Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm

Interim guidance

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Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its extraordinary meeting on 29 April 2021 and updated as a result of another extraordinary SAGE meeting on 5 October 2021. It was further updated based on additional discussions at the extraordinary SAGE meeting on 19 January 2022 with regards to the revised WHO Prioritization Roadmap which now also includes considerations for booster doses.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

The guidance is based on the evidence summarized in the background document on the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm and the annexes which include the GRADE and Evidence to Recommendation Tables. These documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

These interim recommendations refer to the inactivated COVID-19 vaccine (Vero cell), manufactured by the Beijing Institute of Biological Products Co., Limited (BIBP), a subsidiary of the China National Biotec Group (CNBG). The China National Pharmaceutical Group corporation (Sinopharm) is CNBG's parent company. The trade name of the vaccine is Covilo. The vaccine is also known as BBIBP-CorV. In the subsequent text the vaccine will be referred to as the COVID-19 vaccine BIBP.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations *(1)*. A detailed description of the methodological processes as they apply to COVID-19 vaccines can be found in the SAGE evidence framework for COVID-19 vaccines *(2)*. This framework contains guidance on data emerging from clinical trials in relation to the issuance of vaccine-specific evidence-based recommendations.

General goal and strategy for use of the COVID-19 vaccine BIBP

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There is an urgent global need vaccines to make vaccines available at scale and equitably across all countries.

As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, countries are recommended to use the WHO Prioritization Roadmap *(3)* and the WHO Values Framework *(4)* as guidance for their prioritization of target groups. As long as vaccine supplies are very limited (see WHO Prioritization Roadmap), the Roadmap recommends that priority be given initially to high priority-use groups which include older persons, health workers and immunocompromised persons.

As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap *(3)*, taking into account national epidemiological data and other relevant considerations.

Vaccine performance

The COVID-19 vaccine BIBP, is an aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine. A large multi-country phase 3 trial has shown that 2 doses, administered at an interval of 21 days, have an efficacy of 79% (95% confidence interval (CI): 66–87%) against symptomatic SARS-CoV-2 infection, 14 or more days after the second dose. Vaccine efficacy against hospitalization was 79% (95% CI: 26–94%) *(5)*. Women were underrepresented in the trial. The median duration of follow-up available at the time of evidence review was 112 days. More detailed data on the efficacy and safety of the COVID-19 vaccine BIBP can be found in the background document. Data were provided to SAGE in January 2022 on long-term vaccine protection (up to 240 days post administration of the second dose); on vaccine efficacy in older adults and in certain groups with underlying comorbidities, and on booster doses *(6)*. To date, a limited number of studies on vaccine effectiveness have been published. The data reviewed by WHO support the conclusion that the known benefits of the COVID-19 vaccine BIBP outweigh the risks that are known or considered possible.

Older persons: A relatively small number of participants in the phase 3 clinical trial were aged 60 years and older and data for this age group remain limited. Data presented to SAGE indicate that as per the data cut-off date, 31 March 2021, vaccine efficacy in individuals aged 60 years and older against symptomatic disease after a median follow-up time of 213 days was 80% (95% CI: 5–98%) *(6)*. There was no significant difference in post-immunization safety between populations aged 60 years and older and populations aged 18–59 years *(6)*. Given the paucity of data on efficacy and safety in older persons from clinical trials, post-introduction effectiveness and safety studies are needed in this age group. Geometric mean titres (GMT) are lower in those aged over 60 years (109.7 [95% CI: 97.4–123.4]) as compared to 18–59 years (156.2 [95% CI: 149.8–163.0]) *(7)*. Neutralizing antibodies elicited by the standard 2-dose vaccination schedule dropped from a peak of 31.2 AU/ml to 9.2 AU/ml 5 months after the second dose *(8)*.

