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Consensus statements on vaccination in patients with haemophilia—Results from the Italian haemophilia and vaccinations (HEVA) project

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Vaccination against communicable diseases is crucial for disease prevention, but this practice poses challenges to healthcare professionals in patients with haemophilia. Poor knowledge of the vaccination requirements for these patients and safety concerns often result in vaccination delay or avoidance. In order to address this issue, a panel of 11 Italian haemophilia and immunization experts conducted a Delphi consensus process to identify the main concerns regarding the safe use of vaccines in patients with haemophilia. The consensus was based on a literature search of the available evidence, which was used by the experts to design 27 consensus statements. A group of clinicians then rated these statements using the 5-point Likert-type scale (1 = strongly disagree; 5 = strongly agree). The main issues identified by the expert panel included vaccination schedule for haemophilic patients; protocol and optimal route of vaccine administration; vaccination of haemophilic patients with antibodies inhibiting coagulation factor VIII (inhibitors); and vaccination and risk of

*The members of the HEVA Study Group who participated in the Delphi process are listed in Appendix 1.

inhibitor development. This manuscript discusses these controversial areas in detail supported by the available literature evidence and provides evidence- and consensus-based recommendations. Overall, participants agreed on most statements, except those addressing the potential role of vaccination in inhibitor formation. Participants agreed that patients with haemophilia should receive vaccinations according to the institutional schedule for individuals without bleeding disorders; however, vaccination of patients with haemophilia requires comprehensive planning, taking into account disease severity, type and route of vaccination, and bleeding risk. Data also suggest vaccination timing does not need to take into consideration when the patient received factor VIII replacement.

KEYWORDS
bleeding disorder, factor VIII inhibitor, haemophilia, immunization, vaccination

1 | INTRODUCTION

The prevention of communicable diseases by vaccination has been a major public health success over the past century.[1-3] However, vaccination of patients with severe congenital bleeding disorders remains a challenge, and clinicians are often uncertain about immunization recommendations for these patients.

Haemophilia, caused by the deficiency of coagulation factor VIII (haemophilia A) or coagulation factor IX (haemophilia B), is the most common severe congenital bleeding disorder.[4] Patients with haemophilia require lifelong treatment with replacement therapy starting at an early age. While patients experiencing acute bleeding require immediate medical attention, prophylaxis with regular intravenous infusions of coagulation factors is also needed to prevent excessive bleeding and joint damage. However, about 20%-30% of patients with severe haemophilia A and up to 5% of those with haemophilia B who are treated with replacement therapy develop antibodies (inhibitors) that neutralize factors VIII and IX,[5-8] thus compromising treatment outcomes.

A number of issues related to vaccination of patients with haemophilia remain controversial, including the immunogenicity and tolerability of off-label subcutaneous administration of vaccines,[9] and the risk of inhibitor formation with vaccination in patients receiving coagulation factor replacement therapy.[5,10] The risk of bleeding in patients with coagulation disorders needs to be carefully evaluated before intramuscular administration of any vaccine, and the subcutaneous route should only be used if the efficacy is similar to that of the intramuscular route.[11] Most experts agree that individuals with haemophilia should be vaccinated according to the schedule for the general population, and that subcutaneous vaccine administration is preferred over the intramuscular route when feasible.[12,13] Patients with haemophilia should be vaccinated against hepatitis A virus and hepatitis B virus (HBV) infection, particularly if they are candidates for plasma-derived products.[13,14] However, no clear guidelines are available on the vaccination of patients with haemophilia in clinical practice.

To address this information gap, a panel of Italian experts in the areas of haemophilia and immunization was convened within the Haemophilia and Vaccinations (HEVA) project to identify the key concerns regarding vaccination of patients with haemophilia, and provide evidence- and consensus-based recommendations.

2 | METHODS

A modified Delphi consensus[15-17] was conducted between September 2017 and May 2018, consisting of the following steps: (a) establishment of a steering committee of Italian experts in haemophilia, infectious diseases and immunology, to define the topics; (b) validation of the initial statements by a separate group of specialists (hereafter mentioned as reviewers); (c) submission of the validated statements to clinicians from Italian Haemophilia Centres for consensus evaluation; (d) discussion of the results by the steering committee; (e) second-round evaluation of those statements on which no consensus was achieved in the first round, by all first-round participants; and (f) finalization of the consensus-based recommendations.

