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REVIEW

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Sepsis, parenteral vaccination and skin disinfection

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ASBSTRACT

Disinfection should be required for all skin penetrative procedures including parenteral administration of vaccines. This review analyses medically attended infectious events following parenteral vaccination in terms of their microbiological aetiology and pathogenesis. Like 'clean' surgical site infections, the major pathogens responsible for these events were Staphylococcal species, implicating endogenous contamination as a significant source of infection. As 70% isopropyl alcohol swabbing has been shown to effectively disinfect the skin, it would be medico-legally difficult to defend a case of sepsis with the omission of skin disinfection unless the very low risk of this event was adequately explained to the patient and documented prior to vaccination. There was a significant cost-benefit for skin disinfection and cellulitis. Skin disinfection in the context of parenteral vaccination represents a new paradigm of medical practice; the use of a low cost intervention to prevent an event of very low prevalence but of significant cost.

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Introduction

Skin disinfection[1] has been shown to significantly reduce surgical wound infection,[2] infection associated with vascular catheters,[3] blood cultures[4] collection of blood components[5] and yet is not routinely recommended prior to parenteral administration of vaccines and other therapeutic agents.

This procedure is not addressed in the National Immunization Technical Advisory Groups (NITAGs) guidelines from Argentina,[6] Canada,[7] Dubai,[8] India,[9] Sri lanka[10] and USA[11]; is considered unnecessary in Australia[12] and the UK[13]; if used in Ireland[14] and New Zealand,[15] the skin site should be allowed to dry for 30 seconds and 2 minutes after alcohol swabbing respectively, while in Brazil[16] the skin should be cleaned for 30 seconds and allowed to dry for 30 seconds.

There is very limited evidence for the omission of skin disinfection prior to parenteral injection. Hutin et al[17] provides data from 6 small studies with insulin (n = 176) in 2 retrospective and 4 retrospective studies, 16/21 case reports where exogenous sources of infection were implicated and an experimental study[18] involving introduction of coagulase positive Staphylococcus aureus into the skin of 26 young healthy adults. Del Mar et al[19] reported 3 very small randomized trials, 2 venous access studies (Sutton et al,[20] n = 194 and Grabe et al,[21] n = 187) and one small insulin site comparative study (Koivisto & Felig,[22] n = 13). It is noteworthy that Del Mar et al[19] made recommendation about skin disinfection prior to intramuscular injection yet none of their collated studies involved this route of administration. Clearly, accepting these limited data is supporting the null hypothesis that there is no difference between skin disinfection and no skin disinfection in terms of sepsis post parenteral injection is likely to be a type II error.[23]

70% isopropyl alcohol swabbing has been shown to effectively disinfect the skin. Sherman et al[24] reported it decreased the proportion of contaminants (odds ratio 21, 95% CI 3.1–142.2), with 20 of 26 patients who were initially culture positive being culture negative after disinfection. One patient remained culture positive despite disinfection.

Reichel et al[25] observed that disinfection depended on skin site (lumbar area 81–90%, abdomen 57–82%, upper back 55–60% and forehead 32–34%) but was not time dependent with 3 and 4 minutes not being significantly better than 2 minutes.

Khawaja et al[26] concluded that skin disinfection was unnecessary to prevent skin sepsis in a small study (n = 51) where a 47% reduction in colony forming units was found with cultures taken prior to the skin being swabbed for 30 seconds with a drying time of 30 seconds and post injection at the prepared site.

Medically attended infectious events[27] following parenteral vaccination range from any condition for which medical attention is sought to more serious adverse events resulting in hospitalisation, persistent or significant disability and death. Due to their more significant nature, they are likely to be brought to the attention of healthcare workers who report them as case reports and/or to vaccine surveillance programs. However due to their method of reporting[28] there is likely to be a bias toward under-reporting of less severe events like cellulitis, often treated on an outpatient basis without probable report.

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Table 1. VAERS database Cellulitis (Level 1a of certainty) and microbiology.

Sex/Age	Vaccine	Clinical History/ Microbiology
F/61	13-valent pneumococcal vaccine (Prevnar 13®)	Site: warm, swollen, red Culture: Staphylococcal species
M/25	Smallpox (Dryvax®)	Site: tender, indurated area with central eschar and surrounding cellulitis Culture: 4+ Staph aureus
F/11	Meningococcal conjugate vaccine (Menveo®)	Site: oedema, redness, firmness, warmth, pain/ tenderness Culture: Staph aureus
M/1	Measles/Mumps/Rubella (MMRII®)	Site: pain, redness, arm swelling Culture: MRSA at site of vaccine injection
F/53	Influenza (seasonal) (Afluria®)	Site: swelling, pain, redness Culture: Strep/Staph positive

In this review, medically attended infectious events data following parenteral vaccination were collated with a view to assessing the role of skin contamination in the microbiological aetiology and pathogenesis of sepsis following vaccination.

Results

Medically attended infectious events following parenteral vaccination can be subdivided into 2 groups:

1. Localized Clinical Syndromes (cellulitis, infectious abscess, necrotizing fasciitis, pyomyositis, osteomyelitis and septic arthritis).
2. Systemic Syndromes (bacteraemia and sepsis, septic [toxic] shock syndrome) often complicating local syndromes.

Clinical syndrome reports were collated only for healthy patients with case reports with overlapping syndromes entered only once as the most significant syndrome.

Localized clinical syndromes

Cellulitis

Cellulitis is the most common infectious event following parenteral administration of vaccines. It has been defined[29] by the Brighton Collaborative Local Reaction Working Group as "an acute, infectious and expanding inflammatory condition of the skin."

Level 1a of diagnostic certainty – includes at least 3 of the following signs/symptoms: localized pain or tenderness (pain to touch) erythema, induration or swelling and warmth AND reaction at the injection site and laboratory confirmation by culture.

Level 2 of diagnostic certainty – at least 3 of the signs/symptoms for level 1a and reaction at the injection site and diagnosed by a qualified healthcare provider. Exclusion criteria – spontaneous, rapid resolution and fluctuance.

