

COVID-19 vaccines. **Version 6.0, May 27, 2021**

COVID-19 vaccines have been developed, tested, and approved with an unprecedented speed with the aim to control the pandemic. Four vaccines are approved for use within the EU. Two of these based on mRNA technology (Pfizer/BioNTech and Moderna) and two using non-replication competent adenovirus vectors (Oxford AstraZeneca and Johnson & Johnson/Janssen). There are also other vaccines in use in some European countries such as the Gamaleya's Sputnik V vaccine in Russia, Serbia, and Hungary and the Sinopharm inactivated vaccine in Hungary. Additional vaccines are being evaluated by the EMA. The vaccination campaign has proceeded with unprecedented speed with almost 1.5 billion vaccine doses having been administered to date.

Efficacy data

Results from the phase III Pfizer/BioNTech vaccine (BNT162b2) including 43500 subjects have been published¹. This showed 94.6% protection after two doses of vaccine given three weeks apart. When results were split by age, the protective efficacy was 94.6% in adults 18 – 65 and 92.9% in adults > 65 years of age. In the phase III study the safety was good. In early clinical use, two anaphylactic reactions occurred in subjects previously having experienced such reactions. The FDA and CDC have presented advice for the use of this vaccine and it is recommended for immunosuppressed patients although no specific data has been presented². It is recognized that the protection efficacy might be lower in immunosuppressed individuals. More information can be obtained at the FDA (www.fda.gov) and CDC (www.cdc.gov) websites. The Pfizer/BioNTech vaccine has also been approved in the US for children ages 12 – 16 and EMA is currently evaluating the dossier³.

The results from the Moderna/National Institute of Health vaccine (mRNA-1273) have been published as well⁴. This phase III study included 30400 subjects each receiving two doses of vaccine or placebo given 4 weeks apart. The protective efficacy was 94.1% (95.1% in adults 18 – 65 and 86.4% in adults above the age of 65).

In “real world use”, both mRNA vaccines were shown to reduce asymptomatic SARS-CoV-2 infection, COVID-19 related symptoms, hospital admissions, and mortality in adults⁵⁻⁸. Several studies have reported lower rates of immune responses in solid organ transplant recipients⁹⁻¹⁶

as well as in patients with some hematologic malignancies such as CLL, multiple myeloma, lymphoma, and myeloproliferative malignancies with the mRNA vaccines compared to healthy individuals¹⁷⁻²². From these studies, some preliminary conclusions can be drawn. First, even with the use of mRNA vaccines, the response is lower in SOT and oncohematologic patients. Older patients, underlying disease not in remission, active treatment or ongoing immunosuppression with antimetabolites are associated with a lower rate of serology response. Particularly poor serology responses were seen with the use of anti-CD20 in the last 12 months prior to vaccination, patients under BTK inhibitors or daratumumab. Second, the responses after one dose are very poor, leaving the majority of patients unprotected. The second dose increases serology response in the majority of the studies. For this reason, prolonging the interval between doses is not recommended for oncohematologic²¹ or HCT patients. Third, due to the lower serology response after vaccination in SOT and haematological malignancies, it is highly recommended that patients maintain masks and social distancing regardless of vaccination status, and their cohabiting family members receive vaccination in order to reduce the risk of transmission. All these studies in patients with SOT and haematological malignancies have been performed with mRNA vaccines (Pfizer/BioNTech and Moderna). No experience so far has been published with replication-incompetent vector vaccines in these patients. There is so far no data in allogeneic HCT recipients or CAR T cell treated patients.

