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Hrvatski zavod za javno zdravstvo
Služba za epidemiologiju zaraznih bolesti
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Dopuna uputa za cijepljenje i obradu bliskih kontakata COVID-19 bolesnika
Verzija 1b.

S obzirom na to da:
- podaci o cjepivima dopunjavaju se iz dana u dan te više znamo o razini i trajanju zaštite koju pruža jedna doza cjepiva i više je informacija o konačnoj razini zaštite ovisno o razmaku između dviju doza cjepiva;
- cjepiva ne dolaze u Hrvatsku dinamikom koja bi zadovoljila potrebu za cijepljenjem velikog broja stanovnika u kratkom vremenu;
- zbog pojave novih varijanti SARS-CoV-2 važno je što ranije postići što veći obuhvat stanovništva cijepljenjem i ojačati nadzor nad kontaktima oboljelih;

Preporučujemo da se radi postizanja što većeg obuhvata cijepljenjem, uzimajući u obzir fleksibilnost koju dozvoljava registracija cjepiva u EU, **pri budućim cijepljenjima planira razmak između prve i druge doze**
– šest (6) tjedana kod Pfizerova cjepiva protiv COVID-19
- dvanaest (12) tjedana kod Astra Zeneca cjepiva.

S obzirom da:
- neke nove varijante SARS-CoV-2 se lakše prenose, a neke mogu dijelom izbjeći imunosni odgovor stečen ranijim prebolijevanjem ili cijepljenjem;
- u uzorcima iz siječnja su već detektirane potvrđene nove varijante virusa u Hrvatskoj, a u dijelu oboljelih u veljači imamo sumnju na bolest uzrokovanu novim varijantama;
- na rezultate sekvenciranja se čeka dugo;

Podsjećamo na važnost temeljite obrade kontakata oboljelih i određivanja karantene kontaktima oboljelih prema postojećim preporukama, uz napomenu da će se karantena produžiti na 14 dana i zahtijevati negativan rezultat RT-PCR testiranja za izlazak iz karantene ako se u međuvremenu pokaže daje kod izvora potvrđena nova varijanta virusa koja se smatra zabrinjavajućom s obzirom na zaraznost i antigeničnost.

Reference:

Skowronski DDS, G. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine 2021. https://www.nejm.org/doi/pdf/10.1056/NEJMc2036242?articleTools=true

- *Even before the second dose, BNT162b2 was highly efficacious, with a vaccine efficacy of 92.6%, a finding similar to the first-dose efficacy of 92.1% reported for the mRNA-1273 vaccine (Moderna).*
  Tu se referira na FDA dokumente:
  1. Pfizer–BioNTech COVID-19 vaccine (BNT162, PF-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. December 10, 2020 (https://www. fda. gov/ media/ 144246/ download).

2. Vaccines and Related Biological Products Advisory Committee meeting. December 17, 2020. FDA briefing document: Moderna COVID-19 vaccine (https://www . fda . gov/ media/ 144434/ download).

Chodick G, Tene L, Patalon T, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv 2021: 2021.01.27.21250612.

- *We demonstrated an effectiveness of 51% of BNT162b2 vaccine against SARS-CoV-2 infection 13-24 days after immunization with the first dose. Immunization with the second dose should be continued to attain the anticipated protection.*

Hunter PR, Brainard J. Estimating the effectiveness of the Pfizer COVID-19 556BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel. medRxiv 2021: 2021.02.01.21250957

- *A recent paper based on Israel's experience of vaccination suggested that a single dose may not provide adequate protection. Here we extract the primary data from the Israeli paper and then estimate the incidence per day for each day after the first injection and also estimate vaccine effectiveness for each day from day 13 to day 24. We used a pooled estimate of the daily incidence rate during days 1 to 12 as the counterfactual estimate of incidence without disease and estimated confidence intervals using Monte Carlo modelling. After initial injection case numbers increased to day 8 before declining to low levels by day 21. Estimated vaccine effectiveness was pretty much 0 at day 14 but then rose to about 90% at day 21 before levelling off. The cause of the initial surge in infection risk is unknown but may be related to people being less cautious about maintaining protective behaviours as soon as they have the injection. What our analysis shows is that a single dose of vaccine is highly protective, although it can take up to 21 days to achieve this. The early results coming from Israel support the UK policy of extending the gap between doses by showing that a single dose can give a high level of protection.*

Estimated effectiveness of the Pfizer vaccine on each day from 13 to 24 days after the first injection. It can be seen that the at day 14 there was no apparent effect of the vaccine
but from then on till day 21 the effectiveness reached 91% (90% credible intervals: 83 to 98%).

