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KINETICS OF SARS-CoV-2 NEUTRALIZING ANTIBODIES AFTER TWO DOSES OF BNT162b2, (BioNTech/Pfizer) VACCINE

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Abstract

The neutralizing antibody is an antibody that can block the binding and infection process of the virus cell receptor. MAGLUMI ® Neutralizing Antibody kit could detect all those antibodies that can block RBD-ACE2 combination.

Studies evaluating the long-term duration of neutralizing antibodies (NAbs) after SARS-CoV-2 vaccination are important to develop vaccination strategies.

In this study, 131 healthcare workers (HCW) received the two-dose BNT162b2 regimen. Of the 131 HCW enrolled in the study, 85 (64.9%) were female and 46 (35.1%) were male, with a mean age (±SD) of 45.2 ± 10.31 (range 26-55) years. Of them, 91 were seronegative and 40 were seropositive at baseline. The samples were collected at different time points.

Neutralizing antibodies (NAbs) were measured by CLIA method using Maglumi 800 analyzer. The median days that neutralizing antibodies were positive were 96 and 201 days for rapid and slow attenuation, respectively. No age and gender difference were found in Nabs levels.

The decline in Nabs was pronounced (-96.8%) and approximately 47% of those tested were negative at day 180. Whether this decline correlates with a corresponding decline in clinical efficacy against the virus would need to be investigated in appropriate clinical trials. BNT162b2 elicits strong NAb production, especially 28 days after initial inoculation.

Further investigations are urgently needed to improve both the comparability of data and our understanding of which levels should be considered predictive of immune protection

Keywords: COVID-19; SARS-CoV-2; mRNA vaccine;

Introduction

Coronavirus disease 2019 (COVID -19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. In late 2019, a novel coronavirus was identified as the cause of cases of atypical pneumonia in Wuhan, China [2]. The World Health Organization (WHO) declared COVID -19 a pandemic on March 11, 2021 [2].

The first laboratory confirmed case of COVID-19 infection in Republic of North Macedonia was observed in February 2020, escalating to 215995 cases and 7592 deaths as of December 1st 2021.

Several studies have demonstrated that health care workers (HCWs) have an increased risk of COVID-19 infection due to their close contact with patients [3-5].

COVID -19 has important implications for health care workers. First, it has consequences for their health; second, infected health care workers could also spread the infection to vulnerable patients if they are not properly and quickly isolated. Third, a high infection rate among health workers could cause problems because the health system is understaffed.

Fourth, workers may spread the infection to close family members, other HCWs, and the community. Vaccination of medical workers aims to directly protect them from occupational infection with COVID -19 and indirectly protect their patients and critical health infrastructure. It is a turism that health care workers who come into contact with patients have an ethical obligation to be vaccinated.

It is important to monitor the effectiveness of the vaccine over time. In fact, several studies have indicated that protection against infection has declined in recent months. Findings on the durability of the vaccine COVID -19 will inform whether and when certain individuals should receive a booster dose [6-7].

Aim of the study: to evaluate the durability of BNT162b2 neutalizing antibodies (NAbs) in vaccinated HCWs.

Material and methods

In this study, healthcare workers (HCW) received the two-dose Pfizer-BioNTech, BNT162b2, mRNA-based COVID-19 vaccine regimen. Of the 131 HCW enrolled in the study, 85 (64.9%) were female and 46 (35.1%) were male, with a mean age (±SD) of 45.2±10.31 (range 26-55) years. Of them, 91 (69.5%) were seronegative (63.10% female, mean age (±SD) 44±9.35) and 40 (30.5%) were seropositive (73.10% female, mean age (±SD) 46±:8.46) at baseline.

NAbs were measured by CLIA method using Maglumi 800 analyzer. SARS-CoV-2 NAbs present in the sample compete with ACE2 antigen immobilized on magnetic microbeads for binding recombinant SARS-CoV-2-RBD antigen labeled with N-(4-aminobutyl)-N-ethyl- isoluminol (ABEI). For SARS-CoV-2 Neutralizing Antibody reagent, 1 μg/mL is equivalent to 405 IU/mL.