The results with the Oxford-AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine pooling results from four randomized trials have been published²³. This vaccine is based on a replication-deficient chimpanzee adenoviral vector containing the gene for the SARS-CoV-2 spike protein. The primary efficacy endpoint was symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. All participants received two doses 28 days apart. The analysis included 17178 participants and the overall protective efficacy was 66.%. One uncertainty with these results is that patients receiving two full doses of the vaccine showed a protective efficacy of 63.1% vs. 80.7% in participants receiving one half dose followed by one full dose. Exploratory analyses indicated that efficacy following the second doses increased with increasing intervals between the first and second doses (WHO report, 10 February 2021). Vaccine efficacy in older adults aged ≥ 65 years is uncertain, because only 9.8% of the trial participants were 65 or older. This sample size was too small to estimate vaccine efficacy in this age group²⁴. In “real world use”, the Oxford-AstraZeneca vaccine was in one study, similarly to the Pfizer/Biontech vaccine, shown to reduce COVID-19 related symptoms and hospital admissions in adults^{5,25}. The vaccine

effectiveness against COVID-19 analysed at 35 days after one dose of Oxford-AstraZeneca and 14 days after the second dose of Pfizer/BioNTech, was higher for Pfizer/BioNTech vaccine (89% vs 73%, respectively). The Pfizer vaccine reduced the risk of death by 51% (compared to unvaccinated patients) but the follow-up was insufficient to assess the effect of AstraZeneca vaccine on mortality. A post hoc analysis showed clinical efficacy against the “British mutation (B.1.1.7)”²⁶.

Data for the AD26.COV2.S vaccine (Janssen/Johnson&Johnson) has been published and show high immunogenicity and a 66.9% efficacy after one dose of the vaccine²⁷. The efficacy against severe-critical COVID-19 was higher (76.% at 14 days and 85.4% at 28 days after vaccination). The efficacy against the “South African variant” (20H/501Y.V2) was slightly lower (73.1.% at 14 days and 81.7% at 28 days after vaccination).

Safety information

For both the mRNA-based vaccines, there have been reports of anaphylactic although considering the number of individuals vaccinated, these seem to be rare and one third have occurred in individuals with a history of anaphylactic reactions (Until January 18, 2021 a total of 9 943 247 doses of the Pfizer-BioNTech vaccine and 7 581 429 doses of the Moderna vaccine were reported administered in the US. 47 anaphylaxis following Pfizer- BioNTech vaccine were reported, resulting in a rate of 4.7 cases/million doses administered, and 19 cases following Moderna vaccine, for a reporting rate of 2.5 cases/million doses administered²⁸). In addition, there have been reports on Bell’s palsy in a slightly higher frequency in the vaccinated cohorts comparable to other viral vaccines. Cases of myocarditis and pericarditis are currently being investigated but no relation to the vaccines have been established. Furthermore, since both vaccines now have been used in a very large number of individuals, a general assessment can be made of a high degree of safety from serious side effects. From the limited experience available, the safety of mRNA vaccines in patients with haematological malignancies seems to be similar as in healthy individuals^{20,21}.

Safety has become a concern with the Oxford-AstraZeneca and Janssen/Johnson & Johnson vaccines. There have been well-documented reports of Vaccine Induced Thrombosis and Thrombocytopenia (VITT) syndrome related to unusual site thrombosis, raised D-dimer and anti-platelet factor 4 (PF4) antibodies in occasional individuals. Clinical and laboratory

diagnosis are covered in recent reviews²⁹. Although relatively rare, this serious complication has resulted in different countries making decisions to restrict use of associated vaccines in the general population, or, for example, based on age. Current safety updates of all vaccines are presented at the EMA website: (<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorized#safety-updates-for-authorized-covid-19-vaccines-section>).

The preliminary results of a phase III trial with the Gam-Covid-Vac (Sputnik V) performed on 21977 adults showed an efficacy of 91.6% in preventing PCR-confirmed COVID-19 disease calculated at 21 days from the first dose. In this study, the participants received 2 recombinant adenovirus vaccines, rADV26 and rADV5, administered intramuscularly with a 21 day interval between the doses³⁰. The vaccine efficacy in the population > 60 years of age was reported as high as 91.8%.

