, open, phase I study.	Healthy US adults 18–40 y old. n = 80	Experimental Anthrax vaccine n = 60 Anthrax toxoid (AVA) vaccine, n = 20 IM n = 10 SC n = 10	SC > IM, $p < .05$ for subcutaneous nodules for AVA **Immunogenicity** Peak antibody, SC and IM comparable.
Pondo et al[15]	Multi-center, randomized, double-blind, phase IV study.	Healthy US adults 18–61 y old n = 1564	Anthrax toxoid (AVA) vaccine administered according to 7 different protocols.	**Reactogenicity** SC > IM, $p < .05$ for warmth, tenderness, erythema, induration and subcutaneous nodule. **Immunogenicity** IM not inferior to SC administration.
Edelman et al[16]	Randomized, double-blind, Phase II study.	US adults 18–40 y old n = 144	Clostridium botulinum type F toxoid vaccine. Data for 116 patients. Total number of injections n = 419 IM n = 167 SC n = 252	**Reactogenicity** SC > IM, $p < .5$ for subcutaneous nodules at primary injection. **Immunogenicity** Similar immune response in both SC and IM groups.
Carlsson et al[17]	Multi-center, randomized, open study.	Swedish infants, 3 months old. n = 287	D, DT, DT/inactivated polio (IPV) vaccine reconstituted with Haemophilus influenzae type b, Hib-T (Act-Hib) Data for: n = 365 (injections.) IM n = 184 SC n = 181	**Reactogenicity** SC > IM, $p < .05$ for pain, redness and subcutaneous nodules. **Immunogenicity** IM and SC comparable response
Volk et al[18]	Multi-center, observational study.	US children and adults. Ages not given. Adults, n = 1338. Children, n = 2126	Toxoid antigen 3 or 5 antigen preparations; 3 contained diphtheria, pertussis and scarlet fever; 5 contained the above 3 as well as tetanus and typhoid antigens. Data for injections, n = 9236 IM n = 6760 SC n = 2376	**Reactogenicity** SC > IM, $p < .5$ for sterile abscess (antigen cysts). **Immunogenicity** No data recorded
Mark et al[19]	Multi-center, randomized, open study.	Healthy Swedish infants, 3 months old. n = 252	Diphtheria/tetanus toxoid (DT) vaccine. Data for n = 243 IM n = 122 SC n = 121	**Reactogenicity** SC > IM, $p < .5$ for Redness and swelling. SC > IM for pain immediately after injection, but not statistically significant. **Immunogenicity** IM and SC comparable response.

(*Continued*)

Table 1. (Continued).