Post-introduction data:

Data from Argentina, collected from January to June 2021, suggest a vaccine effectiveness, after receipt of 2 doses, of 84% (95% CI: 80–88%) against COVID-19-related mortality in those aged 60 years and older *(9)*. Data from Peru in a large cohort of health workers suggest a vaccine effectiveness of 50% (95% CI: 49–52%) against SARS-CoV-2 infection, and 94% (95% CI: 91–96%) against COVID-19-related mortality *(10)*. In a preprint analysis from Bahrain, the odds ratio for hospitalization in unvaccinated compared to vaccinated adults was 3.5 (p-value <0.001) in those aged 50 years and above; and 2.4 (p-value <0.001) in those aged under 50 years *(11)*. In Hungary, vaccine effectiveness in a large nationwide cohort (approx. 900 000 COVID-19 vaccine BIBP recipients) was 69% (95% CI: 67–70%) against SARS-CoV-2 infection; and 88% (95% CI: 86–89%) against COVID-19-related mortality *(12)*.

Duration of protection and booster doses:

Data suggest that efficacy against symptomatic disease in those vaccinated with 2 primary series doses declined from 70% (95% CI: 57–79%) at 60 days post primary series vaccination, to 57% (95% CI: 50–63%) at 240 days. A significant decline in immunity was seen during phase 1/2 clinical trials at 180 days following completion of the primary vaccine series *(6)*.

In a case–control study from Morocco, vaccine effectiveness against hospitalization with severe or critical COVID-19 was 88% (95% CI: 84–91%) at 1–30 days after completion of the primary vaccine series; 61% (95% CI: 54–67%) at 121–150 days; and 64% (95% CI: 59–69%) at ≥150 days. Overall vaccine effectiveness at any time after the second dose was 73% (95% CI: 71–76%) *(13)*.

Evidence indicates that 3150 participants aged 18 years and older received a booster dose 6 months following primary series vaccination (total study population: 9309). Efficacy against symptomatic disease was 86% (95% CI: 80–91%), and 94% (95% CI: 62–100%) against severe disease *(6)*.

Children and adolescents:

Studies were conducted among children aged 3–17 years to assess immunogenicity, including after a booster dose, and safety of COVID-19 vaccine BIBP. The vaccine was well tolerated in this age group; most adverse events were mild, with a rate of severe reactions of 0.088/100 000 doses administered *(6)*. COVID-19 vaccine BIBP for this age indication has not yet received EUL. A booster dose given at a longer interval (4 months versus 2 months) after completing the primary series, resulted in higher levels of neutralizing antibodies in children, as in all age groups. Antibody levels were higher using a 3-dose versus a 2-dose schedule, though, consistent with adults, immunogenicity declined after around 6 months.

<u>Variants of concern:</u>

No specific estimates of vaccine effectiveness against variants of concern are available. Data from Hungary were generated during a period during which Alpha was the predominant variant *(12)*; data from Morocco were generated in the presence of Delta *(13)*. No data are currently available on vaccine-induced protection against Omicron. A study demonstrated that vaccine-induced immune protection may be lower for Omicron compared to Delta, Beta and wild-type; a booster dose improved neutralization against Omicron *(14, 15)*.

Intended use

Persons aged 18 years and older (in accordance with the WHO Prioritization Roadmap *(3)* .

Administration

The recommended schedule for the primary vaccine series is 2 doses (0.5 ml each dose) given intramuscularly into the deltoid muscle. According to the manufacturer's product label, the vaccine can be administered with an interval of 3 weeks. WHO recommends an interval of 3–4 weeks. If administration of the second dose is delayed beyond 4 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive 2 doses.

Booster doses

Booster doses are administered to a vaccinated population that has completed a primary vaccination series when, with time, vaccine effectiveness has fallen below a rate deemed sufficient in that population *(16)*.