Preliminary results of a randomised phase 3 trial with Novavax performed in the UK was recently released (January 28, 2021. <https://ir.novavax.com/node/15506/pdf>) showing a vaccine efficacy of 89.3%. This is an adjuvanted recombinant prefusion spike protein nanoparticles vaccine. The study enrolled more than 15,000 participants between 18-84 years of age, including 27% over the age of 65. The efficacy was calculated to be 95.6% against the original COVID-19 strain and 85.6% against the UK variant strain [*post hoc* analysis]. In a Phase 2b clinical trial performed in South Africa, with approximately 90% of COVID-19 cases attributed to the South African escape variant, 60% efficacy (95% CI: 19.9 – 80.1) for the prevention of COVID-19 disease was observed.

There are also different vaccines in limited use in China, with only limited information available. One is based on a replication-deficient viral vector and others on inactivated viral particles.

Information about additional vaccines can be expected. It is recognized that there might be national guidelines that need to be followed about which groups will be prioritized and which vaccines will be used. There are 27 vaccines in phase III trials (New York Times Coronavirus Vaccine Tracker, (<https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine->

[tracker.html](#)). These represent different technologies using either mRNA, adenoviral vectors, the spike protein, or inactivated virus as antigens. For some of these vaccines, the information is still limited.

A major concern for possibly reduced efficacy of the vaccines is the rapid spread of mutated variants of SARS-CoV-2. Most recently the “Indian strain” but also the mutation first documented in New York (B.1.526). Data have emerged that these variants can be less sensitive to neutralization by antibodies elicited by vaccines^{31,32}. The efficacy against the British variant “Kent” (B.1.1.7) seems to be relatively unchanged while there is a decrease in neutralization capacity of the South African Strain (B.1.351; 501Y.V2) by antibodies elicited by the Moderna vaccine³². Preliminary data suggest that there is no increase in severity or breakthrough risk of COVID-19 after vaccination for the New York variant³³. The rapid development of new variants is a matter of concern. It is reassuring that the emerging data showing protection from severe infection and death for Pfizer/BioNTech, Janssen/Johnson&Johnson, Novavax and CoronaVac/Sinovac vaccines in all settings, although the prevention of asymptomatic transmission and mild-to-moderate disease is more variable as shown in difference in protection when studies were performed in different regions of the world³⁴.

There has been no data presented on efficacy or safety of any vaccine in HCT or CAR T cell treated patients at the time of approval. Thus, a logical vaccination algorithm will have to be developed without definite information. Furthermore, how SARS-CoV-2 variants will affect patients such as HCT or CAR T cell treated patients, who are likely to develop weaker immune responses will have to be studied but is of concern.

Neither the mRNA nor the vector-based vaccine technology has been used previously in HCT recipients and it is difficult to deduce if one technique would be more likely to produce a more robust immune response in immunosuppressed individuals or would have different safety profiles. It is important to evaluate possible immune activation phenomena when using vaccines based on new technologies. Currently the mRNA vaccines and one replication-incompetent vector vaccine have been deemed safe to use by the CDC/FDA/EMA in immunocompromised patients. As a general rule, the vaccines that use SARS live attenuated virus or replicating viral vectored vaccines (vectored by measles, vesicular stomatitis virus, influenza virus, for example) are contraindicated in HSCT or CART-T cell receptors. Most of this live-attenuated virus or

replicating viral vectored vaccines are currently only in phase 1-2 trials. Similarly, any BCG-approach vaccination is contra-indicated in immunocompromised patients.

The choice of vaccine has become more difficult with the restricted use of some vaccines in some countries. Therefore, national regulations and recommendations should be followed also when vaccinating HCT or CAR T cell treated patients. Prioritization for getting the vaccine will be made by the health authorities in each country. It is our belief that patients early after HCT or CAR T therapy, those on immunosuppression, and those with pulmonary compromise ought to have a high priority together with health care staff caring for these patient groups.