Author	Study design	Patients	Intervention	Outcome
Rothstein et al[20]	Multi-center, randomized, double-blind study.	US infants, 3 months old. n = 80	Diphtheria/tetanus/ acellular pertussis (DTaP) vaccine. Data for n = 80 IM n = 40 SC n = 40	**Reactogenicity** SC > IM, $p < .05$ for redness with 1st, 2nd and 3rd dose. **Immunogenicity** IM and SC comparable response.
Diggle & Deeks[21]	Multi-center, randomized, single-blind study.	UK infants, 4 months old. n = 119	Diphtheria/tetanus/ whole cell pertussis (DTwP) vaccine plus HibTITER vaccine. Data for 110 IM n = 53 SC n = 57	**Reactogenicity** SC > IM, $p < .05$ for redness and swelling. **Immunogenicity** No data recorded.
Diggle et al[22]	Multi-center, randomized, single-blind study.	UK infants 2, 3 and 4 months old. n = 564	DTwP/Hib administered concomitantly with meningococcal C vaccine into contralateral thigh. Data for n = 368 IM n = 189 SC n = 179	**Reactogenicity** Significantly less local reactions for IM compared with SC. **Immunogenicity** IM and SC comparable response.
Jackson et al[23]	Multi-center, open, non-randomized, post licensure safety study.	US children 4–6 y old. n = 1315	DTaP vaccine. Data for n = 1315 IM n = 985 SC n = 430	**Reactogenicity** SC > IM, $p < .05$ for redness, swelling and pain. **Immunogenicity** No data recorded
Ipp et al[24]	Multi-center, open, non-randomized study.	US children 18 months old. n = 205	DTwP- Polio vaccine. Route comparative study. Data for n = 131 IM n = 67 SC n = 64	**Reactogenicity** SC > IM, $p < .05$ for any reaction, any swelling. **Immunogenicity** No data provided.
Holt & Bousfield[25]	Multi-center, open, non-randomized study.	English children, age data not clearly defined. n = 895	Diphtheria toxoid vaccine (PTAP) Data for n = 895 IM n = 556 SC n = 339	**Reactogenicity** No data supplied. **Immunogenicity** IM gave significantly greater Schick conversion rate than SC injection.
Ragni et al[26]	Multi-center open, randomized, phase IV study.	US patients 2–18 y old with hemophilia compared with non-hemophilic siblings. n = 86	Inactivated, adjuvanted Hepatitis A (HAV) virus vaccine. Data for n = 86 IM n = 41 non- hemophilic siblings. SC n = 45, patients with hemophilia. M > F, $p = \leq 0.05$ hemophilia patients compared with non-hemophilic siblings.	**Reactogenicity** SC > IM, but $p > .05$ for swelling. **Immunogenicity** IM > SC. GMT, anti-HAV At 1 month: 233mIU/ml, 185mIU/ml At 8 months: 1022mIU/ml, 584mIU/ml
Frosner et al[27]	Two single- center, open, randomized pilot studies. One compared IM with SC administration.	Healthy Swiss adults, 18–45 y old. n = 115	Virosomal, adjuvanted hepatitis A vaccine. Data for n = 115 IM n = 71 SC n = 44	**Reactogenicity** SC > IM, but $p > .05$ for local reaction, pain and tenderness after primary vaccination. **Immunogenicity** Seroconversion: IM 95.8% vs SC 93.2%.
Fisch et al[28]	Two-center, open, randomized study	French adults 19–59.6 y old. n = 147	Inactivated, adjuvanted Hepatitis A (HAV) vaccine Given by IM or SC by needle injection: Data for n = 99 IM n = 50 SC n = 49	**Reactogenicity** SC > IM, $p < .05$ for local reaction. **Immunogenicity** IM and SC comparable response.

(*Continued*)

Table 1. (Continued).

Author	Study design	Patients	Intervention	Outcome
Parent du Chatelet et al[29]	Multi-center, randomized study	French adults, 18–60 y old. n = 138	Inactivated, adjuvanted Hepatitis A vaccine. Given by IM or SC needle injection. Data for n = 92 IM n = 46 SC n = 46	**Reactogenicity** SC > IM, $p < .05$ for redness. **Immunogenicity** IM and SC comparable response.
Ogawa et al[30]	Retrospective study.	Healthy Japanese University students, age 19–30 y old. n = 1135	Inactivated, adjuvanted Hepatitis B vaccine. Data for n = 620 IM n = 247 SC n = 373	**Reactogenicity** No data supplied. **Immunogenicity** Significantly better seroconversion IM vs SC At 2 months: IM 84.6%, SC 62.7% At 5 months: IM 93.5%, SC 77.0%
Probst et al[31]	Single center, randomized study.	Swiss hemodialysis adult patients, aged 47–50 ± 14 y old. n = 81	Adjuvanted, recombinant Hepatitis B vaccine. Data for n = 54 IM n = 27 Deltoid muscle. SC n = 27 Volar aspect of forearm.	**Reactogenicity** No data supplied. **Immunogenicity** Seroconversion: IM 76%, SC 69% GMT, HBsAb IM 443 mIU/ml SC 79 mIU/ml
Yamamoto et al[32]	Single center, open, randomized, phase I study.	Healthy Japanese adults ≥ 18 y old. n = 124	Adjuvanted, recombinant Hepatitis B vaccine. Data for n = 124 IM n = 62 SC n = 62	**Reactogenicity** No data supplied. **Immunogenicity** Seroconversion: IM 98%, SC 97% GMT, HBsAb, IM > SC, IM 791mIU/ml SC 168mIU/ml
Suzuki et al[33]	Single center, phase I, multicenter, phase II and III, open, non- randomized studies.	Japanese patients, children ≥ 10 y old and adults. n = 2137	Yeast derived, adjuvanted, recombinant, pre S and S containing Hepatitis B vaccine. Data for injections n = 4723 IM n = 2693 SC n = 2030	**Reactogenicity** SC > IM, $p < .05$ for pain, redness, swelling and warmth. **Immunogenicity** At 7 months: IM > SC GMT, HBsAb: IM 1396mIU/ml SC 748mIU/ml Anti-pre S2: IM1185mIU/ml SC 566mIU/ml
Kishino et al[34]	Multicenter, randomized study.	Healthy Japanese adults. Age 20–35 y old. n = 383	Recombinant, inactivated adjuvanted Hepatitis B vaccine. Data for n = 383 IM n = 94 SC n = 279	**Reactogenicity** SC > IM, $p < .5$ for pain, redness, swelling and pruritis. **Immunogenicity** Seroconversion: IM 98.7%, SC 91.6% GMT, HBsAb IM 1064mIU/ml SC 231.5mIU/ml
De Lalla et al[35]	Single center, open, randomized study.	Healthy Italian adults, age range 26.3–28 y old. n = 151	Adjuvanted, recombinant Hepatitis B vaccine. Data for n = 151 IM n = 75, SC n = 76	**Reactogenicity** SC > IM, $p > .05$ **Immunogenicity** Seroconversion: IM 88% SC 75%

