# Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19

Background document to the WHO Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing

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## Contents

## Background

This background document has been prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its 5 January 2021 extraordinary meeting [1], which resulted in the issuance of the 8 January 2021 WHO Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1, accessed 11 January 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.

## General considerations on mRNA vaccines

The advantages of RNA-based vaccines are that they can be developed rapidly. mRNA-based vaccines avoid the risk of integration with the host cell genome and are able to produce pure viral protein. mRNA is transiently expressed, allowing protein to be made within the cell. Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows precise genetic information to be delivered, together with an adjuvant effect, to antigen-presenting cells. It is molecularly well defined, free from materials of animal origin, and synthesized by an efficient, cell-free in vitro transcription process from DNA templates. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, allowing speedy commercial production. The fast and highly scalable mRNA manufacturing and LNP formulation processes allow rapid production of many vaccine doses, which is particularly important during a pandemic.

## Characteristics of COVID-19 vaccine BNT162b2 (Pfizer–BioNTech)

The Pfizer–BioNTech COVID-19 vaccine, BNT162b2, is an mRNA vaccine encoding a P2 mutant spike protein (PS 2) and formulated as an RNA–lipid nanoparticle of nucleoside-modified mRNA (modRNA). BNT162b2 elicits a blunted innate immune sensor activating capacity and thus augments antigen expression. Encapsulation into LNPs allows transfection of the mRNA into host cells after intramuscular (IM) injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol, where it is translated into the encoded viral protein. The mRNA is rapidly degraded intracellularly, while the resulting peptides are presented at the cell surface, triggering a specific humoral T-cell-mediated immune response with activity against the spike protein.

## Development process, contents, formulation

BNT162b2 is produced as a highly purified single-stranded, 5`-capped mRNA; the mRNA encodes the viral spike from SARS-CoV-2. The following excipients are included: ALC-0315, ALC-0159 (polyethylene glycol), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, and water for injection.

## Preclinical studies

A single injection of BNT162b2 elicited high neutralizing antibody titres in mice. Vaccination of mice also resulted in robust T helper 1 ($T_H1$) and T follicular helper ($T_{FH}$) type $CD4^+$ responses as well as a robust $IFN\gamma^+IL\text{-}2^+$ $CD8^+$ T-cell response. This pattern of cell-mediated immunity suggests a low likelihood that the vaccine will induce a hypersensitivity response and resulting vaccine-associated enhanced respiratory disease. In addition, the induction of a $T_{FH}$ response supports the hypothesis that the vaccine may confer durable immunity. Translation of this immunogenicity profile into protection against subsequent viral infection was tested in a non-human primate (NHP) study.

The immunogenicity of BNT162b2 in rhesus macaques paralleled that observed in the murine model (1). Two doses of 100 µg of this mRNA vaccine were given at 0 and 21 days. Seven days after the second dose, the 50% virus neutralization titre of antibodies reached 18 times that of a human SARS-CoV-2 convalescent serum panel; it remained 3.3 times higher than this benchmark five weeks after the second immunization, although the

absolute titre decayed from 1689 to 310. The $T_H1$-based $CD4^+$ response and the $IFN\gamma^+$ $CD8^+$ T-cell response mirrored the cellular immunogenicity profile reported in mice. Two doses of 100 µg of BNT162b2, separated by a three-week interval, protected 2–4-year-old rhesus macaques against viral infection when challenged, intranasally and intratracheally, with $1x10^6$ plaque-forming units (pfu) of SARS-CoV-2 55 days after the second vaccination. Viral RNA, as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR), in the bronchoalveolar lavage fluid (BAL) and nasopharyngeal (NP) and oropharyngeal (OP) swabs, was significantly lower in the vaccinated animals than in the unvaccinated controls. The virus was absent on day 3 and day 6 after challenge. No measurements were made at other times. Histopathological outcomes were not presented in any detail in this NHP study; protective efficacy was limited to virological outcomes. Overall, these preclinical data indicate that BNT162b2 is an immunogenic vaccine that is efficacious in protecting against viral infection in the lower and upper airways of rhesus macaques three days after challenge.