The steering committee included 11 members, whose expertise was proven by reputation, attendance at national and international scientific meetings, and participation in clinical trials and expert panels. A literature search was performed before the first meeting (Milan, Italy; September 2017) to gain insight into current recommendations concerning vaccinations in patients with haemophilia and to identify controversial issues.

Once validated by external reviewers, the statements were submitted to clinicians operating at haemophilia centres across Italy using a secure website (http://www.progettoheva.it). The clinicians expressed their level of agreement/disagreement on each statement anonymously using a 5-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = somewhat agree, 4 = agree and 5 = strongly agree). The number and percentage of participants who scored each item as 1 or 2 (disagreement) or as 3, 4 or 5 (agreement) were calculated.

Consensus was considered to be reached when the sum for disagreement or agreement was ≥66%.

Statements without consensus were discussed by the steering committee during a second meeting (Milan, April 2018) and subjected to a second round of evaluation by the participants of the first Delphi round, using the online system. Finally, a series of practical consensus recommendations were drafted based on the results from the Delphi process.

3 | RESULTS

3.1 | Delphi process

A PubMed search of the peer-reviewed literature published in English until 30 August 2017 (Table 1) identified 985 potentially relevant articles; 966 were excluded after reviewing the title and the abstract (Figure 1). The main reasons for exclusion were (publication prior to 1970) articles describing animal studies, haemophilia-related articles unrelated to vaccination, studies lacking statistical power and articles that were poorly written. The full texts of the remaining 19 articles (plus 1 article that was published after completion of the literature search) were selected for discussion at the first meeting (Table S1).

Based on the selected literature and their clinical experience, the steering committee identified five key areas of uncertainty, namely: (a) vaccination schedules; (b) vaccination protocol and optimal administration route; (c) vaccination of specific subgroups of patients; (d) the risk of inhibitor development with vaccination; and (e) vaccination of patients who have already developed inhibitors. The steering committee produced 27 statements addressing practical issues related to the five controversial areas identified (Table 2).

During the first round of consensus development, 83 participants (including the steering committee) evaluated 27 statements and reached consensus on 22, agreement on 13 and disagreement on nine (Table 2). The five statements on which no consensus was reached were concerned with the timing of vaccination in relation to the administration of coagulation factor replacement therapy (Table 2). All participating clinicians in the first round completed the survey (100% response rate).

Three of the five statements (2.4, 4.2 and 4.3) underwent a second round of evaluation due to availability of a relevant article published after 30 August 2017.[18] Overall, 134 clinicians were contacted during the second round, and 74 (55%) responded. The second round resulted in consensus on two statements (4.2 and 4.3).

All participating clinicians responded to all statements in the two consensus rounds (100% response rate for each statement).

The final consensus statements are discussed in detail below, along with the evidence supporting these decisions.

TABLE 1 Search strategy for the Delphi consensus during the study

Search strategy used for the Delphi consensus
The search terms used were ((((vaccin*[Text Word]) AND ((((((hemophilic*[Text Word] OR haemophilic*[Text Word] OR haemophilia*[Text Word] OR "factor VIII"[Text Word] OR "factor 8"[Text Word] OR BS[Text Word] OR "factor IX"[Text Word])) OR ("factor 9"[Text Word] OR "Christmas Disease"[Text Word])) OR ("Inherited Blood Coagulation"[Text Word] OR "Blood Coagulation disorder"[Text Word] OR "blood coagulation disorders"[Text Word])))))) OR (((((("Hemophilia A"[Mesh]) OR "Hemophilia B"[Mesh])) OR "Factor VIII"[Mesh]) OR (("Blood Coagulation Disorders, Inherited"[Mesh]) OR "Blood Coagulation Disorders"[Mesh])) OR (("Blood Coagulation Factor Inhibitors"[Mesh]) OR "Blood Coagulation Factors"[Mesh])) AND (("Vaccination"[Mesh]) OR "Vaccines"[Mesh]))).

3.2 | Consensus statements

1. Vaccination schedules in patients with haemophilia

1.1 Children with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor (99% consensus).

1.2 There is insufficient scientific evidence to modify the institutional vaccination schedule for paediatric patients with haemophilia (84% consensus).

