

Best vaccination practice and medically attended injection site events following deltoid intramuscular injection

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Analysis of medically attended injection site events data provides a vehicle to appreciate the inadequacies of vaccination practice for deltoid intramuscular injection and to develop best practice procedures. These data can be divided into 3 groups; nerve palsies, musculoskeletal injuries and cutaneous reactions and reflect inappropriate site of injection, needle over or under penetration, local sepsis and vascular complications. The aim of this review is to formulate best vaccination practice procedures for deltoid intramuscular injection of vaccines through the collation and analysis of medically attended injection site events.

Introduction

Increasing public concerns regarding vaccine safety¹ in the context of a decreasing prevalence of vaccine preventable diseases mandates the use of best vaccination practice.

However, it is evident from the increasing range and extent of medically attended injection site event data, following deltoid intramuscular injection of vaccines, retrieved for this review that there are significant inadequacies in current vaccination practice which need prompt attention.

Injection site events following deltoid intramuscular injection are generally² mild and transient with medically attended events being uncommon, usually 'unsolicited' by vaccine trialists and most often reported by the vaccine recipient.

Medically attended events³ range from any condition for which medical attention is sought to serious adverse events resulting in death, hospitalization and persistent or significant disability. Due to their more severe 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 method⁴ of reporting there is likely to be a bias toward under-reporting of less severe events.

The aim of this review is to analyze medically attended injection site events data following deltoid intramuscular injection and to formulate best vaccination practice.

Results

Vaccine associated medically attended injection site events data following deltoid intramuscular injection can be divided into 3 groups; nerve palsies, musculoskeletal injuries and cutaneous reaction.

Nerve Palsies

The radial nerve and the anterior branch of the axillary nerve are susceptible to injury following intended intramuscular injection into the deltoid muscle.

Radial nerve palsy

The radial nerve is susceptible⁵ to injection injury where it passes obliquely around the upper humerus, proximal to and in the spiral groove which ends just distal to the deltoid tuberosity on the lateral margin of the humerus. Radial nerve palsy is the second most common traumatic injection neuropathy seen in developing countries^{6,7} and in this setting is due to injections being given by untrained and unlicensed practitioners.⁷ In a review⁸ of 23 cases of radial nerve palsy following intramuscular injection, the site of injury was above the radial groove in 19 cases and in the groove in the other cases.

Radial nerve palsy has been reported^{9,10,11} post vaccination. Blumstein and Kreithen⁹ and Beredjikhian et al¹⁰ reported complete radial nerve palsies in males 23 and 26 years old, 7 hours and 1 day after receiving painless injection of tetanus toxoid and influenza vaccine respectively. In the latter case Magnetic Resonance Imaging (MRI) and ultrasound were interpreted as showing that the nerve palsy was secondary to an inflammatory demyelinating process around the nerve rather than direct axonal injury. Direct axonal injury may be implicated in the case reported by Ling and Loong¹¹ in which a 47 year old male

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developed a complete radial nerve palsy 2 weeks following severe injection site pain with tetanus toxoid vaccine injection.

Four other cases of radial nerve palsy post vaccination satisfying the inclusion criteria for this review were retrieved from the VAERS database. Two cases were reported with DTap (Adacel[®]), females 22 and 43 years old, 1 day and 1 week post vaccination respectively. The other cases were reported with monovalent influenza vaccine (Sanofi[®]) and tetanus/diphtheria toxoid vaccine (no brand given) in a female 43 years old and a male 49 years old, 2 days and 4 days post vaccination respectively.

Anterior branch of the axillary nerve

The anterior branch of the axillary nerve¹² takes a tortuous path around the surgical neck of the humerus and provides motor innervation to the anterior and middle parts of the deltoid muscle.

Two cases of this nerve palsy have been reported.^{13,14} Imran and Hayley¹³ reported a 73 year old male who had severe local pain after injection of an influenza vaccine and then developed notable deltoid atrophy, inability to abduct his arm and sensory loss over the lower half of the deltoid muscle. Meirelles and Filho¹⁴ reported a 67 year old male who presented with injection site pain one day after vaccination and developed progressive restriction of shoulder abduction and loss in the axillary sensory area over 6 weeks. The clinical diagnosis of anterior branch of the axillary nerve palsy was confirmed by nerve conduction studies.