(*Continued*)

Table 1. (Continued).

Author	Study design	Patients	Intervention	Outcome
Carpenter et al[36]	Retrospective study.	US children with bleeding disorders, n = 207 Testing for HbsAb was done at: SC 53 ± 20 months, IM 60 ± 20 months after vaccinations, p = .02 for time after vaccination.	Adjuvanted Hepatitis B vaccine Data for n = 206 IM n = 114 SC n = 92	**Reactogenicity** SC > IM, p > .05 for intramuscular hematoma **Immunogenicity** IM and SC comparable response.
Vink et al[37]	Single center, open-label, randomized, Phase III study.	Japanese adults, mean age 61.9 y old. n = 60,	Herpes zoster recombinant, adjuvanted, subunit vaccine (HZ/su) containing VZV. Data for n = 58 IM n = 29 SC n = 29	**Reactogenicity** SC > IM, p < .05 for redness and swelling. **Immunogenicity** Seroconversion rates: IM and SC 100% Anti-gE antibody Geometric mean concentration: IM 45521mIU/ml SC 44126mIU/ml
Ikeno et al[38]	Single center, randomized, phase I study.	Japanese males, 20–40 y old. n = 120	Inactivated, adjuvanted, monovalent, whole viruses A/H_5N_1 influenza vaccine. Data for n = 120 3 different doses: (1.7 µg, 5 µg, 15 µg) IM n = 20 each dose, SC n = 20 each dose. 2 doses 21 d apart.	**Reactogenicity** SC > IM, p < .05 for redness and swelling in 1st and 2nd dose. **Immunogenicity** Seroconversion: After 1st dose: 1.7 µg IM 10%, SC 0%, 5 µg IM 35%, SC 10% 15 µg IM 65%, SC 42% After 2nd dose: 1.7 µg IM 20%, SC 20%, 5 µg IM 50%, SC 20% 15 µg IM 75%, SC 68%
Hopf et al[39]	Single center, open, randomized, study.	Healthy Austrian adults, 18–60 y old. n = 116	Adjuvanted, Inactivated tick-borne encephalitis (TBE) virus vaccine. Data for 116 IM n = 58, SC n = 58	**Reactogenicity** SC > IM, p < .05 for pain, redness and swelling. **Immunogenicity** IM and SC comparable response

Seroconversion hepatitis B vaccine – HbsAb ≥ 10mIU/ml
Seroconversion hepatitis A vaccine – anti-HAV level ≥ 20mIU/ml
Seroconversion influenza vaccine – percentage with >4 fold increase in post-vaccination hemagglutinin inhibition (HI) titer.

Table 2. Live virus vaccines and intramuscular compared with subcutaneous administration – reactogenicity and immunogenicity.