Vaccine Adverse Events Reporting Scheme (VAERS) database

Search of the VAERS database for cellulitis codes listed in the methods section, retrieved 5 cases of cellulitis satisfying the Level 1a of diagnostic certainty, 4 due to staphylococcal species (1 MRSA) and 1 due to mixed streptococcal/staphylococcal infection (Table 1).

576 entries from the VAERS database satisfied the Level 2 of diagnostic certainty (major vaccines; combination 179, pneumococcal 166, varicella 90, DTPa 64 and influenza vaccine 41).

The rate of hospitalization for cellulitis in these VAERS patients was 16.2% which is much greater than rates observed n other studies[30,31] and presumably reflects a bias to reporting more severe reactions in passive surveillance systems like the VAERS. Goettsch et al.,[30] using data from the National Morbidity Registration in the Netherlands, estimated that 7% of all patients with bacterial cellulitis and erysipelas of the leg required hospitalization while McCall et al[31] noted a 4% admission rate for cellulitis in Medicare + Choice (M + C) enrolees in the USA.

Vaccine Safety Datalink (VSD) program

Review of studies drawn from data collected through the Vaccine Safety Datalink program,[32] an active collaboration between a number of health maintenance organisations and the National Immunization Program of the Center for Diseases Control, also gave reports of vaccine related cellulitis. Improved diagnostic certainty of these data was made by chart review and only studies with this level of analysis were included in this review. In 5 studies, 288 cases of cellulitis were reported (Table 2).

Other vaccine surveillance programs

Two reports of injection site cellulitis have been reported for influenza vaccines by the National Vaccine Injury Compensation Program[38] and the Korean National Adverse Events Following Immunization Surveillance System.[37]

Table 2. Vaccine Safety Datalink studies and cellulitis.

Author	Study Population	Vaccine	Cellulitis
Jackson et al[33]	Children 4–6 y old.n = 233, 616	5th dose of DTaP	230 cellulitis and 378 prescribed antibiotics for injection site infection
Jackson et al[34]	Children and young adults, 9–25 y old. n = 128,297	DT	11 cellulitis, 8 treated with antibiotics
Jackson et al[35]	Children and young adults, 9–25 years old. n = 436, 828	Td	23 cellulitis, 20 treated with antibiotics (16 oral and 4 parenteral)
Jackson et al[36]	Older adults (mean age 73 ± 7 years) n = 603	3rd dose of 23-valent pneumococcal vaccine	2 cellulitis, treated with oral cephalexin
Hambidge et al[37]	Children 6–23 months n = 45,356	Inactivated trivalent influenza vaccine	22 cellulitis

Choe et al.[38] reported cellulitis in 7/45 vaccine recipients with serious adverse events following administration of trivalent, inactivated influenza vaccine over the period 2003–2010, with 2 satisfying the level 1 and 5, the level 2 of diagnostic certainty. Kim et al[39] reported an 8 y old male who developed cellulitis following injection of a novel influenza A (H_1N_1) vaccine.

In the Italian region of Veneto, 13 patients were reported[40] as having cellulitis as a serious event following vaccination during the period 1992–2008.

In the Canadian Province of Ontario, 19 cases of cellulitis were reported[41] in recipients of DTaP-IPV over the period 2009–2013.

Post-marketing vaccine safety studies

Schmidt et al[42] reported 36 cases of cellulitis in a retrospective study in Kaiser Permanente Northwest (KPNW) clinics, 7/13,210 patients who received 2 doses of an inactivated, trivalent influenza vaccine within 28 days and 29/59,905 patients who received a single dose of this vaccine.

Burwen et al[43] reported 42 cases of cellulitis/abscess (ICD-9-CM code 682.3) requiring hospital admission in a retrospective study of Medicare vaccination data.

Case reports of cellulitis

Twenty-three reports of vaccine related cellulitis have been made in 6 studies (Table 3).

In two VSD studies, with zoster vaccine in adults[51] and trivalent inactivated influenza in children aged 24–59 months,[52] relative risks of 1.30 (95%CI 1.18–1.44) and 3.27 (95% CI 0.36 – 29.70) were reported for cellulitis and infection and cellulitis and skin reaction respectively.

Also in a study[53] of emergency department visits and hospital admission following quadrivalent human papilloma vaccines, vaccination odds ratio for skin infection days 1 to 14 post vaccination was 1.8 (95% CI 1.3–24). However in those 3 studies the number of patients satisfying the case definitions for cellulitis are unknown.

Table 3. Vaccine studies and cellulitis.

Author	Study/Vaccine	Adverse Events
Aberibigbe et al.[45]	Nigerian tertiary health institute, 2004–2006	17 cellulitis
Gattas et al.[45]	2009 Southern Hemisphere inactivated seasonal Influenza vaccine, given as a 2 dose regimen 30 days apart to children/adolescents 6–19 y in Brazil, n = 1021, total number of injections given n = 2042.	1 cellulitis
Agnandji et al.[46]	Malaria vaccine RTS,S/$ASO1_E$ given as a 0, 1, 2 monthly regimen with measles/yellow fever vaccine at vaccine visit 4 to infants in Ghana, Tanzania & Gabon. n = 170, total number of injections given n = 667.	1 cellulitis
Tregnaghi et al.[47]	DTP-Hep B/Hib vaccine given as booster dose to children 18–24 months old in Argentina, Colombia, Dominican Republic and Nicaragua. n = 143, total number of injections given n = 143.	1 cellulitis
Abdelnour et al.[48]	Quadrivalent meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY-CRM) given as 2, 4, 6 and 12 month regimen to 2 month old infants in US, Guatemala, Peru, Taiwan, Costa Rica and Panama. n = 5772, Total number of injections given, n = 22,070.	1 cellulitis
Kepfer et al.[49]	Measles/Mumps/Rubella/Varicella vaccine (ProQuad) given as a 2 dose regimen 3–6 months apart in 5 studies, studies 3, 4, 5 conducted with other vaccines in children 12–23 months old in the US, n = 2027, total number of injections given n = 3772.	1 cellulitis
Rivera-Medina et al.[50]	HPV-16/18 AS04-adjuvanted vaccine given at 0, 1, 6 month regimen to females mean age 12 y in 12 countries (Australia, Colombia, Czech Republic, France, Germany, Spain, Honduras, Korea, Norway, Panama, Sweden and Taiwan. n = 1017, total number of injections at least n = 3051	1 cellulitis

Infectious abscess

The Brighton Collaboration Local Reaction Working Group level 1 of diagnostic certainty for abscess of infectious aetiology requires[54] "spontaneous or surgical drainage of material from the mass" and "laboratory confirmation (Gram stain, culture or either test) of microbiological organisms with or without polymorphonuclear leukocytes in material drained or aspirated from the mass."

