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CLINICAL RESEARCH

Incidence and prevention of post-immunisation bleeding complications in people with haemophilia at a treatment centre in India

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Background: Haemophilia is an inherited bleeding disorder characterised by a deficiency in coagulation factors, leading to an increased risk of bleeding, including after procedures such as immunisation. While immunisation is crucial for preventing infectious diseases, it poses a bleeding risk in people with haemophilia, particularly when administered intramuscularly. **Aims:** This study aims to assess the incidence of bleeding complications following immunisation and the use of prophylactic measures among people with haemophilia (PwH) at a haemophilia treatment centre (HTC) in Manipal, India. **Methods:** A descriptive cross-sectional study was adopted with a purposive sample of 65 PwH. Data was collected using a demographic proforma and a structured questionnaire on post-immunisation complications and the use of prophylactic measures. Data was collected from the PwH and the caregivers of PwH through an interview. The analysis is reported using descriptive and inferential statistics. **Results:** Sixty-five PwH were included in the study (55 (84.6%) haemophilia A; 10 (15.3%) haemophilia B). The study found that 23.1% of participants experienced bleeding complications following intramuscular immunisation, while 76.9% of participants did not experience any bleeding complications. The prophylactic measures reported include administration of clotting factor concentrates, close monitoring for bleeding

symptoms, and using icepacks and compressions. The shift towards subcutaneous immunisation was evident, with 83.1% receiving their first immunisation subcutaneously, and 100% receiving subsequent immunisations via the subcutaneous route post-diagnosis. Additionally, 56.9% received clotting factor replacement therapy prior to immunisation, significantly reducing the risk of bleeding. **Conclusion:** This study gives an overview of the incidence of bleeding complications following immunisations and the prophylactic measures used to prevent it. It is evident that there has been a shift towards subcutaneous immunisation and a decrease in cases of bleeding complications among PwH.

Keywords: *Haemophilia; Immunisation; Vaccine, intramuscular; Bleeding complication; Prophylaxis; Developing country*

Haemophilia is an inherited genetic disorder characterised by a deficiency in clotting factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B. This leads to prolonged bleeding, even from minor injuries or procedures such as immunisation [1]. The complications associated with intramuscular injection in people with haemophilia (PwH) can range from the development of intramuscular bleeding and minor bruising to muscle haematomas. The management of bleeding risks associated with routine vaccinations is a critical aspect of care for PwH [2,3]. Immunisations are essential in preventing infectious diseases but pose a challenge for PwH due to the risk of bleeding at the injection site [1]. Conventionally, intramuscular injections have been avoided in PwH due to concerns about the risk-benefit balance. Recent data from the European Paediatric Network for Haemophilia Management found no link between vaccination timing and inhibitor development in previously untreated patients with severe haemophilia, with 18.9% receiving intramuscular injections, 74.0% subcutaneous, and 6.9% via an unknown route [4]. Vaccines are well-tolerated in PwH, but special considerations need to be taken for immunisation given through the intramuscular route [5].

According to the National Family Health Survey report for 2019-2021 (NFHS-5), India's full immunisation coverage stands at 76.1%, meaning that one in four children miss essential vaccines [6,7]. The National Immunization Schedule recommends administering the birth dose of hepatitis B (HBV) vaccine, three doses of HBV, three doses of the combined diphtheria, tetanus and polio (DPT) vaccine, three doses of haemophilus influenza type B (Hib) vaccine, and two doses of DPT booster to be given intramuscularly before the age of five. It also recommends two doses of tetanus toxoid (TT) vaccine via the intramuscular route at 10 years and 16 years of age [8]. For PwH, a 2010 consensus report supports subcutaneous vaccination to avoid the need for concurrent factor substitution [9]. Considering the associated risks and complications, the World Federation of Hemophilia (WFH) recommends that children with haemophilia receive subcutaneous immunisation to lower the risk of bleeding complications [2]. This approach has led to increased adoption of the subcutaneous route of immunisation for PwH [10]. To better understand the bleeding risk associated with immunisation in PwH, a study was conducted at the haemophilia treatment centre (HTC) in Manipal, India, to assess the incidence of bleeding complications following immunisation and the prophylactic measures implemented to prevent such complications.