1.3 Adults with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor (99% consensus).

The near-complete consensus on the need for paediatric and adult patients with haemophilia to be immunized reflects the universal acceptance of vaccinations as the most effective way to prevent infectious diseases.[3,19] While special attention is required in patients with congenital bleeding disorders, the benefits of vaccination clearly outweigh the risks. The recommended vaccinations and their

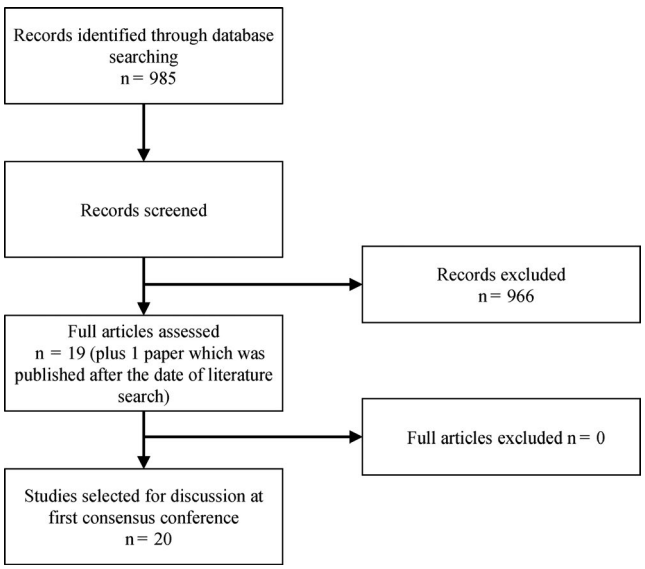

FIGURE 1 Flow diagram of the literature search and selection process

TABLE 2 Statements and results of the Delphi consensus process

No.	Statement	Consensus degree (%)	
		First round	Second round
1. Vaccination in patients with haemophilia			
1.1	Children with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor	99% agreement	-
1.2	There is sufficient scientific evidence to modify the institutional vaccination schedule for paediatric patients with haemophilia	84% disagreement	-
1.3	Adults with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor	99% agreement	-
2. Vaccine administration in patients with haemophilia			
2.1	Subcutaneous administration of vaccines is preferred over intramuscular administration in patients with haemophilia, regardless of disease severity, to reduce the risk of bleeding	83% agreement	-
2.2	There is no evidence that the vaccines delivered by the intramuscular route are more effective than those administered subcutaneously	82% agreement	-
2.3	Antibody titration should not be performed before vaccination in patients with haemophilia	71% agreement	-
2.4	If intramuscular administration of vaccine is mandatory, it is advisable for patients with haemophilia to receive factor replacement prior to vaccination	No consensus	No consensus
2.5	The routine application of ice to the injection site is recommended before and after vaccine administration in patients with haemophilia	93% agreement	-
2.6	Rubbing of the injection site should be avoided in patients with haemophilia; instead, compression at the injection site is recommended	98% agreement	-
2.7	When vaccinating patients with haemophilia, use the thinnest possible needle	94% agreement	-
3. Vaccinating subgroups of patients with haemophilia			
3.1	The use of live attenuated vaccines is contraindicated in immunocompromised[a] patients with haemophilia	84% agreement	-
3.2	Immunocompromised[a] patients with haemophilia should be vaccinated against pneumococcus and influenza	94% agreement	-
3.3	Patients with haemophilia who are travelling to areas where yellow fever and/or typhus are endemic should be vaccinated against these diseases	94% agreement	-
3.4	Patients with haemophilia aged ≥65 years should be vaccinated against pneumococcus and influenza as per the institutional vaccination schedule	99% agreement	-
3.5	The administration of hyposensitizing therapy by subcutaneous and/or intradermal route is not contraindicated in patients with haemophilia and atopy	92% agreement	-

(Continues)

TABLE 2 (Continued)

