

Consensus Recommendations for Intramuscular COVID-19 Vaccination in Patients with Hemophilia

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Hämostaseologie

Abstract

Background Currently available coronavirus disease 2019 (COVID-19) vaccines are approved for intramuscular injection and efficacy may not be ensured when given subcutaneously. For years, subcutaneous vaccination was recommended in patients with hemophilia to avoid intramuscular bleeds. Therefore, recommendations for the application of COVID-19 vaccines are needed.

Methods The Delphi methodology was used to develop consensus recommendations. An initial list of recommendations was prepared by a steering committee and evaluated by 39 hemophilia experts. Consensus was defined as $\geq 75\%$ agreement and strong consensus as $\geq 95\%$ agreement, and agreement as a score ≥ 7 on a scale of 1 to 9. After four rounds, a final list of statements was compiled.

Recommendations Consensus was achieved that COVID-19 vaccines licensed only for intramuscular injection should be administered intramuscularly in hemophilia patients.

Keywords

- hemophilia
- COVID-19
- vaccination
- recommendation

received

February 14, 2021

accepted after revision

February 25, 2021

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Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1401-2691>.
ISSN 0720-9355.

Prophylactic factor replacement, given on the day of vaccination with a maximum interval between prophylaxis and vaccination of 24 hours (factor VIII and conventional factor IX concentrates) or 48 hours (half-life extended factor IX), should be provided in patients with moderate or severe hemophilia. Strong consensus was achieved that patients with mild hemophilia and residual factor activity greater than 10% with mild bleeding phenotype or patients on emicizumab usually do not need factor replacement before vaccination. Swelling, erythema, and hyperthermia after vaccination are not always signs of bleeding but should prompt consultation of a hemophilia care center. In case of injection-site hematoma, patients should receive replacement therapy until symptoms disappear.

Conclusions Consensus was achieved on recommendations for intramuscular COVID-19 vaccination after replacement therapy for hemophilia patients depending on disease severity.

Introduction

Coronavirus-19 disease (COVID-19) caused by the infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a pandemic affecting millions of people all over the world. Especially older people and patients with comorbidities are at high risk for COVID-19-associated complications.^{1–3} Pharmacologic treatment of COVID-19 including antibody strategies,^{4,5} direct or indirect antiviral treatment,^{6–9} and targeted therapies¹⁰ have shown limited or no efficacy.¹¹ Therefore, there is an urgent need for effective vaccinations to prevent a SARS-CoV-2-infection. Vaccines currently approved by the European Medical Association (EMA)^{12–14} and other vaccines, that are under investigation and might be approved in the near future,^{15,16} have been investigated for intramuscular application only. In people living with hemophilia, it has traditionally been recommended to administer vaccinations subcutaneously to avoid the risk of bleeding or the need for additional prophylactic replacement therapy. Thus, patients, caregivers, and healthcare providers might be concerned about the safety of intramuscular vaccination in hemophilia.

To address these concerns, a panel of experts in the field of hemophilia treatment was constituted to develop consensus recommendations for the use of the SARS-CoV-2 vaccination in patients with hemophilia.

Methods

To establish consensus recommendations, a Delphi consensus procedure^{17–19} was conducted and headed by a steering committee of 16 hemophilia experts. Prior to the start of the Delphi procedure, a literature research was conducted searching for current guidelines and expert recommendations for the administration of vaccinations in patients with bleeding disorders^{20–24} and for SARS-CoV-2 vaccination in patients with hemophilia.²⁵

Delphi Process

After literature review, all members of the Hemophilia Board of the GTH were asked to answer an online survey including

17 questions about the administration of the SARS-CoV-2 vaccine in patients with hemophilia. A total of 55 physicians responded. The results are provided in the supplementary material. Based on these results, a list of 24 statements was sent to 39 members of the Hemophilia Board of the GTH willing to participate in the consensus process. The clinicians were asked to express their agreement/disagreement on a scale of 1 = strongly disagree to 9 = strongly agree. Agreement was defined as a score ≥ 7 . Participants were asked to provide explanations in case of disagreement (score ≤ 6). Consensus was defined as $\geq 75\%$ agreement and strong consensus as $\geq 95\%$ agreement. After the first round, strong consensus was achieved in 7, consensus in 16, and no consensus in 1 statement. The results including the comments of the participants were evaluated by the steering committee. Four statements were removed because they were considered outside the main focus or achieved low consensus; these statements are provided at the end of the “Recommendations” section. The remaining 20 statements were modified according to participant feedback and reevaluated by the participants. In the second round, 34 participants responded with strong consensus in 15 and consensus in 5 statements. After review by the steering committee, two statements were modified and sent for evaluation in the third round. These two statements were again evaluated by 39 participants reaching consensus in both. In the last round, one statement had to be clarified, and reached strong consensus from 36 participants.

