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.

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 to develop effective and safe vaccines and to make them available at scale and equitably across all countries.

The COVID-19 vaccine BIBP, is an aluminium-hydroxide-adjuvanted, inactivated whole virus vaccine. A large multi-country phase 3 trial has shown that two 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%). The trial was not designed and powered to demonstrate efficacy against severe disease, in persons with comorbidities, in pregnancy, or in persons aged 60 years and above. Women were underrepresented in the trial. The median duration of follow-up available at the time of evidence review was 112 days. Two other efficacy trials are under way but data are not yet available.
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More detailed data on the efficacy and safety of this vaccine can be found in the background document. 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. As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, it is recommended that countries use the WHO Prioritization Roadmap(3) and the WHO Values Framework(4) as guidance for prioritized vaccine use based on population subgroup. As long as vaccine supplies are very limited (stage I in the WHO Prioritization Roadmap), in settings with community transmission, the Roadmap recommends that priority of vaccine use be given initially to health workers and older people with and without comorbidities. As more vaccine becomes available, additional priority-use groups should be vaccinated as outlined in the WHO Prioritization Roadmap(4), taking into account national epidemiological data, vaccine-specific characteristics as outlined in product information approved by regulatory authorities, and other relevant considerations.

Intended use
Persons aged 18 years and above.

Administration
The recommended schedule for the primary vaccine series is two doses (0.5 ml) 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 two doses.

Additional doses
Additional doses of a vaccine may be needed as part of an extended primary series for target populations where the immune response following the standard primary series is deemed likely to be insufficient. The objective of including an additional dose in the primary series is to increase the proportion of individuals who are protected against disease (https://www.who.int/news/item/04-10-2021-interim-statement-on-booster-doses-for-covid-19-vaccination). Emerging evidence suggests that older persons and immunocompromised individuals mount a lower immune response after a standard primary series compared to younger individuals and those without immunocompromising conditions. Therefore, for older adults and immunocompromised persons who have received a standard 2-dose primary series of the COVID-19 vaccine BIBP, WHO recommends an additional dose, see under “Older persons” and “Immunocompromised persons” below.

The benefit of an additional dose has largely been assessed using the same vaccine product as for the first two doses (homologous doses) (5). Evolving evidence suggests that a heterologous series (using a different vaccine platform for the third dose) may be more immunogenic than a homologous series. However, data on safety, immunogenicity, and vaccine effectiveness are currently limited as to the relative merits of heterologous versus homologous additional doses. Advice as to whether the additional dose should be a homologous or heterologous vaccine (COVID-19 vaccines from another vaccine platform such as mRNA or viral-vector vaccines) will be updated once more data are available.

In situations of interrupted vaccine supply used for the primary series, or for countries with access to COVID-19 vaccines from another vaccine platform which has received WHO emergency use listing, a heterologous third dose can be considered. 1

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 (6). For the COVID-19 vaccine BIBP, the need for, and timing of, booster doses is being assessed. Recommendations with regards to booster doses will be updated as data become available.

Interchangeability with other COVID-19 vaccines
Limited data are available on using a dose of the COVID-19 vaccine BIBP and a dose of another COVID vaccine in the primary series. It is currently recommended that the same product should be used for both doses. Recommendations may be updated as further information becomes available.

1 Additional doses to the primary series, with either a homologous or heterologous vaccine product, are currently considered off-label use.
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Co-administration with inactivated influenza vaccines

Limited evidence on co-administration of COVID-19 vaccines with inactivated influenza vaccines (derived mainly from co-administration studies with other COVID-19 vaccines) suggests that adverse events and reactogenicity are not increased as a result of co-administration. The COVID-19 vaccine BIBP can be co-administered with inactivated influenza vaccines. Different arms for injection should be used when both vaccines are delivered during the same visit. Continued pharmacovigilance monitoring is recommended.

Co-administration with vaccines other than inactivated influenza vaccines

No co-administration data are available for live-attenuated influenza vaccines given with COVID-19 vaccines. Data gaps also remain for co-administration of this vaccine with other vaccines. There should be a minimum interval of 14 days between administration of this vaccine and vaccines other than inactivated influenza vaccines. This recommendation will be updated as data on co-administration with other vaccines, including live vaccines, become available.