One important issue is regarding vaccination of donors. As always in case of donors, safety of the donor is paramount and there are recommendations to postpone donations in donors developing side effects. Use of live attenuated and replication-competent vaccines in the donors must result in delay of the transplantation according to recommendations by the ECDC. However, no such vaccine is currently licensed in Europe. There is currently no data supporting a transfer of protective or disease attenuating immunity from donors to HCT recipients and therefore high-risk HCTs should not be delayed allowing vaccination of the donor.

The use of a vaccine for SARS-CoV-2 modifies the interpretation of the serologic test. As the four EMA licensed vaccines induce antibodies against the spike glycoprotein, to evaluate for evidence of infection in an individual vaccinated, a test specifically evaluating IgM/IgG to the nucleocapsid protein should be used.

Since the immunity to SARS-CoV-2 seems to wane over time and reinfections have been reported, vaccination should be offered to persons regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection. In the general population, reinfection is uncommon in the 90 days after initial infection. Thus, persons with documented acute SARS-CoV-2 infection in the preceding 90 days may delay vaccination until near the end of this period, if desired. There are currently no data on the duration of protection due to the resolved SARS-CoV-2 infection in the immunocompromised, but this period might be shorter than in the immunocompetent. Therefore, it might be reasonable not to postpone vaccination in those with a recent resolved SARS-CoV-2 infection.

Currently our assumptions and recommendations are:

- 1) HCT patients could be vaccinated against SAR-CoV-2. They could be given whatever vaccine is made available **in their country** as long as they are not live-attenuated or contain replicating viral vectors. Considering the results of the phase III trials in healthy individuals, we can assume that the HCT patient population is among the ones, who should have the highest benefit/risk ratio of the vaccination.
- 2) **Currently there is no data on the capacity of any vaccine to induce immune responses in HCT or CAR T cell treated patients. Nonetheless, based on the preliminary experience of patients with haematological malignancies and SOT that show a lower serology response compared to the general population, it seems logical to use those vaccines that showed a $\geq 90\%$ response in the phase 3 trials. Considering the rapid emergence and spread of SARS-CoV-2 variants with possibly higher risk of vaccine breakthroughs, HCT and CAR T cell treated patients should continue to follow recommendations with the aim to limit the risk for exposure.**
- 3) If the transmission rate in the surrounding society is high, vaccination could be initiated at the earliest three months after HCT. Whether an earlier start would give any protective effect is currently unknown.
- 4) Vaccination against COVID-19 should take priority over the regular vaccinations program. The vaccine should routinely be administered alone. It is prudent to avoid influenza or pneumococcal vaccines within 14 days or any other vaccine within 28 days, before and after the administration of mRNA or replication-incompetent vector vaccines against SARS-CoV-2 unless the indication for the other vaccine(s) is strong. With the currently approved two-dose vaccines, this means a postponement of approximately 6 – 8 weeks for other vaccines.
- 5) If transmission in the surrounding society is well controlled, it would be logical to wait until six months after transplantation to initiate vaccination.
- 6) Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without obvious risks to result in worsening of the GVHD. These patients should therefore not be excluded. Although side effects are expected as with any vaccine, there is no example of a non-live vaccine having more frequent or more severe side effects in HCT recipients than in the healthy population of the same age range.
- 7) **However, safety has to be assessed in well-designed clinical trials using vaccines based on new technologies such as mRNA or replication-incompetent vector vaccines.**