## Clinical studies: phases 1 and 2

### Safety

Two candidate mRNA vaccines were tested in phase 1 trials: BNT162b1 and BNT162b2. The latter was ultimately advanced to phase 3 trials because it was better tolerated and represented a greater breadth of T-cell epitopes (2). Overall, the vaccine, given as a two-dose regimen at one of three doses (10 µg, 20 µg, 30 µg) was tolerated well in two age groups: 18–55 years and 65–85 years. Local and systemic adverse events were generally mild and were more frequent in the two higher dose groups. Systemic adverse events were generally milder in the older age group. Perturbations in laboratory values that were deemed related to vaccine administration were also milder in older individuals. No serious adverse events were reported, and no stopping rules met.

### Immunogenicity

Neutralizing antibody titres (50% neutralizing geometric mean titres (GMTs)) elicited by BNT162b2 peaked one week after the second vaccination and began decaying one week after that. There was a trend towards higher titres in individuals who had received the highest vaccine dose of 30 µg. Vaccination with this dose elicited titres that were lower than those seen in animal studies; titres were 1.7–4.6 times higher than that seen in a convalescent serum panel among the 18–55-year-olds and 1.1–2.2 times higher among the 65–85-year-olds. The adult population studied for safety and immunogenicity was stratified by age but skewed towards a Caucasian background (85%). The population in the phase 3 trial assessing efficacy of BNT162b2 was more diversified.

## Clinical studies: phase 2/3 trials (3)

### Efficacy

#### *Trial population*

The phase 2/3 pivotal registration trial of the vaccine was conducted at sites in six countries (Argentina, Brazil, Germany, South Africa, Turkey and the USA) and involved about 43 000 participants aged 16 to 85 years, who were healthy or had stable medical conditions, randomized equally between vaccine and placebo groups. About 6% of participants had serological evidence of a past SARS-CoV-2 infection at entry to the trial. The vaccine was administered in two doses separated by 21 days, with a range of 19 to 42 days. Most participants were white (83%) and from sites in the USA (77%). Similar numbers of males and females were included; 42% of the trial population was aged over 55 years, and 22% over 64 years, with a median age at vaccination of 52 years. About 46% of participants were obese or had a co-morbid condition that was likely to increase their risk of severe COVID-19. The primary analysis of the trial results was conducted when participants had been followed for an average of two months after the second vaccine dose; 92% had been followed for at least one month after the second dose.

#### *Efficacy against COVID-19*

Two primary endpoints were specified: efficacy among all participants and efficacy among participants who had no evidence of a previous SARS-CoV-2 infection 7 days after the second vaccine dose. The primary assessment of efficacy was based on the 178 cases of symptomatic laboratory-confirmed SARS-CoV-2 infection that

occurred between 7 days after the second vaccine dose and the end of the follow-up period. Of these cases, 9 were in the vaccinated group and 169 in the placebo group, giving an estimated vaccine efficacy (VE) of 94.6% (95% credibility interval (CI) 89.9–97.3%). When analysis was confined to participants without evidence of a previous SARS-CoV-2 infection, the case numbers were 8 in the vaccine group and 162 in the placebo group, with an estimated VE of 95.0% (95% CI 90.3–97.6%).

Analyses were also conducted including all cases from the time of the first dose. There was evidence of protection both between the first and second doses (VE 52.4%, 95% CI 29.5–68.4%) and between the second dose and 7 days after the second dose (VE 90.5%, 95% CI 61.05–98.9%). More detailed analyses indicated that there was no evidence of protection until about 12 days after the first dose, but subsequently the incidence of COVID-19 was lower among vaccinated participants.

For the period starting 7 days after the second vaccination, no significant variations in the estimates of vaccine efficacy were apparent when the primary analyses were stratified according to sex, age, race, ethnicity, country, comorbid conditions or obesity, and obesity alone. In particular, among those aged 65 years or older, without evidence of prior infection up to 7 days after the second dose, there was 1 case in the vaccinated group and 19 cases in the placebo group (VE 94.7%, 95% CI 66.7–99.9%).

### *Efficacy against severe COVID-19*

A total of 10 cases of severe COVID-19 occurred in trial participants, 1 in the vaccinated group and 9 in the placebo group (VE 88.9%, 95% CI 20.1–99.7%). Of these cases, 5 occurred 7 or more days after the second vaccine dose, 1 in the vaccine group and 4 in the placebo group (VE 75%, 95% CI –152.6–99.5%).