In accordance with the WHO Prioritization Roadmap *(3)*, a booster dose is recommended for the highest and high priority-use groups (i.e. older adults, health workers, persons with comorbidities), administered 4–6 months after completion of the primary series. Countries with moderate-to-high rates of primary series coverage in higher priority-use groups should usually prioritize available resources to first achieve high booster dose coverage rates in higher priority-use groups before offering vaccine doses to lower priority-use groups.[1]

If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity.

Interchangeability with other COVID-19 vaccines (heterologous schedules)

As inferred by other inactivated vaccines *(17)*, and supported by limited data from Bahrain *(18)*, evidence suggests that immunogenicity and vaccine effectiveness is superior with a heterologous booster (COVID-19 vaccine from a different vaccine platform) following a primary vaccine series with COVID-19 vaccine BIBP compared to a homologous booster. Any of the EUL COVID-19 vaccines (mRNA vaccines, or viral vectored vaccines) can be used as a booster dose following a primary series of COVID-19 vaccine BIBP *(17)*.

Co-administration with other vaccines

For adults, based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other adult vaccines, COVID-19 vaccines may be given concomitantly, or any time before or after, other adult vaccines including live-attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines *(19)*. When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. For children and adolescents, evidence from co-administration studies is currently insufficient to make a recommendation for concomitant administration with COVID-19 vaccines.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of this vaccine should not receive a second dose of the same vaccine.

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[1] In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

Precautions

No severe (≥ grade 4) hypersensitivity and anaphylaxis reactions caused by the vaccine have been recorded in clinical trials, but were occasionally observed post-introduction. As for all COVID-19 vaccines, the COVID-19 vaccine BIBP should be given under health-care supervision, with the appropriate medical treatment available in case of allergic reactions. As a precautionary measure, an observation period of 15 minutes after vaccination should be ensured.

Anyone with an acute febrile illness (body temperature over 38.5 ºC) should postpone vaccination until they are afebrile. However, the presence of a minor infection, such as a cold, or low-grade fever should not delay vaccination.

Vaccination of specific populations

Persons aged 60 years and older

The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a very high priority-use group in the WHO SAGE Prioritization Roadmap *(3)*. Vaccination is recommended for older persons without an upper age limit.

Persons with comorbidities

Certain comorbidities such as diabetes, hypertension, obesity and neurodevelopmental and neurodegenerative conditions have been identified as increasing the risk of severe COVID-19 disease and death. Vaccination is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19.

Children and adolescents below the age of 18 years

Most children and adolescents are at very low risk of severe COVID-19. A phase 2 paediatric study has been completed, but the COVID-19 vaccine BIBP has not yet received EUL for this age indication. Until EUL has been obtained, routine vaccination of individuals below 18 years of age with the COVID-19 vaccine BIBP is not recommended.

Pregnant women

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality *(20, 21)*. Pregnant women who are aged 35 years or older, or have high body mass index, or have an existing comorbidity such as diabetes or hypertension are at particular risk of serious outcomes from COVID-19.

Developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects of the vaccine in pregnant animals and their foetuses. Available data from clinical trials are insufficient to assess vaccine safety or efficacy of the COVID-19 vaccine BIBP in pregnancy. This vaccine is an inactivated vaccine with an adjuvant that is routinely used in many other vaccines with a documented good safety profile, including in pregnant women. On the basis of previous experience with use of other inactivated vaccines during pregnancy, the effectiveness of the COVID-19 vaccine BIBP in pregnant women is expected to be comparable to that observed in non-pregnant women of similar age. Studies should be conducted to evaluate safety and immunogenicity in pregnant women.

WHO has identified pregnant women as a priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes. WHO recommends the use of the COVID-19 vaccine BIBP in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of safety data in pregnant women. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Breastfeeding women

WHO recommends the same use of the COVID-19 vaccine BIBP in breastfeeding and non-breastfeeding women. This is based on the following considerations: breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children, and vaccine effectiveness is expected to be similar in breastfeeding women as in non-breastfeeding women. Data are not available on the potential benefits and risks of the vaccine to breastfed children. However, as the COVID-19 vaccine BIBP is not a live virus

vaccine, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. WHO does not recommend discontinuing breastfeeding after vaccination.