- 8) If an HCT recipient has received COVID-19 vaccine before HCT or CAR T cell therapy, the procedures will most likely wipe out all immune memory as for other vaccines. Thus, they most likely need to be vaccinated as COVID-19 naïve patients post HCT.
- 9) It should be recognized that the current labels for all the licensed vaccines do not include additional doses after the first vaccine series. Thus, it is off label, and this must be taken into consideration if additional doses are contemplated post-HCT.
- 10) Reasonable criteria to postpone COVID-19 vaccination based on our current knowledge are:
 - a. Severe, uncontrolled acute GVHD grades III – IV.
 - b. Recipients, who have received anti-CD20 antibodies such as rituximab during the past six months or other B-cell depleting therapy such as obinutuzumab, inotuzumab, blinatumomab .
 - c. CAR T cell patients with B-cell aplasia earlier than six months after treatment.
 - d. Recent therapy with ATG or alemtuzumab.
 - e. Children < 16 since there is no information regarding vaccination of this group in any of the studies. The Pfizer-BioNTech vaccine is licensed from 16 years in the EU (now from 12 years in the US) and it can be used from that age, while the Moderna and Oxford-AstraZeneca vaccines are licensed from 18 years. This might change if the EMA approves the Pfizer-BioNTech vaccine for children from 12 years.
- 11) There is no information available allowing guidance regarding COVID-19 vaccination in patients on maintenance therapy with lenalidomide or TKIs after HCT. These cases have to be assessed on an individual situation basis.
- 12) Studies of safety, efficacy and immunogenicity of COVID-19 vaccines are recommended, but positive antibody testing (both to spike or nucleocapsid proteins) is not equivalent with clinical protection; and general preventive practices should be continued.
- 13) It is likely that stem cell donors will have been vaccinated prior to donation and the ECDC has issued recommendations as have several registries. The ECDC recommendations state that there is no risk to vaccinate donors with mRNA or protein subunit vaccines and such individuals can donate as long as they are feeling well (<https://www.ecdc.europa.eu/en/publications-data/coronavirus-disease-2019-covid-19-and-supply-substances-human-origin>). For non-replicating vaccines (mRNA or virus vector-based), it might be reasonable to wait a few days (3-7) after vaccination before

starting G-CSF for stem cell mobilization to avoid overlapping toxicities or before collection.

- 14) The transplant donation should not be delayed due to vaccination of the donor in case the transplant is urgent.
- 15) The ECDC also recommends that donors, who receive attenuated vaccines (virus vector-based or live-attenuated virus vaccines), have to be deferred for four weeks after vaccination.
- 16) Healthcare workers should be vaccinated to protect the patients.
- 17) Adult house-hold contacts should be vaccinated, especially when the HCT recipient is early after transplant or receiving intensive immunosuppression, as such patients are unlikely to respond to COVID-19 vaccine.
- 18) The duration of protection is unknown, but it is possible that it will be shorter in immunocompromised patients than in healthy individuals as has been shown with other vaccines^{35,36}. Thus, booster doses are most likely needed but it is unclear when such should be given.

Other vaccines: Influenza vaccination is strongly recommended in HCT and CAR T cell treated patients. It is also logical to ensure that the patient's vaccination status against *S. pneumoniae* is up to date.

Prepared by: Per Ljungman, Simone Cesaro, Catherine Cordonnier, Malgorzata Mikulska, Jan Styczynski, Rafael de la Camara.

Approved by: Nicolaus Kröger, John Snowden, Harry Dolstra, Andreu Gusi

References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
2. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(50):1922-1924.
3. Frenck RW, Jr., Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *N Engl J Med*. 2021.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416.

5. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ*. 2021;373:n1088.
6. Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged \geq 65 Years - United States, January-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(18):674-679.
7. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021;384(15):1412-1423.
8. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet*. 2021;397(10287):1819-1829.
9. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. *JAMA*. 2021.
10. Rozen-Zvi B, Yahav D, Agur T, et al. Antibody response to mRNA SARS-CoV-2 vaccine among kidney transplant recipients - Prospective cohort study. *Clin Microbiol Infect*. 2021.
11. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. *Eur J Heart Fail*. 2021.
12. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA*. 2021.
13. Rabinowich L, Grupper A, Baruch R, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol*. 2021.
14. Grupper A, Rabinowich L, Schwartz D, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant*. 2021.
15. Marion O, Del Bello A, Abravanel F, et al. Safety and Immunogenicity of Anti-SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants. *Ann Intern Med*. 2021.
16. Benotmane I, Gautier-Vargas G, Cognard N, et al. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int*. 2021;99(6):1498-1500.
17. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. *Blood*. 2021.
18. Terpos E, Trougakos IP, Gavriatopoulou M, et al. Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose. *Blood*. 2021.
19. Roeker LE, Knorr DA, Thompson MC, et al. COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia. *Leukemia*. 2021.
20. Pimpinelli F, Marchesi F, Piaggio G, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol*. 2021;14(1):81.
21. Monin L, Laing AG, Munoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021.
22. Agha M, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. *medRxiv*. 2021.
23. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881-891.
24. WHO. AZD1222 vaccine against COVID-19 developed by Oxford University and Astra Zeneca: Background paper. Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines 10 February 2021;