Results

We tested NAbs antibodies in a real-life setting during the 3rd-4th week, 3 months and 6 months after complete BNT162b2 vaccination in healthcare workers and residents of a Macedonian health care facilities.

Our data clearly show that vaccination with two doses of BNT162b2 spaced of 21-28 days determines a detectable antibody production in 99.88% of tested subjects, confirming the effectiveness of this vaccine also in a real-life setting.

Our study showed a significantly higher NAb titer in those who had a previous SARS-CoV-2 infection (950 vs 485 IU/mL; $p < 0.001$).

All participants had high NAb 21-28 days post-vaccination **(206-6.359 IU/ml, median 1.053 IU/ml)**. All subjects experienced a significant decline in NAb levels by day 40 post-vaccination but antibodies appeared to plateau by day 60 and 90.

Table 1. NAb levels in days post-vaccination.

Days post vaccination	NAb (μg/mL)	NAb (IU/mL)
21-28	2.6	1.053
40	1.365	552.02
60	0.605	245.01
90	0.595	241.01
180	0.437	176.98
Positive cut-off	0.30	121.50
Measuring range	0.05-30	20.25-12.150

Discussion

Our results do not indicate a complete loss of neutralizing antibodies over the duration of the study. This suggests that protection against symptomatic infection persists for months after vaccination. Vaccination appears to permanently reduce risk over time, despite the early evidence of declining protection that we present here [7,8,9].

It is noteworthy that several reports suggest that the efficacy of BNT162b2 against symptomatic infections decreases over time [10-13].

Consistent with this, recent studies have shown that antibody titers decrease over time after complete vaccination with BNT162b2 [12-14]. This is particularly important because the concentration of neutralizing antibodies is considered highly predictive of protection against SARS-CoV-2 infection [15].

In one study, spike protein antibody concentrations decreased by about two fold between 21-41 days and 70+ days after the second dose [16].

In the study of Terpos et al. [17], concentrations of neutralizing antibodies decreased significantly several months after vaccination with two dose regimen [17].

We emphasize the need to collect additional prospective clinical data to make recommendations for booster vaccinations, particularly with regard to their safety, immunogenicity, and efficacy in severe disease progression [18-22].

Conclusions

These findings motivate further investigation of strategies to prolong vaccine-induced immunity, such as combining vaccination with nonpharmaceutical interventions or administering additional doses of additional doses of vaccine to vulnerable populations.

References

1. Lippi G, Plebani M. The novel coronavirus (2019-nCoV) outbreak: think the unthinkable and be prepared to face the challenge. Diagnosis (Berl) 2020;7:79–81.
2. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
3. Rudberg AS, Havervall S, Månberg A, Jernbom Falk A, Aguilera K, Ng H, Gabrielsson L, Salomonsson AC, Hanke L, Murrell B, McInerney G, Olofsson J, Andersson E, Hellström C, Bayati S, Bergström S, Pin E, Sjöberg R, Tegel H, Hedhammar M, Phillipson M, Nilsson P, Hober S, Thålin C. SARS-CoV-2 exposure, symptoms and seroprevalence in healthcare workers in Sweden. Nat Commun. 2020;11(1):5064.
4. Von Huth S, Lillevang ST, Røge BT, Madsen JS, Mogensen CB, Coia JE, Möller S, Justesen US, Johansen IS. SARS-CoV-2 seroprevalence among 7950 healthcare workers in the Region of Southern Denmark. Int J Infect Dis 2021;112:96-102.
5. Tosheska-Trajkovska K, Babacic H, Toseska-Spasova N , Kostovska I, Bogdanska J, Labudovikj D, Cekovska S, Brezovska S, Ampova H, Emin M, Stanojevska-Petrusevska E, Topuzovska S. Anti-SARS-CoV-2 antibodies in Macedonian healthcare workers: an interim analysis. Acad Med J 2021;1(1):18-25.
6. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA, Li P, Koury K, Kalina W, Cooper D, Fontes-Garfias C, Shi PY, Türeci Ö, Tompkins KR, Lyke KE, Raabe V, Dormitzer PR, Jansen KU, Şahin U, Gruber WC. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020;383(25):2439-50.
7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group.

