Subcutaneous diphtheria and tetanus vaccines in children with haemophilia: A pilot study and review of the literature

B. A. Schaefer | R. A. Gruppo | E. S. Mullins | C. Tarango

Introduction: Subcutaneous (SQ) vaccination has emerged as standard of care in children with severe bleeding disorders to reduce unnecessary factor exposure and avoid provoking an intramuscular bleed, but little is known about comparative immunogenicity to intramuscular (IM) vaccination.

Aim: To confirm immunogenicity of Diphtheria Tetanus acellular Pertussis (DTaP) vaccines administered SQ to individuals <6 years old with haemophilia.

Methods: We performed a retrospective and prospective pilot study of tetanus and diphtheria antibody titres among patients evaluated at our Haemophilia Treatment Centre between 2015-2016. Children with haemophilia who had received three to four doses of DTaP containing vaccine administered SQ were eligible.

Results: Eight children met inclusion criteria. The mean age at the time of diphtheria and tetanus antibody testing was 21.1±17.8 months. All children who received SQ diphtheria and tetanus developed a positive antibody titre to both antigens. There was no statistically significant difference in distribution of titre values. The average time between the last dose of vaccine and antibody testing was 6.6±3.9 months among SQ vaccinated subjects. Minor injection site reactions were common with SQ vaccines.

Conclusion: SQ administration of diphtheria and tetanus vaccination appears to be immunogenic in a pilot study of Haemophilia patients and supports this practice as the standard of care for this population.

Keywords: diphtheria, haemophilia, immunization, severe bleeding disorders, subcutaneous vaccination, tetanus

1 | INTRODUCTION

The Advisory Committee on Immunization Practices (ACIP) and the American Academy of Paediatrics (AAP) recommend that all immunocompetent children receive scheduled vaccinations to prevent diphtheria, tetanus, polio, and other communicable diseases.\(^1,2\) Many adjuvant-containing vaccines in childhood are given via an intramuscular (IM) route primarily due to decreased local reactions (oedema, erythema, pruritis, granuloma formation) and improved immunogenicity in a subset of vaccines given to elderly adults, including Hepatitis B and influenza.\(^3,4\) In individuals with haemophilia and severe bleeding disorders however, the IM administration of vaccines or medications may cause significant intramuscular haematomas, and commonly alternative therapies exist.\(^5\) Because of this risk, the World Federation of Haemophilia (WFH) guidelines for management of haemophilia recommend that all vaccinations be administered subcutaneously (SQ) or given IM after a dose of replacement factor.\(^5\) The necessity to administer factor concentrate concurrently with IM immunizations makes the administration of vaccines impractical in a community physician’s office. In addition, there is a concern that immunizations administered at the same time as clotting factor concentrates may be a risk factor for inhibitors in minimally treated children.\(^7-9\) These concerns make the SQ administration of vaccines in young children a reasonable alternative to IM administration. Although conclusive data on the risk of inhibitor formation with
concomitant administration of factor replacement and immunizations do not exist, clinicians often opt to administer immunizations SQ without factor replacement.\textsuperscript{10} The consensus among many providers is that if SQ administration results in a lower rate of successful immunization then it is offset by the avoidance of the well-documented risk of muscle haematoma.\textsuperscript{11} Studies examining safety of intramuscular injections in individuals on anticoagulation are equally limited.\textsuperscript{12,13}

Prior studies have demonstrated that SQ administration of Hepatitis A and Hepatitis B vaccines are immunogenic,\textsuperscript{14-27} however, there is incomplete evidence regarding immunogenicity and tolerability of SQ administration of diphtheria and tetanus vaccines.\textsuperscript{28,29} We report on a pilot study of the immunogenicity of subcutaneously administered tetanus and diphtheria vaccines in individuals with haemophilia, as well as review available evidence to support this vaccination practice for individuals with severe bleeding disorders. The data generated from this pilot study provides a rationale for a larger controlled study of IM vs SQ vaccines.

2 | MATERIALS AND METHODS

We conducted a prospective single-institution pilot study of haemophilia patients of any severity who were receiving all their immunizations subcutaneously. This study was approved by the Cincinnati Children’s Hospital Medical Center Institutional Review Board, and informed consent was obtained from parents or legal guardians. In addition to the pilot study, we performed a retrospective chart review to gather data on patients who may have already had vaccine titres drawn as part of routine clinical care and who had received all immunizations SQ.