METHODOLOGY

A descriptive cross-sectional study was adopted with a purposive sample of 65 PwH and their caregivers. Data were collected using a demographic proforma and a structured questionnaire on vaccination complication and use of prophylactic measures. The inclusion criteria for the study were: (1) People diagnosed and living with haemophilia, up to the age of 30 years; (2) People who have family members (mother/father).

A demographic proforma and a structured questionnaire were used to collect data from the participants. The proforma gathered information on participants' age, education level, age at diagnosis, type and severity of haemophilia, and family history of the disease. The structured questionnaire included details on immunisation status, the route of administration for the first immunisation, any bleeding complications, the management of those complications, whether clotting factor replacement was received prior to immunisation, and the route of immunisation after diagnosis if clotting factor replacement was not administered. The immunisation criteria established by the Ministry of Health and Family Welfare, India were followed for this investigation, and vaccines delivered intramuscularly (IM) were considered for the study (Table 1). Details regarding the following immunisations were collected: three doses each of HBV, HiB and DPT vaccine, and two doses of DPT booster and two doses of TT vaccine.

The data was collected during a clinic visit. Participants were informed about the study and consent

Table 1. Immunisation schedule criteria established by the Ministry of Health and Family Welfare, India [8]

VACCINE	TIME TO ADMINISTER	DOSE	ROUTE	SITE	INTRODUCTION TIME IN INDIA (MHFW)
HBV	At birth	0.5ml	Intramuscular	Anterolateral side of mid-thigh	2002
HBV 1,2,3	6 weeks, 10 weeks, 14 weeks	0.5ml	Intramuscular	Anterolateral side of mid-thigh	1970s
DTwP/DTaP 1,2,3	6 weeks, 10 weeks, 14 weeks	0.5ml	Intramuscular	Anterolateral side of mid-thigh	
Hib	6 weeks, 10 weeks, 14 weeks	0.5ml	Intramuscular	Anterolateral side of mid-thigh	2008
DTwP/ DTaP booster 1	16-18 months	0.5ml	Intramuscular	Anterolateral side of mid-thigh	1970
DTwP/DTaP booster 2	4-6 years	0.5ml	Intramuscular	Upper arm	
TT	10 years and 16 years	0.5ml	Intramuscular	Upper arm	1970

HBV: Hepatitis B, **DTwP:** Diphtheria, Tetanus, and Whole cell Pertussis vaccine
DTaP: Diphtheria, Tetanus, and Acellular vaccine **Hib:** Haemophilus influenzae type B,
TT: Tetanus Toxoid

was obtained from the parents if the child was under 18 years old. Data collected through interviews were the experiences expressed by the caregivers when their child received vaccination as per the vaccination schedule.

The Institutional Ethics Committee, Kasturba Hospital, Manipal approved the study protocol with CTRI Reg. No: CTRI/2024/04/066207.

Data analysis

Data analysis was undertaken using R software and Microsoft Excel. Descriptive statistics using frequency tables and percentages were used to describe the demographic characteristics of the study participants. The statistical analysis was implemented using R software.

RESULTS

A total of 79 participants were approached to participate in the study, of whom 65 were deemed eligible. Fourteen participants who did not receive any vaccinations were asked about their reasons for not doing so.

Participant demographics

Among the 65 PwH to participated in the study, 22 (33.8%) were under 10 years old and 22 (33.8%) were between 11 and 20 years old. The majority (46; 70.7%), were diagnosed before the age of two, whereas 8 (12.3%) were diagnosed between ages 3 to 5, and 11 (16.9%) were diagnosed after the age of 5. Haemophilia A was the predominant type, affecting 55 participants (84.6%), while 10 (15.3%) had haemophilia B. The severity distribution indicated that 47 participants (72.3%) had severe haemophilia (Table 2).

Incidence of bleeding complications

Among the 79 participants surveyed, 65 (82.2%) had received immunizations (Table 2). Of these, 50 (76.9%) did not experience any post-vaccination bleeding complications. However, 15 (23.1%) reported issues including haematoma, swelling, and pain at the injection site, primarily occurring between 16 to 24 months (Figure 1).

Vaccination routes/Sites used

A notable trend in immunisation practices was observed, with an increasing preference for subcutaneous vaccine administration. Initially, 83.1% of participants received their first vaccination subcutaneously (Figure 2). Following diagnosis, 100% of participants were exclusively vaccinated via the subcutaneous route, aligning with WFH recommendations [2] that emphasise this method to reduce bleeding risk.