The sensory loss noted in these cases can not be accounted for on the basis of lone injury to the anterior branch of the axillary nerve, as the posterior branch subserves this function. It has been suggested¹² that sensory deficit in these cases may be due to a cutaneous neuropathy due to the injectate. This effect has been reported with an antiemetic¹² but not with a steroid injection.¹⁵

Musculoskeletal Lalsies

The deltoid muscle covers the subacromial/subdeltoid bursa proximally and the humerus distally. The bursae are intimately related and in direct communication with each other in 80% or more of patients¹⁶ and cover the tendons of the rotator cuff (supraspinatus, infraspinatus, subscapularis and teres minor) which provide dynamic stabilization of the glenohumeral joint.¹⁷

Magnetic Resonance Imaging (MRI) offers a paradigm shift in the diagnosis and management of medically attended injection site reactions as it allows concurrent assessment of both soft tissue and bony injury following vaccination.

Bone and articular injury

Six cases of periosteal reaction (bony contusion) following vaccination have been reported, 4 from published reports and 2 with adequate clinical and MRI data from the VAERS database. The four published cases were with influenza vaccine (Okur et al,¹⁸ males 36 and 39 years old; Barnes et al,¹⁹ female 22 years old and Schafer,²⁰ female 25 years old). The two VAERS

database retrieved cases were a female 18 years old and a male 30 years old vaccinated with the human papilloma virus vaccine (Gardasil[®]) and an influenza vaccine respectively.

Osteonecrosis

Three cases of osteonecrosis due to probable osseus injection have been reported. Two published cases are with influenza vaccine (Kuether et al²¹ and Messerschmidt et al²² in a 48 year old female and a 46 year old male respectively) and a single case report from the VAERS, a 45 year old patient vaccinated with hepatitis B vaccine (Recombivax HB[®]) who had 2 bone biopsies showing osteonecrosis.

Intra-articular injection

Three cases of inadvertent intra-articular injection of vaccines have been reported. One with quadrivalent human papilloma virus vaccine (Gardasil[®])²³ in which no additional clinical data were given and 2^{24,25} with 23 valent pneumococcal polysaccharide vaccine (Pneumovax[®]). The latter cases reported in females 59 and 76 years old respectively were diagnosed as pseudoseptic arthritis of the glenohumeral joint.

Subacromial/subdeltoid bursitis/rotator cuff tendinopathy

The first report of vaccination-related shoulder dysfunction was published by Bodor and Montalvo,²⁶ a 71 year old female and an 89 year old male vaccinated with 23-valent pneumococcal polysaccharide vaccine (Pneumovax[®]) and influenza vaccine (Fluzone[®]) were diagnosed without MRI/ultrasound imaging with “frozen shoulder” and bicipital tendonitis, subacromial bursitis, mild C6 sensory radiculopathy respectively. These authors postulated that vaccines were administered into the subdeltoid bursa with its communication with the subacromial bursa resulting in its inflammation and subsequent inflammation of the biceps tendon and shoulder capsule.

Subsequently, 20 reports of subacromial/subdeltoid bursitis/rotator cuff tendinopathy have been obtained from a combination of published case reports and the VAERS database. Cook²⁷ and Uchida et al²⁸ have reported cases of subacromial/subdeltoid bursitis in a 76 year old male and a 45 year old female vaccinated with influenza and human papilloma virus vaccine respectively. Bathia and Stitik²⁹ reported a case of infraspinatus tendonosis without frank tear in a 34 year old female following influenza vaccination.

Search of the VAERS database retrieved data on 17 patients (16 females, 1 male) who received 19 vaccines and who had MRI demonstrated subacromial bursitis/tendinopathy (influenza vaccine 10, tetanus toxoid 5, DTaP vaccine 2, 23 valent pneumococcal polysaccharide vaccine 1 and tetanus toxoid 1) Some of these data were probably reported by Atanasoff et al.³⁰

Frozen shoulder

Frozen shoulder has been defined³¹ as “a condition characterized by functional restrictions of both active and passive shoulder motion for which radiographs of the glenohumeral joint are essentially unremarkable except for the possible presence of osteopenia or calcific tendonitis.” It has been

classified into primary and secondary groups with the latter including intrinsic, extrinsic and systemic groups. The intrinsic group is associated with tendinopathies which as previously discussed can be a consequence of vaccine administration.