VAERS database infectious abscess (Level 1 of certainty and microbiology)

Fifty three cases of infectious abscess with level 1 of certainty were retrieved from the VAERS database, 30 Staphylococcus aureus (including 5 MRSA, 5 coagulase negative strains), 6 group A (GAS) Streptococcus, 4 mixed growth (Staphylococcus/Streptococcus), 3 Serratia Marcescens, 2 acid fast bacillus and 1 each of Streptococcus viridans, Haemophilus influenzae type b, Haemophilus influenzae (not specified), Haemophilus parainfluenzae, Streptococcus pneumoniae, Enterobacter faecalis, Enterobacter agglomerans, and mixed skin flora. The vaccines involved were Combination 18, DTP 10, influenza 7, Hepatitis B 5, TD/TT 5, pneumococcal 3, DTaP 2, Hepatitis A 2 and DaTP – IPV/Hib/Hepatitis B 1.

Published reports of infectious abscess formation

Mycobacteral infection (254/307) accounted for the majority of infectious abscess formation. Mycobacterium tuberculosis (167 cases), Mycobacterium chelonae (47 cases) and Mycobacterium fortuitum (40 cases) (Table 4). Oka and Sato[55] and Tamura et al[56] reported 62 and 102 cases of cutaneous Mycobacterium tuberculosis infection following vaccination with pertussis and typhoid vaccines respectively. Although the role of infected vaccinators is uncertain, the potential for needle contamination as the source of these infections is supported[57] by a recent outbreak of Mycobacterium tuberculosis following acupuncture in which failure to disinfect needles was implicated.

Table 4. Infectious abscess post vaccination.

Author	Sex/Age	Vaccine	Clinical History/Investigation	Cause
Oka & Sato[55]	62 infants	Pertussis	209 infants aged 4 months to 2 y old were vaccinated subcutaneously with pertussis vaccine. 62 infants were diagnosed as having "inoculation" tuberculosis with lesions at the subcutaneous vaccination site. 17 and 33 speciments from the vaccination site and axilliary nodes were smear/culture and culture positive positive respectively.	The doctor and nurse who administered the vaccine were found to have sputum positive pulmonary tuberculosis.
Tamura et al.[56]	102 children	Typhoid vaccine	102 of 631 children vaccinated with a double course of typhoid vaccine developed lesions at the site of injection, 1 to 6 months after vaccination, tubercule bacilli were identified in 29 cases and cutaneous and axillary lymph nodes had positive histopathology for tuberculosis was in 17 and 45 patients respectively.	One of the vaccinators, female physician, was found to have pulmonary tuberculosis. The authors noted that there was a relationship between the infected vaccinator and tubercule introduction but that there was not sufficient correlation between the children who reacted and who were inoculated by this person to suggest that this was the only or even possible source of contamination. They also note that the infected vaccinator gave injections of the same typhoid vaccine at another school where no cases of tuberculosis were found.
Dixit et al.[58]	5 month old female	DTP	'cold' abscess left thigh grew Mycobacterium tuberculosis	Source of infection not determined.
Mishra et al.[59]	8 month old female	DTP	'cold' abscess in right thigh after vaccination, fine needle aspiration showed caseating granulomata suggestive of a tubercule and staining for acid fast bacilli was positive.	No source for infection identified.
Agrawal & Jain[60]	11 month old female	DTP	'cold' abscess right gluteal for 8 months, given DTP at age 31/2 months. Zeil Neilson staining was positive for AFB, PCR was positive for Mycobacterium tuberculosis.	No source of infection found.
Borghans & Sanforth[62]	47 children, 3 to 15 months	DTP-IPV	Children developed lump at the injection site 1–13 months after injection. 7 abscesses showed the same strain type of Mycobacterium chelonae	The contamination of a number of vials with the same mycobacterium strain over a 6 month period is unexplained.
Owen et al.[63]	40 patients	36 Polyvalent influenza, 4 DTP-IVP	Lesions developed on average about 3 months after injection. 15 given influenza vaccine grew Mycobacterium fortuitum	The source of infection could not be found
Cayton & Morris[64]	4 children	DTP	4/10 children vaccinated developed abscess at injection site. Group A Streptococcus (GAS)	Same serotype isolated from nose of doctor, throat of nursing attendant and the scissors used at the clinic.
Chi-Thuong et al.[65]	3 (2 male, 1 female) 5–13 months	Hep B x 2, MMR x 1	Developed abscess with community acquired MRSA encoding gene for the Panton-Valentine-Leukocidin toxin	One Vaccinator had asymptomatic carriage of this MRSA in her nose and throat.
Simon et al.[66]	9 children	DTP	9 children injected with vaccine from the same vial at a clinic in Colorado. 8 developed abscesses which required surgical drainage. Group A streptococcus was cultured from all abscesses with staphylococcus aureus being also isolated from 4 abscesses.	Infection was likely caused by use of a single vaccine vial with the mixed infections in 4 cases suggesting skin contaminant.
Stetler et al.[67]	12 children in Georgia and 7 in Oklahoma	DTP	In Georgia, of 14 children who received lot A vaccine 12 developed abscess on 19 & 20/7/82, no abscesses were found in 31 children vaccinated with the same lot of vaccine on 15/7/82. In Oklahoma 7 children, 6 children had received vaccine from the same vial. Group A Streptococcus was isolated from 9/12 abscesses in Georgia and 4/7 in Oklahoma. All isolates were the same strain in both states but with different strains in both states	Infection of a multidose vial implicated.
Greaves et al.[68]	7 children in Indiana	DTP	Culture positive in 6 children with Group A Streptococcus, same streptococcal strain in all cases	Infection of a multidose vial implicated.