Recommendations

1. Indication for SARS-CoV-2 vaccination:
 - 1.1. Hemophilia is not a contraindication for a SARS-CoV-2 vaccination.
Consensus: 100%.
 - 1.2. The prioritization of vaccination in patients with hemophilia should follow official regulations, considering age, care dependency, and concomitant diseases as risk factors for a severe course of COVID-19.
Consensus: 100%.

1.3. Patients with known allergy to factor concentrates containing polyethylene glycol (PEG) should receive a PEG-free vaccine.

Consensus: 97.1%.

Comments: Concerns were expressed regarding the weighting of possible harms of an allergic reaction related to the vaccine and the benefits of a COVID-19 vaccination. As there are currently no PEG-free vaccines licensed, one participant raised the question whether the vaccine could be applied with a standby medication containing antihistamines and prednisolone, especially in patients with a low allergic disposition. However, it should be noted that an allergy to any component including PEG is a contraindication according to the summary of product characteristics.

2. Administration of the vaccine:

2.1. SARS-CoV-2 vaccines should be administered by intramuscular injection in patients with hemophilia as long as this is the only approved route of administration.

Consensus: 94.1%.

2.2. The smallest available needle size should be used for injection, following the manufacturer's instructions.

Consensus: 97.2%.

2.3. Local compression should be applied for at least 10 minutes after intramuscular injection.

Consensus: 100%.

2.4. The injection site should be examined and palpated a few minutes and 2 to 4 hours after the end of compression. In case of progressive swelling or hematoma, the hemophilia center should be contacted immediately.

Consensus: 100%.

Comments: The high consensus regarding the officially approved intramuscular administration route reflects the high priority given to the efficacy of vaccination and the consideration that any hemophilia-related bleeding risk could be mitigated by appropriate prophylaxis. Nevertheless, some participants suggested that subcutaneous administration would be the preferable way of administration once data become available to support its safety and efficacy, as previously for the hepatitis B vaccine.²⁶

There was strong consensus that the smallest possible needle size recommended by the manufacturer should be used and local compression for 10 minutes applied after the vaccination, in line with recently updated guidelines for the management of hemophilia by the World Federation of Hemophilia (WFH).²⁰ There was no consensus to recommend a specific Gauge needle size as done by the WFH, due to concerns that vaccination might be declined if only larger needles were available.

3. Prophylaxis prior to vaccination:

3.1. Patients with severe or moderate hemophilia and patients with inhibitors should receive prophylactic

replacement therapy prior to intramuscular vaccination.

Consensus: 97.1%.

3.2. Patients with residual factor activity greater than 10 IU/dL and mild bleeding phenotype usually do not need prophylactic therapy prior to intramuscular vaccination. Individual consideration is required for patients with residual factor activity between 5 and 10 IU/dL.

Consensus: 100%.

3.3. Patients on regular prophylactic therapy should receive prophylaxis preferably on the day of intramuscular vaccination. If necessary, prophylaxis should be brought forward to the day of vaccination.

Consensus: 100%.

3.4. The interval between prophylaxis and intramuscular vaccination should be a maximum of 24 hours for conventional or extended half-life (EHL) factor VIII (FVIII) and conventional factor IX (FIX), and a maximum of 48 hours for EHL FIX.

Consensus: 97.1%.

3.5. Patients on prophylaxis with emicizumab may not need additional prophylactic replacement therapy prior to intramuscular vaccination.

Consensus: 97.1%.

3.6. Patients treated with on-demand therapy requiring prophylaxis for intramuscular vaccination should receive a single dose of 20 to 40 IU/kg body weight FVIII or FIX concentrate prior to vaccination.

Consensus: 97.1%.