Author	Study design	Patients	Intervention	Outcome
Bernstein et al[40]	Single-center, double-blind, randomized, placebo controlled phase I study.	Healthy US adults, 18–45 y old n = 40	Cytomegalovirus vaccine. IM n = 16 SC n = 16 Placebo n = 8 Low dose n = 16, IM n = 8 SC n = 8 High dose n = 16 IM n = 8 SC n = 8	**Reactogenicity** Redness and swelling only seen in those who received active vaccine by SC administration. **Immunogenicity** Similar antibody response IM and SC groups.
Diez-Domingo et al[41]	Multi-center, randomized, open-label study.	Healthy German and Spanish adults ≥ 50 y old n = 354	Live attenuated herpes zoster vaccine. Data for 352 IM n = 175 SC n = 177	**Reactogenicity** SC > IM, $p < .05$ for injection site reaction (0–21 d) **Immunogenicity** Similar antibody titers IM and SC groups.
Koblin[42]	Multi-center, randomized, open-label study.	US and Peru adults 18–50 y old n = 90	HIV DNA prime and booster with rAd5 vaccine. Data for n = 40 IM n = 20 SC n = 20	**Reactogenicity** SC > IM, $p < .05$ for redness/induration and pain. **Immunogenicity** Similar antibody titers in both IM and SC groups
Peters et al[43]	Double-blind, randomized, placebo-controlled, dose-escalation study.	UK and Kenya Adults. 18–59 y old n = 70 Nairobi, n = 45 London. n = 115	PTHr HIVA DNA and recombinant MVA HIVA vaccines. Data for n = 68 IM n = 35 SC n = 33	**Reactogenicity** SC > IM, $p < .05$ for Moderate/severe local reactions **Immunogenicity** Similar antibody titers IM and SC groups.
Enama et al[44]	Single-center randomized, open, phase I study.	US adults 18–50 y old. n = 60	HIV, DNA and comparator rAd5 HIV vaccines Data for DNA primes, IM n = 10 SC n = 10 Data for rAd5 prime, IM n = 10 SC n = 10	**Reactogenicity** HIV DNA SC > IM, $p < .05$ for swelling. rAd5 SC > IM, $p < .05$ for swelling, redness and injection site reaction, subcutaneous nodules. (SC 2, IM 0). **Immunogenicity** Similar antibody titers IM and SC groups.
Lafeber et al[45]	Single-center randomized, open study.	Dutch children 14 months old n = 67	MMR vaccine Data for n = 67 IM n = 33 SC n = 34	**Reactogenicity** SC > IM, $p > .05$ for pain immediately after injection. **Immunogenicity** Response to vaccine antigens not significantly different.
Kuter et al[46]	Post-licensure analysis of 33 studies.	Infants/children 11–18 months old. n = 752	MMRII – rHA vaccine and Varivax® (Varicella vaccine). No data for numbers given by IM or SC administration.	**Reactogenicity** SC > IM, $p < .05$ for injection site reactions. **Immunogenicity** Seropositivity rates after IM and SC administration were comparable.
Knuf et al[47]	Multi-center, randomized study.	German infants/children 11–21 months old. n = 328	MMR vaccine. Data for n = 318 IM n = 161 SC n = 157	**Reactogenicity** SC > IM, $p > .05$ **Immunogenicity** IM and SC comparable antibody responses for all antigens.

(*Continued*)

Table 2. (Continued).