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.

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

A relatively small number of participants in the phase 3 clinical trial were aged 60 years and older, and there were no cases of COVID-19 in either the vaccine or the placebo group in this age category; thus, vaccine efficacy could not be estimated from randomized controlled trials, and safety data from these clinical trials are limited. There are no theoretical reasons to believe that the vaccine has a different safety profile in older than in younger populations for which there is evidence specific to this vaccine. Given the paucity of efficacy and safety data 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 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 two-dose vaccination schedule dropped from a peak of 31.2 AU/ml to 9.2 AU/ml 5 months after the second vaccination(8). In a preprint, lower vaccine effectiveness was reported in Bahrain in persons aged 50 years and older versus younger adults(9).

The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority-use group in the WHO Prioritization Roadmap. The currently available evidence, despite its limitations, suggests lower immunogenicity and effectiveness in older persons. Therefore, WHO recommends an additional (third) dose in persons aged 60 years. Given the significant risk of severe COVID-19 for older adults, 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. These recommendations will be updated when more evidence becomes available.

Countries that have not yet achieved high coverage with the 2-dose primary series in priority-use groups, as per WHO Prioritization Roadmap, should focus on achieving high 2-dose vaccination coverage before implementing an additional (third) dose in persons aged 60 years and older. Given limited vaccine supplies, countries administering an additional (third) dose for persons aged 60 years and older should follow the WHO Prioritization Roadmap and first vaccinate persons aged 80 years or older before moving to vaccinating those aged 60 years or older.
For the additional (third) dose in an extended primary series, WHO recommends an interval of 3-6 months between the second and third doses. If more than 6 months have elapsed since the second dose, the third dose should be administered as soon as possible.

Persons with comorbidities

Certain comorbidities have been identified as increasing the risk of severe COVID-19 disease and death. The phase 3 clinical trial data are insufficient to determine vaccine efficacy among participants with comorbidities. The limited trial data to date are promising but more data will be needed through other phase 3 efficacy and phase 4 effectiveness studies. Experience with other inactivated vaccines suggests that vaccine effectiveness in persons with comorbidities – other than immunocompromising conditions – is likely to be similar or only slightly lower than that in persons of the same age without comorbidities. Considering the favourable benefit-risk assessment, 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. There are currently no efficacy or safety data for children or adolescents below the age of 18 years, although a phase 2 paediatric study is underway. Until such data are available, 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. Pregnant women who are older (age 35 years and above), 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.

The available data on the COVID-19 vaccine BIBP in pregnant women are insufficient to assess vaccine efficacy or vaccine-associated risks in pregnancy. Developmental and reproductive toxicology (DART) studies in animals have not shown harmful effects in pregnancy. In addition, 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.

In the interim, 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 this vaccine 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 to other adults. 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 (5).
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 (5). 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, and therefore this recommendation applies regardless of the level of 2-dose coverage achieved in a country.

Available evidence suggests (5) that an additional (third) dose should be given at least 1 month, and within 3 months, after the second dose in the standard primary series in order to increase protection as quickly as possible in ICPs. 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.

Information and, where possible, counselling about the limitations around the data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment.

Given that protection may remain inadequate in a portion of immunocompromised persons even after the administration of an additional dose, 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. Available data show that, in the 6 months after an initial natural infection, symptomatic reinfection is uncommon. If vaccine supply is limited, persons who have had PCR-confirmed SARS-CoV-2 infection in the preceding 6 months may therefore choose to delay vaccination until near the end of this period. However, emerging data from settings where variants of concern circulate indicate that there is a higher risk of symptomatic reinfection. In these settings, earlier immunization after natural infection may be advisable. When more data on duration of immunity after natural infection become available, the recommendation on the length of this time period may be revised.

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 a natural infection and vaccination is not yet known.