Regarding injection sites, the thigh was the most common site for both primary series and booster vaccinations in children under 24 months. Among the 15 participants who experienced bleeding complications, 10 (15.3%) reported bleeding at the thigh injection site, while five (7.7%) reported bleeding in the upper arm.

Table 2. Frequency and percentage distribution of demographic characteristics of study participants (n=65)

VARIABLE	FREQUENCY (F)	PERCENTAGE (%)
Age (years)		
<10	22	33.8
11-20	22	33.8
>21	21	32.3
Education		
No schooling	7	10.7
Primary	12	18.4
Secondary	19	29.2
Higher secondary	9	13.8
University	18	27.6
Age at diagnosis (years)		
0-2	46	70.7
3-5	8	12.3
Over 5	11	16.9
Type of haemophilia		
Haemophilia A	55	84.6
Haemophilia B	10	15.3
Disease severity		
Mild	3	4.6
Moderate	15	23
Severe	47	72.3
Family history of haemophilia		
Yes	30	46.1
No	35	53.8

Table 3. Frequency and percentage distribution of prophylactic measures to prevent complications after vaccination

ITEM	FREQUENCY (N)	PERCENTAGE (%)
Have you/your child received vaccination? (n=79)		
Yes	65	82.2
No	14	17.7
Did you have any bleeding complications after the vaccination? (n=65)		
Yes	15	23.1
No	50	76.9
If yes, how was it managed? (n=15)		
Factor injection	9	13.8
Icepack and compression	6	9.2
Did you receive any clotting factor replacement therapy before your vaccination? (n=65)		
Yes	37	56.9
No	28	43.1
Route of administration of first vaccination? (n=65)		
Subcutaneous	54	83.1
Intramuscular	11	16.9

Figure 1. Distribution of site of bleeding complications (%)

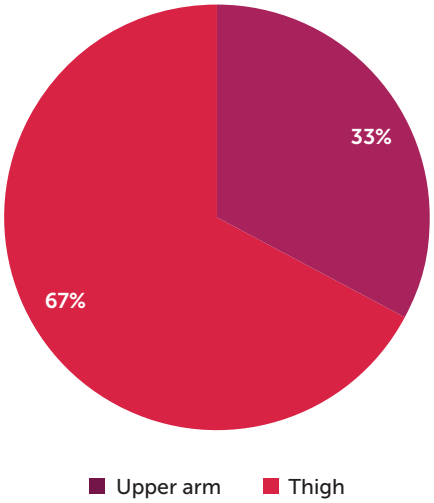


Figure 2. Shift in route of vaccination (%)

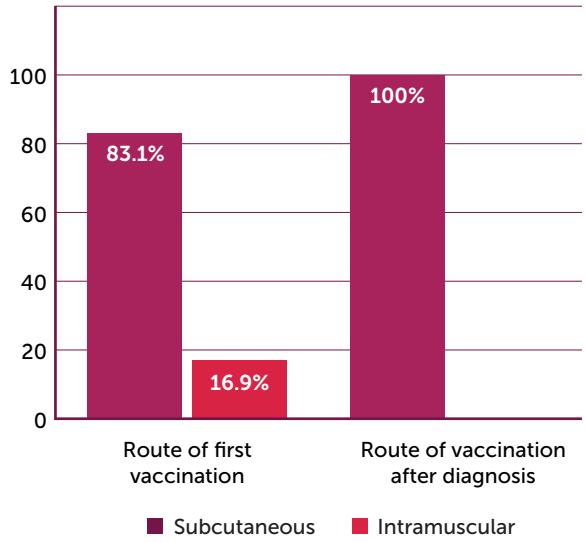
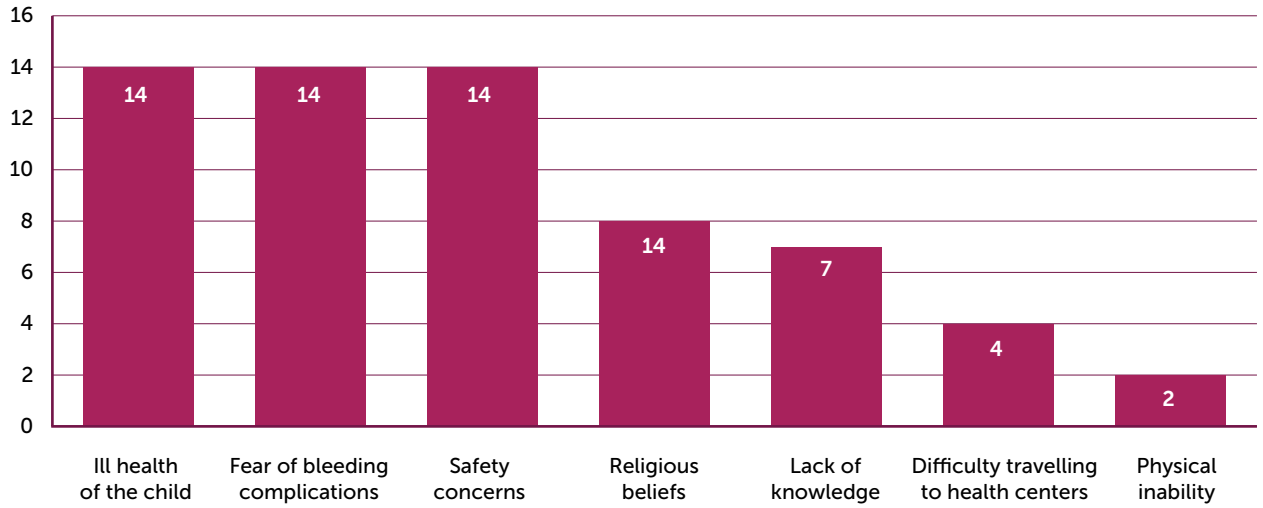