(*Continued*)

Table 4. (*Continued*)

Author	Sex/Age	Vaccine	Clinical History/Investigation	Cause
Tan et al.[69]	7 children (5 female, 2 male) 4–7 months 1, 3 month old female	DTaP-IVP-Hib Hepatitis B vaccine (Hbvaxpro®)	7 children developed thigh abscess; methicillin-resistant Staphylococcus aureus. 4 Center A, 1 Center B, C, D. Staphylococcus aureus cultured right thigh.	The authors report that "a breach of sterility during immunization at Center A most likely accounted for a cluster of 4 cases post vaccination.
Kuyubasi et al.[70]	30 day old healthy female	Hepatitis B	Swelling one week after vaccination with erythema, tenderness, induration and fluctuation being reported. Abscess aspirated and Staphylococcus aureus cultured.	Authors state that "abscess in this case was caused by use of inappropriate vaccination technique without paying attention to sterility.
Niederman & Marcinak[71]	7 months old female	DTP	11 d after vaccination a firm 3×4 cm non-fluctuating mass was felt in the left thigh extending to the groin area. Incision revealed a pseudo-capsule within the adductor muscle with thick pus which grew Haemophilus influenzae type b.	Source of infection not defined.

In three other cases [58,59,60] of primary cutaneous tuberculosis (PCTB) caused by M. tuberculosisc ontamination of the needle could not be excluded.

M. fortuitum and M. chelonae are rapidly growing mycobacteria (RGM) with contaminated tap water considered to be major reservoir of these pathogens.[61] This source is more likely to explain the 47 cases reported by Borghans & Stanford,[62] than the contamination of a number of vials with the same mycobacterial strain over a 6 month period. Similarly, this source could explain the 40 cases of M. fortuitum reported by Owen et al.[63]

Exogenous source of infection also accounted for infectious abscess formation in another 43 cases (7 contaminated vaccinator, 4 Group A Streptococcus [GAS][64] and 3 MRSA encoding the Panton-Valentine-Leukocidin toxin[65]) and contaminated multi-dose vials (9 children Colorado,[66] 12 children Georgia and 7 children Oklahoma[67] and 7 children Indiana[68]). In 10 cases, (8 Singapore,[69] 1 Turkey[70] and 1 USA[71]) the source of infection was not identified.

Abscesses following vaccination have been reported in clinical trials, number in parenthesis, from Niger[72] (5), Burkina Faso[73,74] (16, 1), Kenya[75] (17), India[76](16) and Ethiopia[77] (10) and also in the review by Klar et al.[41] However as microbiological data were not provided in these reports it is uncertain whether these were infectious or "sterile" abscesses.

Necrotizing fasciitis

Necrotizing fasciitis is an infection of the subcutaneous tissue (between the skin and the underlying muscle) which often overlaps with myconecrosis and is complicated by sepsis.[78] It has been classified[78] in 4 groups; Type 1 (polymicrobial), Type 2 (Group A Streptococcus), Clostridium fasciitis and Clostridium myonecrosis.

Seven case reports of this condition have been reported post vaccination with an additional 5 cases being retrieved from the VAERS database (Table 5). Definitive treatment of this condition involves early debridement of all necrotic tissue.

Pyomyositis

Pyomyositis is a very uncommon primary infection of skeletal muscle mainly caused by Staphylococcus aureus.[85]

Bae et al.[86] reported this condition in a 17 month old female patient due to Mycobacterium tuberculosis following Hepatitis A (Havrix®) vaccination. The case was considered to have incidentally occurred at the vaccination site "rather than being a syringe-transmitted infection or that it was associated with BCG vaccination.."

Two cases of pyomyositis were retrieved from the VAERS database;

A 17 y old female vaccinated with HPV (Gardasil®) vaccine developed an oval, tender, swollen and erythematous reaction with fever. Blood culture and aspiration culture negative, WCC 13.7×10^9, (80% neutrophils), CT scan showed subcutaneous infiltration, no abscess formation and MRI positive for inflammation.

A 4 y old female vaccinated with 23-valent pneumococcal vaccine (Pneumovax®) developed severe leg pain, fever and difficulty walking. MRI and Ultrasound revealed diffuse fasciitis with abscess formation and patient was diagnosed with cellulitis and myositis.

Osteomyelitis

Osteomyelitis is a not uncommon disease[87] of bone which can be divided into 3 categories in terms of its source of infection; haematogenous, contiguous spread with or without vascular insufficiency.

Search of the VAERS database retrieved 10 cases of osteomyelitis, 9 due to contiguous spread and one due to haematogenous spread (Table 6).

Septic arthritis

Septic arthritis, infection of the joint, can occur via 3 routes[88]; haematogenous, direct contamination into the joint and indirect contamination – spread from nearby structures.

Search of the VAERS database revealed 7 cases of septic arthritis, 4 due to haematogenous spread, 2 due to direct contamination and 1 due to indirect contamination (Table 7).

Systemic syndromes

Bacteraemia

A consensus conference between the American College of Chest Physicians (ACCP) and the Society of Critical Care

Table 5. Necrotozing fasciitis post vaccination.

