According to the protocol decision of NITAG
dated 09.03.2021 №6

National Immunization Technical Advisory Group (NITAG)

POSITION PAPER № 09-03/2021-1

(official statement)

Regarding the recommendation of the Ministry of Health of Ukraine on certain issues of COVID-19 vaccination in Ukraine

These NITAG recommendations address specific issues of COVID-19 vaccination and are recommendatory in nature.

Question 1:

Determination of the list of professions, industries and organizations whose employees are subject to mandatory preventive vaccinations against acute respiratory disease COVID-19 caused by the coronavirus SARS-CoV-2.

The Law of Ukraine "On Protection of the Population against Infectious Diseases" (https://zakon.rada.gov.ua/laws/show/1645-14#Text) Article 12 "Preventive Vaccinations" provides: "Employees of certain professions, industries and organizations whose workers may be exposed to the infectious virus due to their activities and/or contribute to the spread of infectious diseases are subject to mandatory preventive vaccinations against other infectious diseases as well. In case of refusal or evasion of mandatory preventive vaccinations in accordance with the procedure established by law, these employees should be suspended from performing these types of work. The list of professions, industries and organizations whose employees are subject to mandatory preventive vaccinations against other infectious diseases is established by the central executive body that ensures the formation of state health policy." This article also reads: "In case of threat of a particularly dangerous infectious disease or mass spread of a dangerous infectious disease in the relevant territories and facilities, mandatory preventive vaccinations against this infectious disease may be carried out according to epidemic indications".

The Chief State Sanitary Doctor makes the decision to conduct mandatory preventive vaccinations according to epidemic indications in the respective territories and facilities of Ukraine, Chief State Sanitary Doctor of the Autonomous Republic of Crimea, Chief State Sanitary Doctors of the regions, of Kyiv and Sevastopol cities, Chief State Sanitary Doctors of Central Executive Authorities implementing state policy in the areas of defence and military construction, protection of public order, execution of criminal penalties, protection of the state border, Security Service of Ukraine."

This article uses the concepts of "mandatory preventive vaccinations", "vaccinations for epidemic indications." The Order of the Ministry of Health of Ukraine dated 16.09.2011 No. 595 (as amended by the Order of the Ministry of Health of Ukraine 11.08.2014 No.

551) "National Immunization Schedule" (https://zakon.rada.gov.ua/laws/show/z1159-11#Text), registered in the Ministry of Justice of Ukraine on October 10, 2011. No. 1159/19897 uses the wording "mandatory vaccinations", which is further explained as "other mandatory vaccinations established in accordance with this Schedule for the following groups of population: by age; vaccinations of children who missed the vaccination according to the National Immunization Schedule; vaccination of HIV-infected persons; by health condition; vaccination of children after allogeneic hematopoietic stem cell transplantation (allo-hsct); **vaccinations** in endemic and enzootic territories **and according to epidemic indications**". Thus, the definition "mandatory vaccinations" provides for vaccinations according to epidemic indications. Section IV, art. 4 of the same Order reads "4. The decision to carry out mandatory preventive vaccinations according to epidemic indications in the endemic and enzootic territories is made by the Chief State Sanitary Doctor of Ukraine, the Chief State Sanitary Doctors of the Autonomous Republic of Crimea, regions, cities of Kyiv and Sevastopol."

Today, in accordance with the amendments to Article 39 of the Law of Ukraine "On Protection of the Population against Infectious Diseases" (regarding additional guarantees of the rights of medical and other employees engaged in the protection of the population against infectious diseases and their family members) (http://w1.c1.rada.gov.ua/pls/zweb2/webproc4_1?pf3511=68757), insurance payments are provided in case of illness or death of health workers due to infection of acute respiratory disease COVID-19 caused by the coronavirus SARS-CoV-2. The procedure for making insurance payments and determining their sizes was approved by the Resolution of the Cabinet of Ministers of Ukraine No. 498 dated June 17, 2020.

At this stage, vaccination against COVID-19 in Ukraine is voluntary but not mandatory. The roadmap for the introduction of the vaccine against acute respiratory disease COVID-19, caused by the coronavirus SARS-CoV-2, and mass vaccination in response to the COVID-19 pandemic in Ukraine in 2021-2022, approved by the Order of the Ministry of Health of Ukraine No. 213 of 09.02.2021 reads: "Vaccination against coronavirus disease COVID-19 in Ukraine will be voluntary for all groups of the population and professional groups".