Figure 3. Reasons for not taking vaccination (n=14)*



*It is to be noted that this table the participants may have more than one reason for not taking vaccination. The data includes all the options mentioned by the participants.

Prophylactic measures

A summary of prophylactic measures to prevent bleeding complications after vaccination is shown in Table 3. Of the 65 participants, 37 (56.9%) received clotting factor replacement therapy before their first vaccination, highlighting the high standard of preventive care in managing haemophilia. Among those who experienced post-vaccination bleeding, 9/15 (60%; 13.84% of total cohort) required clotting factor infusion to control the bleeding. One had moderate haemophilia, and the remaining eight had severe haemophilia. The other six participants who experienced post-vaccination bleeding (40%; 9.23% of total cohort) managed their symptoms with ice packs and compression therapy; of these, three had mild haemophilia and three had moderate haemophilia.

These findings reinforce the effectiveness of pre-vaccination clotting factor replacement in preventing severe complications. The results suggest that careful selection of vaccination routes and prophylactic measures can effectively mitigate bleeding complications in people with haemophilia. The widespread adoption of subcutaneous immunisation and pre-vaccination clotting factor administration in this study reflects adherence to best practices in haemophilia management.

J Haem Pract 2025; 12(1). doi: 10.2478/jhp-2025-0007

Reasons for not taking vaccination

In this study, a small proportion of PwH (14 out of 79) had not received the vaccination. The reasons for this are outlined in Figure 3. Primary factors for non-vaccination included fear of bleeding, safety concerns, and existing illness in the child. Similarly, a study by Azarpanah et al. (2021), emphasizes that vaccine hesitancy is often influenced by concerns about vaccine safety and potential adverse events [11].

DISCUSSION

This study provides valuable insights into the incidence of bleeding complications following immunisation and the prophylactic measures implemented for PwH at tertiary care centre. This discussion uses the findings, compares them with existing literature, and explores the implications for clinical practice. A similar study on bleeding after immunisation in children with inherited bleeding disorders, including haemophilia, was undertaken in 2012 by Tasar et al. Like the current study, it suggests that with appropriate management, including pre-immunisation factor replacement, the risk of bleeding can be significantly reduced [12].

Incidence of bleeding complications

In our study, 15 participants (23.1%) experienced bleeding complications after intramuscular vaccination, consistent with existing research that highlights the heightened bleeding risk in PwH due to coagulation deficiencies [13]. These complications ranged from minor bruising to more significant bleeding, primarily occurring at common intramuscular injection sites such as the upper arm and thigh. Notably, 76.9% of participants in our study did not experience bleeding complications, indicating that prophylactic measures and careful management protocols are effective. Similarly, a study by Carpenter et al. found that among 114 children who received intramuscular vaccinations, 23 (20.2%) developed a total of 38 intramuscular haematomas; however, the difference in haematoma occurrence between vaccination routes was not statistically significant (P=0.07). Due to data limitations, it was unclear whether haematoma formation was directly attributable to vaccine administration [14].