Author	Sex/Age	Vaccine	Clinical History/ Investigation	Comment
Pitta et al.[79]	M/30	Influenza	Pain, oedema, erythema left upper limb with fever 12 hours after vaccination. Arm debrided with fasciotomy. No bacteria cultured	The authors report "one can suspect that some kind of contamination occurred during the process – in the handling of needles - or even some break in aseptic technique, allowing skin micro-organisms to penetrate the patient's tissues"
Senaran et al.[80]	M/ 18 months old	Hepatitis B vaccine	Admitted 2 d after vaccination with erythema and swelling of his left shoulder. Patient required debridement of shoulder muscles. All cultures were negative.	The authors note: "The possible cause of local soft tissue infection and NF in our case might be contamination of needle during handling or manipulation and direct inoculation of the microorganism into the subcutaneous and muscular tissues rather than the vaccine itself"
Thapa et al.[81]	F/7 days old, healthy, negative parental history of HIV	BCG	Baby was presented 18 hours after vaccination in the left arm with warm, tender, erythematous swelling of the outer aspect of the middle third of the left arm. The baby had radical debridement of the shoulder. Blood cultures positive MRSA The baby was revaccinated with BCG at 1 month of age in the right arm and "spirit and cotton swab was used for preparation of the proposed vaccination site."	Authors report that "isolation of the pathogenic organism from the lesion confirmed the etiology."
Okeniyi et al.[82]	F/13 days old, healthy child, negative TB and HIV	BCG	Child was presented 6 d after BCG vaccination in left arm with extensive skin necrosis with the limb being hyperaemic and oedematous. The child had radical excision of necrotic tissue. Wound culture grew mixed growth of Pseudomonas aeruginosa and Staphylococcus aureus	Authors note that "most plausibly, the inoculation provided a nidus for bacterial infection.
Thomas[83]	F/80 Excellent health except recent diagnosis of Type 2 diabetes managed by diet	Influenza (Influvac)	Two days prior to admission influenza vaccine was administered to the left upper arm. The left forearm and hand had blue discolouration with bullae and soft tissue crepitus and cold, pulseless left hand. Bullae aspirate grew Clostridium septicum with no growth from the batch of influenza vaccine. Despite left forequarter amputation patient died post operatively.	Author noted "an alternative explanation is that C. septicum spores were inoculated along the tract of the intramuscular injection."
Pora et al.[84]	F/71 Patient had depression, no history of immuno-compromise, Including neoplasia	H_1N_1 influenza vaccine	Patient presented 3 d after H1N1 influenza vaccination with fever and progressive left shoulder pain. She was febrile (38.2°c), hypotensive (100/70) and the left arm was swollen, discoloured with crepitus. X-ray showed extensive subcutaneous emphysema The patient died a few hours after presentation. Blood and wound cultures were positive for Clostridium septicum	The authors suggest "a causative association" between fatal gas gangrene and influenza vaccine administration.

(*Continued*)

Table 5. (*Continued*)

Author	Sex/Age	Vaccine	Clinical History/ Investigation	Comment
Chi- Thuong et al.[65]	M/17/12	MMR	Necrotising fasciitis, MRSA encoding Panton-Valentine-Leukocidin toxin gene.	MRSA cultured from nose and throat of vaccinator.
VAERS	M/11 No comorbid health issues reported	Influenza vaccine (Fluzone®) And 23-valent pneumococcal vaccine (Pneumovax®)	Patient developed right arm pain the morning after vaccinations. The arm had swelling, erythema, pain and discolouration. Patient had 2 debridements and skin grafts, wound cultured pseudomonas thought to be a colonizing bacteria.	
VAERS	M/52 No comorbid health issues reported	Influenza vaccine (Fluvirin®) and 23 valent pneumococcal vaccine (Pneumovax®)	Patient admitted 1 day after vaccination with necrotizing fasciitis of right shoulder which was surgically debrided. Gram stain and wound culture was negative.	
VAERS	F/42 No history of comorbid diagnoses given	23-valent pneumococcal vaccine (Pneumovax®)	Patient had pain and ache at injection site with fever. MRI showed necrotizing fasciitis. Patient had debridement which was culture negative.	
VAERS	F/62, no history of comorbid diagnoses given.	23-valent pneumococcal vaccine (Pneumovax®)	Patient reported painful, blistering reaction over right deltoid muscle after vaccination. CT scan revealed gas and extensive oedema consistent with necrotizing fasciitis. Blood and wound cultures were negative Patient required debridement of right deltoid muscle.	
VAERS	M/30 Patient had sigmoid diverticulitis and chronic back pain	23-valent pneumococcal vaccine (Pneumovax®)	Following vaccination the patient developed erythema, warmth, tenderness and oedema at the injection site. The patient had a debridement of the soft tissue of the left upper arm which showed acute inflammation and focal gangrenous necrosis.	

Medicine (SCCM) defined bacteraemia[90] as the presence of viable bacteria in the blood. This condition can be divided into complicated and uncomplicated bacteraemia with the criteria for the latter[91] being:

i. Exclusion of endocarditis
ii. No implanted prosthesis
iii. Negative results of follow-up blood cultures drawn 2–4 d after the initial set
iv. Defervescence within 72 hours after the initiation of effective antibiotic therapy and
v. No evidence of metastatic infection

Uncomplicated bacteraemia

A case of uncomplicated Staphylococcus aureus bacteraemia was drawn from the VAERS database. A 64 y old male given influenza (H1N1) [Sanofi®] vaccine had induration, swelling and pain at the injection site with blood culture positive for coagulase negative S. aureus. Using the 5 predictors of systemic inflammatory response syndrome (SIRS) validated by Elzi et al[92] to differentiate between blood culture contamination and blood stream infection due to coagulase-negative S. aureus, the probability of blood stream infection in this case was 42.4%, as the while cell count was greater than 12×10^9/l.

Complicated bacteraemia

Complicated bacteraemia has been reported[93] to include a wide range of metastatic infectious syndromes (infective endocarditis, septic arthritis, deep tissue abscess, vertebral osteomyelitis, epidural abscess, septic thrombophlebitis, psoas abscess, meningitis and embolic stroke).

Chae et al.[94] reported a case of multiple subcutaneous abscesses complicating Staphylococcus aureus bacteraemia in a 42 day old female vaccinated with BCG.

One case of haematogenous osteomyelitis (Table 6) was drawn from the VAERS database, a 73 y old female vaccinated with influenza vaccine developed L3/4 vertebral osteomyelitis.

Four cases of septic arthritis (Table 7) were drawn from the VAERS database

(M/age not given, MSSA; M/16, MRSA; M/72, GAS; F/1.1, Alcaligenes faecalis. A case of arterial stroke was also drawn from the VAERS database, a 1.1 y old male presented with febrile seizure and left arm weakness the morning after vaccination with a combination of hepatitis A (Vaqta®), 7-valent pneumococcal conjugate vaccine (Prevnar7®) and varicella (Varivax®) vaccines. MRI showed thrombosis of the right middle cerebral artery and blood cultures were positive for S.