There are discussions around the world about whether it is lawful for employers to direct essential workers or those working with the vulnerable population to obtain a COVID-19 vaccine, when failure to do so may mean that they are restricted to perform their work (USA) (https://www.lexology.com/library/detail.aspx?g=24ccb199-b49e-489c-b3fe-b99c8363b502).

All European Union and the European Economic Area (EEA) countries have launched their national vaccination campaigns against COVID-19. Countries have confirmed that vaccination is not mandatory, but is voluntary (https://www.ecdc.europa.eu/sites/default/files/documents/Overview-of-COVID-19-vaccination-strategies-deployment-plans-in-the-EU-EEA.pdf

https://www.health.gov.au/sites/default/files/documents/2020/11/australian-covid-19-vaccination-policy.pdf

https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021.pdf)

Given the limited availability of the vaccine, the lack of precise data on the prevention of virus transmission by vaccinated persons, at this stage of the vaccine campaign, we deem it reasonable to give the preference to vaccination to persons who are

most susceptible to severe illness or mortality (older adults, residents of boarding schools – nursing homes, residents and staff of long-term care institutions, people with special needs, as well as people with concomitant pathology (obesity, diabetes, etc.), as well as medical workers, especially at high risk of infection.

It is also important to ensure the protection of employees of rapid response and rescue units, firefighters (the State Emergency Service of Ukraine) – (for example, earthquake in Croatia); soldiers taking part in Joint Force Operations, employees of critical structures (for example, nuclear power plants), police, border guard service.

Simultaneously, effective communication on the priority of population groups and justification of the choice of categories of the population for vaccination will be extremely important.

According to the information publicly disclosed from the Social Insurance Fund of Ukraine (published November 18, 2020; https://www.kmu.gov.ua/npas/deyaki-pitannya-nadannya-strahovih-viplat-u-razi-zahvoryuvannya-abo-smerti-medichnih-pracivnikiv-u-t170620) at the time of publication, Social Insurance Fund of Ukraine (hereinafter SIFU) allocated monthly insurance payments for four healthcare workers with determined disability group linked to COVID-19. Also, at the time of publication, SIFU has allocated monthly insurance payments for two healthcare workers who have determined permanent disability linked to COVID-19.

From open sources of information (https://ua-news.liga.net/society/articles/skilki-koshtue-jittya-likarya-chomu-mediki-ne-otrimuyut-viplati-za-pereneseniy-koronavirus) it is known that that SIFU, in response to a request from Liga.net, reported that 36 families of health workers who died of coronavirus (that is, 7.5% of the number of deaths) and nine doctors who were diagnosed with disability linked to COVID-19 (publication 21.01.2021) received one-time and monthly payments of different amounts in Ukraine. It was also reported that in total, in Ukraine, about 800 health workers or their families received one-time and monthly payments of various amounts.

Since the beginning of the vaccination roll-out against COVID-19 in Ukraine, a significant percentage of health workers refused vaccination for various reasons. The first phase of the ongoing vaccination foresees the inoculation of health care workers providing care to patients with COVID-19 in hospitals. The low adherence of healthcare workers to vaccination against COVID-19 can lead to significant staff shortages due to the suspension of those who refused the COVID jab from working with COVID-19 patients.

Cancellation of insurance payments to healthcare workers who refused vaccination against COVID-19 in case of an insured event can lead to increased social tension, deepening the crisis in relations between healthcare workers and public authorities. It should also be taken into account that from the very beginning of communication campaign related to the COVID-19 vaccination roll-out, it was highlighted that the vaccination against COVID-19 among medical professionals is voluntary, and no sanction will be imposed on those refusing vaccination.

The position of Ukrainian NITAG:

Vaccination against COVID-19 should be carried out on a voluntary basis with no sanctions/restrictions imposed on individuals and the representatives of professional groups subject to immunisation in accordance with the designated priority groups if these individuals refused vaccination against COVID-19 for various reasons.

It is recommended to continue communicating to the public the benefits of vaccination against COVID-19 to increase vaccination coverage in Ukraine.