### *Summary of efficacy evidence in phase 2/3 trials*

The vaccine was highly efficacious against laboratory-confirmed COVID-19 from 7 days after the second vaccine dose until the end of the follow-up period, which was, on average, 2 months. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variations in efficacy were found in the various subgroups that were analyzed. Importantly, in subgroups likely to be at higher risk of severe COVID-19, including those aged over 65 years and those with comorbid conditions or obesity, the estimates of efficacy were very high. Few participants in the trial developed severe COVID-19, so efficacy against this endpoint is less certain, but from the time of the first dose, there was only 1 severe case in the vaccinated group and 9 in the placebo group, consistent with high efficacy.

## Vaccine safety

Safety data from 37 586 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow-up after the second dose suggested a favourable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the seven days after vaccination, were frequent and mostly mild to moderate. Reactogenicity and adverse events (AEs) were generally milder and less frequent in the older group (≥55 years of age) than the younger group (18–55 years of age) and tended to be more frequent and severe after the second dose. Reactogenicity was mostly mild to moderate and short-lived for both age groups (median onset was 0–2 days after either dose for a median duration of 1–2 days). The vaccine's AE profile did not suggest any specific safety concerns. The median onset of systemic AEs was 1–2 days after either dose for a median duration of 1 day. Severe adverse reactions occurred in 0.0–4.6% of participants. The incidence rates of serious adverse events (SAEs), deaths, and discontinuation due to AEs were low and comparable for the vaccine and placebo groups. No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

### *Adverse events*

The most common solicited adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%). The mean duration of pain at the injection site after dose 2 was 2.5 days (range 1 to 36 days), redness 2.6 days (range 1 to 34 days), and swelling 2.3 days (range 1 to 34 days).

### *Adverse events of special interest, that would potentially require longer follow up*

#### *Lymphadenopathy*

Lymphadenopathy was reported in 64 participants (0.3%). There were more cases in the vaccine group (64) than the placebo group (6). In the vaccine group, 54 (0.5%) occurred in the younger age group (16–55 years) and 10 (0.1%) in the older age group (>55 years). Lymphadenopathy occurred in the arm and neck region, and was reported within 2–4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off.

#### *Bell's palsy*

Bell's palsy was reported by four participants in the vaccine group and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days post-vaccination) was reported as resolved with sequelae within three days of onset, and the other three were reported as continuing or resolving as of the 14 November 2020 data cut-off, with ongoing durations of 10, 15, and 21 days, respectively. The usual incidence of Bell`s palsy is 15–30 per 100 000 per year (4). The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population. An association between COVID-19 and Bell's palsy has been reported. At this point in time, there is no clear basis upon which to conclude a causal relationship, but surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations is an absolute requirement. Bell`s palsy has been addressed in the risk management plan.

#### *Allergic reactions*

The Food and Drug Administration of the USA independently conducted standard MedDRA queries (SMQs) on the phase 2/3 all-enrolled safety population using FDA-developed software. This was to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including allergic, neurological, inflammatory, and autoimmune conditions. The SMQs revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137, 0.63%) compared with the placebo group (111, 0.51%). No imbalances between treatment groups were evident for any of the other SMQs evaluated (5).

Severe allergic reactions have been reported following administration of the Pfizer–BioNTech COVID-19 vaccine during mass vaccination outside of clinical trials. Severe allergic reactions to any ingredient of this vaccine, or a previous dose of this vaccine, are a contraindication.

Additional adverse reactions may become apparent with more widespread use of the Pfizer–BioNTech COVID-19 vaccine.

### *Serious adverse events*

Two of the SAEs considered as possibly related to the vaccine were shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla ipsilateral to the vaccine injection site. The lymphadenopathy was temporally associated and biologically plausible.

### *Special populations*

#### *Comorbidities*

Across both treatment groups, 20.5% of participants had a comorbidity (as per the Charlson Comorbidity Index). The most frequently reported comorbidities were diabetes, with or without chronic complications (8.4%) and pulmonary disease (7.8%), which were reported at similar frequencies in each group. More participants had comorbidities in the older population (31.1%) than the younger population (12.8%), including diabetes (14.6% and 3.8%), malignancy (7.4% and 1.0%), and pulmonary disease (8.8% and 7%).