Table 6. Osteomyelitis cases and VAERS database.

No.	Sex/Age(years)	Vaccine/Site	Clinical History/ Investigations	Source, Mode of Spread
1.	F/12	HPV (Gardasil®), right arm	Pain and swelling 48 hours after injection. CT scan right humerus – osteomyelitis. Blood cultures positive for S. aureus. Had necrotic bone resected.	Contiguous
2.	M/0.1	DTaP-IPV-HepB (Pentacel®) and 13-valent pneumococcal vaccine, left leg.	Developed MSSA abscess, X-ray – periosteal elevation left femur.	Contiguous
3.	F/0.3	DTaP-IPV-HepB (Pediarix®), left leg	MRSA left periosteal abscess with CT scan confirmation inflammatory changes in subcutaneous fat and muscle.	Contiguous
4.	F/4	DTaP (Infanrix®), Varicella (Varivax®), right leg	Fever and pain. Surgery to aspirate infection in bone, staph – species unknown.	Contiguous
5.	M/0.3	Hib (Pedvaxhib®) Polio (Ipol®), Left leg	Fever and pain. MRI – myositis of left lower thigh and mild periosteal reaction left mid distal femur.	Contiguous
6.	F/age unknown	Tdap (Adacel®), right arm	Pain and limited arm movement. MRI revealed osteomyelitis	Contiguous
7.	M/4	13-valent pneumococcal (Prevnar®), Left leg	Fever, headache. MRI – left femoral osteomyelitis	Contiguous
8.	F/11	23-valent pneumococcal (Pneumovax®), right arm	Severe redness, tenderness at injection site. MRI – cellulitis/osteomyelitis right humerus	Contiguous
9.	M/2	Dtap (Daptacel®), Hepatitis A (Vata®), MMRV (Proquad®), left leg. Hib (Pedvaxhib®) left arm.	Left arm and left leg swelling and erythema. MRI multi-loculated abscess of distal humeral shaft, osteomyelitis proximal radius and ulna. Gram +ve cocci.	Contiguous, possible haematogenous spread.
10.	F/73	Influenza (no brand name given), right arm	Right arm cellulitis, L3–4 vertebral osteomyelitis due to Group B Strep.	Haematogenous

aureas. Fullerton et al[95] have concluded that "infection may act as a trigger for childhood arterial ischaemic stroke, while routine vaccinations appear protective."

Two other cases of complicated bacteraemia were obtained from the VAERS database. A 72 y old male vaccinated with influenza H_1N_1 (Novartis®) developed sudden onset of pain and swelling in right wrist and arm and left ankle had GAS cultured from the right wrist. A 0.6 y old female vaccinated with a combination of Hib and Hep B (Comvax®), DTaP (Tripedia®), 7 valent pneumococcal vaccine (Prevnar®) and polio inactivated (IPOL®) developed Streptococcus pneumoniae bacteraemia with bacterial meningitis.

Sepsis/severe sepsis/septic (toxic) shock syndrome

Systemic inflammatory response syndrome (SIRS), is characterized[96] by more than one of the following clinical findings: body temperature higher than 38°c, heart rate higher than 90/minute, hyperventilation evidenced by respiratory rate higher than 20/min or $PaCO_2$ lower than 32 mm Hg or white cell count higher than 12×10^9/l or lower than 4×10^9/l. Sepsis[96] is defined as SIRS in the presence of infection with severe sepsis being associated with organ dysfunction, hypoperfusion or hypotension and septic shock being sepsis-induced hypotension despite adequate fluid resuscitation.

Septic/Toxic shock is rarely seen following vaccination and then likely to be due to contamination of needles/syringes or vaccines or transfer of infectious agents from the vaccinator to the vaccine recipient (Table 8).

In total 1534 reports of sepsis following parenteral vaccination were retrieved from databases and published reports in this review with this number being dominated by cellulitis, 1011 (65.9%).

Discussion

"Clean" surgical site infections (an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital or uninfected urinary tract is not entered) have been suggested[101] to be due to endogenous Staphylococcal species at the site of incision. This contention has been supported[102] by a study using Technetium-99 m pertechnetate labeled albumin microspheres to differentiate between surgeon and patient derived infection.

Staphylococcal species infection prevalence at "clean" surgical sites varies from 54.8% (orthopaedic surgery),[103] 67.3% (superficial site, open heart surgery)[104] to 87.9% (post arthroscopy)[105] with the latter authors concluding that "their predominance supports the need for careful skin preparation and sterile technique when performing arthroscopy."

Similarly in this review, Staphylococcal species were identified in 59/92 (64.1%) cases, when suspected/proven cases due to exogenous infection were excluded; cellulitis 5/5, infectious abscess 43/63, necrotising fasciitis 1/4, osteomyelitis 4/6, septic

Table 7. Septic arthritis.

No.	Sex/Age (years)	Vaccine/Site	Clinical Features/Investigations	Route of Spread
1.	M/72	Influenza (H_1N_1) [Novartis] Left arm	Pain and swelling right wrist, arm and left ankle. GAS cultured from right wrist aspirate.	Haematogenous spread
2.	F/1.1	Hepatitis A (Vaqta®) and Varicella (Varivax®) Left leg	Unable to move left elbow. Aspirate from left elbow grew light growth of Alcaligenes faecalis	Haematogenous spread
3.	M/ age not given	Hepatitis B (Foreign) left leg	Pain and decreased movement in left leg. Septic arthritis left hip and ankle. Blood cultures MSSA, left ankle ulcer cultured MSSA	Haematogenous spread
4.	M/16	Meningococcal conjugate (Menactra®) and Tdap (Adacel®) Right arm	MRSA bacteraemia with left sacroiliac joint Septic arthritis on bone scan and MRI	Haematogenous spread
5.	F/74	23-valent pneumococcal vaccine right arm. Influenza [seasonal] (Fluvirin®) left arm	Pain, swelling, redness right deltoid. Ultrasound showed large glenohumeral joint effusion. Synovial fluid 86,033 neutrophils[85*] (90% polymorphs), culture negative.	Direct contamination
6.	M/91	13-valent pneumococcal vaccine (Prevnar®) Right arm	Pain, redness, swelling and severe bruising around injection site. Ultrasound – joint effusion right shoulder	Direct contamination
7.	F/0.9	Haemophilus B conjugate-Hib (Acthib®) left leg Hepatitis B (Engerix-B®) left leg 7 valent pneumococcal vaccine (Prevnar®) left leg	Cellulitis left thigh, septic arthritis left knee. Culture MRSA WCC 30.7×10^9/l	Indirect contamination

