

COVID-19 vaccines. Version 4.03, February 2, 2021

COVID-19 vaccines have been developed, tested, and approved with an unprecedented speed with the aim to control the pandemic. Two vaccines are currently approved by the FDA for emergency use in the USA (Moderna/National Institutes of Health, Pfizer/BioNTech) both based on mRNA technology. The EMA has approved the Pfizer/BioNTech vaccine December 21, the Moderna vaccine on January 6, and the Oxford-AstraZeneca vaccine on January 29. The British competent authority has approved the Pfizer/BioNTech vaccine, the Moderna vaccine, and the Oxford-AstraZeneca vaccine for use in the UK. This vaccine has also been approved in some non-European countries. 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.

Results from the phase III Pfizer/BioNTech vaccine 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 results from the Moderna/National Institute of Health vaccine have been published as well³. 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).

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 in most cases have occurred in individuals with a history of anaphylactic reactions (i.e 11.1 per million of doses of Pfizer/BioNTech vaccine, MMWR Jan, 6 2021). Furthermore, there have been reports on Bell's palsy in a slightly higher frequency in the vaccinated cohorts. However,

since both vaccines 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.

There has been an interim publication of the results with the Oxford-AstraZeneca vaccine pooling results from four randomized trials⁴. 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 preliminary analysis included 11600 participants and the overall protective efficacy was 70.4%. One uncertainty with these results is that patients receiving two full doses of the vaccine showed a protective efficacy of 62.1% vs. 90.0% in participants receiving one half dose followed by one full dose.

Two other vaccines use similar technology (Johnson & Johnson, Gamaleya Research Institute; Sputnik-V) and the latter is in clinical use in Russia, but no data has been published from the phase III studies with either of these vaccines. **Interim data from one phase III study including 44325 adult volunteers with the Johnson & Johnson vaccine have been released and showed 68% efficacy in preventing moderate and severe COVID-19 disease including those infected with an emerging mutated strain.** 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 20 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.

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 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. 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.

One important question is if any of the vaccines is preferable for use in HCT or CAR T cell treated patients? The efficacy data in the pivotal studies suggest stronger immunogenicity by the approved mRNA vaccines from Pfizer-BioNTech and Moderna than the Oxford-AstraZeneca vaccine and concerns have been expressed regarding the latter vaccine's efficacy in the elderly. Thus, if there is a choice, it seems logical to use one of the mRNA vaccines in HCT and CAR T cell patients. However, if the only alternative is the Oxford-AstraZeneca vaccine, this should be given. This tentative recommendation might be changed when more data is presented.

Prioritization of HCT or CAR T patients 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 to allow vaccination of the donor.

The use of a vaccine for SARS-CoV-2 modifies the interpretation of the serologic test. As the three 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 SARS-CoV-2. They could be given whatever vaccine is made available in Europe 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) If there is a choice, it seems logical to use one of the mRNA vaccines in HCT and CAR T cell patients based on the results from the pivotal trials pending more data. However, if the only alternative is the Oxford-AstraZeneca vaccine, this should be given.
- 3) This message is important to explain to patients and their relatives.
- 4) 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.
- 5) 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.

- 6) If transmission in the surrounding society is well controlled, it would be logical to wait until six months after transplantation to initiate vaccination.
- 7) 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.
- 8) So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD is low.
- 9) 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.
- 10) 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.
- 11) 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.
 - 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 and it can be used from that age, while the Moderna and Oxford-AstraZeneca vaccines are licensed from 18 years.
- 12) 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.

- 13) 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.
- 14) 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.
- 15) The transplant donation should not be delayed due to vaccination of the donor in case the transplant is urgent.
- 16) 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.
- 17) 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.
- 18) Healthcare workers should be vaccinated to protect the patients.
- 19) 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.
- 20) 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^{5,6}. 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.

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Table 2

General considerations

- **Available vaccines**

- **Two vaccines are currently approved by the FDA** for emergency use in the USA (Moderna/National Institutes of Health, Pfizer/BioNTech) **and three by EMA** for conditional marketing authorisation in Europe (Moderna/National Institutes of Health, Pfizer/BioNTech, Oxford-AstraZeneca). The British competent authority has approved the Pfizer/BioNTech vaccine and Astra-Zeneca vaccine for use in the UK. This last vaccine has also been approved in some non-European countries (India, Argentina). **The EMA has approved the Pfizer/BioNTech vaccine on December 21, 2020, Moderna vaccine on January 6, 2021, and Oxford-AstraZeneca on January 29, 2021**

- The Moderna and Pfizer licensed vaccines are based on mRNA technology. The Astra-Zeneca vaccine is based on a replication-deficient chimpanzee adenoviral vector. All these 3 vaccines contain the gene for the SARS-CoV-2 spike protein

- **One important question is if any of the vaccines is preferable for use in HCT or CAR T cell treated patients**

- The efficacy data in the pivotal studies suggest stronger immunogenicity by the approved mRNA vaccines from Pfizer-BioNTech and Moderna than the Oxford-AstraZeneca vaccine and concerns have been expressed regarding the latter vaccine's efficacy in the elderly. Thus, if there is a choice, it seems logical to use one of the mRNA vaccines in HCT and CAR T cell patients. However, if the only alternative is the Oxford-AstraZeneca vaccine, this should be given. This tentative recommendation might be changed when more data is presented

- **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**

- Since both vaccines (Pfizer and Moderna) 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 11.1 per million of doses of Pfizer/BioNTech vaccine) **and Bell's palsy in vaccinated people.**
- **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-Tcell 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

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.
2. **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.
3. **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
4. **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.
5. **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.
6. **Reasonable criteria to postpone vaccination** with our current knowledge are:
 - Severe, uncontrolled acute GVHD grades III – IV.
 - Recipients, who have received anti-CD20 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.
7. There is no information available allowing guidance regarding COVID-19 vaccination in patients **on maintenance therapy with lenalidome or TKIs after HCT.** These cases have to be assessed on an individual situation basis
8. **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.
9. **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)

10. **Healthcare workers should be vaccinated** to protect the patients.
11. **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.
12. **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.