No.	Statement	Consensus degree (%)	
		First round	Second round
4. Vaccination and the risk of inhibitor development in patients with haemophilia			
4.1	There is sufficient scientific evidence supporting the association between vaccination of patients with haemophilia and development of neutralizing antibodies (inhibitor) against the deficient factor	84% disagreement	-
4.2	It is advisable to avoid vaccination on the same day as administration of factor replacement therapy to prevention inhibitor development	No consensus	70% disagreement
4.3	When possible, the administration of prophylactic factor replacement therapy should be delayed ≥24 hours after vaccination	No consensus	66% disagreement
4.4	When possible, the administration of prophylactic factor replacement therapy should be delayed ≥48 hours after vaccination	75% disagreement	-
4.5	When possible, the administration of prophylactic factor replacement therapy should be delayed ≥72 hours after vaccination	77% disagreement	-
4.6	The risk of inhibitor development increases if haemophilia patients are given a vaccine during a switch between different types of factor replacement therapy	67% disagreement	-
4.7	The risk of inhibitor development increases if haemophilia patients are given a vaccine concurrently with replacement therapy for trauma	No consensus	No consensus
4.8	The risk of inhibitor development increases if haemophilia patients are given a vaccine concurrently with replacement therapy for acute bleeding	No consensus	No consensus
5. Vaccination of haemophilia patients with inhibitors			
5.1	In patients with haemophilia and inhibitors, there is no evidence to that any type of vaccination should be postponed until the levels of inhibitor become undetectable	86% agreement	-
5.2	Any type of vaccination can promote the persistence of inhibitors	77% disagreement	-
5.3	There is evidence that vaccination can compromise the efficacy of immune tolerance induction therapy in patients with haemophilia and inhibitors	77% disagreement	-
5.4	All types of vaccination should be postponed in haemophilia patients with inhibitors who are undergoing immune tolerance induction therapy until there is a complete response to immune tolerance	75% disagreement	-

[a]Patients receiving biologic therapy; patients with HIV aged >5 years with CD4+ count <200; patients with HIV aged 1-5 years with CD4+ count <500; patients with HIV aged <1 year with CD4+ count <750.

schedules may vary between countries; those issued by the Italian Ministry of Health are summarized in Table S2.

2. Vaccine administration in patients with haemophilia

2.1 Subcutaneous administration of vaccines is preferred over intramuscular administration in patients with haemophilia, regardless of disease severity, to reduce the risk of bleeding (83% consensus).

2.2 There is no evidence that vaccines delivered by the intramuscular route are more effective than those administered subcutaneously (82% consensus).

2.3 There is no need to measure antibody titre prior to administration of booster doses of vaccine in patients with haemophilia; patients

with haemophilia should receive booster doses by the standard schedule, without reference to antibody coverage (71% consensus).

2.5 The routine application of ice to the injection site is recommended before and after vaccine administration in patients with haemophilia (93% consensus).

2.6 Compression of the injection site is recommended after vaccination of patients with haemophilia; rubbing the injection site should be avoided (98% consensus).

2.7 When vaccinating patients with haemophilia, a needle with the smallest possible gauge should be used (94% consensus).

The group agreed (>90% consensus) with the currently recommended protocol for administering vaccines intramuscularly to individuals with bleeding disorders, which involves applying an ice pack to the injection site before and after vaccination, using the smallest gauge needle available, and applying firm pressure to the injection site without rubbing, for ≥5 minutes after vaccination.[20]

Some discrepancies exist in the recommendations regarding the route of vaccination in patients with bleeding disorders,[20,21] with concerns that the subcutaneous route may not provide the same level of immunogenicity as intramuscular administration.[20,22,23] Studies have shown that subcutaneous injections were associated with vaccine failure due to lower rates of seroconversion, the effect being more pronounced in elderly patients.[24,25] A recent retrospective analysis found no significant difference in the immunogenicity of HBV vaccine in children (n = 767) with bleeding disorders who received the vaccine subcutaneously compared with those who received it intramuscularly, but there was a higher incidence of local haematoma formation in those receiving intramuscular vaccination.[21] A pilot study investigating the immunogenicity of 3-4 doses of subcutaneous diphtheria and tetanus vaccines in children with haemophilia (aged <6 years; n = 8) reported the development of a positive antibody titre to both antigens, thus confirming the feasibility of the subcutaneous route for diphtheria and tetanus vaccines in this population.[9]

Choosing the subcutaneous route is not always possible because some vaccines are only suitable for intramuscular use. Evidence supporting the prophylactic administration of coagulation factor concentrate before intramuscular vaccine administration is lacking. During the first consensus round, the participants were not in agreement about this practice, with 54% of the participants agreeing on the need to administer a clotting factor concentrate before intramuscular vaccine administration to minimize the risk of muscle haematoma (statement 2.4, Table 2). The lack of consensus persisted after the second round, when 50% agreed and 50% disagreed.

It was previously thought that administering factor VIII at the same time as a vaccine increased the risk of inhibitor development in patients with severe haemophilia. However, this is no longer considered to be true, and the Medical and Scientific Advisory Council of the US National Hemophilia Foundation recommends that patients may be given prophylactic factor replacement within 1 day after intramuscular vaccination to decrease the risk of injection site haematoma.[20]

3. Vaccination for subgroups of patients with haemophilia

Immunocompromised individuals

3.1 The use of live attenuated vaccines is contraindicated in immunocompromised patients with haemophilia (84% consensus).

