10.2478/inmed-2022-0201

VACCINATION AND COVID 19 INFECTIONS

Florin Mihălțan, Ancuța Constantin
U.M.F. "Carol Davila, Bucharest"

Abstract
In a world plagued by the same multifaceted Covid 19, pros-cons discussions about vaccines, their effectiveness, side effects, fears, and their inclusion in therapeutic strategies have taken on innumerable colors. In this article we will look at the impact of vaccines from the booster regimens to the effects of the booster, all this being seen through the light of the latest research conducted this year.
Keywords: *vaccines, Covid 19.*

Rezumat
Într-o lume asaltată de același Covid 19 cu multiple fațete, discuțiile pro și contra despre vaccinuri, eficiența lor, efectele adverse, temeri și includerea lor în strategiile terapeutice au căpătat nenumărate colorituri. În acest articol vom privi impactul vaccinurilor, de la schemele cu un rapel, până la efectele boosterului, toate acestea fiind privite prin prisma ultimelor cercetări realizate în acest an.
Cuvinte cheie: *vaccinuri, Covid 19.*

Introduction

The world has been aggressively assaulted for two consecutive years by COVID 19. All this period our life changed radically. Vaccine and the idea of vaccination were in all our thoughts. That's why we decided to see exactly what the arguments in favor of vaccines are and at the same time to bust the myths about the dangers of the vaccinations and revaccinations campaigns.

Of course, when we received this first important prevention tool all people were enthusiastic, but now, mass media disparage in many cases this instrument of protection for our countrymen.

Currently, in September 2021, only 43% of the world's population has received at least one dose of a covid-19 vaccine[1]. In our article, we are focusing more on the second dose or the booster administration in cases where this is appropriate. Changes in viral strains is also a major concern for the scientific societies and remain a challenging problem for vaccines campaign.



Internal Medicine

General Reviews

Vaccination and infections (general considerations)

Natural immunity "varies from person to person" and "experts don't know yet how long someone is protected"[2]. The percentage of vaccinated people after infection is variable: 57% of those previously infected got vaccinated in the US[3]. Some experts found up to eight months "durable immune responses" after infection, in 95% of the 200 participants[4]. There are other pieces of evidence suggesting that memory of B cells increased over time, and the half-life of memory CD8+ and CD4+ T cells suggests a steady presence[5]. Another discussion is focusing on the antibody level. Some experts like Dr Anthony Fauci claim that people that had Covid 19 still need a booster for obtaining sky-high level of antibody[6]. Instead, other authors[7] declare that the "protective effect" of a previous infection "is high and similar to the protective effect of vaccination". Looking at this pros-cons discussion, there is a certainty: antibodies are higher in participants who were seropositive at baseline than in those who were seronegative[8]. In the same time, we don't know what are the best protective level of antibodies[8].

Another discussion is concerning T cells; there are more important than antibodies, explaining why people with asymptomatic infections "mount a highly functional virus-specific cellular immune response[9]. It is clear that those who were unvaccinated had more than twice the odds of reinfection[10]. That's why some studies tried to see exactly what happened after the second dose versus the first of vaccination, concerning the rate of infections. In India, mild symptomatic breakthrough infections where present at 16.9% post any dose of vaccine, with 13.3% having these symptoms after ≥14 days from the second dose[11].

Another example is referring to medical stuff, more exposed in all the settings. In the US, an extensive survey in 22,729 healthcare providers founds that 114 (60.3%) of infections occurred within 14 days of first vaccine dose (early post-vaccination), 49 (25.9%) within 14 days of the second vaccine dose (partially vaccinated), and 26 (13.8%) >14 days after the second dose (fully vaccinated)[12]. The great majority of post-vaccine SARS-CoV-2 cases (PVSCs) occurred prior to the expected onset of full, vaccine-derived immunity[12].

One possible vaccine failure could result from partial vaccine degradation due to inadequate cold chain or other issues during shipping, storage, or administration[13]. In the same time, many concerns are related to five emerged SARS-CoV-2 variants that contain mutations in the spike glycoprotein (i.e., B.1.1.7- United Kingdom, B.1.351- South Africa, P.1-Brasil, B.1.427-, and B.1.429-

California; Centers for Disease Control and Prevention. SARS-CoV-2 variants)[14,15,16]. If plasma in patients who were not vaccinated had less neutralizing activity against the variants B.1.1.7 (alpha), B.1.351 (beta), B.1.526 (iota), and P.1 (gamma), with the greatest loss of activity against the beta variant first detected in South Africa for those who had received at least 1 dose experts found higher plasma anti-RBD antibodies and a nearly 50-fold increase in neutralizing activity.