Hall V, Foulkes S, Saei A,et al.Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399

- We found a vaccine effectiveness, at a given site, of at least 70% overall (72% in the negative cohort) against both asymptomatic and symptomatic infection, from 21 days post-first dose of the BNT162b2 vaccine. This is comparable to a single-centre Israeli HCW cohort study vaccine effectiveness of 75% (95% CI 72 – 84), 15-28 days following first dose of BNT162b2 vaccine. However, this study had no routine laboratory surveillance to pick up asymptomatic cases and only detected cases if symptomatic, whereas SIREN had regular asymptomatic testing; in addition, their adjustment for other potential risk factors was more limited. Another population-level study in Israel reported a 51% reduction in PCR-confirmed SARS-CoV-2 infections 13-24 days after individuals received the first dose of BNT162b2 vaccine, compared to historical controls' 1-12 days 21. This mirrors the 52.4% (95% CI: 29.5 - 68.4) vaccine efficacy estimated by Pfizer-BioNTech researchers, between the first and second dose.6 Whilst follow up periods differed, the RCT included true controls and the Israeli study included PCR-positivity regardless of symptom status compared to symptomatic confirmed cases in the phase III BNT162b2 RCT. A preprint from researchers re-analysing the data from the Israeli study using daily incidence of infection, calculated a vaccine effectiveness of 91% at day 21 post-vaccination. This estimate is closer to the 92.6% vaccine efficacy 14–21 days after the first dose, calculated by researchers using data submitted by the manufacturers to the Food and Drug Administration from vaccine trials.

AmitS, Regev-YochayG, AfekA, KreissY, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. Lancet 2021 https://doi.org/10.1016/ S0140-6736(21)00448-7. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900448-7

Compared with a symptomatic COVID-19 rate of 5.0 per 10000 per-son-days in unvaccinated HCWs, disease rates were 2.8 and 1.2 per 10000 person-days on days 1–14 and days 15–28 after the first dose of the vaccine, respectively. Adjusted rate reductions of COVID-19 disease were 47% (95% CI 17–66) and 85% (71–92) for days 1–14 and days 15–28 after the first dose, respectively.

WHO. AZD1222 vaccine against COVID-19 developed by Oxford University and Astra Zeneca: Background paper (draft) [Internet]. 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-background-2021.1
Evidence of efficacy emerged from about 22 days after the first vaccine dose. The vaccine was efficacious against laboratory-confirmed Covid-19 from 22 days after the first dose and persisted until at least 12 weeks until a second dose was given (VE=71.42%).

Regulatory Medicines and Healthcare products, Agency. Public Assessment Report Authorisation for Temporary Supply; COVID-19 Vaccine AstraZeneca, solution for injection in multidose container COVID-19 Vaccine (ChAdOx1-S [recombinant]) [Internet]. 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949772/UKPAR_COVID_19_Vaccine_AstraZeneca_05.01.2021.pdf

Table 11: Vaccine efficacy for incidence of first SARS-CoV-2 virologically-confirmed COVID-19 occurring ≥ 15 days post dose 2 in participants seronegative at baseline by dose interval

	Participants with events				VE (%)	95% CI
	AZD1222		Control			
Dosing interval	N	n (%)	N	n (%)		
< 6 weeks	3905	35 (0.90)	3871	76 (1.96)	55.09	(32.99, 69.90)
6-8 weeks	1124	20 (1.78)	1023	44 (4.30)	59.72	(31.68, 76.25)
9-11 weeks	1530	14 (0.92)	1594	52 (3.26)	72.25	(49.95, 84.61)
≥ 12 weeks	2038	15 (0.74)	2093	76 (4.16)	79.99	(65.20, 88.50)

Škotska studija - **Vasileiou E, Simpson CR, Robertson C, et al. Effectiveness of first dose of covid-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. [Preprint.] 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264**
*- The first dose of the **BNT162b2** vaccine was associated with a vaccine effect of 85% (95% confidence interval [CI] 76 to 91) for COVID-19 related hospitalisation at 28-34 days post-vaccination. Vaccine effect at the same time interval for the **ChAdOx1** vaccine was 94% (95% CI 73 to 99). Results of combined vaccine effect for prevention of COVID-19 related hospitalisation were comparable when restricting the analysis to those aged ≥80 years (81%; 95% CI 65 to 90 at 28-34 days post-vaccination).*

ECDC. Rapid Risk Assessment. Risk related to the spread of new SARS-CoV-2 variants of concern in the EU/ EEA, first update. 21 January 2021. Available from:https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-risk-related-to-spread-of-new-SARS-CoV-2-variants-EU-EEA-first-update.pdf

ECDC. Rapid Risk Assessment. SARS-CoV-2 – Increased circulation of variants of concern and vaccine rollout in the EU/ EEA, 14th update. 15 February 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-covid-19-14th-update-15-feb-2021.pdf