Inclusion criteria included children aged 6 months–6 years of age with Factor VIII or IX deficiency of any severity, and who had received at least three, and no more than four diphtheria and tetanus vaccines (DTaP or DTaP-IPV/HIB) that were documented as administered SQ. Children were excluded if they had received IM immunization, if more than 24 months between diphtheria and tetanus vaccines had elapsed, or if they carried a diagnosis of concurrent immunodeficiency or if they were prescribed chronic systemic steroids. Vaccine records were obtained and reviewed on all subjects. IgG antibody titers to diphtheria and tetanus were obtained at least 30 days following diphtheria or tetanus vaccination. After informed consent, serum samples were collected at any point venepuncture was being performed for routine clinical care such as for laboratory testing, factor infusions, or during hospitalization. Testing of diphtheria and tetanus antibody titres was performed by Arup Laboratories (Salt Lake City, UT, USA), using established reference ranges (greater than 0.1 IU/mL considered protective for both).

3 | RESULTS

A total of eight male children enrolled on the study in a one year period. There were five children with Factor VIII deficiency (four severe, one mild) and three with Factor IX deficiency (two mild, one moderate). One patient with severe Factor VIII deficiency was receiving prophylactic recombinant factor infusions for a history of intracranial haemorrhage in infancy, however he continued to receive vaccinations subcutaneously. None of the children had inhibitors. Five children received immunizations at their community paediatrician’s office, and three at the Haemophilia Treatment Centre at Cincinnati Children’s Hospital Medical Center.

The average age at the time of tetanus antibody testing was 21.1±17.8 months. The average time between the last dose of vaccine and antibody testing was 6.6±3.9 months among all subjects. Three patients had received four injections of diphtheria and tetanus, and five had received three injections. All children developed a positive diphtheria antibody titre with a mean titre of 1.25 IU/mL±1.2 (>0.1 IU/mL considered seroprotective) and 1.6±1.6 for tetanus (>0.1 IU/mL, considered seroprotective). Children who had received three vaccines (N=5) were younger with an average age of 11.4 months, had titres drawn an average of 4.8 months following vaccination, and were found to have an average diphtheria titre of 1.2 IU/mL±1.0 (>0.1 IU/mL), and tetanus titre of 1.9 IU/mL±1.8 (>0.1 IU/mL). This is similar to previous trial results of IM administration of diphtheria and tetanus vaccines, with titres obtained one month following third dose of DTaP with a mean diphtheria titre of 0.84 IU/mL, and mean tetanus titre of 0.19 IU/mL.\textsuperscript{29,30} Children who received four vaccines (N=3), were older with an average age 37.3 months, had titres drawn an average of 9.7 months following vaccination, with an average diphtheria titre of 1.4 IU/mL±1.7 (>0.1 IU/mL) and tetanus titre of 1.1 IU/mL±1.2 (>0.1 IU/mL), similar to previously published findings.\textsuperscript{30} At time of enrollment, parents were interviewed regarding history of injection site reactions (oedema, erythema, pruritis, palpable nodule), with four of the eight parents reporting mild injection site reactions, none of which required medical evaluation for these signs and symptoms. There were no episodes of vaccination related bleeding or haematoma formation, and no patients developed an inhibitor during the study.

4 | DISCUSSION

Prophylactic vaccination against communicable diseases has been the major public health victory of the past century, in part due to meticulous and exhaustive research regarding safety and efficacy.\textsuperscript{31} In individuals with severe bleeding disorders who are at risk of intramuscular haematomas with IM administration of medications, SQ vaccination has emerged as the standard of care,\textsuperscript{6} and there is ongoing debate regarding vaccine immunogenicity and tolerability with this alternate route of administration. Historically, SQ injection has been cited as a cause of vaccine failure, with lower rates of seroconversion due to poor vascularity of the subcutaneous tissues, resulting in slower mobilization and antigen processing;\textsuperscript{3} this effect is most pronounced in elderly adults with more prominent adipose tissue.\textsuperscript{3,4}

There are few published studies that compare immunogenicity and tolerability between SQ and IM administration of recommended childhood vaccines, and primary care providers are often unable to extensively review literature during their busy practice.\textsuperscript{32,33} All
live-attenuated vaccines including MMR and varicella vaccines are recommended to be given SQ, and several other live-attenuated vaccines are in development or in use in other countries. In Japan, SQ vaccination is the preferred route of administration of all childhood vaccines. A meta-analysis conducted by Ajana et al. identified nine studies with direct comparison of SQ to IM administration of various vaccines in healthy individuals, and concluded that immunogenicity was equivalent, although tolerability was superior in IM injections.