Comments: In the first Delphi round, a residual factor activity cutoff of less than 10 IU/dL was suggested as an indication for prophylaxis with factor concentrates. Several respondents expressed that this cutoff was not evidence based and that the individual bleeding tendency should be taken into account. A recent retrospective study evaluated the rate of bleeding complications in hemophilia patients with residual activity less than 2 IU/dL receiving intramuscular vaccination prior to the diagnosis of hemophilia and thus without prophylaxis.²⁷ Hematomas were reported in 11 of 549 (2%) vaccinations, of which 3 needed medical consultation and just 1 required factor replacement therapy. The low complication rate suggested that intramuscular vaccination was safe without factor replacement in most patients. The cutoff activity less than 5 IU/dL suggested here provides an additional safety margin. Emicizumab has been estimated to provide an equivalent of greater than 10 IU/dL FVIII activity²⁸; clinical trial data and real-world experience suggest that minor surgery often does not need additional replacement therapy.²⁹ In consequence, we do not recommend additional factor replacement for intramuscular vaccination in patients on prophylaxis with emicizumab.

The rationale for the maximum time interval between prophylaxis and intramuscular vaccination was based on a target factor activity greater than 10 IU/dL at the

time of injection. As the individual half-life of factor concentrates varies and different doses are used for prophylaxis, a maximum interval between prophylaxis and vaccination of 24 hours for FVIII and conventional FIX products and 48 hours for EHL-FIX was chosen with preference toward safety. Other intervals may be sufficient if individual pharmacokinetic data are known. The suggested factor dose of 20 to 40 IU/kg body weight in patients not on prophylaxis was chosen to achieve factor levels recommended for minor surgeries.²⁰

4. Treatment of bleeding complications:

4.1. In case of clinically relevant injection-site hematoma, patients should receive replacement therapy until symptoms disappear.

Consensus: 97.1%.

4.2. Adjunctive therapy of injection-site hematoma includes immobilization, cooling, and antiphlogistic/analgetic therapy if necessary.

Consensus: 94.1%.

4.3. In case of injection-site hematoma after the first vaccination, more intense prophylactic replacement prior to the second injection may be justified.

Consensus: 94.1%.

Comments: There was strong consensus that a clinically relevant hematoma should be treated adequately. The duration of treatment may vary according to hematoma size and patient-related features, but symptoms such as pain and swelling will usually guide individual decisions. Two participants recommended against the use of nonsteroidal anti-inflammatory drugs. According to the WHO recommendation, selective COX2 inhibitors could be used instead.²⁰ There was consensus that an injection-site hematoma would justify a more intense prophylaxis before the second injection. Nevertheless, it was noted that bleeding might have been caused by incorrect administration, inadvertent vessel injury, or insufficient compression during the first vaccination, and that these aspects should be addressed as well.

5. Treatment of nonbleeding complications:

5.1. Injection-site reactions (swelling, erythema, and hyperthermia) are not always signs of bleeding but also occur in the general population. Hemophilia patients with such symptoms should contact their hemophilia care center.

Consensus: 87.2%.

5.2. Patients should receive both injections of the vaccine as approved, unless serious side effects prohibit further application after the first injection. A hematoma after the first injection is not a contraindication for the second injection.

Consensus: 97.1%.

5.3. The management of adverse events of vaccination is similar to that in the general population. In case of local or systemic adverse events, the bleeding risk should be assessed and additional FVIII or FIX replacement therapy should be considered.

Consensus: 94.9%.

Comments: The participants agreed that injection-site reactions are not necessarily related to bleeding. Not all participants agreed that a contact with the hemophilia center is always needed, as patients would be able to distinguish bleeds from other local reactions and contact to the general practitioners might often be sufficient or even preferred. The panel noted that local or systemic reactions may sometimes warrant replacement therapy, even if the complication itself did not involve bleeding, because inflammation or swelling may increase the hemorrhagic risk as such. Consensus was achieved that in these situations, the bleeding risk and the need for replacement therapy should be assessed by the hemophilia care center.

6. Additional consideration in minimally pretreated patients:

6.1. There is currently no evidence that vaccinations in general increase the risk of inhibitors against FVIII or FIX.

Consensus: 100%.