Degreef and Deboer³² reported 3 cases of “frozen shoulder;” a 36 year old female and a 73 year old male vaccinated with hepatitis A and tetanus toxoid vaccines respectively and a 54 year old male vaccinated with influenza vaccine. Two cases were retrieved from the VAERS database, a 49 year old male and a 56 year old female vaccinated with influenza vaccine (Fluzone[®] and Fluvirin[®] respectively).

Cutaneous Reactions

Cutaneous reactions can be divided into 3 groups; sequelae of inadvertent subcutaneous rather than intramuscular injection, local sepsis and vascular complications.

Adverse events due to inadvertent subcutaneous rather than intramuscular injection

Subcutaneous nodules

The Brighton Collaboration Local Reaction Working Group defines³³ a nodule at the injection site with a level 1 of diagnostic certainty as: “the presence of—a discrete or well demarcated soft tissue mass or lump THAT IS FIRM AND - is at the injection site in the absence of abscess formation erythema and warmth.” They noted that the paucity of data on the time of onset, duration and size of nodules prevented the inclusion of this information in the case definition.

The central role of route of administration in the genesis of subcutaneous nodules is seen in clinical trials with anthrax and botulinum F toxoid vaccines.

Pittman et al³⁴ in a route comparative study with anthrax vaccine (n = 173, 109M, 64F) observed that intramuscular injection generated no subcutaneous nodules while subcutaneous injection generated subcutaneous nodules in 63.4% of females and 24.2% of males.

Wright et al³⁵ reported nodule formation in 161/2762 (5.8%) of females and 98/2554 (3.8%) of males and 409/947 (43.2%) of females and 133/825 (16.1%) of males with intramuscular and subcutaneous injection respectively.

Marano et al³⁶ reported nodule formation in 21/332 (6.3%) of females and 5/300 (1.7%) of males and 161/313 (51%) of females and 73/219 (22.0%) of males with intramuscular and subcutaneous injection respectively.

In a study with type F botulinum toxoid, Edelman et al³⁷ reported that subcutaneous nodules were more frequent after primary and booster injection given subcutaneously 64/264 (24%) compared with intramuscularly administered vaccine 4/97 (4.0%).

Localized lipoatrophy

Localized lipoatrophy is characterized³⁸ clinically by a non-inflammatory focal loss of subcutaneous tissue, and histologically

by fat lobule involution. This reaction has been seen at the injection site of a number of medications³⁸ (antibiotics, corticosteroids, human growth hormone, insulin and vasopressin) and vaccines.³⁹⁻⁴²

Thirty nine cases of localized lipoatrophy following vaccination were obtained from a combination of published case reports and the VAERS database.

Ojaimi et al³⁹ and Stephan et al⁴⁰ reported cases in females 23 and 25 years old and a female 27 years old respectively following quadrivalent human papilloma virus vaccine (Gardasil[®]). Mayet et al⁴¹ and Javelle et al⁴² reported cases in a female (no age given) and a female 30 years old respectively given AS03 – adjuvanted influenza A (H₁N₁) 2009 vaccine.

Thirty four cases (33F, 1M) with 35 vaccines (influenza 17, human papilloma virus 9, hepatitis B 5, hepatitis A 2, diphtheria/tetanus 1, measles/mumps/rubella 1, typhoid 1) were retrieved from the VAERS database (“injection site atrophy”) which satisfied the inclusion criteria for this review.

Localized lipoatrophy has been suggested⁴³ as being due to non-vaccine specific administration trauma to subcutaneous tissue. Support for this thesis can be drawn from the observation of this reaction following acupuncture⁴⁴ and the suggestion⁴⁵ that trauma rather than immune activation of macrophages underpins the localized lipoatrophy following steroid injection. The female dominance of this reaction may be accounted for on the basis of a greater sensitivity of their subcutaneous tissue to this reaction than males, as reflected by the greater rate of injection site reactions reported by females compared with males with a number of vaccines⁴⁶ (anthrax, DT booster in adolescents, Hib-tetanus toxoid conjugate in infants, influenza and pneumococcal vaccines).