Moderately and severely immunocompromised persons, including persons living with HIV with CD4 cell count of <200 cells/µl

Moderately and severely immunocompromised persons (ICPs) are at higher risk of severe COVID-19, regardless of age, although increasing age remains an important co-factor. For purposes of this interim recommendation, moderately and severely immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes people living with HIV with a current CD4 cell count of <200 cells/µl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease). For more details, see the interim recommendations for an extended primary series in immunocompromised persons (22).

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity is lower in ICPs compared to persons without immunocompromising conditions (22). The emerging evidence suggests that an additional dose included in an extended primary series enhances immune responses in ICPs. Reactogenicity data on an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered. Given the significant risk of severe COVID-19 for ICPs, if infected, WHO considers that the benefits of an additional (third) dose in an extended primary series outweigh the risks based on available data, though additional safety monitoring is required.

WHO recommends an extended primary series including an additional (third) dose for ICPs aged 18 years and older. Given the relatively small population of individuals covered by this additional dose recommendation, the impact on vaccine supply is expected to be limited. Available evidence (22) suggests that an additional (third) dose should be given at 1 to 3 months after the second dose in the standard primary series. If more than 3 months have elapsed since the second dose in the primary series, the additional (third) dose should be given at the earliest opportunity. The most appropriate timing for the additional dose may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy, and should be discussed with the treating physician.

Given the limited vaccine effectiveness in this population, a booster (fourth) dose administered 3–6 months after the additional (third) dose may be considered. As a fourth homologous dose does not appear to further increase immunogenicity in health workers (23), heterologous boosters should be considered.

Given that protection may remain inadequate in a portion of immunocompromised persons even after the administration of additional doses, WHO further recommends that close contacts (in particular caregivers) of such individuals should be vaccinated if eligible (according to the product-specific vaccines that have received EUL). Additional public health and social measures at household level to protect immunocompromised persons are also warranted depending on the local epidemic circumstances.

Persons living with HIV who are stable on antiretroviral therapy (ART)

Persons living with HIV may be at higher risk of severe COVID-19. Persons living with HIV were not included in the trials. Data on administration of the vaccine are currently insufficient to allow assessment of vaccine efficacy for persons living with HIV. It is possible that immune responses to the vaccine may be reduced, which may lower clinical effectiveness. Studies in persons living with HIV are under way. In the interim, given that the vaccine is nonreplicating, persons living with HIV that is well-controlled (e.g. current CD4 count >200 cells/µl and/or viral suppression) who are part of a group recommended for vaccination may be vaccinated with the standard primary series of 2 doses. Information and, where possible, counselling should be provided to inform individual benefit–risk assessment. It is not necessary to test for HIV infection prior to vaccine administration.

Persons who have previously had SARS-CoV-2 infection

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Viral or serological testing for prior infection is not recommended for the purpose of decision-making about vaccination. Data from the pooled analyses indicate that the vaccine is safe in people with evidence of prior SARS-CoV-2 infection. With the emergence of Omicron, reinfections after prior infection appear to be common. Hybrid immunity is superior to immunity induced by vaccine or infection alone (24). The optimal time interval between infection and vaccination is not yet known. Persons with laboratory-confirmed SARS-CoV-2 infection before primary series vaccination may choose to delay vaccination for 3 months. Persons with breakthrough infections following any dose could also consider delaying the next dose by 3 months. When more data on duration of immunity after infection become available, the length of this time period may be revised as well as the number of doses needed.

Persons with current acute COVID-19

Persons with acute PCR-confirmed COVID-19 should not be vaccinated until after they have recovered from acute illness and the criteria for discontinuation of isolation have been met. The optimal minimum interval between infection and vaccination is not yet known.

