



# Immunosuppressed non-responders to two doses of mRNA SARS-CoV-2 vaccines achieve an immune response comparable to those of immunocompetent individuals after a third dose

Andrew N. Margioris<sup>1</sup>

Received: 27 August 2021 / Accepted: 5 April 2022 / Published online: 24 June 2022  
© Hellenic Endocrine Society 2022

## Abstract

The SARS-CoV-2 vaccines trigger the production of neutralizing antibodies to the SARS-CoV-2 spike (S) protein and induce a T cell-mediated immune response. However, the antibody titers that confer protection against the SARS-CoV-2 virus are currently not well-established. While immunocompetent individuals achieve a high level of immune response after SARS-CoV-2 vaccination, it now appears that a high proportion of immunosuppressed or immunocompromised, patients exhibit low or no response to two doses of the vaccines. Most non-responders are on treatment with either glucocorticoids, mycophenolate-mofetil (MMF), the anti-CD20 monoclonal antibody rituximab, calcineurin inhibitors like cyclosporine and tacrolimus, rapamycin (mTOR) signaling cascade inhibitors (i.e., sirolimus and everolimus), azathioprine, or methotrexate given for a variety of diseases including autoimmune disorders, hematological malignancies, and solid cancers, while recipients of solid organ transplants also fall within this category. Recently, several published reports have suggested that a third dose of these vaccines induces an elevated antibody response against the SARS-CoV-2 S protein.

**Keywords** mRNA SARS-CoV-2 vaccines · Third dose · Immunosuppression · Cancers · Transplantation

It is now well established that most COVID-19 vaccines are highly effective in eliciting a robust immune response in immunocompetent individuals, their seroconversion being between 90 and 100% [1–3]. Immune response is assessed by measuring humoral immunity, i.e., antibodies against the SARS-CoV-2 S protein, or by estimating cellular immunity. The most common method for assessing antibody response to SARS-CoV-2 vaccination is assessment of SARS-CoV-2-specific IgG levels; this method uses ELISA for the measurement of anti-SARS-CoV-2 Spike S1 IgG. Another method is a microblot-array for COVID-19 IgG using a mix of recombinant antigens. A third method is a chemiluminescent immunoassay using a SARS-CoV-2 trimeric S IgG against trimeric Spike S1 protein. These, and a few other serological assays, although exhibiting a significant number of false negatives and/or positives, generally appear to be valid screening tools for assessing antibody response to SARS-CoV-2 vaccination [4].

It should, however, be noted that the antibody levels conferring protection against the SARS-CoV-2 virus are as yet not well-established. Several methods have been developed to assess SARS-CoV-2 vaccine-mediated cellular immune response, though the available procedures are cumbersome. One of them consists in measuring SARS-CoV-2-specific T-cells via detection of their intracellular cytokine interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF- $\alpha$ ) following 4 h stimulation of peripheral blood mononuclear cells. It has been observed that the frequency of memory Th cell subsets (CD3 + CD4 + CD45RO+) appears to increase following the second dose of the vaccine, most of the cells being of the Th1 type (CXCR3 + CCR6-). In one study, the mobilization of T follicular helper and B follicular cells was measured in the circulation following BNT162b2 vaccination. Interestingly, the humoral response appears to be detectable before the cellular response. Several other assays are also available for measurement of cellular immune-response, including an INF $\gamma$ -release assay (IGRA) and one consisting of overnight blood incubation with an overlapping set of spike protein peptides, followed by the measurement of cytokine production using a cytometric bead array [5–9].

✉ Andrew N. Margioris  
margiori@uoc.gr

<sup>1</sup> School of Medicine, University of Crete, Heraklion, Greece

Up to few months ago, there were no data regarding the response of immunosuppressed patients to the SARS-CoV-2 vaccines, since the latter patients were excluded from the phase 3 trials that led to the emergency authorization of these vaccines. As our experience grew, it became apparent that, although immunocompetent individuals had an excellent immune response to the vaccines, a large proportion of immunosuppressed patients had low or no response at all following two doses of SARS-CoV-2 vaccines. Non-responders included patients on immunosuppressive treatment for a variety of diseases, including autoimmune disorders, hematological malignancies, and solid cancers, as well as recipients of solid organ transplants. The medications implicated are glucocorticoids, mycophenolate mofetil (MMF) (a reversible inhibitor of inosine monophosphate dehydrogenase, IMPDH, the rate-limiting enzyme in the *de novo* synthesis of guanosine nucleotides crucial for development of T- and B-lymphocytes), the B cell depletion medication anti-CD20 monoclonal antibody rituximab, immunophilin-binding drugs including calcineurin inhibitors like cyclosporine and tacrolimus (calcineurin is involved in the production of interleukin-2, crucial for the development and proliferation of T cells), rapamycin (mTOR) signaling cascade inhibitors (i.e., sirolimus and everolimus, which prevent cytokine signals that activate T-cells), pyrimidine synthesis inhibitors like leflunomide and FK778, and antimetabolites such as azathioprine. This commentary will not address the impact of these medications on the clinical course of patients suffering from COVID-19 disease, i.e., glucocorticoids and IL-6 inhibitors (for instance, tocilizumab) which reduce mortality and prevent mechanical ventilation. [10–12].

Impaired immunogenicity to SARS-CoV-2 mRNA vaccines in immunosuppressed patients was reported in April, 2021. Since then, multiple reports have confirmed these observations in several groups of patients on immunosuppressive treatment.