Sterile abscess

The Brighton Collaboration Local Reactions Working Group for abscess at injection site defined⁴⁷ a sterile abscess with level 1 diagnostic certainty as – spontaneous or surgical drainage from the mass AND material obtained from the mass prior to initiating antimicrobial therapy, but with negative evaluation for infectious etiology (which may include Gram stain, culture or other tests).

Route of administration of adjuvanted vaccines has been shown to be a determinate of sterile abscess formation. Volk et al⁴⁸ reported significant differences in “antigen cyst” (sterile abscess) formation in an observational study with aluminum adjuvanted vaccines administered by subcutaneous injection (135/2215, 6.1% institutionalized patients; 6/161, 3.7% community dwelling patients) compared with intramuscular injection (21/4562, 0.5% institutionalized patients, 1/2298, 0.04% community dwelling patients).

In a more recent case report⁴⁹ with aluminum adjuvanted plague vaccine, subcutaneous rather than intramuscular injection of the vaccine generated a sterile abscess in a 22 year old serviceman.

Non-infectious subcutaneous emphysema

Subcutaneous emphysema has been reported following deltoïd intramuscular injection of vaccines. Douglas⁵⁰ reported a

case in a 21 year old female following injection of quadrivalent human papilloma virus vaccine (Gardasil®) and Urdaneta et al⁵¹ reported a case in a patient given SPF malaria vaccine. The latter authors note that the reaction was “probably due to improper application technique.”

Non-infectious subcutaneous emphysema is uncommon but has been reported⁵² after high pressure injection injury and in dermal injury where a small laceration can act as a ‘one-way’ valve. In a no longer used vaccination practice⁵³ each dose of vaccine was terminated with 0.1ml of air to rid the needle tract of adjuvanted vaccine particles to prevent injection site reactions. However, it seems unlikely that this practice could introduce enough air to cause subcutaneous emphysema.

Local sepsis

Cellulitis

The Brighton Collaboration Local Reaction Working Group for cellulitis at injection site defined⁵⁴ cellulitis as “an acute, infectious and expanding inflammatory condition of the skin that is characterized by the following inclusion and exclusion criteria.” Level 1a of diagnostic certainty—at least 3 of the following 4 signs/symptoms: localized pain or tenderness (pain to touch), erythema, induration or swelling and warmth AND reaction is 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 is at the injection site AND has been diagnosed by a qualified health care provider. Exclusion criteria – spontaneous rapid resolution AND/OR fluctuance.

Lapphra and Schiele assert⁵⁵ that “injection-related bacterial cellulitis is vanishingly rare” after pre-school booster. Certainly there is a paucity of data on injection site cellulitis satisfying the Brighton Collaboration criteria following deltoid intramuscular injections of vaccine with a single case report and limited data from surveillance programs. Owensby and Elliott reported⁵⁶ a case of cellulitis/myositis in a 44 year old female due to *Agrobacterium radiobacter* and *Haemophilus parainfluenzae* following influenza vaccine injection.

Search of the VAERS database for “injection-site-cellulitis” retrieved 1625 entries with manual search of these reports finding 109 entries (23-valent pneumococcal polysaccharide 71, DT/DTP 16, influenza 11, meningococcal 6, anthrax 3, hepatitis and varicella vaccines 1 each), satisfying the level 2 criteria of the Brighton Collaboration Local Reaction Working Group for cellulitis and the inclusion requirements of this review. This data collection certainly contains reactions of a non-infectious etiology, as the majority of cases were reported for 23-valent pneumococcal polysaccharide vaccine for which there has been an increasing number of reports⁵⁷⁻⁵⁹ of a non-infectious cellulitic reaction. This syndrome reported in children^{57,58} and adults⁵⁹ is suggested⁵⁷ to present with earlier erythema and induration and fever than bacterial cellulitis and is unresponsive to antibiotics.

Vaccine safety datalink (VSD) program – cellulitis data

Review of studies drawn from data collected by the Vaccine Safety Datalink program,⁶⁰ an active collaboration between a

number of health maintenance organizations and the National Immunization Program of the Centers for Disease Control also gave reports of vaccine-related cellulitis. Improved diagnostic certainty of the VSD project data is achieved by chart review of those with presumptive events. In this review only studies with this level of analysis are included.