In haemophilia, Hepatitis B vaccination has been the most well studied due to risk of transfusion-acquired hepatitis. A compilation of comparative vaccine studies conducted within the bleeding disorder population and the general population are reviewed in Table 1

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Author (year)</th>
<th>Type of trial</th>
<th>Population studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, Tetanus (DTaP)</td>
<td>Schaefer (2016)</td>
<td>Prospective/Retrospective</td>
<td>SQ: 8 children, mean age 21 mo</td>
<td>100% seroprotection</td>
</tr>
<tr>
<td>Hepatitis A Vaccine</td>
<td>Ragni (2000)</td>
<td>Phase IV, prospective</td>
<td>SQ: 45 children, IM: 41 unaffected sibling controls; mean age 8.7 y</td>
<td>Similar rates of seroconversion to anti-HAV-IgG at 1, 6 and 8 mo</td>
</tr>
<tr>
<td></td>
<td>Zuckerman (1996)</td>
<td>Prospective</td>
<td>SQ: 30 children &lt;16 y, 67 adults &gt;16 y</td>
<td>Adequate rates of seroconversion; children superior to adults</td>
</tr>
<tr>
<td></td>
<td>Tilzey (1996)</td>
<td>Prospective</td>
<td>SQ: 26 HIV+ adults, 8 HIV− adults, and 25 HIV− unaffected controls</td>
<td>Similar rates of seroconversion to anti-HAV-IgG at 1, 6 and 8 mo, higher anti-HAV titres in HIV−</td>
</tr>
<tr>
<td></td>
<td>Dentico (1996)</td>
<td>Prospective</td>
<td>SQ HAV 3 dose: 91 adults and children; mean age 14 y; HIV+/−</td>
<td>98% seroconvert, Higher anti-HAV titres in HIV−</td>
</tr>
<tr>
<td></td>
<td>Rothschild (1995)</td>
<td>Prospective</td>
<td>SQ: 39 children, including 7 HIV+; mean age 7 y</td>
<td>97% seroconversion, failure in child with HIV and low CD4 count</td>
</tr>
<tr>
<td></td>
<td>Santagostino (1994)</td>
<td>Prospective</td>
<td>SQ HAV 3 dose: 113 adults and children with haemophilia, including 47 HIV+</td>
<td>100% seroconversion after two doses, higher immunogenicity in HIV−</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Carpenter (2015)</td>
<td>Retrospective</td>
<td>SQ: 92, IM: 114, mean age 56 mo</td>
<td>No difference in immunogenicity SQ to IM</td>
</tr>
<tr>
<td></td>
<td>Roznovsky (2010)</td>
<td>Retrospective</td>
<td>SQ: 51 children and adults</td>
<td>98% seroconversion</td>
</tr>
<tr>
<td></td>
<td>Pillay (1994)</td>
<td>Retrospective</td>
<td>SQ: 122 children and adults, ID: 36, including HIV+</td>
<td>SQ superior to ID, lower seroconversion in older adults and HIV+</td>
</tr>
<tr>
<td></td>
<td>Miller (1989)</td>
<td>Prospective</td>
<td>SQ: 8 children, 19 HIV negative adults, ID: 8 children, 26 HIV negative adults</td>
<td>100% of children responded, 17/19 adults seroconverted, SQ superior to intradermal, higher immunogenicity in HIV−</td>
</tr>
<tr>
<td></td>
<td>Zanetti (1986)</td>
<td>Prospective</td>
<td>SQ HBV 4 dose: 113 adults and children</td>
<td>98% seroconversion</td>
</tr>
<tr>
<td></td>
<td>Janco (1985)</td>
<td>Prospective</td>
<td>SQ: 36 adults, HIV status unknown</td>
<td>96% seroconversion</td>
</tr>
<tr>
<td></td>
<td>Hedner (1984)</td>
<td>Prospective</td>
<td>SQ: 30 adults, HIV status unknown</td>
<td>Adequate rates of seroconversion</td>
</tr>
<tr>
<td>Influenza, trivalent</td>
<td>Brydak (1998)</td>
<td>Prospective</td>
<td>SQ: 38 children</td>
<td>76%-97% seroconversion at 6 mo, similar to IM controls</td>
</tr>
</tbody>
</table>

ID, intradermal; HAV, hepatitis A virus; IM, intramuscular.
and Table S1 respectively. Although these studies vary in patient demographics, country of origin, composition of vaccine, and timing of vaccination, they consistently demonstrate similar immunogenicity between SQ and IM vaccination in children. Rates of seroconversion are consistently lower in individuals with HIV and in older adults. There is insufficient evidence to support the practice of obtaining post-vaccination titres in children who have received SQ diphtheria and tetanus vaccines. Post-vaccination titres are recommended for Hepatitis B depending on patient risk factors and may be of utility in children with concurrent immunologic disorders, liver disease or HIV.