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-background-2021.1; 2021.

25. Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet*. 2021;397(10285):1646-1657.
26. Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet*. 2021;397(10282):1351-1362.
27. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021.
28. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. *JAMA*. 2021.
29. Platton S, Bartlett A, MacCallum P, et al. Evaluation of laboratory assays for anti-Platelet Factor 4 antibodies after ChAdOx1 nCoV-19 vaccination. *J Thromb Haemost*. 2021.
30. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. 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.
31. Xie X, Liu Y, Liu J, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. *Nat Med*. 2021.
32. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*. 2021.
33. Thompson CN, Hughes S, Ngai S, et al. Rapid Emergence and Epidemiologic Characteristics of the SARS-CoV-2 B.1.526 Variant - New York City, New York, January 1-April 5, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(19):712-716.
34. Gupta RK. Will SARS-CoV-2 variants of concern affect the promise of vaccines? *Nat Rev Immunol*. 2021.
35. Robin C, Bahuaud M, Redjoul R, et al. Antipneumococcal Seroprotection Years after Vaccination in Allogeneic Hematopoietic Cell Transplant Recipients. *Clin Infect Dis*. 2020;71:e301-e307.
36. Cordonnier C, Labopin M, Chesnel V, et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. *Clin Infect Dis*. 2009;48(10):1392-1401.

COVID-19 vaccines. Version 5 February 22, 2021

Table 2

General considerations

- **Available vaccines**

- Four vaccines are approved for use within the EU. Two of these based on mRNA technology (Pfizer/BioNTech and Moderna) and two using non-replication competent adenovirus vectors (Oxford AstraZeneca and Johnson & Johnson/Jansen).
- One important question is if any of the vaccines is preferable for use in HCT or CAR T cell treated patients
 - The choice of vaccine has become more difficult with the restricted use of some vaccines in some countries. Therefore, national regulations and recommendations should be followed also when vaccinating HCT or CAR T cell treated patients.
 - Currently there is no data on the capacity of any vaccine to induce immune responses in HCT or CAR T cell treated patients. Nonetheless, based on the preliminary experience of patients with haematological malignancies and SOT that show a lower serology response compared to the general population, it seems logical to use those vaccines that showed a $\geq 90\%$ response in the phase 3 trials.

- **Preliminary results of phase III trials, not approved yet**

- Gam-Covid-Vac (Sputnik V), recombinant adenovirus vaccine (first dose: ADV26; second dose: rADV5) showed an efficacy of 91.6% in preventing PCR-confirmed COVID-19 disease (in patients > 60 years of age was 91.8%)
- Novavax, recombinant prefusion spike protein nanoparticles vaccine, showed an efficacy of 95.6% against the original COVID-19 strain and 85.6% against the UK variant strain.

- **Regulatory agencies recommendation**

- **The FDA and CDC have presented advise** for the use of these vaccines and it is recommended for immunosuppressed patients although no specific data has been presented.
- **EMA** recognized that the protection efficacy might be lower in immunosuppressed individuals, but there are no particular safety concerns. Immunocompromised people can still be vaccinated as they are at higher risk of COVID-19

- **Vaccine data for HCT or CAR T cell treated patients**

- There has been no data presented on efficacy or safety of any vaccine in HCT or CAR T cell treated patients at the time of approval. Thus, a logical vaccination algorithm will have to be developed without definite information
- **Neither the mRNA or the vector-based vaccine technology** has been used previously in HCT recipients and it is difficult to deduce if one technique would be more likely to produce a more robust immune response in immunosuppressed individuals or would have different safety profiles.