Author	Study design	Patients	Intervention	Outcome
Gillet et al[48]	Multi-center, randomized, Open-label study.	French infants/children 12–18 months old. n = 752	Measles, mumps, rubella vaccine. Data for n = 712 IM n = 349 SC n = 363	**Reactogenicity** MMR SC > IM, $p < .05$ for any injection site reaction and redness. Varicella SC > IM, $p < .05$ for any injection site reaction and redness. **Immunogenicity** comparable immune response SC and IM.
Haas et al[49]	Multi-center randomized, open-label, Phase III study.	Healthy French infants/ children 12–18 months old. n = 405	Measles/Mumps/ Rubella/Varicella vaccine. Data for n = 405 IM n = 202 SC n = 203	**Reactogenicity** SC > IM, $p < .05$ for injection site reaction. **Immunogenicity** GMTs comparable for SC and IM groups.
Pittman et al[50]	Single-center, randomized, open-label, phase I study.	Healthy US adults, at least 18 y old. n = 43	Rift Valley Fever vaccine (MP-12) IM n = 6 ($10^{3.4}$ pfu) SC n = 10($10^{4.7}$pfu) IM n = 27($10^{4.4}$pfu)	**Reactogenicity** SC and IM comparable for tenderness. **Immunogenicity** IM and SC comparable
Wilck et al[51]	Multi-center, randomized, open, dose escalation study.	US adults 18–34 y old. n = 72	Live attenuated Vaccinia vaccine; Modified Vaccine Ankara (MVA) 10^7 or 10^8 $TCID_{50}$ Data for n = 40 IM n = 20 SC n = 20	**Reactogenicity** SC > IM, $p < .05$ for severe local erythema and induration (31–70 mm) **Immunogenicity** IM and SC comparable antibody responses.
Vollmar et al[52]	Single-center, randomized, double-blind, phase I study.	Healthy German males 20–55 y old n = 86	Live attenuated Vaccinia vaccine MVA-BN 10^8 $TCID_{50}$ Data for n = 36 IM n = 18 SC n = 18	**Reactogenicity** SC > IM, $p < .05$ for Redness and swelling **Immunogenicity** IM and SC comparable antibody responses.
Frey et al[53]	Single-center, randomized, partially-blinded, phase I study.	Healthy US adults aged 18–32 y old n = 90	Live attenuated Vaccinia vaccine MVA-BN 10^8 $TCID_{50}$ Data for n = 30 IM n = 15 SC n = 15 for each group.	**Reactogenicity** 1st dose SC > IM, $p < .05$ for redness and induration **Immunogenicity** IM and SC comparable antibody responses.
Seaman et al[54]	Single-center, randomized, double- blind, placebo controlled study.	Healthy US adults 18–34 y old. n = 36	Live attenuated MVA Vaccinia vaccine. 10^7 $TCID_{50}$ challenge with Vaccinia vaccine Dryvax® Data for n = 12 IM n = 5 SC n = 7	**Reactogenicity** No data supplied **Immunogenicity** SC < IM, $p > .05$
Dennehy et al[55]	Two-center, randomized, study.	US infants and children, 12 months – 10 y old n = 132	Varicella vaccine. Data for n = 132 IM n = 67 SC n = 65	**Reactogenicity** SC > IM, $p < .05$ for injection site reaction **Immunogenicity** GMTs comparable for IM and SC administration.
Fox et al[56]	Non- randomized study.	Brazilian male military personnel. 15–40 y old. n = 552	Yellow Fever Vaccine 17D-NY104, dose escalation, route comparative studies. Minimum immunizing dose assessed as a 50% lethal dose of a mouse lot.	**Reactogenicity** No data supplied **Immunogenicity** Minimum Immunizing Dose (mid) IM 1.6 SC 2.5

pfu – plaque forming units
$TCID_{50}$ – Median tissue culture infectious dose
mid – minimum immunizing dose

Table 3. Non-adjuvanted (whole cell, split cell and subunit) vaccines and intramuscular compared with subcutaneous administration – reactogenicity and immunogenicity.