Comment: In the past, vaccination was discussed as a potential danger signal that might cause inhibitor development.^{30,31} Data from the PedNet Registry showed no association of the time interval between vaccination and factor replacement with inhibitor development in 375 previously untreated patients (PUPs) during the first 75 exposure days.³² In the hemophilia mouse model, the combination of factor replacement with measles-mumps-rubella or influenza vaccines resulted in similar or even lower inhibitor formation compared with nonvaccinated controls.³³ These results suggested that antigenic competition via T-cell chemotaxis toward the vaccination site may have resulted in decreased FVIII immunogenicity and supported the notion that vaccination does not increase the risk of inhibitor development.

Statements Excluded after the First Delphi Round

1. SARS-CoV-2 vaccination is not contraindicated in patients receiving immunosuppressive agents as part of an immune tolerance therapy. Immunocompromised patients may have a lower response to the vaccine.

Consensus: 94.9%.

Comment: Although this statement achieved consensus, the steering committee decided to exclude it from further Delphi rounds because it was outside the main focus. Immunosuppression is not a typical treatment in patients with hereditary hemophilia. In addition, there is a German guidance document on vaccination in patients with autoimmune disorders and patients under treatment with immunosuppressants³⁴ and a recommendation of the German Society of Hematology and Oncology (DGHO)³⁵ addressing this issue in more detail.

2. If available, an ice pack should be applied to the injection site for 5 minutes before injection of the intramuscular vaccination.

Consensus: 74.4%.

Comment: This recommendation appearing in the WFH guideline²⁰ did not achieve high consensus. Concerns were expressed regarding the lack of evidence and rationale.

3. SARS-CoV-2 vaccine is not contraindicated in previously untreated or minimally treated patients with hemophilia. Consensus: 82.1%.

4. Recommendations for prophylactic and therapeutic replacement therapy for intramuscular vaccination apply for previously or minimally treated patients as for other patients with hemophilia.

Consensus: 82.1%.

Comment: Although there was consensus on these statements, the steering committee excluded these statements from the further Delphi evaluation process. SARS-CoV-2 vaccines are currently not approved for children younger than 16 years and therefore will not apply to most PUPs.

Discussion and Conclusions

This Delphi process was initiated to provide consensus statements for SARS-CoV-2 vaccination in patients with hemophilia. In the past, and also in the most recent WFH guidelines, it was recommended that patients with hemophilia “should preferably receive vaccination subcutaneously rather than intramuscularly or intradermally, as it is as safe and effective as the latter and does not require clotting factor infusion.”²⁰ In part, the preference for subcutaneous vaccination was also based on the lack of evidence that vaccines delivered by the intramuscular route were more effective than those administered subcutaneously.²³ Currently licensed SARS-CoV-2 vaccines have not been studied by other than the intramuscular route; moreover, the first vaccines licensed to date employ novel modes of action: (1) single-stranded messenger RNA formulated in lipid nanoparticles in the BioNTech/Pfizer and Moderna vaccines and (2) double-stranded DNA packaged in an adenovirus vector in the Oxford/AstraZeneca product.³⁶ It cannot be assumed, nor can it be excluded, that these vaccines were effective when given subcutaneously.

Our recommendations are in line with recent ad hoc guidance published by the WFH, the European Association for Haemophilia and Allied Disorders (EAHAD), the European Haemophilia Consortium (EHC), and the National Hemophilia Foundation (NHF) on SARS-CoV-2 vaccination.²⁵ This guidance currently consists of 13 statements that are planned to be updated whenever new information becomes available. In fact, SARS-CoV-2 vaccines for intradermal use are in development,³⁶ and even with the currently approved vaccines growing experience may ultimately support their use through other than the intramuscular route.

The current uncertainty regarding the route of administration of currently approved SARS-CoV-2 vaccines should be weighed against the risk of bleeding and the burden of additional factor replacement in hemophilia patients. Our aim was to provide practical guidance based on a broad consensus among physicians treating patients with hemo-

philia within the GTH. Therefore, we invited all members of the GTH Hemophilia Board (70 members) to join this Delphi consensus process. Thirty-nine members completed the first and third rounds; 34 and 36 members also completed the second and fourth rounds, respectively. Consensus (>75% agreement) was achieved on all 20 statements, and strong consensus (>95% agreement) on 15 of those. With this high rate of consensus, we are confident that our recommendation for intramuscular vaccination of hemophilia patients—after adequate replacement therapy if needed—will be followed by our colleagues in the national vaccination centers.