* Margaretten et al[89] likelihood ratio for infection wcc aspirate <25,000/ui, LR, 0.32, 95%CI 0.23–0.41; <25,000/ui LR 2,9 m 95%CI 2.5–3.4; <50,000/iu, LR 7.7, 95%CI 5.7–11.0 and <100,000/iu LR 28.0, 95%CI 12–66. Polymorphs nuclear cell count for septic arthritis, at least 90% LR 3.4, 95%CI 2.8–4.2 while a count lower than 90% LR 0.34, 95%CI 0.25–0.47.

arthritis 3/5, bacteraemia 3/5, sepsis 0/4. This implicates endogenous contamination as a significant source of infection during parenteral vaccination, a thesis supported by the probable/proven exogenous contamination in only 421 of the 1534 (27.4%) of the medically attended infectious events collated in this review.

Table 8. Septic/toxic shock.

Author	Sex/ Age	Vaccine	Clinical Details	Source of Infection
Sood[97]		Measles vaccine	Severe reaction 115 children, 79 deaths, 105 fever, 92 vomiting, 91 diarrhea	Unsterile syringe and needles and perhaps use of contaminated vaccines.
Sokhey[76]	F/9yrs	Tetanus toxoid	48 hours after vaccination with fever, vomiting	Re-used syringes and needles
Plueckhahn & Banks[98]	M/51yrs M/52yrs	Influenza vaccine	Group A streptococcal toxic shock. Blood cultures positive for group A streptococcus	Contamination of multidose vaccine vials
Chi Thuong et al.[65]	M/13/12 M/13/12 F/16/12	MMR MMR Varicella	Two children vaccinated with MMR, one died and one had neurological sequelae. Varicella vaccinated child recovered.	Contamination originating from vaccinator
Rutishauser et al.[99]	F/55yrs	Tetanus toxoid	Toxic shock syndrome Group A streptococcus	Contamination originating from vaccinator
Italiano et al.[100]	F/49yrs	Varicella	Streptococcal toxic shock syndrome Group A streptococcus	Unknown source of Infection
VAERS	F/11yrs	Hepatitis A (Havrix®), Meningococcal conjugate (Menactra®), HPV (Gardasil®), Tdap (Boostrix®)	Necrotising fasciitis complicated by fatal GAS toxic shock syndrome	
VAERS	M/0.4yrs	DTaP-IPV/Hib (Pentacel®), 13-valent pneumococcal conjugate vaccine (Prevnar®)	Patient died due to toxic shock syndrome, Group A streptococcus	
VAERS	No sex given/ 2.5yrs	Hepatitis A (Havrix®), 7-valent pneumococcal conjugate vaccine (Prevnar®)	Patient died due to toxic shock syndrome Group A streptococcus	

Consequently it would be difficult to defend[106] a case of sepsis if skin preparation was omitted unless the risk of this very low prevalence event was adequately explained to the patient and documented prior to vaccine administration.

Cellulitis, a syndrome of uncertain microbiological etiology,[107] was the major event post parenteral vaccination in this review, 1011/1534 (65.9%). In a review[108] of prospective and retrospective laboratory studies of the 16% of patients with positive needle aspirate and/or punch biopsy cultures from intact skin, the ratio of Staphylococcus aureus to group A streptococcus was almost 2:1 (51% : 27%).

This trend was reversed when microbiological diagnosis was made with blood culture[109] and serology,[110] (anti-streptolysin O (ASOT) and anti-DNase B) (beta haemolytic streptococcus 57–75% and 70% respectively).

A Kaiser Permanente of Northern California study[111] of the microbiology of skin and soft tissue infections (2006–2009) held beta haemolytic streptococci accounted for 9% of cultured cellulitis and abscess.

In the presented review, GAS accounted for 13.5% of cultured cellulitis and abscesses when mixed growth culture with Staphylococcus aureus were combined.

Cutaneous tuberculosis can be classified[112] as, inoculation tuberculosis from an exogenous source, tuberculosis from an endogenous source and haematogenous tuberculosis.

In this review Mycobacterial infection was dominant in the infectious abscess post vaccination group, 254/307 (82.7%), 167 cases due to Mycobacterium tuberulosis and 87 cases due to rapid growing mycobacteria (Mycobactyerium chelonae 47 and Mycobacterium fortuitum 40). These infections are "inoculation" tuberculosis due to inadequately sterilised needles[112] in the M tuberculosis group and probable use of contaminated tapwater,[61] the major reservoir of rapidly growing mycobacteria (RGM) in the cluster of cases of Mycobacterium chelonae and Mycobacterium fortuitum.

A cost benefit analysis for skin disinfection with 70% isopropyl alcohol swabs can be made for cellulitis from the data collated in this review.

The prevalence of cellulitis in the 6 randomized, controlled trials collated[45-50] in this review ranged from 1/143 to 1/22,070 injections with the mean being 1/5290 injections. If the 2 extreme outliers are excluded then mean prevalence of cellulitis is 1/2383 injections. The cost per swab is 2.2 c USA[113] and 2.9c Australian,[115]

As decontamination rates after swabbing with isopropyl alcohol have varied from 47% to 77%, with the former measurement made after injection, a mean effectiveness of swabbing of 66% would seem to be acceptable with this presumably translating into a similar rate of reduction of injection site cellulitis.

The cost of swabbing 2383 patients is $52.5 USA and $69.1 Australia.

The cost of managing a case of cellulitis includes outpatient and inpatient components. The outpatient component is $37.05 standard consultation (concession card holders) and $68 (private billing) jwith $6.10 to $10 respectively for a course of Cephalexin in Australia. In the USA the consultation charge would be $10–50 for insured patients and $50–200 for uninsured patients respectively with $7 for a course of Cephalexin.