Persons who previously received passive antibody therapy for COVID-19

In people who have previously received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment, vaccination does not need to be delayed. Although some reduction in vaccine-induced antibody titers was observed in people who previously received antibody products, the clinical significance of this reduction is unknown, and the balance of benefits versus risks favours proceeding with vaccination even considering the possibility of diminished vaccine effectiveness in this situation.

Special settings

Persons in settings with high population densities, such as refugee and detention camps, prisons and slums, where physical distancing is not implementable, should be prioritized for vaccination as outlined in the WHO Prioritization Roadmap *(3)*, taking into account national epidemiological data, vaccine supply and other relevant considerations.

As noted in the WHO Prioritization Roadmap, national programmes should give special consideration to groups that are disproportionately affected by COVID-19, or that face health inequities as a result of social or structural inequities. Such groups should be identified, barriers to vaccination should be addressed, and programmes should be developed to allow equitable access to vaccines.

Other considerations

SARS-CoV-2 tests
Prior receipt of the vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests for diagnosis of acute/current SARS-CoV-2 infection. However, it is important to note that currently available antibody tests for SARS-CoV-2 assess levels of IgM and/or IgG to the spike or the nucleocapsid protein. The vaccine contains inactivated SARS-CoV-2 virus, which elicits an immunological response to the spike and nucleocapsid protein; thus, a positive result in a test for spike protein IgM or IgG or a test that specifically evaluates IgM or IgG to the nucleocapsid protein could indicate either prior infection or prior vaccination. Antibody testing is not currently recommended to assess immunity to COVID-19 following vaccination with the COVID-19 vaccine BIBP.

Role of vaccines among other preventive measures

As recent data suggest limited effect of the vaccine on transmission, particularly against Omicron, it is advisable that public health and social measures to reduce SARS-CoV-2 transmission continue, including use of well-fitted face masks, physical distancing, handwashing, appropriate ventilation and other measures as appropriate in particular settings, depending on the COVID-19 epidemiology and potential risks of emerging variants. Each country is facing a different situation in the pandemic depending on several factors including the intensity of SARS-CoV-2 circulation, amount of population level immunity, capacities to respond and agility to adjust measures. As the pandemic continues and the virus evolves, policy adjustments related to SARS-CoV-2 public health and social measures, will be needed. Government advice on public health and social measures should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated.

Community engagement, and effective communication

Community engagement and effective communication (including risk communication) are essential to the success of COVID-19 vaccination programmes. Prioritization decisions should be made through transparent processes that are based on shared values, the best available scientific evidence, and appropriate representation and input by affected parties. Furthermore, communication about the mechanism of action of inactivated vaccines, and efficacy and safety data derived from clinical trials and post-marketing studies, as well as background mortality, maternal and neonatal outcomes and rates of adverse events of special interest (AESI) in groups prioritized for vaccination, needs to be strengthened. Strategies should include: (i) culturally acceptable and linguistically accessible communications regarding COVID-19 vaccination made freely available; (ii) active community engagement and involvement of community opinion leaders and trusted voices to improve awareness and understanding of such communications; and (iii) inclusion of diverse and affected stakeholder opinions in decision-making. Such efforts are especially important in subpopulations who may be unfamiliar with or distrustful of health-care systems and immunization.

Vaccination logistics

The vaccine is provided as a refrigerated liquid formulation stored at a temperature of 2–8 ºC, in a single-dose vial or prefilled syringe. The product should be protected from light.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded in patient records.

When scheduling vaccination for occupational groups, e.g. health workers, consideration should be given to the reactogenicity profile of the COVID-19 vaccine BIBP observed in clinical trials, which may occasionally lead to time off work in the 24–48 hours following vaccination.

In considering the programme implications of implementing these recommendations, particular attention should be given to equity, including the feasibility, acceptability, and effectiveness of the programme in resource-constrained settings.

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