Vaccine Safety Datalink Cellulitis data have been reported by Jackson et al⁶¹⁻⁶⁴ with; fifth dose of DTaP in children 4–6 years old (n = 233, 616), 186 diagnosed with cellulitis and 304 prescribed antibiotics for arm reaction; Td (7), Tdap (9) and MCV₄ (6) medically attended local reactions in a study of adolescents and young adults 9–25 years old (n = 128, 297) 11 were given a clinical diagnosis of cellulitis and 8 treated with oral antibiotics; 23 chart review validated local reactions were assigned the clinical diagnosis of cellulitis (4 treated with parenteral antibiotics and 16 with oral antibiotics) in a study of Td in adolescents and young adults 9–25 years old (n = 436, 828); 2 patients, (71 year old male and 74 year old female) were assigned the diagnosis of cellulitis versus allergic reaction and given a prescription for cephalexin in a study (n = 603) of adults (mean age 73 ± 7 years old) given a third dose of 23-valent pneumococcal polysaccharide vaccine.

Other vaccine surveillance program cellulitis data

Two reports^{65,66} of post-vaccination cellulitis have been made for influenza vaccine by the South Korean Passive Surveillance System. Choe et al⁶⁵ reported cellulitis in 7/45 vaccine recipients with serious adverse reactions following trivalent, inactivated influenza vaccination over the period 2003–2010 with 2 satisfying Level 1 and 5 satisfying Level 2 criteria of the Brighton Collaboration Local Reaction Working Group for cellulitis. Kim et al⁶⁶ reported an 8 year old male who developed cellulitis as a serious adverse reaction following novel influenza A (H₁N₁) 2009 vaccination.

Thirteen patients were reported⁶⁷ as having cellulitis as a serious adverse reaction during the period 1992–2008 in the Veneto region of Italy for all vaccines and age groups. Thus including some patients given other than deltoid intramuscular injection. One patient was reported⁶⁸ with cellulitis requiring hospitalisation following Dtap-IPV as a pre-school booster by the Ontario, Canada Surveillance program.

Abscess of infectious etiology and pyomyositis

The Brighton Collaboration Local Reactions Working Group Level 1 of diagnostic certainty for abscess of infection etiology requires⁴⁷ laboratory confirmation of microbiological organisms. There are 4 case reports^{57,65,69,70} and 8 cases from the VAERS database which satisfy this level of certainty.

Borghans and Stanford reported⁶⁹ abscesses due to *Mycobacterium chelonae* after injection of diphtheria-pertussis-tetanus-polio vaccine in 47 children, 5 injected in the upper arm. It was suggested that these cases were most likely due to contamination of multidose vials but the contamination of a number of vials with the same mycobacterial strain over a 6 month period being unexplained.

A single case of pyomyositis due to *Mycobacterium tuberculosis* has reported⁷⁰ the following hepatitis A (Havrix®) injection into the left deltoid muscle of a healthy 17 month old female. It

was suggested that this infection occurred co-incidentally with vaccination and was not due to syringe contamination as a non re-usable syringe was used.

Two other single case reports of abscess of infectious etiology were reported following administration of inactivated influenza vaccine⁶⁵ and 23 valent pneumococcal polysaccharide vaccine.⁵⁷ The latter cultured coagulase-negative staphylococcus and was concluded by the authors to be a “contaminant.”

Search of the VAERS database for “injection site-abscess” retrieved 8 case reports (5F, 3M) which satisfied the criteria for inclusion in this review. Four patients were culture positive for commensal bacteria (M/25yrs, DT, *Staphylococcus epidermidis*; M/59yrs, TT, Mixed skin flora; F/24.9yrs, 23 valent pneumococcal polysaccharide, *Staphylococcus hominis* and M/64yrs, DTaP, *Staphylococcus coagulase negative*), one was culture positive for Group A beta-haemolytic streptococcus (F/1.1yr, DTP) and 3 were culture positive for *Serratia marcescens* (F/11yrs, DT; F/33.5yrs, DT; F/24.7yrs, DT). *Serratia marcescens* a Gram negative facultative anaerobic bacillus is a rare cause of dermal abscess in immunocompetent patients following injection⁷¹ and skin injury.⁷² Park and Seo reported,⁷¹ abscess formation following filler injection in a 62 year old female and recommended “clean preparation of the skin” “prior to filler placement.”