Relations infections rate-vaccine protection is very complex. It's a hybrid immunity (a single dose of an mRNA vaccine substantially enhances the immune response to SARS-CoV-2 variants among patients with a prior infection)[17]. At least 12 weeks after their second dose of Pfizer's mRNA vaccine, people who were not previously infected developed a surprisingly high number of SARS-CoV-2 spike protein - targeting B cells in the germinal centers of their lymph nodes, where these cells are trained to produce and perfect antibodies.

In the UK, after one or two - doses of BNT162b2 and one dose of ChAdOx1 nCoV-19, a significant reduction in infection risk were seen starting by the 12th day after the first dose, reaching 60% (95% CI 49-68) for ChAdOx1 nCoV-19 and 69% (66-72) for BNT162b2 at 21-44 days and, 72% (63-79) for BNT162b2 after 45-59 days. This data suggests that both vaccines decrease the risk of SARS-CoV-2 infection after 12 days[18].

Another problem remains the rates of side effects in patients with a history of SARS-CoV2 infection (those with a history of covid-19 were 56% more likely to experience a severe side effect that required hospital care)[19].

There are recently some researchers more pessimistic concerning the role of vaccination compared to natural infection, sustaining a change of governments vaccination policy because 6 deaths are prevented by vaccination versus 4 deaths, reported by Dutch Lareb, occurring after vaccination, yielding a potential risk/benefit ratio of 2:3[20]. Other arguments are coming from recent CDC reports: in fully vaccinated patients the rates of hospitalizations and deaths raised from 0.01 to 9%, respectively from 0 to 15.1%, between January to May 2021[21]. We have also some more optimistic researchers sustaining those current vaccines boost neutralizing responses to all strains but the responses to the variants typically remain proportionally lower[22]. Reformulated vaccines expressing variant Spike are undergoing evaluation and are likely to improve the neutralizing response to variants[23]. Every time when we are weighing the benefits of the vaccination, we have not to forget two things:

1. among fully vaccinated health care workers (the most exposed sample of the population), the occurrence of breakthrough infections (mild or asymptomatic) with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period[24].
2. presence of comorbidities was not associated with severe disease or death among persons with breakthrough infection after SARS-CoV-2 vaccination[25].

Second dose effects

Vaccine effectiveness (VE) against new SARS-CoV-2 infections, ≥14 days after the 2nd dose of either BNT162b2 (Comirnaty, Pfizer/BioNTech) or ChAdOx1 (Oxford-AstraZeneca), during the Delta (B.1.617.2) period, was similar to the VE during the Alpha (B.1.1.7) period. These were the results of an



observational study realized in Great Britain on more than 380000 cases. Protection was important and from the moment of the Alpha period to the Delta one VE against SARS-CoV-2 infections with high viral burden and symptomatic infections were reduced 10-13% (with BNT162b2) and 16% (with ChAdOx1)[26].

Infections and second dose

There are some pieces of evidence in this moment, studies proving that there are equally low levels among people who are fully vaccinated and those who have previously had Covid-19[27,28,29,30].

A lack of understanding of the complexity of immunity to respiratory viruses can explain the pro-con discussions concerning the coverage obtained by natural infection or vaccination protective effect.

Reinfections after vaccination

An evaluation of the association between vaccination and SARS-CoV-2 reinfection in Kentucky, during May - June 2021, among persons previously infected with SARS-CoV-2 in 2020 Kentucky residents who were not vaccinated discovered 2.34 times the odds of reinfection compared with those who were fully vaccinated (odds ratio [OR] - 2.34; 95% confidence interval [CI] = 1.58–3.47)[31].

The booster effect on the new infections

Neutralization of Omicron was undetectable in most vaccinated individuals. Individuals boosted with mRNA vaccines exhibited potent neutralization of Omicron only 4-6-fold lower than the wild type, suggesting that boosters enhance the cross-reactivity of neutralizing antibody responses. There are already studies highlighting the importance of boosters to broaden neutralizing antibody responses against highly divergent SARS-CoV-2 variants[32].

Data from the US indicate that infections with the Omicron variant occur after the previous infection, 2 doses of mRNA Covid-19 vaccines, and boosting albeit with characteristically mild outcomes[33]. There are many unknown faces of omicron, but one thing remains important reducing the prevalence of new SARS-CoV-2 infections, in general, should reduce the rate of emergence of further new post-Omicron variants, that have equal or even greater potential adverse impact[34].