- **Vaccines safety**

- The four vaccines now approved by EMA now have been used in a large number of individuals, **a general assessment can be made of a high degree of safety from serious side effects. Nonetheless, there are reports of anaphylactic reactions** (i.e 4.7 cases per million of doses of Pfizer/BioNTech vaccine and 2.5 cases/million dose of Moderna vaccine) **and rare but potentially fatal vaccine-induced immune thrombotic thrombocytopenia cases (VITT).**
- **Vaccines that use SARS-CoV-2 live attenuated virus or replicating viral vectored vaccines** (vectored by measles, vesicular stomatitis virus, influenza virus, for example) **are contraindicated** in HSCT or CART-T cell receptors. **Similarly, any BCG-approach vaccination is contra-indicated**

in immunocompromised patients

- **Prioritization of HCT or CAR T patients for getting the vaccine**
 - It is our belief that patients early after HCT or CAR T therapy, those on immunosuppression, and those with pulmonary compromise ought to have a **high priority** together with health care staff managing these patient groups
- **Other vaccines**
 - **Influenza vaccination** is strongly recommended in HCT and CAR T cell treated patients. It is also logical to ensure that the patient's vaccination status against ***S. pneumoniae*** is up to date
 -
- **Variants of SARS-CoV-2 and vaccines**
 - **Neutralization activity induced by vaccination**
 - **The neutralization capacity induced by the mRNA vaccines** (Moderna, Pfizer) seems to be relatively unchanged against the British variant "Kent" (B.1.1.7) while there is a decrease in neutralization capacity of the South African Strain (B.1.351; 501Y.V2). B.1.351 variant showed high resistance to vaccine sera on neutralisation assays in patients who received **AstraZeneca vaccine**
 - The clinical effect of this potential decrease in neutralization is currently unknown
 - **Clinical efficacy of vaccines**
 - Emerging data shows protection from severe infection and death for Pfizer/BioNTech, Jansen/Johnson&Johnson, Novavax and CoronaVac/Sinovac vaccines in all settings, although the prevention of asymptomatic transmission and mild-to-moderate disease is more variable as shown in difference in protection when studies were performed in different regions of the world. The protection of Oxford-AstraZeneca vaccine against death and severe disease by B.1.351 is uncertain as it didn't prevent mild-moderate cases in a randomised trial.

Recommendations

1. **HCT patients could be vaccinated with whatever vaccine is made available in Europe as long as they are not live-attenuated or contain replicating viral vectors.** See comments in the section of general considerations for the choice of available vaccines. Considering the results of the phase III trials in the healthy population, we can assume that the HCT patient population is among the ones who should have the best benefit/risk ratio of the vaccination.
 - This message is important to explain to patients and their relatives.
 - **Variants of SARS-CoV-2** can impact on the neutralization activity of antibodies induced by vaccines and on vaccine efficacy (see comments in the section of general considerations)
 - **Prolonging the interval between vaccine doses is not recommended for HCT patients**

2. **Vaccination in patients that have received convalescent plasma or anti-SARS-CoV2 monoclonal antibodies**
 - Both types of passive antibody therapies may influence immune response to COVID-19 vaccines SARS-CoV-2. If vaccination is considered despite that the patient has had COVID-19, it is recommended to defer vaccination for at least 90 days as a precautionary measure to avoid potential interference of the antibody therapy with vaccine-induced immune responses

3. **Vaccination against COVID-19 should take priority over the regular vaccinations program.**
 - **The vaccine should routinely be administered alone.**
 - **It is prudent to avoid influenza or pneumococcal vaccines within 14 days or any other vaccine within 28 days, before and after** the administration of mRNA or replication-incompetent vector vaccines against SARS-CoV-2 unless the indication for the other vaccine(s) is strong. With the currently approved two-dose vaccines, this means a postponement of approximately 6 – 8 weeks for other vaccines.