An observational study has been started concurrently to collect data on the safety and efficacy of SARS-CoV-2 vaccination. New information obtained from this study as well as other sources may warrant future updates of our recommendations. Physicians taking care of the vaccination of hemophilia patients are advised to visit the GTH Web site in regular intervals.

In summary, the consensus statements published here provide practical guidance to clinicians on how to administer SARS-CoV-2 vaccination in patients with hemophilia and how to address concerns and worries associated with the bleeding risk of intramuscular vaccination.

Authors' Contributions

C.P., K.H., C.K., and A.T. developed the initial survey and the first set of recommendations. C.P. managed the consensus process and analyzed data. C.P. and A.T. wrote the final manuscript. All authors participated in the discussion of recommendations and Delphi results, reviewed the manuscript, and agreed with its final content.

Conflicts of Interest

C.P. reports grants and personal fees from Roche, grants and personal fees from Takeda, personal fees from Bayer Healthcare, personal fees from Chugai, personal fees from CSL Behring, personal fees from Novo Nordisk, personal fees from Shire, grants from Fujimori, grants from LeoPharma, personal fees from BMS, and personal fees from Pfizer, outside the submitted work.

K.H. reports grants, personal fees, and other from Bayer; personal fees and other from Biotest; personal fees from Chugai/Roche; personal fees and other from CSL Behring; personal fees and other from Novo Nordisk; grants, personal fees, and other from Pfizer; personal fees from Shire/Takeda; and personal fees and other from Sobi, outside the submitted work.

C.K. reports grants and personal fees from Bayer, grants from Biotest, grants and personal fees from CSL Behring, grants from Intersero, grants and personal fees from Novo Nordisk, grants from Pfizer, grants and personal fees from Roche/Chugai, grants and personal fees from Takeda, and grants and personal fees from Sobi/Sanofi, outside the submitted work.

C.H. reports grants from Bayer, grants and personal fees from Biotest, grants from CSL Behring, grants and personal fees from Intersero, grants from Novo Nordisk, grants

from Pfizer, grants and personal fees from Roche/Chugai, grants and personal fees from Takeda, and grants and personal fees from Sobi/Sanofi, outside the submitted work.

M.K. reports personal fees from Bayer Healthcare, CSL Behring, Chugai Pharma, Novo Nordisk, and Roche, outside the submitted work.

M.O. reports grants and personal fees from Bayer, grants and personal fees from Biotest, grants and personal fees from Takeda, grants and personal fees from CSL Behring, grants from Octapharma, grants and personal fees from Pfizer, grants from Shire, grants and personal fees from Roche, grants and personal fees from Sobi, and personal fees from Novo Nordisk, outside the submitted work.

C.B. reports personal fees from Bayer, grants and personal fees from CSL Behring, personal fees and other from Roche, personal fees from Biotest, personal fees from Takeda, personal fees from Pfizer, and personal fees from Sobi, outside the submitted work; and C.B. is coinvestigator of the German Pediatric Hemophilia Research Database. This registry is funded by most manufacturers of factor and nonfactor therapies for patients with hemophilia.

M.S.-K. reports grants from Pfizer, personal fees from Biotest AG, and personal fees from Novo Nordisk, outside the submitted work.

J.W. has nothing to disclose.

S.Ha. reports grants and personal fees from Bayer Healthcare, grants and personal fees from Baxalta Innovations, grants and personal fees from Biotest, grants and personal fees from CSL Behring, grants and personal fees from Novo Nordisk, grants and personal fees from Octapharma, grants and personal fees from Pfizer, grants and personal fees from Sobi, and personal fees from Roche, outside the submitted work.

S.Ho. reports personal fees from Takeda/Shire, Bayer Healthcare, Novo Nordisk, Octapharma, Pfizer, Sobi und Roche, outside the submitted work.

H.R. reports grants from Bayer, Biotest, CSL Behring, Novo Nordisk, Pfizer, Roche/Chugai, Sobi, and Takeda, outside the submitted work.