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. The HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition, but their safety data were not available to contribute to the safety analyses at the time of the data cut-off.

### *Pregnancies*

Female study participants with childbearing potential were screened for pregnancy prior to each vaccination. Anyone who tested positive was excluded or discontinued from the study. The study is collecting data on outcomes of all reported pregnancies that occurred either after vaccination or before vaccination but without being detected by prevaccination screening tests. Twenty-three such pregnancies were reported up to the data cut-off date of 14 November 2020 (12 in the vaccine group, 11 in the placebo group). Pregnancy outcomes are currently not known. Available data on the BNT162b2 vaccine administered to pregnant women are insufficient to allow assessment of vaccine-associated risks in pregnancy.

## ***Special considerations***

### *PEGylation (or pegylation)*

The Pfizer BioNTech BNT162b2 vaccine contains four lipids. The lipids encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles. The four lipids are:

- cholesterol
- 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
- ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate))
- ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

Two of the lipids are commonly used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)). ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid). The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the lipid nanoparticle, which contributes to storage stability and reduces nonspecific binding to proteins.

### *Severe allergies*

Of the excipients, ALC-0159 has the ability to cause allergic reactions, since it contains polyethylene glycol or macrogol.

First published data on anaphylaxis following mass roll-out in the United States after emergency use authorization

During December 14–23, 2020, monitoring by the Vaccine Adverse Event Reporting System detected 21 cases of anaphylaxis after administration of a reported 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million doses); 71% of these occurred within 15 minutes of vaccination (6).

## ***Summary of vaccine safety aspects***

Reactogenicity and adverse events associated with the vaccine were generally milder and less frequent in the older group (≥55 years of age) than the younger group (18–55 years of age) and tended to increase after the second dose. Reactogenicity was mostly mild to moderate and short-lived for both adult age groups (median onset was 0–2 days after either dose for a median duration of 1–2 days). Available data on the vaccine administered to pregnant women are insufficient to allow assessment of vaccine-associated risks in pregnancy. Adverse events of special interest (that would require longer follow up) include lymphadenopathy, Bell's palsy and allergic reactions.

# Vaccine storage

This vaccine requires an ultra-low-temperature freezer for storage up to 6 months. Temperature-controlled thermal shippers using dry ice to maintain the recommended temperature of –70 °C ± 10 °C for up to 10 days will be needed for transportation. Each thermal shipper should have a reusable global positioning system (GPS) temperature-monitoring device.

The intent is to use Pfizer strategic transportation partners to ship by air to major hubs within a country or region and by ground transport to dosing locations. GPS-enabled thermal sensors will be used and a control tower will track the location and temperature of each vaccine shipment along their pre-set routes. These GPS-

enabled devices will allow detection of unwanted deviations. Shipment and transfer of vaccines is directed to "points of use" (POU).

Once a POU receives a thermal shipper with the vaccine, there are three options for storage.

- Ultra-low-temperature freezers, which are commercially available and can extend shelf-life for up to six months.
- Refrigeration units, which are commonly available in hospitals: the vaccine can be stored for five days in such refrigerators at 2–8 °C.
- The Pfizer thermal shippers in which doses arrive can be refilled with dry ice and used as temporary storage units for up to 15 days. After the 15 days, the vials may be transferred to refrigerated storage at 2–8 °C for an additional five days, giving a total storage time of 20 days.

Once thawed and stored at 2–8 °C, the vials may not be refrozen or stored in frozen condition.

The various storage options at the POU allow equitable access to the Pfizer vaccine for areas with differing infrastructure.

## Manufacturer's recommended dosage and schedules including boosters

The Pfizer–BioNTech COVID-19 vaccine BNT162b2 (30 µg) is administered intramuscularly as a series of two 30-µg doses of the diluted vaccine solution (0.3 ml each) according to the following schedule: a single dose followed by a second dose 21 days later. The interval between the two doses in the trial ranged from 19 to 45 days. Studies to determine the need for, and timing of, boosters have been initiated. For the current timing, the schedule determines two doses only.

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