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383(27):2603-15.

8. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott A, Flach B, Doria-Rose NA, Corbett KS, Morabito KM, O'Dell S, Schmidt SD, Swanson PA 2nd, Padilla M, Mascola JR, Neuzil KM, Bennett H, Sun W, Peters E, Makowski M, Albert J, Cross K, Buchanan W, Pikaart-Tautges R, Ledgerwood JE, Graham BS, Beigel JH; mRNA-1273 Study Group. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020; 383(20):1920-31.
9. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384(5):403-16.
10. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, Goepfert PA, Truyers C, Fennema H, Spiessens B, Offergeld K, Scheper G, Taylor KL, Robb ML, Treanor J, Barouch DH, Stoddard J, Ryser MF, Marovich MA, Neuzil KM, Corey L, Cauwenberghs N, Tanner T, Hardt K, Ruiz-Guiñazú J, Le Gars M, Schuitemaker H, Van Hoof J, Struyf F, Douoguih M; ENSEMBLE Study Group. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med 2021;384(23):2187-201.
11. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernán MA, Lipsitch M, Reis B, Balicer RD. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021;384(15):1412-23.
12. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Polack FP, Zerbini C, Bailey R, Swanson KA, Xu X, Roychoudhury S, Koury K, Bouguermouh S, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Yang Q, Liberator P, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Gruber WC, Jansen KU; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med 2021;385(19):1761-73.
13. Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson K; HEROES-RECOVER Cohorts. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021;70(34):1167-9.
14. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G, Myers R, Campbell CNJ, Amirthalingam G, Edmunds M, Zambon M, Brown KE, Hopkins S, Chand M, Ramsay M. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385(7):585-594.
15. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205-11.
16. Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, Beale S, Fong WLE, Patel P, Kovar J, Hayward AC, Aldridge RW; Virus Watch Collaborative. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet 2021;398(10298):385-7.
17. Terpos E, Trougakos IP, Karalis V, Ntanasis-Stathopoulos I, Gumeni S, Apostolakou F, Sklirou AD, Gavriatopoulou M, Skourti S, Kastritis E, Korompoki E, Papassotiriou I, Dimopoulos MA. Kinetics of Anti-SARS-CoV-2 Antibody Responses 3 Months Post Complete Vaccination with BNT162b2; A Prospective Study in 283 Health Workers. Cells 2021;10(8):1942.
18. Patel MM, Jackson ML, Ferdinands J. Postlicensure Evaluation of COVID-19 Vaccines. JAMA 2020;324(19):1939-40.
19. Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 Vaccine Effectiveness in a High-Risk National Population in a Real-World Setting. Ann Intern Med 2021;174(10):1404-8.

20. Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, Olsho LEW, Caban-Martinez AJ, Fowlkes A, Lutrick K, Kuntz JL, Dunnigan K, Odean MJ, Hegmann KT, Stefanski E, Edwards LJ, Schaefer-Solle N, Grant L, Ellingson K, Groom HC, Zunie T, Thiese MS, Ivacic L, Wesley MG, Lamberte JM, Sun X, Smith ME, Phillips AL, Groover KD, Yoo YM, Gerald J, Brown RT, Herring MK, Joseph G, Beitel S, Morrill TC, Mak J, Rivers P, Harris KM, Hunt DR, Arvay ML, Kutty P, Fry AM, Gaglani M. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. Morb Mortal Wkly Rep 2021;70(13):495-500.
21. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, Malek JA, Coyle P, Ayoub HH, Al Kanaani Z, Al Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul Rahim HF, Nasrallah GK, Al Kuwari MG, Al Romaihi HE, Al-Thani MH, Al Khal A, Butt AA, Bertollini R, Abu-Raddad LJ. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021;27(9):1614-21.
22. Callaway E. COVID vaccine boosters: the most important questions. Nature 2021; 596(7871):178-80.