I.W. reports grants and personal fees from Bayer; grants and personal fees from Biotest; grants and personal fees from CSL; nonfinancial support from Pfizer; grants and personal fees from Roche/Chugai; grants, personal fees, and nonfinancial support from Sobi; and grants, personal fees, and nonfinancial support from Shire/Takeda, outside the submitted work.

R.K. reports grants and personal fees from Bayer, personal fees from CSL Behring, personal fees from Roche, personal fees from Pfizer, grants and personal fees from BioMarin, grants and personal fees from Takeda/Shire, grants and personal fees from Novo Nordisk, and grants and personal fees from SOBI, outside the submitted work.

J.O. reports grants and personal fees from Bayer, personal fees from Biogen Idec, personal fees from BioMarin, grants and personal fees from Biotest, personal fees from Chugai, grants and personal fees from CSL Behring, personal fees

from Freeline, personal fees from Grifols, grants and personal fees from Novo Nordisk, grants and personal fees from Octapharma, personal fees from Pfizer, personal fees from Roche, personal fees from Sanofi, personal fees from Sparks, personal fees from Swedish Orphan Biovitrum, grants and personal fees from Takeda, outside the submitted work.

A.T. reports grants and personal fees from Bayer, grants and personal fees from Biotest, grants and personal fees from Chugai/Roche, personal fees from CSL Behring, grants and personal fees from Novo Nordisk, grants and personal fees from Octapharma, grants and personal fees from Pfizer, grants and personal fees from SOBI, and grants and personal fees from Takeda, outside the submitted work.

Acknowledgment

We thank all colleagues who participated in the Delphi consensus process (in alphabetical order): Cihan Ay, Wien; Wolfgang Behnisch, Heidelberg; Wolfgang Eberl, Braunschweig; Carmen Escuriola, Mörfelden; Clemens Feistritzer, Innsbruck; Sven Gutsche, Lübeck; Christina Hart, Regensburg; Inga Hegemann, Zürich; Sabine Heine, Zweibrücken; Susanne Holzhauer, Berlin; Karim Kentouche, Jena; Paul Knöbl, Wien; Ralf Knöfler, Dresden; Karin Kurnik, München; Florian Langer, Hamburg; Wolfgang Miesbach, Frankfurt; Claudia Niekrens, Delmenhorst; Ingrid Pabinger, Wien; Kristina Schilling, Jena; Monika Sparber-Sauer, Stuttgart; Werner Streif, Innsbruck; Katharina Thom, Wien; Vera Vaillant, Giessen; Barbara Zieger, Freiburg.

References

- 1 Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020;94:91–95
- 2 Fathi M, Vakili K, Sayehmiri F, et al. The prognostic value of comorbidity for the severity of COVID-19: a systematic review and meta-analysis study. *PLoS One* 2021;16(02):e0246190
- 3 Langer F, Kluge S, Klamroth R, Oldenburg J. Coagulopathy in Covid-19 and its implication for safe and efficacious thromboprophylaxis. *Hamostaseologie* 2020;40(03):264–269
- 4 Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT-COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2021;384(07):610–618
- 5 Weinreich DM, Sivapalasingam S, Norton T, et al. Trial Investigators. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384(03):238–251
- 6 Goldman JD, Lye DCB, Hui DS, et al; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020;383(19):1827–1837
- 7 Kalil AC, Patterson TF, Mehta AK, et al; ACTT-2 Study Group Members. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med* 2021;384(09):795–807
- 8 Mitjà O, Corbacho-Monné M, Ubals M, et al. BCN-PEP-CoV-2 Research Group. A cluster-randomized trial of hydroxychloroquine for prevention of COVID-19. *N Engl J Med* 2021;384(05):417–427
- 9 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020