Question 2:

Regarding the optimal interval between the administration of the first and second doses (28 days or 8 (eight) weeks) of Oxford/AstraZeneca vaccines (ChAdOx1 nCov-19 Sorona Virus (recombinated), in particular produced by the Serum Institute of India, SK Bioscience, etc.

In accordance with the instructions for using registered in Ukraine COVIESHILD™ vaccine (registration certificate UA/18593/01/01; address: http://www.drlz.com.ua/ibp/ddsite.nsf/all/shlist?opendocument&rs=UA/18593) the article 4.2 "Dosage and Administration Method" reads that "the COVIESHILD vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered 4 to 12 weeks after the first dose. The instructions for the use of this vaccine posted on the website of the vaccine manufacturer, SSI, contains similar information (https://www.seruminstitute.com/pdf/covishield_ChAdOx1_nCoV19_corona_virus_vaccine_insert.pdf).

On February 26, 2021, WHO published the recommendations for the emergency use of the COVIESHILD ™ vaccine (https://extranet.who.int/pqweb/sites/default/files/documents/COVISHIELD_TAG_REPORT_EULvaccine.pdf™), which reads: "COVISHIELD™ vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose".

On February 10, 2021, WHO published interim recommendations of the Strategic Advisory Group on Immunization (SAGE) on using the COVID-19 vaccine AZD1222, also coded ChAdOx1 nCoV-19. You can read the SAGE recommendations at - https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials. As stated in the SAGE interim recommendation data: "The recommended schedule is two doses (0.5 ml) given intramuscularly into the deltoid muscle. According to the manufacturer's product label, the vaccine can be administered at an interval of 4-12 weeks (6). In light of the observation that two-dose efficacy and immunogenicity increase with a longer interdose interval, WHO recommends an interval of 8 to 12 weeks between the doses. If the second dose is inadvertently administered less than 4 weeks after the first, the dose does not need to be repeated. If the administration of the second dose is inadvertently delayed beyond 12 weeks, it should be given at the earliest possible opportunity. It is recommended that all vaccinated individuals receive two doses".

As can be seen from the table, the immunogenicity of the vaccine ChAdOx1 nCoV-19 was higher when extending the interval between the introduction of the first and second doses of the vaccine: the difference in geometric mean titres (GMTs) is for groups that have been vaccinated at different intervals when determining the level of antibodies 28 days after receiving the second dose of the vaccine. Thus, the Serum Institute of India provides in its materials that the efficacy of the vaccine reaches 78.79% only with an increase in the interval between vaccinations (>12) weeks, the gap between vaccinations is less than 9-11 weeks (60.55%) ensures efficiency at the level of 51.08%, which is much lower than the declared Ministry of Health of Ukraine. Similar patterns are established in

determining the geometric mean titres of antibodies to S-protein. The difference in level is almost 2 times (>12 weeks - GMTs 63181.59; 9-11 weeks - GMTs 34754.1)

When assessing the impact of administering two doses of vaccines at different intervals, there was also an increase in the vaccine's efficacy regarding the symptomatic course of COVID-19.

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Overall	(N=882) 57.18 (52.8, 62.0)	(N=817) 8386.46 (7758.6, 9065.1)	(N=819) 29034.74 (27118.2, 31086.7)
Dose Interval			
< 6 weeks	(N=481) 60.51 (54.1, 67.7)	(N=479) 8734.08 (7883.1, 9676.9)	(N=443) 22222.73 (20360.50, 24255.3)
6-8 weeks	(N=137) 58.02 (46.3, 72.6)	(N=99) 7295.54 (5857.4, 9086.7)	(N=116) 24363.10 (20088.5, 29547.3)
9-11 weeks	(N=110) 48.79 (39.6, 60.1)	(N=87) 7492.98 (5885.1, 9540.2)	(N=106) 34754.10 (30287.2, 39879.8)
≥ 12 weeks	(N=154) 52.98 (44.4, 63.2)	(N=152) 8618.17 (7195.4, 10322.3)	(N=154) 63181.59 (55180.1, 72343.4)