3.2 Immunocompromised patients with haemophilia should be vaccinated against pneumococcus and influenza (94% consensus).

A substantial number of adults with haemophilia are human immunodeficiency virus (HIV)-positive due to blood products received before routine screening of donated blood began.[13] In this vulnerable population, vaccination against preventable disease is fundamental to avoid co-infections that may have particularly detrimental effects. Currently, no data are available on vaccination of HIV-infected patients with bleeding disorders. However, vaccination in the general HIV-positive population is considered safe. Early studies reported transient increases in plasma viral load following vaccination in HIV-positive patients[26,27]; more recent studies did not confirm these results.[28-32] International guidelines consistently recommend vaccination of HIV-positive individuals using inactivated vaccines. Live vaccines are not recommended in adults with a CD4 count <200 cells/mm^3, but are feasible and safe when the CD4 count is ≥200 cells/mm^3.[33-36]

For the present consensus, immunocompromised individuals were defined as patients receiving biologic therapy, and patients with HIV infections and low CD4+ T lymphocyte counts (<200 cells/mm^3 if aged >5 years). The HEVA participants believed that evidence on vaccination from the general HIV population can be extrapolated to HIV-infected haemophilia patients. There was good agreement that HIV-infected patients with haemophilia and severe immunodeficiency (<200 CD4$^+$ cells/mm^3) should not be given live attenuated vaccines and almost full agreement that these patients should be vaccinated against pneumococcus and influenza virus.

Travellers

3.3 Patients with haemophilia who are travelling to areas where yellow fever and/or typhus are endemic should be vaccinated against these diseases (94% consensus).

The HEVA group agreed that patients with haemophilia who travel to countries where specific infectious diseases are endemic should be vaccinated. Depending on the country of destination, proof of vaccination for certain diseases including yellow fever or polio may be required, and other vaccinations are strongly recommended; patients with haemophilia should receive vaccinations as recommended for their travel destinations.

Elderly patients

3.4 Patients with haemophilia aged ≥65 years should be vaccinated against pneumococcus and influenza as per the institutional vaccination schedule (99% consensus).

Improved care and access to safe factor replacement products have substantially increased the life expectancy of patients with

haemophilia,[37,38] resulting in the need to manage age-related diseases in this population. Current guidelines recommend immunizing people aged ≥65 years against pneumonia, influenza and herpes zoster. These vaccinations can also be given to elderly patients with haemophilia based on the available evidence showing that older adults vaccinated against influenza or pneumococcal disease have a lower risk of developing these illnesses compared with unvaccinated age-matched individuals.[39,40]

Atopic patients

3.5 The use of hyposensitizing therapy administered by the subcutaneous or intradermal route is not contraindicated in atopic patients with haemophilia (92% consensus).

4. Vaccination and the risk of inhibitor development in patients with haemophilia

4.1 There is insufficient scientific evidence supporting the association between vaccination of patients with haemophilia and development of neutralizing antibodies (inhibitor) against the deficient factor (84% consensus).

4.2 There is no need to avoid vaccination in association with the administration of the replacement therapy with the deficient factor (on the same day) in patients with haemophilia to prevent inhibitor development (70% consensus).

4.3 There is no need to delay administration of prophylactic therapy with the deficient factor by at least 24 hours after vaccination in patients with haemophilia (66% consensus).

4.4 There is no need to delay administration of prophylactic therapy with the deficient factor by at least 48 hours after vaccination in patients with haemophilia (75% consensus).

4.5 There is no need to delay administration of prophylactic therapy with the deficient factor by at least 72 hours after vaccination in patients with haemophilia (77% consensus).

4.6 The risk of inhibitor development does not appear to be increased if haemophilia patients undergo vaccination during a switch between different factor replacement therapies (67% consensus).

Some authors have suggested that vaccination may lead to the development of inhibitors in patients receiving factor replacement therapy, but this association remains speculative. Most HEVA participants agreed that there is currently insufficient evidence supporting an association between vaccination and inhibitor formation in haemophilia patients. At the end of the first round of evaluation, no consensus was reached on whether to avoid concurrent vaccination and factor replacement therapy to prevent inhibitor formation (statement 4.2; 37% agreement), or if the administration of factor replacement therapy should be postponed by ≥24 hours (statement 4.3; 43% agreement). After the second round of evaluation, only 30% of participants agreed on statement 4.2 (postpone by ≥24 hours) and 34% agreed with statement 4.3 (postpone by ≥48 hours). Therefore, the final consensus was that there is no need to postpone the administration of replacement therapy by 24-72 hours following vaccination.