The booster dose consequences

Systemic side-effects were reported by 13·5% of individuals after the first dose of BNT162b2, by 22·0% after the second dose of BNT162b2. Local side-effects were also reported by 71·9% of individuals after the first

dose of BNT162b2 and by 68·5% (9025 of 13 179) after the second dose of BNT162b2[35].

Boosting vaccinated individuals with currently available mRNA vaccines will increase plasma neutralizing activity but may not produce antibodies with the equivalent breadth to those obtained by vaccinating convalescent individuals[36].

Homologous and heterologous booster vaccinations were well-tolerated and immunogenic in adults who completed a primary Covid-19 vaccine regimen at least 12 weeks earlier. The neutralizing activity against Booster vaccines increased the neutralizing activity against a D614G pseudovirus (4.2-76-fold) and binding antibody titers increased also (4.6-56-fold) for all combinations; in this research homologous boost increased neutralizing antibody titers 4.2-20-fold whereas heterologous boost increased titers 6.2-76-fold[37].

And, also the reactogenicity was similar to that reported for the primary series (injection site pain, malaise, headache, and myalgia occurred in more than half the participants. This effect is reconfirmed by a study realized recently in Israel[38].

They found across all age groups, rates of confirmed infection (≈10-fold lower in the booster sample) and severe illness (18.7-fold lower for ages over 60 and 22 for 40-6- years old sample) substantially lower among those who received a booster dose of the BNT162b2 vaccine. Safety evaluations after the third BNT162b2 dose included reports of local reactions (injection site pain, redness, swelling) and systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain, joint pain) and use of antipyretic medications in the 7 days after BNT162b2 administration as reported by participants in electronic diaries[38].

Omicron and other variants of concerns and vaccination

Three strains have recently been defined as VOCs (variants of concerns) by the WHO (World Health Organization): the B.1.1.7 strain (first detected in the UK), the B.1.351 strain (first detected in South Africa), and the P.1 strain (first detected in Brazil). Recent findings suggest reduced vaccine effectiveness against both VOCs within particular time windows emphasizing the importance of rigorously tracking viral variants, and of increasing vaccination to prevent the spread of VOCs[39]. Studies have shown that, immunizations are proving to be less potent against the variant first identified in South Africa (B.1.351), which might have acquired a partial resistance to neutralizing antibodies generated by natural infections or vaccinations[40,41].

In case vaccinations follow Omicron infections (*variant* B.1.1.529), a longer-lasting protection might be achieved, in contrast to just recurrent monospecific mRNA vaccinations; the authors are encouraging the patients to monitor their anti-N-capsid-titres post-Omicron infection (2 weeks and 4 to 8 weeks)[42].

Another study suggests that the third dose with BNT162b2 could prolong protection (100% observed vaccine efficacy of BNT162b2 against COVID-19 in the subgroup of participants from South Africa) and further increase the breadth of protection without knowing exactly at this moment the durability of protection from vaccination and the required frequency of booster doses[43,44].

Vaccinations Pass

There are different national strategies concerning the duration and the obligation to



have a vaccination pass. In UE people are eligible for an EU digital covid certificate after a single dose of an mRNA vaccine, if they have had a positive test result within the past six months, allowing travel between 27 EU member states[45]. In Great Britain citizens with a positive polymerase chain reaction (PCR) test result can obtain the NHS covid pass up until 180 days after infection[46]. In Israel, the recommendations are: people who have had covid-19 wait three months before getting one mRNA vaccine dose they offer a "green pass" (vaccine passport) to those with a positive serological result regardless of vaccination[47].

The CDC still recommends a full vaccination dose for all, because the immune response from vaccination is more predictable" and that based on current evidence and antibody responses after infection "vary widely by individual"[6]. Looking to some strategies applied in the last two years in Singapore, New Zeeland and Australia[48] the conclusions and recommendations of experts are more flexible:

- "the social and economic stressors on populations as a result of elimination strategies that were feasible during the first year of the COVID-19 pandemic might not be sustainable in the future.
- nations need to ensure maximum vaccination coverage while taking into account risk prioritization, vaccine dose sparing, and equity principles.
- nations need to foster extensive surveillance and stronger community social responsibility to detect and isolate COVID-19 cases quickly through more self-testing and home-based isolation while transferring risk assessment skills from institutions to individuals through codesigned risk communication and community engagement strategies, so communities can understand and mitigate their own risks".