Author	Study design	Patients	Intervention	Outcome
Leung et al[57]	Non-randomized study. Every 2nd child given SC injection.	Canadian children 15 months to 5 y. n = 498	Inactivated, whole cell Haemophilus influenzae type b polysaccharide vaccine. Data for n = 398 IM n = 194 SC n = 194	**Reactogenicity** IM > SC, $p < .05$ for crying **Immunogenicity** No data supplied
Cook et al[58]	Single-center, randomized, observer-blind study.	Australian adults ≥65 y old, 55 y old if had physician diagnosed chronic disease. n = 720	Split-virus influenza vaccine. Data for n = 709 IM n = 356 SC n = 353	**Reactogenicity** SC > IM, $p < .05$ for redness, swelling and tenderness. **Immunogenicity** Seroconversion: H_3N_2 IM 80.5%, SC 71.1%, $p = .0045$. H_1N_1 IM 37.2%, SC 26.9%, $p = .0043$. B, IM 57.0%, SC 51.0%, $p = .1948$.
Ruben & Jackson[59]	Multi-center, randomized study.	US Adults 18–25 y old with small number of older subjects.	Four subunit influenza vaccines, A_2/Aichi and B/Mass. No number given for IM and SC injection.	**Reactogenicity** SC > IM – 2 fold for local pain. SC > IM – 8 fold for erythema and induration. **Immunogenicity** Fold increase in titer (post:pre vaccination) A_2/Aichi: IM 20.5, SC 6.8 A_2/Aichi vs B/Mass IM 20.5 and 8.0 respectively.
Sanchez et al[60]	Two-center, randomized, phase I/II, double-blind study.	Japanese adults ≥65 y old. n = 120	High dose, split virus influenza vaccine. Data for n = 110 IM n = 55 SC n = 55	**Reactogenicity** SC > IM for injection site pain, erythema, swelling and induration. $p < .05$ **Immunogenicity** Fold increase: H_3N_2 IM 16.93, SC8.31 H_1N_1 IM 16.0, SC 9.25 B Yamagata IM 7.51, SC 4.68 B Victoria IM 10.69, SC 6.92
Delafuente et al[61]	Multi-center, randomized, single-blind study	Elderly males, mean age 68 y old, range 61–81 y. On warfarin anticoagulant. n = 26	Split virus influenza vaccine, 1991–1992. Data for n = 26 IM n = 13, SC n = 13	**Reactogenicity** No difference in adverse events between IM and SC administration. **Immunogenicity** Comparable immune response in IM and SC.
Ballester-Torrens et al[62]	Single-center, randomized, single-blind, phase IV study	adults n = 59	Split-virus influenza vaccine. Data for n = 59 IM n = 30 SC n = 29	**Reactogenicity** SC > IM, $p < .05$ for local reaction and pain. **Immunogenicity** No data provided
Casajuana et al[63]	Multi-center, randomized, single-blind study.	Spanish adults older than 18 y on oral anticoagulants n = 229	Split virus influenza vaccine. Data for n = 207 IM n = 92 SC n = 115	**Reactogenicity** SC > IM, $p < .05$ for erythema **Immunogenicity** No data supplied
Laurichesse et al[64]	Single-center, double-blind, randomized, placebo-controlled study.	French adults 18–40 y old. n = 84	Inactivated, whole cell Leptospira interrogans (Serogroup icterohaemorrhag-iae) vaccine. Data for n = 60 IM n = 30 SC n = 30	**Reactogenicity** SC > IM, $p < .05$ for local reaction at 14 d. **Immunogenicity** Similar antibody response for IM and SC routes.

(*Continued*)

Table 3. (Continued).

Author	Study design	Patients	Intervention	Outcome
Ruben et al[65]	Single-center, randomized study.	US adults. Mean age: IM 21.9 y old SC 20.6 y old n = 141	Inactivated, whole cell meningococcal vaccine (A,C,Y, W-135). Data for n = 132 IM n = 66 SC n = 66	**Reactogenicity** SC > IM, $p < .05$ for erythema. **Immunogenicity** IM and SC comparable response.
Scheifele et al[66]	Single-center, non-randomized study.	Canadian children 4–6 y old n = 101	Inactivated, whole cell meningococcal polysaccharide vaccine (A, C, Y, W-135) First 53 given SC immunization, subsequent 48 given IM immunization.	**Reactogenicity** SC > IM, $p < .05$ for any redness or swelling. **Immunogenicity** No data provided
Cook et al[67]	Single-blind, randomized, prospective trial	Australian adults ≥65 y old, 55 y old if had physician diagnosed chronic disease. n = 254	Inactivated, whole cell pneumococcal 23 valent vaccine Data for n = 254. IM n = 127 SC n = 127	**Reactogenicity** SC > IM, odds ratio 3.2 95% CI (1.13–1.93) **Immunogenicity** Comparable antibody response IM and SC route.