Dose interval	Participants with events, n (%)		Vaccine efficacy %	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
< 6 weeks	9 / 1702 (0.53)	19 / 1698 (1.12)	53.28	(-3.21, 8.86)	0.060
6-8 weeks	5 / 562 (0.88)	9 / 521 (1.73)	51.08	(-45.57, 3.56)	0.199
9-11 weeks	9 / 1056 (0.85)	24 / 1110 (2.16)	60.55	(15.23, 81.64)	0.017
≥ 12 weeks	4 / 1120 (0.36)	19 / 1126 (1.69)	78.79	(37.63, 92.79)	0.005

However, on March 6, 2021, the Lancet (weekly peer-reviewed general medical journal) (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00528-6/fulltext published information on the efficacy of a single-dose vaccination scheme with the administration of the second, revaccinal dose in a 12-week period of time. Earlier, following the interim results of four randomized controlled trials conducted in Brazil, South Africa and the United Kingdom, and to quickly achieve the greatest health benefits, the UK government adopted a policy of ensuring the vaccination with as many first doses as possible and delaying the administration of the second dose of the ChAdOx1 nCoV-19 vaccine until 12 weeks after the vaccination with the first dose. It is noteworthy that in the analysis of clinical trials, the efficacy of the vaccine after a single standard dose was 76.0% (59.3–85.9) from day 22 to 90, and antibody levels persisted during this period with minimal decrease. Supporting the immunization strategy with a longer interval, **the vaccine efficacy was significantly higher – 81.3% (60.3-91.2) after two standard doses introduced at intervals of 12 weeks or longer, compared to 55.1% (33.0–69.9) at the**

interval between doses of less than 6 weeks. These findings were confirmed by immunogenic studies, conducted in participants under the age of 55, which was demonstrated through the response of IgG antibodies against SARS-CoV-2: more than twice as high in those who had a dose interval of at least 12 weeks than those who had an interval of less than 6 weeks (geometric average ratio of 2.32 [95% CI 2 · 01–2 · 68]).

Modeling tests showed an increase in the vaccine efficacy after administering two standard **doses from 55.1%** (95% CI 33.0 to 69.9) with an interval of less than 6 weeks **between doses to 81.3%** (60.3 to 91.2) with an interval of at least 12 weeks. The efficacy after a single standard dose against symptomatic COVID-19 in the first 90 **days stood at 76.0%** (59.3 to 85.9) but did not provide protection against asymptomatic infection (vaccine efficacy – 17.2% [–248.6 to 60.6]). It is notable that efficacy against any PCR positive case of COVID-19, symptomatic and asymptomatic or unknown cases, was 63.9% (46.0 to 75.9) after a single standard dose, indicating the possibility of reducing viral transmission.

Canadian NITAG (https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html) recommends in the conditions of a limited supply of vaccines against COVID-19 to maximize the number of people who will be vaccinated with the first dose of the vaccine, extending the interval for the second dose of the vaccine to four months.

French NITAG https://www.nitag-resource.org/media-center/vaccination-strategy-against-covid-19-covid-19-vaccine-astrazeneca has withdrawn its recommendation to administer two doses of the AZD1222 vaccine with the intervals between the doses from 4 to 12 weeks. However, given the available data on the efficacy and immunogenicity, which indicate a positive effect from increasing the interval between doses and lasting protection of 12 weeks ensured by the first dose, NITAG recommends an interval of 9 to 12 weeks between doses.

German NTGEI (STIKO)

(https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/AstraZeneca-Impfstoff.html) on March 4, 2021, noted that two doses of the AstraZeneca vaccine are required for complete vaccination. The interval between the two vaccinations should be 12 weeks, if possible.

Position of Ukrainian NITAG:

Recommend the Ministry of Health of Ukraine a 12-week interval between first and second doses of Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19 Corona Virus (recombinated), produced by the Serum Institute of India and SK Bioscience, taking into account the shelf life of vaccines currently available in the country. Compliance with this interval will allow achieving higher immunogenicity and efficacy compared to a smaller interval between the administration of the first and second doses of the vaccine. At the same time, extending the interval between the doses up to 12 weeks will free up resources, both human and vaccine doses, in order to accelerate the coverage of target population groups with the first dose of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19 Corona Virus (recombinated), produced by the Serum Institute of India and SK Bioscience. The maximum possible coverage of the population with the first dose will positively affect

reducing the incidence of COVID-19 compared to the approach to maximize the coverage with two doses of COVISHIELD™ vaccine of target groups over the same time period. This approach can only be used for the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19 Corona Virus (recombined), produced by the Serum Institute of India and SK Bioscience, and not for other vaccines against COVID-19.