Conclusions

Vaccines remain a centerpiece of protection against SARS-CoV-2 and the Delta viral variant. The need to vaccinate previously infected individuals is one of the final conclusions of the Israel studies[29]. At the same time, their data coming from recent studies and experts are sustaining the same recommendations that the recovered have better protection than people who were vaccinated[6]. Even so, the principle claimed by all experts remains after this mini review made by us of literature: "better safe than sorry". Of course, it's an important discussion still running generated also by the recent Omicron variant: pandemic strategy should not be covering all the variants but it seems that universal vaccination is a more predictable, feasible, and quantifiable modality to protect the world population.

References

1. Coronavirus (covid-19) vaccinations. Our World in Data. https://ourworldindata. org/covid-vaccinations.

2. CDC. Frequently asked questions about covid-19 vaccination. 25 Jan 2021. ncov/vaccines/faq.html.

3. KFF COVID-19 Vaccine Monitor: June 2021.https://www.kff.org/coronavirus-covid-19/poll-finding/ kff-covid-19-vaccine-monitor-june-2021.

4. NIH. Lasting immunity found after recovery from COVID-19. 2021. https://www.nih.gov/newsevents/ nih-research-matters/lasting-immunity-found-after-recovery-covid-19#main-content.

5. Dan JM, Mateus J, Kato Y, etal. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371:eabf4063. doi: 10.1126/ science.abf4063 pmid: 33408181.

6. Block J. Vaccinating people who have had covid-19: why doesn't natural immunity count in the US? BMJ. 2021 Sep 13;374:n2101. doi: 10.1136/bmj.n2101. Erratum in: BMJ. 2021 Sep 15;374:n2272. PMID: 34518194.

7. Klausner J. Op-Ed: Quit ignoring natural covid. Medpage Today 2021 May 28. Immunity. https://www. medpagetoday.com/ infectiousdisease/ covid19/92836.

8. FDA. Pfizer-BioNTech covid-19 vaccine EUA amendment review memorandum. Table 9. 2021. https://www.fda.gov/media/148542 /download# page=19.

9. Le Bert N, Clapham HE, Tan AT, etal. Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection. J Exp Med 2021;218:e20202617. . doi: 10.1084/jem.20202617 pmid: 33646265).

10. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced risk of reinfection with SARS-CoV-2 after COVID-19 vaccinationKentucky, May-June 2021.MMWR Morb Mortal Wkly Rep 2021;70:1081-3. doi: 10.15585/mmwr.mm7032e1 pmid: 34383732.

11. Tyagi K, Ghosh A, Nair D, Dutta K, Singh Bhandari P, Ahmed Ansari I, Misra A. Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India. Diabetes Metab Syndr. 2021 May-Jun;15(3):1007-1008. doi: 10.1016/j.dsx.2021.05.001. Epub 2021 May 3. PMID: 33991805; PMCID: PMC8091733.

12. Jacobson KB, Pinsky BA, Montez Rath ME, Wang H, Miller JA, Skhiri M, Shepard J, Mathew R, Lee G, Bohman B, Parsonnet J, Holubar M. Post-vaccination SARS-CoV-2 infections and incidence of presumptive B.1.427/B.1.429 variant among healthcare personnel at a northern California academic medical center. Clin Infect Dis. 2021 Jun 17:ciab554. doi: 10.1093/cid/ciab554. Epub ahead of print. PMID: 34137815; PMCID: PMC8344553.

13. Public health investigations of COVID-19 vaccine breakthrough cases Case investigation protocol-march 2021-CDC.

14. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html. Access date, March 2021.

15. Galloway SE, Paul P, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 Lineage United States, December 29, 2020January 12, 2021. MMWR Morb Mortal Wkly Rep 2021;70:9599.

16. Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E. Emergence of a novel SARS-CoV-2 variant in Southern California. JAMA 2021. doi:10.1001/jama.2021.1612.

17. Abbasi J. Study Suggests Lasting Immunity After COVID-19, With a Big Boost From Vaccination. JAMA. 2021 Aug 3;326(5):376-377. doi: 10.1001/jama. 2021.11717. PMID: 34259836.).

18. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, Sudre CH, Nguyen LH, Drew DA, Merino J, Hu C, Selvachandran S, Antonelli M, Murray B, Canas LS, Molteni E, Graham MS, Modat M, Joshi AD, Mangino M, Hammers A, Goodman AL, Chan AT, Wolf J, Steves CJ, Valdes AM, Ourselin S, Spector TD. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis. 2021 Jul;21(7):939-949. doi: 10.1016/S1473-3099(21)00224-3. Epub 2021 Apr 27. PMID: 33930320; PMCID: PMC8078878.

19. Mathioudakis AG, Ghrew M, Ustianowski A, et al. Self-reported real-world safety and reactogenicity of covid-19 vaccines: a vaccine recipient survey. Life (Basel) 2021;11:249. doi: 10.3390/life11030249 pmid: 33803014

20. Walach H, Klement RJ, Aukema W. Retracted: The Safety of COVID-19 Vaccinations-We Should Rethink the Policy. Vaccines (Basel). 2021 Jun 24;9(7):693. doi: 10.3390/vaccines9070693. Retraction in: Vaccines (Basel). 2021 Jul 02;9(7):null. PMID: 34202529; PMCID: PMC8294615)

21. McMorrow M. (rep.). Improving communications around vaccine breakthrough and vaccine effectiveness. 2021. Retrieved from https:// context- CDC. Washington post. com/ notes/ prod/ default/ documents/ 8a726 408-07bd- 46bd- a945- 3af0a e2f3c 37/ note/ 57c98 604-3b54- 44f0- 8b44- b148d 8f751 65.

22. Cromer D, Steain M, Reynaldi A, et al. SARS-CoV-2 variants: neutralizing antibodies required for protective immunity. MedRxiv 2021 pre-print. doi: 10.1101/ 2021.08.11.21261876

23. Wu K, Choi A, Koch M, et al. Preliminary analysis of safety and immunogenicity of SARS-CoV-2 variant vaccine booster. MedRxiv 2021 pre-print. doi: 10.1101/ 2021.05.05.21256716.

24. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, Mandelboim M, Levin EG, Rubin C, Indenbaum



Internal Medicine

General Reviews

V, Tal I, Zavitan M, Zuckerman N, Bar-Chaim A, Kreiss Y, Regev-Yochay G. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med. 2021 Oct 14;385(16):1474-1484. doi: 10.1056/NEJMoa2109072. Epub 2021 Jul 28. PMID: 34320281; PMCID: PMC8362591.

25. Butt AA, Nafady-Hego H, Chemaitelly H, Abou-Samra AB, Khal AA, Coyle PV, Kanaani ZA, Kaleeckal AH, Latif AN, Masalmani YA, Bertollini R, Raddad LJA. Outcomes Among Patients with Breakthrough SARS-CoV-2 Infection After Vaccination. Int J Infect Dis. 2021 Sep;110:353-358. doi: 10.1016/j.ijid.2021.08.008. Epub 2021 Aug 8. PMID: 34375762; PMCID: PMC8349447.

26. Pauwels K.B., Pritchard, E., Matthews, P.C. et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nat Med (2021). https://doi.org/10.1038/s41591-021-01548-7.

27. Bertollini R, Chemaitelly H, Yassine HM, Al-Thani MH, Al-Khal A, Abu-Raddad LJ. Associations of vaccination and of prior infection with positive PCR test results for SARS-CoV-2 in airline passengers arriving in Qatar.JAMA 2021;326:185-8. doi: 10.1001/jama.2021.9970 pmid: 34106201

28. Hall VJ, Foulkes S, Charlett A, etalSIREN Study Group. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet 2021;397:1459-69. doi: 10.1016/S0140-6736(21)00675-9 pmid: 33844963

29. Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel. [Preprint.] medRxiv 2021.04.20.21255670. doi: 10.1101/2021. 04.20. 21255670

30. Shrestha NK, Burke PC, Niowacki AS, Terpeluk P, Gordon SM. Necessity of COVID-19 vaccination in previously infected individuals.[Preprint.] medRxiv 2021.06.01.21258176; doi: 10.1101/2021. 06.01. 21258176

31. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination - Kentucky, May-June 2021. MMWR Morb Mortal Wkly Rep. 2021 Aug 13;70(32):1081-1083. doi: 10.15585/mmwr.mm7032e1. PMID: 34383732; PMCID: PMC8360277.

32. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. Preprint. medRxiv. 2021;2021.12.14.21267755. Published 2021 Dec 14. doi:10.1101/ 2021.12.14. 2126775

33. CDC COVID-19 Response Team. SARS-CoV-2 B.1.1.529 (Omicron) variant-United States, December 1-8, 2021. Morb Mortal Weekl Rep. 2021; 70(50):1731-1734 [PMC free article] [PubMed] [Ref list]

34. Ingraham NE, Ingbar DH. The omicron variant of SARS-CoV-2: Understanding the known and living with unknowns. Clin Transl Med. 2021;11(12):e685. doi:10.1002/ctm2.685.

35. Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis 2021;21:939-49. doi: 10.1016/S1473-3099(21)00224-3 pmid: 33930320.

36. Cho, A., Muecksch, F., Schaefer-Babajew, D. et al. Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination. Nature 600, 517522 (2021). https://doi.org/10.1038/s41586-021-04060-7).

37. Atmar, R. L., Lyke, K. E., Deming, M. E., Jackson, L. A., Branche, A. R., El Sahly, H. M., Rostad, C. A., Martin, J. M., Johnston, C., Rupp, R. E., Mulligan, M. J., Brady, R. C., Frenck, R. W., Bäcker, M., Kottkamp, A. C., Babu, T. M., Rajakumar, K., Edupuganti, S., Dobryzynski, D., Posavad, C. M., ... DMID 21-0012 Study Group (2021). Heterologous SARS-CoV-2 Booster Vaccinations - Preliminary Report. medRxiv : the preprint server for health sciences, 2021.10.10.21264827. https:// doi.org/ 10.1101/2021.10.10.21264827)

38. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-Preis S, Ash N,

Milo R, Huppert A. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021 Oct 7;385(15):1393-1400. doi: 10.1056/NEJMoa2114255. Epub 2021 Sep 15. PMID: 34525275; PMCID: PMC8461568.)

39. Kustin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, Caspi I, Levy R, Leshchinsky M, Ken Dror S, Bergerzon G, Gadban H, Gadban F, Eliassian E, Shimron O, Saleh L, Ben-Zvi H, Keren Taraday E, Amichay D, Ben-Dor A, Sagas D, Strauss M, Shemer Avni Y, Huppert A, Kepten E, Balicer RD, Netzer D, Ben-Shachar S, Stern A. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nat Med. 2021 Aug;27(8):1379-1384. doi: 10.1038/s41591-021-01413-7. Epub 2021 Jun 14. PMID: 34127854; PMCID: PMC8363499.

40. Stamatatos L, Czartoski J, Wan Y-H, et al. mRNA vaccination boosts crossvariant neutralizing antibodies elicited by SARS-CoV-2 infection. Science 2021; 25: eabg9175).

41. Planas D, Bruel T, Grzelak L, et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat Med 2021 March 26 (Epub ahead of print.

42. Thiesen H.J /CEO, IndyMed, Rostock, Germany-7xfnit-yquaf5h phapa2hz2r8fpx5lwxj.pdf article under press.

43. Falsey AR, Frenck RW Jr, Walsh EE, Kitchin N, Absalon J, Gurtman A, Lockhart S, Bailey R, Swanson KA, Xu X, Koury K, Kalina W, Cooper D, Zou J, Xie X, Xia H, Türeci Ö, Lagkadinou E, Tompkins KR, Shi PY, Jansen KU, ªahin U, Dormitzer PR, Gruber WC. SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3. N Engl J Med. 2021 Oct 21;385(17):1627-1629. doi: 10.1056/NEJMc2113468. Epub 2021 Sep 15. PMID: 34525276; PMCID: PMC8461567.

44. Thomas SJ, Moreira ED, Kitchin N, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med 2021 [Submitted].

45. Questions and answers EU digital covid certificate. Jun 2021. https:// ec.europa.eu/ commission/ presscorner/detail/en/QANDA_21_2781).

46. UK Department of Health and Social Care. Who can get an NHS COVID Pass in England. 26 Aug 2021. https://www.gov.uk/guidance/nhs-covid-pass#who-can-get-an-nhs-covid-pass-in england)

47. What is a green pass? https://corona. health.gov.il/ en/ directives/green-pass-info/.

48. De Foo C, Grépin KA, Cook AR, Hsu LY, Bartos M, Singh S, Asgari N, Teo YY, Heymann DL, Legido-Quigley H. Navigating from SARS-CoV-2 elimination to endemicity in Australia, Hong Kong, New Zealand, and Singapore. Lancet. 2021 Oct 30;398(10311):1547-1551. doi: 10.1016/S0140-6736(21)02186-3. Epub 2021 Oct 4. PMID: 34619099; PMCID: PMC8489883.