Seroconversion influenza vaccine – percentage with > 4 fold increase in post-vaccination hemagglutinin inhibition(HI) titer.
Fold increase influenza vaccine – Ratio of post- to pre-vaccination titer.

meningococcal polysaccharide (4vMenPV), varicella (VV), measles-mumps-rubella/varicella (MMR/V), herpes zoster vaccine) and vaccines recommended to be given by either IM or SC route (influenza and 23-valent pneumococcal (23vPPV)).

Direct route comparative studies have not been reported for inactivated polio (IPV), Japanese encephalitis (Imojev®), Q fever and rabies vaccine. Studies with IPV[17,68] given IM or SC with other antigens have shown comparable immunogenicity for IPV. Consequently, the recommendation for IPV alone to be given by SC injection is inconsistent with these data.

Older rabies vaccines were derived from animal neural tissue and given by subcutaneous injection.[69] Currently recommended[70] rabies vaccines are derived from cell cultures and are given by IM injection. The latter are more immunogenic and associated with less severe adverse reactions than the older rabies vaccines.

Subcutaneous nodules are uncommonly reported in this review and almost entirely with adjuvanted vaccines (anthrax[10–15], botulinum toxoid[16] and diphtheria combination vaccine[17]). A single report[44] of the transient formation of two nodules was made with an HIV vaccine. Subcutaneous nodules have been considered[71] to be benign, self-limiting AEFIs but this is clearly not the case as demonstrated by Bernstein et al.[72] who reported 11.4% of nodules persisting at 180 d post anthrax vaccination. These nodules may persist[73] for years and are often associated with pruritis and superficial dermatological features such as eczema, lichenification and hyperpigmentation.

Route of administration and use of aluminum salt adjuvants are recognized[71] determinants of their formation. However, the role of aluminum hydroxide sensitivity in the pathogenesis of these nodules is controversial with some authors demonstrating this phenomenon[74] whilst others[75] claiming that nodule formation reflects SC rather than IM injection of aluminum adjuvanted vaccines. Sterile abscess formation was also significantly greater with SC than IM injection for an adjuvanted diphtheria toxoid vaccine in an observational study.[18]

Pain immediately after injection might be expected[76] to be greater with IM compared with SC injection as the former has a dense supply of nociceptive nerve endings with the subcutaneous space being relatively devoid of pain receptors. Pain assessed (using standardized pain assessment scales) was significantly greater with SC than IM with anthrax vaccine[11] in this review. The same trend was seen with MMR[45] and DT toxoid vaccines[19] using the same methodology but did not reach statistical significance.

This review provided moderate grade evidence that IM injection significantly improved the immunogenicity of vaccines compared with SC injection. This grade of evidence was drawn from better antibody response/seroconversion data with adjuvanted vaccines n = 6, live virus vaccines n = 1 and non-adjuvanted, inactivated (whole cell, split and subunit) vaccines n = 3 for IM compared with SC injection. In this review, no study with SC injection was observed to be more immunogenic than IM injection. The extent and availability of the immunogenicity data were influenced by trial design factors (e.g. set to demonstrate non-inferiority between routes of administration and Phase I studies)

Phase I studies[77] are safety and tolerance studies with one of their objectives to identify preferred routes of administration.

In the randomized trials of this review, 33% had less than 100 patients (3/21 adjuvanted vaccines,[14,20,37] 9/15 live virus vaccines[40,42,44,45,50-54] and 3/9 non-adjuvanted, inactivated (whole cell, split cell and subunit vaccines)).[61,62,64]

The combination of high-grade reactogenicity evidence with the moderate grade immunogenicity evidence allows a strong recommendation[78] that all vaccines, except BCG (intradermal) and rotavirus (oral), should be given by IM injection. This will simplify vaccination practice and prevent the inadvertent misadministration of vaccines (meningococcal conjugate vaccine[79] and recombinant zoster vaccine[80]). It may potentially reduce vaccine hesitancy/refusal[2,3] due to a lower rate of ISRs with IM compared with SC injection.

The use of evidence-based medicine in vaccinology should replace highly idiosyncratic and divergent practices that are outmoded by promoting accountability based on best scientific principles.

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