Prophylactic measures and vaccination routes

The study revealed that nine participants (13.84%) received factor replacement therapy, while six (9.23%) used ice packs and compression as a preventive measure to minimise post-vaccination complications. According to the WFH Guidelines [2], if an intramuscular injection is necessary, it should be administered after coagulation factor replacement therapy. Additionally, it is recommended to apply an ice pack to the injection site for five minutes beforehand, use a small-gauge needle (23G), and to apply firm pressure to the site for five minutes post-vaccination [15]. Dochart et al. examined the risk of bleeding associated with intramuscular vaccination in individuals with haemophilia and concluded that, with appropriate management, it can be safely administered without significant bleeding complications [16].

In the current study, we found that 83.1% of participants received their first vaccination via the subcutaneous route, aligning with WFH recommendations [2]. This shift towards subcutaneous administration minimises the risk of bleeding compared to intramuscular injections. The fact that 100% of participants received subsequent vaccinations subcutaneously after diagnosis further supports the effectiveness of this approach. Although most vaccines can be administered subcutaneously, some require intramuscular administration. However, PwH should preferably receive vaccines subcutaneously rather than intramuscularly as this is a safer method and does not require infusion of clotting factor as a preventive measure.

It was noted in this study that prior to vaccination, 56.9% of participants received clotting factor replacement, which is a critical prophylactic measure to reduce bleeding risks [10]. The use of factor injections for managing bleeding complications was reported by 13.8% of participants, indicating that factor replacement is a standard practice in addressing post-vaccination bleeding issues. A survey in HTCs in Germany showed the need for standardised vaccination protocols, improved training for healthcare providers, and better patient education to ensure effective and safe vaccination practices for PwH [1]. Our study aligns with existing studies emphasising the safety of subcutaneous vaccination routes in haemophilia people [5]. The low incidence of significant bleeding complications among those who received factor replacement shows the importance of this practice reducing risks associated with immunisation.

Clinical implications

Our study indicates the effectiveness of subcutaneous vaccination routes and the role of prophylactic measures in reducing the incidence of bleeding complications. Healthcare professionals should continue to emphasise these practices to enhance

safety. Additionally, the findings advocate for continued education and training for healthcare professionals on the importance of appropriate vaccination routes and timely prophylactic measures.

The study findings reflect the successful implementation of recommended practices and highlight the importance of ongoing vigilance and adaptation of clinical protocols to ensure the safety and well-being of PwH. Parental attitudes and knowledge towards vaccination is likely to increase the uptake of childhood vaccination. Vaccine information for the parents should focus on vaccine safety and engage communities to increase and sustain the uptake of childhood vaccines.

Limitations

This study has several limitations, primarily its retrospective design, which may affect the accuracy and completeness of the data. This is especially relevant for vaccination, as it is often administered by a child's primary care provider. Additionally, information on the frequency of factor product administration before intramuscular vaccination, specifically to prevent haematoma formation, was not available. The small sample size further limits the generalisability of the findings.

CONCLUSION

Our study demonstrates that the incidence of bleeding complications following immunisation in PwH can be effectively managed through careful selection of vaccination routes and the use of prophylactic measures. The predominant use of the subcutaneous route and pre-vaccination clotting factor replacement therapy have proven to be effective in minimising bleeding risks in PwH in this clinic and is confirmed in other studies. Future research could further explore long-term outcomes of these practices and seek to refine protocols based on evolving clinical evidence.

ACKNOWLEDGEMENTS

Conflict of interest

The authors have advised no interests that might be perceived as posing a conflict or bias.

Consent

Informed consent has been obtained from the participants in the study reported in this paper. In the case of participants under the age of 18 years, informed consent was obtained from their parents or caregivers.

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HOW TO CITE THIS ARTICLE:
Zompa T, Abraham SM, Tseten T, Palkyi T, Muhammed A, Archana MV, Nayak R, Badaganbettu S. Incidence and prevention of post-immunisation bleeding complications in people with haemophilia at a treatment centre in India. *J Haem Pract* 2025; 12(1): 57-64. *https://doi.org/10.2478/jhp-2025-0007*