Subcutaneous emphysema of infectious etiology

Two fatal cases of gas gangrene due to *Clostridium septicum* have been reported^{73,74} in females aged 80 and 71 years old following influenza vaccine.

Vascular complications

Nicolau Syndrome or embolia cutis medicamentosa is a rare complication⁷⁵ of intramuscular injection of medications leading to ischemic necrosis at the injection site due to direct trauma to vascular structure or trauma induced vasospasm or a combination of both mechanisms.

The syndrome has only been reported after vaccination in children and with one case reported⁷⁶ after intramuscular injection of Infanrix hexa[®] into the deltoid muscle of a 21 month old female.

Discussion

Data collated in this review draws attention to 4 aspects of vaccination practice with regards to deltoid intramuscular injection.

Selection of a ‘safe’ site for injection

Intramuscular injection of the deltoid muscle should be given along a line drawn vertically downwards from the mid acromion, as posterolateral injection has the potential to compromise the radial nerve. There are currently 4 different methods recommended⁷⁷ for site selection along this line. Three of these methods involve ‘land marking’ using the acromion:

Injection given variable distances below this structure measured as centimeters or finger breadths/widths.

Injection given into the midpoint of a triangle (apex on a line drawn laterally across the deltoid muscle from the apex of the

axilla and with its base on or 2 or 3 finger breadths below the acromion). This technique is recommended by National Immunization Technical Advisory Groups (NITAGs) in Ireland,⁷⁸ New Zealand⁷⁹ and USA.⁸⁰

Injection into the site midpoint between the acromion and the deltoid tuberosity, a technique recommended in Australian NITAG guidelines.⁸¹

A fourth method involving injection into the middle third of the deltoid muscle has also been recommended.

However, in an anthropometric study⁷⁹ measuring the position of anatomical landmarks in adults (≥ 65 years old) and mapping the location of structures potentially injured by injection it was observed that all these methods could result in injury to these structures.

Injury to the anterior branch of the axillary nerve can result from the 2 site selection methods endorsed by NITAGs with the vaccine recipients’ arm by their side (neutral position). However, in a cadaver study⁸² it was observed the anterior branch of the axillary nerve was moved 1.3 to 1.4cms toward the acromion and away from the midpoint of muscle (acromion to deltoid tuberosity) if the shoulder was abducted to 60°.

Consequently, a ‘safe’ method for injection site selection can be obtained⁷⁹ by having the vaccine recipient place their hand on their hip (abducting the shoulder 60°) and giving the injection into the mid-point of the muscle.

Individualising needle length selection for muscle penetration and using a standardised injection technique

The needle over and under penetration medically attended injection site event data presented in this review may reflect errors in either the selection of an appropriate length needle^{83,84} and/or injection technique (angle of needle insertion⁸⁵ and whether the muscle was ‘bunched’ or ‘flattened’ prior to injection⁸⁶).

Needle length selection data in adults has been obtained by ultrasonographic studies^{83,84} of the deltoid fat pad with the transducer not compressing the skin and measurement being made at 90° to the skin’s surface. These studies suggested that a 25 mm long needle would routinely penetrate 5mm of the deltoid muscle if entered at this angle and inserted to the hub in males <118 kg and females 60–90 kg and all males and females body mass index (BMI) <35. This needle length is recommended in NITAGs in Argentina,⁸⁷ Australia,⁸¹ Canada,⁸⁸ Dubai,⁸⁹ Ireland,⁷⁸ New Zealand,⁷⁹ Sri Lanka,⁹⁰ United Kingdom⁹¹ and the USA⁸⁰ for injection in most adults.

However, needle length should be individualized as a 25 mm long needle would result in under penetration in males >118 kg and females >90 kg and BMI >35 and over penetration in females <60 kg. Moreover, there are no data on needle length to be used when the skin is ‘bunched’ or ‘flattened’ prior to injection or when the needle is entered at an angle of other than 90° to the skin’s surface.