- 10 Stone JH, Frigault MJ, Serling-Boyd NJ, et al; BACC Bay Tocilizumab Trial Investigators. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med* 2020;383(24):2333–2344
- 11 Fachgruppe COVRIIN Am Robert-Koch-Institut. Medikamentöse Therapie bei COVID-19 mit Bewertung durch die Fachgruppe COVRIIN am Robert-Koch-Institut 2020 [cited February 6, 2020]. Accessed March 10, 2021 at: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Therapieuebersicht.pdf?__blob=publicationFile
- 12 Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(05):403–416
- 13 Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383(27):2603–2615
- 14 Voysey M, Clemens SAC, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397(10269):99–111
- 15 Logunov DY, Dolzhikova IV, Shchelyakov DV, et al; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397(10275, Suppl 1):671–681
- 16 Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine. *N Engl J Med* 2021
- 17 Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess* 1998;2(03):i–iv, 1–88
- 18 Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs* 2000;32(04):1008–1015
- 19 Cuhls K. Die Delphi-Methode – eine Einführung. In: Niederberger M, Renn O, eds. *Delphi-Verfahren in den Sozial- und Gesundheitswissenschaften*. Wiesbaden: Springer Fachmedien Wiesbaden; 2019:3–31
- 20 Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020; (26, Suppl 6):1–158
- 21 CDC/NCIRD. ACIP General Best Guidance for Immunization – Special Situations [cited February 1, 2021]. Accessed March 10, 2021 at: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html>
- 22 Robert Koch-Institut. Impfen bei Blutungsneigung. Accessed March 10, 2021 at: https://www.rki.de/DE/Content/Infekt/Impfen/Stichwortliste/G/Injektionsort_Tabelle.pdf?__blob=publicationFile
- 23 Santagostino E, Riva A, Cesaro S, et al; the HEVA Study Group. Consensus statements on vaccination in patients with haemophilia—results from the Italian haemophilia and vaccinations (HEVA) project. *Haemophilia* 2019;25(04):656–667
- 24 Pfrepper C, Krause M, Sigl-Kraetzig M, Königs C, Wendisch J, Olivieri M. Vaccination in patients with haemophilia—Results from an online survey among haemophilia treatment centres in Germany. *Haemophilia* 2019;25(04):e304–e306
- 25 COVID-19 vaccination guidance for people with bleeding disorders [cited January 26, 2021]. Accessed March 10, 2021 at: <https://news.wfh.org/covid-19-vaccination-guidance-for-people-with-bleeding-disorders/>
- 26 Carpenter SL, Soucie JM, Presley RJ, et al; Hemophilia Treatment Center Network Investigators. Hepatitis B vaccination is effective by subcutaneous route in children with bleeding disorders: a universal data collection database analysis. *Haemophilia* 2015;21(01):e39–e43
- 27 Hochart A, Falaise C, Huguenin Y, Meunier S. Intramuscular vaccination of haemophiliacs: Is it really a risk for bleeding? *Haemophilia* 2019;25(05):e322–e323
- 28 Lenting PJ. Laboratory monitoring of hemophilia A treatments: new challenges. *Blood Adv* 2020;4(09):2111–2118
- 29 Holstein K, Albisetti M, Bidlingmaier C, et al; ‘Ständige Kommission Hämophilie’ (Haemophilia board) of the German, Swiss Austrian Society for Thrombosis Haemostasis Research (GTH) Practical guidance of the GTH Haemophilia Board on the use of emicizumab in patients with haemophilia A. *Hamostaseologie* 2020;40(05):561–571
- 30 Matzinger P. The danger model: a renewed sense of self. *Science* 2002;296(5566):301–305
- 31 Lövgren KM, Søndergaard H, Skov S, Wiinberg B. Non-genetic risk factors in haemophilia A inhibitor management – the danger theory and the use of animal models. *Haemophilia* 2016;22(05):657–666
- 32 Platokouki H, Fischer K, Gouw SC, et al. Vaccinations are not associated with inhibitor development in boys with severe haemophilia A. *Haemophilia* 2018;24(02):283–290
- 33 Lai JD, Moorehead PC, Sponagle K, et al. Concurrent influenza vaccination reduces anti-FVIII antibody responses in murine hemophilia A. *Blood* 2016;127(26):3439–3449
- 34 Wagner N, Assmus F, Arendt G, et al. Impfen bei Immundefizienz. *Bundesgesundheitsbl* 2019;62(04):494–515
- 35 Aktualisierte Empfehlungen zur COVID-19 Schutzimpfung bei Patienten mit Blut- und Krebserkrankungen [cited January 24, 2021]. Accessed March 10, 2021 at: <https://www.dgho.de/publikationen/stellungnahmen/gute-aerztliche-praxis/coronavirus/covid-19-vakzine-20210107.pdf>
- 36 Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. *Adv Drug Deliv Rev* 2020; 170:1–25