Our pilot study is the first study in children with haemophilia to confirm adequate immunogenic responses to SQ diphtheria and tetanus vaccination. Factors that affect the immune response to vaccine antigens are complex and include host factors like obesity, smoking, genetic polymorphisms as well as vaccine related factors, including site of injection, and whether antigens are given as separate injections or combined with other antigens. In our study, all children received combined vaccines. Historically the rates of seroconversion for DTaP-IPV/HIB are noninferior when compared with infants receiving separately administered vaccines, and have not shown decreased immunogenicity when administered with other vaccines. Local reactions were common in our cohort, and historically they have been reported in up to 78% of children receiving SQ DTaP and in 65% of children receiving IM DTaP. There were no reports of sterile abscesses in our patients. A larger prospective study would be needed to assess for significant differences in local reactions and complications between SQ and IM administered vaccines.

As the landscape of therapeutic options for preventative immunizations continues to evolve, it is likely that the debate to administer IM vs SQ will continue with the advent of each new agent. The anti-viral human papillomavirus vaccine is recommended for all adolescents, and to date SQ administration has not been studied. Currently, the SQ administration of palivizumab to prevent respiratory syncytial virus in at-risk infants has not been studied, but has been adopted by some centres.

Limitations of this study include small sample size and use of historical controls rather than controls receiving vaccines at similar time points. In examining true immunogenicity, evaluation of pre- and post-vaccination titres is helpful, given individual variability in response to vaccines. A larger, prospective study would be required to study the impact of subcutaneous administration of vaccines, as well as to identify rare complications.

Many children with bleeding disorders receive their immunizations by a community paediatrician or family practitioner at routine well-child visits. Community providers are often unfamiliar with the recommendation for universal subcutaneous vaccination in children with severe bleeding disorders and may have concerns regarding efficacy and safety (see Table S1). Good communication between haematologists and community providers is key to clarify misconceptions and provide education about safety and technique. At our institution, our practice is to instruct our paediatric colleagues to apply cool compresses to the area for five minutes prior, have an experienced nurse administer the vaccine subcutaneously using the smallest gauge needle possible (26 gauge or smaller), and hold pressure for five minutes afterwards. We counsel families about this practice and the potential for local inflammatory reactions as well as risk of bleeding.

Our pilot study has provided evidence that subcutaneous DTaP vaccination generates an apparent adequate immune response in children with haemophilia. The data from our cohort provides a foundation for a prospective controlled trial to confirm the noninferiority of SQ administration of the DTaP vaccine compared with IM administration.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to the patients and families, as well as the research staff, particularly Rebecca Thompson. This work was supported by the Tri-State Bleeding Disorder Foundation (a chapter of the National Hemophilia Foundation). BS, CT performed the research and designed the research study. BS analysed the data. BS, CT, wrote the manuscript. RG, EM reviewed the manuscript. RG has served on the advisory boards for Shire, Grifols, Biogen and CSL Behring. EM has received honoraria from Shire, has served on the advisory board for US World Meds, Shire and Bayer. CT has received honoraria and served on the advisory board for Shire.

DISCLOSURES

ESM: Honoraria Shire Advisory Board: US World Meds, Shire, Bayer; CT: Honoraria Shire and Octapharma Advisory Board; RG has been on the advisory boards for Shire, Grifols, Biogen and CSL Behring.

REFERENCES

25. Zanetti AR, Mannucci PM, Tanzi E, et al. Hepatitis B vaccination of
28. Mark A, Carlsson RM, Granström M. Subcutaneous versus intramus-
12. Delafuente JC, Davis JA, Meuleman JR, Jones RA. Influenza vac-
14. Ragni MV, Lusher JM, Koerper MA, Manco-Johnson M, Krause DS.
13. Raj G, Kumar R, McKinney WP. Safety of intramuscular influenza im-
10. Makris M, Conlon CP, Watson HG. Immunization of patients with
11. Seale JR. Importance of injecting vaccines into muscle. Parenteral
21. Roznovský L, Orságová I, Tvrdík J, et al. [Hepatitis B immunization of

Rothstein EP, Kamiya H, Nii R, et al. Comparison of diphtheria-

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Schaefer BA, Gruppo RA, Mullins ES, Tarango C. Subcutaneous diphtheria and tetanus vaccines in children with haemophilia: A pilot study and review of the literature. Haemophilia. 2017;00:1–6. https://doi.org/10.1111/hae.13316