There is no consensus on needle length for intramuscular injection at this site for children aged 12 months and older with a 16mm long needle recommended in India⁹² and New Zealand⁷⁹; needle 16–25 mm long being recommended in Argentina,⁸⁷ Dubai,⁸⁹ and USA⁸⁰; needles 22–25 mm long being

recommended in Canada⁸⁸ and 25 mm long needles being recommended in Australia,⁸¹ Ireland,⁷⁸ Sri Lanka⁹⁰ and UK.⁹¹

Skin preparation prior to injection

Skin preparation prior to vaccination is not mentioned in NITAG recommendations from Argentina,⁸⁷ Canada,⁸⁸ Dubai,⁸⁹ India,⁹² Sri Lanka,⁹⁰ considered unnecessary in Australia⁸¹ and UK⁹¹ and if used in Ireland⁷⁸ and New Zealand⁷⁹ the skin site should be allowed to dry for 30 seconds and 2 minutes respectively after alcohol swabbing.

The Australian⁸¹ and UK,⁹¹ recommendations are underpinned by a one page report⁹³ by proponents of evidence based medicine who have argued on the basis of 2 small vascular access studies and one small insulin site comparative study that there is no need to clean the skin prior to intramuscular injection because there are no randomized controlled trials which have resulted in a *p* value of ≤ 0.05 for skin cleaning, so indicating “no evidence” for any benefit of hygiene in this case.

This conclusion, a false negative result, reflects the limitations⁹⁴ of EBM to assess the impact of a low cost treatment in the context of a very low risk/high cost event. Consequently the very low prevalence of significant cost infectious sequelae following deltoid intramuscular vaccination (cellulitis 363, abscess formation 16 and subcutaneous emphysema 2) would make it difficult to defend⁹⁵ a case of local sepsis if skin preparation (a very low cost treatment) was omitted prior to vaccination.

Preparation of the skin is recommended by the WHO⁹⁶ for intramuscular injection of therapeutic agents, this involves application of a single use 70% isopropyl swab for 30 seconds and allowing skin to dry. Cocoman & Murray⁹⁷ suggest the skin be allowed to dry for 30 seconds.

Syringe aspiration before injection

Aspiration before injection is not recommended by any National Immunization Technical Advisory Group. Certainly only one case of Nicolau syndrome (ischemic necrosis at the injection site), the complication this procedure is potentially intended to prevent, was retrieved from the extensive literature search for this review. Moreover, omission of this procedure results in faster injection which is associated⁹⁸ with greater parental acceptance of their children's vaccination. Consequently this procedure cannot be recommended.

Conclusion

Analysis of medically attended injection site event data provides a vehicle to appreciate the inadequacies of current vaccination practice for deltoid intramuscular injection. This analysis demonstrates that best practice requires; selection of a ‘safe’ site for injection, individualising needle length for muscle penetration, using a standardised injection technique and skin preparation prior to injection.

Implementation of these best practice recommendations should help reduce public concerns about the safety of deltoid intramuscular administration of vaccines.

Methods

Data for this review were sought from the following data bases; Medline via Ovid (1966 to present), Embase via Ovid (1980 to present), The Cochrane Central Register of Controlled Trials, CINAHL via EBSCO (1982 to present).

Word searches

Using word searches “injection site reactions/shoulder injury/radial and axillary nerve palsy/periosteal reaction/boney contusion/osteonecrosis/septic and pseudoseptic arthritis/subacromial/subdeltoid bursitis/rotator cuff tendinopathy/frozen shoulder/nodules/panniculitis/lipoatrophy/cellulitis/abscess formation/subcutaneous emphysema/Nicolau syndrome/embolia cutis medicamentosa” and “vaccine studies/trials.”

Additional data were obtained by hand searching journals for “safety data” and “vaccine studies/trials.” The following journals were searched from the date in parenthesis to June 2014:

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 Disease 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 was searched manually by the author, for “injection site nerve damage,” “nerve injury,” “axillary and radial nerve injury,” “bone contusion,” “osteonecrosis,” “injection site joint inflammation/effusion/swelling,” “bursitis,” “tendon injury,” “tendonitis,” “peri-arthritis,” “injection site nodule,” “injection site granuloma,” “injection site atrophy,” “lipoatrophy,” “panniculitis,” “injection site abscess” and “injection site abscess sterile,” “subcutaneous emphysema,” “injection site cellulitis and embolia cutis medicamentosa.”

Data were included from this database if an adverse reaction was reported or reviewed by a healthcare professional and if demographic data (age,sex) and vaccine name and route and site of injection (intramuscular, arm) were provided.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed in the submitted article are the author's and not an official position of the University of Newcastle.

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