4. **If an HCT recipient has received COVID-19 vaccine before HCT or CAR T cell therapy,** the procedures will most likely wipe out all immune memory as for other vaccines. Thus, they most likely need to be vaccinated as COVID-19 naïve patients post HCT.
 - However, it should be recognized that the current labels for all the licensed vaccines do not include additional doses after the first vaccine series. Thus, it is off-label and this must be taken into consideration if additional doses are contemplated post-HCT

5. **Moment after HSCT for vaccine administration**
 - **If the transmission rate in the surrounding society is high,** vaccination could be initiated at the earliest **three months after HCT**
 - **If transmission in the surrounding society is well controlled,** it would be logical to wait until **six months after transplantation** to initiate vaccination.

6. **Not exclude HSCT patients with GVHD**
 - Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without the risk of worsening of the GVHD. These patients should therefore not be excluded. Although side effects are expected as with any vaccine, there is no example that side effects of non-live vaccines be more frequent or more severe in HCT than in the healthy population of the same age range. So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD low.

7. **Reasonable criteria to postpone vaccination** with our current knowledge are:
 - Severe, uncontrolled acute GVHD grades III – IV.
 - Recipients, who have received anti CD20 or other anti-B cell antibodies during the last six months.
 - CAR T cell patients with B-cell aplasia earlier than six months after treatment.
 - Recent therapy with ATG or alemtuzumab.
 - Children < 16 since there is no information regarding vaccination of this group in any of the studies. The Pfizer-BioNTech vaccine is licensed from 16 years and it can be used from that age, while the Moderna and Astra-Zeneca vaccines are licensed from 18 years.

8. There is no information available allowing guidance regarding COVID-19 vaccination in patients **on maintenance therapy with lenalidomide or TKIs after HCT**. These cases have to be assessed on an individual situation basis

9. **General preventive practices should be continued after vaccination**

- Studies of safety, efficacy and immunogenicity of COVID-19 vaccines are recommended, but positive antibody testing (both to spike or nucleocapsid proteins) is not equivalent with sufficient protection; and general preventive practices should be continued.
- **Considering the rapid emergence and spread of SARS-CoV-2 variants with possibly higher risk of vaccine breakthroughs, HCT and CAR T cell treated patients should continue to follow recommendations with the aim to limit the risk for exposure**

10. **Donor vaccination against SARS-CoV-2**

- **It is likely that stem cell donors will have be vaccinated prior to donation**
 - The ECDC recommendations state that there is no risk to vaccinate donors with mRNA or protein subunit vaccines and such individuals can donate as long as they are feeling well.
 - They also recommend that donors, who receive attenuated vaccines (virus vector-based or live-attenuated virus vaccines), have to be deferred for four weeks after vaccination.

For non-replicating vaccines (mRNA or virus vector-based), it might be reasonable to leave a few days (3-7) after vaccination before starting G-CSF for stem cell mobilization to avoid overlapping toxicities or before collection.

- **There is no recommendation against the use of replication-deficient vector vaccines** such as the Oxford-AstraZeneca, **Sputnik V, and Johnson & Johnson** vaccines in immunocompromised individuals and this ought to mean that also donors can receive these vaccines.
- **Transplant donation should not be delayed due to vaccination of the donor** with the aim to protect the patients in case the transplant is urgent (i.e., acute leukemia)

11. **Healthcare workers should be vaccinated** to protect the patients.

12. **Adult House-hold contacts should be vaccinated**, especially when the HCT recipient is early after transplant or receiving intensive immunosuppression, as such patients are unlikely to respond to COVID-19 vaccine.

13. **The duration of protection is unknown**, and it is possible that it will be shorter in immunocompromised patients than in healthy individuals as has been shown with other vaccines. **Thus, booster doses as most likely needed** but it is unclear when such should be given.