An inpatient component is added to the cost of managing cellulitis as 4–7% of these patients require hospital admission.[30,31] In the USA this is costed at between $6,000 to $25,000 while in Australia (2011–2012) this was costed[116] at an average of $3800 with a range of $1900 to $4000 for major metropolitan hospitals and at an average of $4000 (range 2700 to 5300) for major regional hospitals. If this is averaged at $4000 per admission in 2016 and the mean rate of admission for cellulitis is also averaged at 5.5% then the increment of cost added to the care of all cases of cellulitis is $220.

The total cost per patient for the management of cellulitis in Australia is thus $263.15 and $298 for concession card holders and privately billed patients respectively and as 66% of patients are protected against cellulitis by swabbing the cost saved per patient is $173.6 and $196.7 for these groups.

The cost-benefit for skin disinfection prevention of cellulitis is the cost saved per case ($173.6 and $196.7) minus the cost of swabbing to prevent 1 case of cellulitis (2.9 c × 2383 = $69.1), $104.5 and $127.6. This significant cost-benefit takes no account of indirect costs such as loss of income.

Evidence based medicine has been championed[117] as a paradigm which results in improved medical practice. However, it is evident from the body of data collated in this review that very large randomized trials would be needed to adequately address the issue of skin disinfection prior to vaccine administration and the prevention of sepsis.

Consequently, a new paradigm[118] might be evoked to cover this clinical issue, namely the use of a very low cost intervention (disposable skin swab) to prevent a very low prevalence event (sepsis related to parenteral vaccination) of high cost (medical attention including hospitalisation with morbidity/ mortality).

Methods

Data for this review were sought from the following databases: Medline via Ovid (1996 to present), Embase via Ovid (1980 to present, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO (1982 to present), using search terms and their word variants; "cellulitis," "infected abscess formation," "necrotizing fasciitis," "pyomyositis," "osteomyelitis," "septic arthritis," "bacteraemia," "sepsis" and "toxic shock syndrome" and "vaccine administration," "vaccine studies," "vaccine trials" and "post marketing vaccine safety."

Additional data were obtained by hand searching journals for "safety data" and "vaccine studies/trials." The following journals were searched for these data from the date in parentheses to December 2015; Acta Paediatrica (1998), Acta Tropica (1989), American Journal of Medicine (1946), American Journal of Public Health (1971), American Journal of Tropical Medicine and Hygiene (1998), Annals of Internal Medicine (1960), Archives of Diseases of Child Health (1926), Bio Drugs (1998), Biologicals (1990), British Medical Journal (1991), Canadian Medical Association Journal (1911), Clinical Infectious Diseases (1999), Clinical Therapeutics (1995), Clinical and Vaccine Immunology (2006), European Journal of Clinical Microbiology and Infectious Diseases (1997), European Journal of Pediatrics (1997), Infection and Immunity (1970), Infection (1997), International Journal of Infectious Diseases (1996), Journal of American Medical

Association (1983), Journal of Hygiene (1903), Journal of Infectious Disease (1999), Journal of Medical Microbiology (1996), Journal of Pediatrics and Childhood (1998), Journal of Pediatrics (1999), Journal of Travel Medicine (1997), Journal of Tropical Pediatrics (1996), Lancet (1990), Medical Journal of Australia (2004), New England Journal of Medicine (1993), Pediatrics (1966), Pediatric Infectious Diseases Journal (1995), Public Health (1995), Scandinavian Journal of Infectious Disease (1997), Transactions of the Royal Society of Tropical Medicine and Hygiene (1920) and Vaccine (1983). Bibliographies of all relevant publications obtained by these searches were then searched for additional data.

The Vaccine Adverse Events Reporting System (VAERS) database November 2015 was searched manually by the author for code 10075095 (administration site cellulitis), code 10007882 (cellulitis), code 10007921 (cellulitis staphylococcal), code 10007922 (cellulitis streptococcal) and code 10050057 (injection site cellulitis); code 10022044 (injection site abscess), code 10041917 (staphylococcal abscess), 10042343 (subcutaneous abscess), code 10069556 (vaccination site abscess), code 10028885 (necrotising fasciitis), code 10028887 (necrotizing fasciitis staphylococcal), code 10021918 (infective myositis), code 10028653 (myositis), code 10037652 (pyomyositis), code 10031252 (osteomyelitis), code 10031253 (osteomyelitis acute), code 10031256 (osteomyelitis chronic), code 10064250 (staphylococcal osteomyelitis), code 10053555 (arthritis bacterial), code 10060968 (arthritis infective), code 10064111 (injection site inflammation), code 10040059 (septic arthritis haemophilus), code 10067323 (septic arthritis streptococcal); code 10003997 (bacteraemia), code 10058922 (haemophilus bacteraemia), code 10058859 (pneumococcal bacteraemia), 10051017 (staphylococcal bacteraemia), code 10051018 (streptococcal bacteraemia), code 10014665 (endocarditis), code 1001466 (endocarditis bacterial), code 10014684 (endocarditis staphylococcal); code 10058875 (haemophilus sepsis), code 10054047 (pneumococcal sepsis), code 10056430 (staphylococcal sepsis), code 10048960 (streptococcal sepsis); code 10044248 (toxic shock syndrome), code 10044250 (toxic shock syndrome staphylococcal), code 10044251 (toxic shock syndrome streptococcal) AND all vaccine products. Data were included from these search domains if adverse events were reported or reviewed by a healthcare professional and if the vaccine name was provided.

Abbreviations

NITAGs	National Immunization Technical Advisory Groups
VAERS	Vaccine Adverse Effect Reporting System
VSD	Vaccine Safety Datalink
KPNW	Kaiser Permanente North West
PCTB	Primary Cutaneous Tuberculosis
RGM	Rapid Growing Mycobacteria
MRSA	Methicillin Resistant Staphylococcus Aureus
SIRS	Systemic Inflammatory Response Syndrome
GAS	Group A Streptococcus

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No potential conflicts of interest were disclosed.

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