Few studies have investigated the potential effect of vaccination on inhibitor formation, and the generalizability of these studies is limited by small sample size and short follow-up duration.[41] A pilot study comparing an early versus standard prophylaxis regimen in previously untreated severe haemophilia A patients (n = 26) reported a significantly lower risk of inhibitor formation with early versus standard prophylaxis.[41]

The timing of vaccination relative to factor VIII infusion may be relevant, but data from the PedNet Registry suggested otherwise.[18] This study compared the risk of inhibitor development between previously untreated patients with severe haemophilia (n = 375) who did and did not receive vaccinations within 24, 72 or 120 hours of factor VIII infusion,[18] and found that vaccination administered close to factor VIII exposure did not increase the risk of inhibitor formation.[18]

5. Vaccination of patients who have already developed inhibitors

5.1 In patients with haemophilia and inhibitors, there is no evidence that any type of vaccination should be postponed until the levels of inhibitor become undetectable (86% consensus).

5.2 Vaccination does not promote the persistence of inhibitors in patients with haemophilia who have developed inhibitors (77% consensus).

5.3 There is no evidence that vaccination can compromise the efficacy of immune tolerance (77% consensus).

5.4 Vaccination does not need to be postponed in haemophilia patients with inhibitors who are undergoing immune tolerance induction therapy (75% consensus).

The HEVA participants agreed that, based on current evidence, inhibitor antibodies do not need to be eradicated before vaccination, and vaccination does not induce inhibitor persistence. Furthermore, the current evidence indicates that vaccination does not have a negative impact on immune tolerance induction with daily high-dose coagulation factor in haemophilia patients who have inhibitors, and vaccination does not need to be postponed until the achievement of a complete response to immune tolerance therapy.

4 | CONCLUSIONS AND PERSPECTIVES

This article describes issues that may be of interest not only to haemophilia experts, but also to general practitioners, paediatricians and healthcare professionals at vaccination centres in Italy, and provides consensus-based recommendations in key areas of uncertainty (Table 3). Participants agreed on most statements, except those addressing the potential role of vaccination in inhibitor formation. Available data showed no association between vaccination and the risk of inhibitor development, and the final consensus statements of HEVA study reflect these data.

The overall results of the HEVA consensus suggest that patients with haemophilia should receive vaccinations according to the institutional schedule for individuals without bleeding disorders. The only difference is that vaccination of patients with haemophilia requires comprehensive planning, taking into account

TABLE 3 Finalized consensus statements and results of the Delphi consensus process

No.	Statement	Consensus degree (%)
1. Vaccination schedules in patients with haemophilia		
1.1	Children with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor	99
1.2	There is insufficient scientific evidence to modify the institutional vaccination schedule for paediatric patients with haemophilia	84
1.3	Adults with haemophilia should receive mandatory and recommended vaccinations as per the institutional vaccination schedule, irrespective of the residual level of activity of the deficient factor	99
2. Vaccine administration in patients with haemophilia		
2.1	Subcutaneous administration of vaccines is preferred over intramuscular administration in patients with haemophilia, regardless of disease severity, to reduce the risk of bleeding	83
2.2	There is no evidence that vaccines delivered by the intramuscular route are more effective than those administered subcutaneously	82
2.3	There is no need to measure antibody titre prior to administration of booster doses of vaccine in patients with haemophilia; patients with haemophilia should receive booster doses by the standard schedule, without reference to antibody coverage	71
2.5	The routine application of ice to the injection site is recommended before and after vaccine administration in patients with haemophilia	93
2.6	Compression of the injection site is recommended after vaccination of patients with haemophilia; rubbing the injection site should be avoided	98
2.7	When vaccinating patients with haemophilia, a needle with the smallest possible gauge should be used	94
3. Vaccination for subgroups of patients with haemophilia		
3.1	The use of live attenuated vaccines is contraindicated in immunocompromised[a] patients with haemophilia	84
3.2	Immunocompromised[a] patients with haemophilia should be vaccinated against pneumococcus and influenza	94
3.3	Patients with haemophilia who are travelling to areas where yellow fever and/or typhus are endemic should be vaccinated against these diseases	94
3.4	Patients with haemophilia aged ≥ 65 years should be vaccinated against pneumococcus and influenza as per the institutional vaccination schedule	99
3.5	The use of hyposensitizing therapy administered by the subcutaneous or intradermal route is not contraindicated in atopic patients with haemophilia	92
4. Vaccination and the risk of inhibitor development in patients with haemophilia		
4.1	There is insufficient scientific evidence supporting the association between vaccination of patients with haemophilia and development of neutralizing antibodies (inhibitor) against the deficient factor	84
4.2	There is no need to avoid vaccination in association with the administration of the replacement therapy with the deficient factor (on the same day) in patients with haemophilia to prevent inhibitor development	70
4.3	There is no need to delay administration of prophylactic therapy with the deficient factor by at least 24 hours after vaccination in patients with haemophilia	66
4.4	There is no need to delay administration of prophylactic therapy with the deficient factor by at least 48 hours after vaccination in patients with haemophilia	75
4.5	There is no need to delay administration of prophylactic therapy with the deficient factor by at least 72 hours after vaccination in patients with haemophilia	77
4.6	The risk of inhibitor development does not appear to be increased if haemophilia patients undergo vaccination during a switch between different factor replacement therapies	67