Question 3:

The use of Oxford/AstraZeneca vaccines (ChAdOx1 nCov-19 Sorona Virus (recombined) among older age population groups (≥ 65 years), in particular produced by the Serum Institute of India, SK Bioscience, etc.

In accordance with the instructions to COVISHIELD™ vaccine, which is registered in Ukraine (registration certificate UA/18593/01/01; address: http://www.drlz.com.ua/ibp/ddsite.nsf/all/shlist?opendocument&rs=UA/18593) in article 4.2 "Dosage and Administration Method" reads "currently, efficacy and safety data are limited for persons aged ≥65 years. For the elderly, ≥65 years, there is no need to adjust the dose." Such information in the instructions to COVISHIELD™ vaccine is due to the low number of COVID-19 cases among 660 participants of ≥65 y.o. to draw conclusions about its efficacy.

However, by looking into the results of stage I/II of clinical trials (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)32466-1.pdf), the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19 Corona Virus (recombined) demonstrated a high safety profile and, on the contrary, showed lower reactogenic potential among patients of the older age group (from 55 to 81 years).

SAGE's findings of February 10, 2021 (https://apps.who.int/iris/bitstream/handle/10665/339477/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222-2021.1-eng.pdf?sequence=5&isAllowed=y) read: "Because a relatively small number of participants aged 65 years or over were recruited into the clinical trials, there were few cases of COVID-19 in either the vaccine or the control group in this age category, and thus the confidence interval on the efficacy estimate is very wide. More precise efficacy estimates for this age group are expected soon, from both ongoing trials and vaccine effectiveness studies in countries using this vaccine. Immune responses induced by the vaccine in older persons are well documented and similar to those in other age groups. This suggests it is likely that the vaccine will be found to be efficacious in older persons. The trial data indicate that the vaccine is safe for this age group. The risk of severe disease and death due to COVID-19 increases steeply with age. Older adults are identified as a priority group in the WHO SAGE Prioritization Roadmap. This prioritization is supported by vaccine impact modelling work, even for vaccine efficacy that is substantially below that observed among younger adults administered AZD1222. Taking the totality of available evidence into account, WHO recommends the vaccine for use in persons aged 65 years and older."

On March 4, 2021 **German NTGEI (STIKO)** (https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/AstraZeneca-Impfstoff.html) released the position paper, where the use of the AstraZeneca vaccine was approved for all age groups. This STIKO solution is based on intensive analysis and evaluation of new research data that have only become available in the form of preprint

over the past few days. Data collected from the mass use of the vaccine in England and Scotland for the first time give reliable results on the vaccine efficacy in older age groups after only one dose of the vaccine. Efficacy has been demonstrated in the prevention of COVID-19 diseases and, in particular, in the prevention of severe forms of this disease.

According to the results released in the form of preprint https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1.full.pdf, Oxford-AstraZeneca vaccine has demonstrated high efficacy in reducing COVID-19 infections among the elderly over the age of 70. The study involved individuals aged 70 years and older. The sample of the study was more than 7.5 million people. Protection against symptomatic COVID 4 weeks after the first dose ranged from 60 to 73% for the Oxford-AstraZeneca vaccine. The vaccine's efficacy was observed 14-20 days after vaccination, reaching the efficacy at 60% (95% CI 41-73%) between 28-34 days and further growing to 73% (95% CI 27-90%) from the 35th day.

In people over the age of 80, a single dose of any vaccine (Pfizer and Oxford-AstraZeneca) by more than 80% prevents hospitalization after about 3-4 weeks of vaccination. Cases that were vaccinated with one dose of ChAdOx1 showed additional 37% (95% CI 3-59%) reduction in the risk of emergency hospitalization. However, there was not enough observation to assess the impact of ChAdOx1 on mortality due to the short period of using this vaccine. The findings also show that the number of symptomatic infections in patients over 70 y.o. decreases after approximately 3 weeks following the administration of one dose of both vaccines.

Position of Ukrainian NITAG:

Recommend to the Ministry of Health of Ukraine the use of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19 Corona Virus (recombined), produced by the Serum Institute of India and SK Bioscience, for vaccination of people over 65 years of age.