Persons who previously received passive antibody therapy for COVID-19

Currently, there are no data on the safety or efficacy of vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. As a precautionary measure, vaccination should be deferred for at least 90 days to avoid interference of the antibody treatment with vaccine-induced immune responses.
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 (4), 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 variants

SARS-CoV-2 undergoes evolution (12). Some new virus variants, referred to as variants of concern (VOCs), may be associated with higher transmissibility, disease severity, risk of reinfection, or a change in antigenic composition resulting in lower vaccine effectiveness.

WHO currently recommends the use of the COVID-19 vaccine BIBP according to the WHO Prioritization Roadmap (4), even if variants are present in the country. Countries using the vaccine in the presence of variants are encouraged to monitor vaccine effectiveness and to capture data on the frequency and severity of any breakthrough infections due to virus variants. Limited data exist with regards to the vaccine effectiveness of the COVID-19 vaccine BIBP against VOCs.

There is an urgent need for a coordinated approach to surveillance and evaluation of variants and their potential impact on vaccine effectiveness. WHO will continue to monitor the situation; as new data become available, recommendations will be updated accordingly.

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 the vaccination with the COVID-19 vaccine BIBP.

Role of vaccines among other preventive measures

As there is not yet sufficient evidence of an effect of the vaccine on transmission, nonpharmaceutical interventions must continue, including use of face masks, physical distancing, handwashing and other measures as appropriate in particular settings, depending on the COVID-19 epidemiology and potential risks of emerging variants. Government advice on nonpharmaceutical interventions should continue to be followed by vaccinated individuals, as well as those who have not yet been vaccinated. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.

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 2–8°C 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.

**Recommendations on addressing current knowledge gaps through further research**

WHO recommends the following post-authorization monitoring activities and research.

- **Safety surveillance and monitoring:**
  - all serious adverse events (e.g., death, life-threatening event requiring in-patient hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly/birth defect or an important medical event as considered by the health care provider), including thromboembolic events, thrombosis with thrombocytopenia syndrome (TTS), anaphylaxis and other serious allergic reactions, Bell’s palsy, transverse myelitis;
  - cases of multisystem inflammatory syndrome following vaccination, cases of COVID-19 following vaccination that result in hospitalization or death;
  - background rates of AESIs (including thromboembolic events), maternal and neonatal outcomes, and mortality in groups prioritized for vaccination;
  - vaccine-associated enhanced disease and vaccine-associated enhanced respiratory disease following immunization;
  - vaccine safety assessment in the context of phase IV studies, particularly in older persons and persons with comorbidities

- **Vaccine effectiveness:**
  - vaccine effectiveness in relation to new virus variants;
  - vaccine effectiveness in persons 60 years and above;
  - vaccine effectiveness in persons with comorbidities;
  - vaccine effectiveness against severe COVID-19;
  - vaccine effectiveness in relation to time interval between the first and second dose;
  - vaccine effectiveness over time and whether protection can be prolonged by booster doses;
  - vaccine effectiveness against post-COVID-19 conditions
  - studies to investigate whether this vaccine reduces SARS-CoV-2 transmission and viral shedding;
  - assessment and reporting of breakthrough infections and virus sequence information;
  - head-to-head studies with other vaccines on extent and duration of immunity using standardized neutralization, T-cell and mucosal immunity assays;
  - booster studies with homologous and heterologous vaccines.

**Subpopulations:**

- prospective studies on the safety of this vaccine in pregnant and breastfeeding women;
- immunogenicity and safety studies in persons below the age of 18 years;
- safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease;
- optimal dose interval for additional doses for immunocompromised and older persons;
- safety and vaccine effectiveness of additional doses;
- studies to assess the need for and timing of booster doses in the general population.

Correlates of protection and of duration of immunity

Vaccination logistics:
- immunogenicity and safety studies of co-administration with other vaccines, including influenza and pneumococcal vaccines, to adults and older persons;
- safety, immunogenicity, and impact of a delayed second dose;
- interchangeability and “mix and match” studies within and across COVID-19 vaccine platforms.

• Virus variants:
  - global surveillance of virus evolution and the impact of virus variants on vaccine effectiveness to support update of vaccines;
  - modelling to determine the trade-offs in the use of vaccines with reduced effectiveness against emergent variants;
  - effectiveness studies against virus variants.

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References


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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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