(Continues)

TABLE 3 (Continued)

No.	Statement	Consensus degree (%)
5. Vaccination of patients who have already developed inhibitors		
5.1	In patients with haemophilia and inhibitors, there is no evidence that any type of vaccination should be postponed until the levels of inhibitor become undetectable	86
5.2	Vaccination does not promote the persistence of inhibitors in patients with haemophilia who have developed inhibitors	77
5.3	There is no evidence that vaccination can compromise the efficacy of immune tolerance	77
5.4	Vaccination does not need to be postponed in haemophilia patients with inhibitors who are undergoing immune tolerance induction therapy	75

[a]Patients receiving biologic therapy; patients with HIV aged >5 years with CD4+ count <200; patients with HIV aged 1-5 years with CD4+ count <500; patients with HIV aged <1 year with CD4+ count <750.

disease severity, type and route of vaccination, and bleeding risk. The available data also suggest vaccination timing does not need to take into consideration when the patient received factor VIII replacement.

However, a number of questions still remain unanswered and prospective studies are needed to (a) compare the immunogenicity, safety and efficacy of vaccines administered by the subcutaneous versus the intramuscular route, especially when the subcutaneous route is off-label; and (b) elucidate the impact of vaccination on inhibitor formation in these patients. It should also be noted that these recommendations were designed by Italian experts using the Delphi consensus method, which might affect their generalizability to a broader patient population.

It is hoped that these evidence- and consensus-based recommendations will provide valuable guidance for clinicians and healthcare professionals involved in the vaccination of patients with haemophilia.

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DISCLOSURES

Elena Santagostino has acted as a member of advisory boards and/or speaker bureaus for Bayer, Shire, CSL Behring, Sobi, Bioverativ, Roche, Octapharma, Grifols, Kedrion, Novo Nordisk and Pfizer. Agostino Riva has received speaker's honoraria from Gilead, ViiV Health Care, Merck Sharp & Dohme, Novartis, Sobi, Sanofi and Roche. Simone Cesaro has received a fee for participation to advisory boards from Sobi. Davide Matino has received unrestricted educational grants and research funding from Pfizer, Bayer, Sobi and BIOviiix, and has also received honoraria for participating in educational events and advisory boards funded by Bayer, Sobi, Pfizer and BIOviiix. Renata Ilde Mazzucchelli is an employee of Swedish Orphan Biovitrum srl (Sobi). Giovanni Di Minno has received honoraria for scientific activities from Bayer, Novo Nordisk, Pfizer, Kedrion, CSL Behring and Boehringer Ingelheim. Susanna Esposito, Angelo Claudio Molinari, Rosamaria Mura, Lucia Dora Notarangelo, Annarita Tagliaferri, and Mario Clerici declare no conflicts of interest related to the present work.

AUTHOR CONTRIBUTIONS

The authors were the members of the HEVA steering committee. They contributed to literature search, participated in the two meetings, identified the statements to be evaluated in the Delphi process, discussed the Delphi results and drafted the final recommendations. They critically revised the various drafts of the manuscript and approved the final version before submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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