**Patients on treatment for autoimmune disorders** SARS-CoV-2 antibodies were measured at baseline and prior to the second vaccine dose in patients suffering from inflammatory arthritis, systemic lupus erythematosus, Sjogren's syndrome, and overlap connective tissue diseases. After the first vaccine dose, 74% had detectable antibody titers, the lowest being among patients on MMF and rituximab, while all the patients on anti-tumor necrosis factor (TNF) inhibitors had good responses. [13] In another study, humoral and cellular immune responses to the COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) were evaluated in patients taking methotrexate. Humoral immunity to a single dose of BNT162b2 was impaired by methotrexate but not by targeted biologics, whereas cellular responses were good for both treatment modalities [14].

Because of the uncertainty regarding the efficacy and safety of vaccination in patients with autoimmune inflammatory rheumatic disease (AIIRD), the Korean College of Rheumatology Task Force for COVID-19 Vaccine Guidance for Patients with Autoimmune Inflammatory Rheumatic Diseases recommended that prior to vaccination, these patients should decrease the amount of corticosteroids to the lowest possible dose, while those on methotrexate were advised to discontinue it for a couple of weeks until the timing of rituximab or abatacept infusion was adjusted as per clinical evaluation [15].

**Patients with hematologic malignancies** patients with hematological malignancies treated with BTKIs, ruxolitinib, venetoclax, or anti-CD20 antibody appeared to have suboptimal responses to the two doses of the BNT162b2 mRNA vaccination [16, 17]. In a study in patients suffering from hematologic malignancies, 77% had a poor response following two doses of anti-SARS-CoV-2 vaccination. The patients with B cell chronic lymphocytic leukemia had the lowest response [18].

**Patients on chemotherapy for solid cancers** The patients on treatment of solid cancers had blunted humoral response to two doses of the BNT162b2 mRNA vaccination [19]. The titers of anti-spike antibodies were significantly lower in patients with solid cancers in comparison to those in healthy volunteers and significantly lower than in patients receiving chemotherapy. Titers of anti-spike antibodies did not differ depending on age, sex, cancer location, and metastatic status [20]. Similarly, seroconversion rates were low in these patients compared to healthy controls, with the lowest rate observed in patients on methotrexate. On the other hand, cellular immune responses were induced in all groups, even in patients receiving methotrexate [21].

**Patients on hemodialysis** Humoral immune response was measured in patients on hemodialysis after two doses of mRNA-based SARS-CoV-2 vaccine BNT162b2 (Pfizer-BioNTech). Antibody responses were evaluated with an anti-SARS-CoV-2 IgG ChemiLuminescent ImmunoAssay 2 weeks after the second dose and compared with those of controls (healthy healthcare workers). The control group had a strong antibody response with a median antibody titer of 800.0 AU/mL; meanwhile, though hemodialyzed patients of less than 60 years of age responded as well as did controls; those over 60, had significantly lower antibody titers [22]. In another study, SARS-CoV-2-vaccination induced seroconversion efficacy in dialysis patients to a degree similar to that of the medical personnel (>95%), but was markedly impaired in kidney transplant recipients (42%). T cellular immunity largely mimicked humoral results. Major risk factors of seroconversion failure were immunosuppressive drugs

(e.g., belatacept, MMF-MPA, and calcineurin-inhibitors) [23]. In one other study, serological response was assessed at 0, 14, 28, 36, and 58 days after the first injection of the Pfizer/BioNTech (BNT162b2) mRNA vaccine in 78 patients undergoing hemodialysis, 74 kidney transplant recipients, and seven healthy controls. The controls had antibodies at a positive level ( $> 13$  arbitrary units per ml; AU/ml) on day 14 post-injection, which increased progressively to peak on day 36 (1082 AU/ml). The patients undergoing hemodialysis had lower titers that peaked on day 58 (276 AU/ml). A small percentage of kidney transplant recipients had positive antibody levels on day 36, suggesting that the humoral response following a single dose of the vaccines was strongly inhibited by the immunosuppressant therapy [24].

**Solid organ transplant recipients** Kidney transplant patients (136) were vaccinated with the BNT162b2 (Pfizer-BioNTech) vaccine and compared with 25 controls. While all the controls had humoral immune response against the SARS-CoV-2 nucleocapsid protein, this was true of only 37.5% of the transplanted patients. MMF and corticosteroids were the main variables [25]. In another recent study, the majority of solid organ transplant recipients did not exhibit a significant anti-spike antibody response to the first dose of the mRNA SARS-CoV-2 vaccine. Younger participants and those who received the mRNA-1273 (Moderna) vaccine were more likely to develop an antibody response [26]. Among lung transplant recipients, none developed anti-SARS-CoV-2 antibodies after two doses of the mRNA BNT162b2 vaccine (Pfizer-BioNTech), while 85% presented an antibody response after SARS-CoV-2 infection [27]. Liver recipients vaccinated with the Pfizer-BioNTech SARS-CoV-2 mRNA-based vaccine developed a substantially lower immunological response compared to healthy controls. Factors influencing the serological antibody responses included age, renal function, and the type of immunosuppressive medications [28]. Only 50% of liver recipients, 33% of kidney, 20% of pancreas, and 12% of thoracic organ recipients developed anti-SARS-CoV-2 antibodies at 4 weeks after the second vaccine dose [29]. Two-thirds of kidney or kidney-pancreas transplant recipients developed either cellular or humoral response following two doses of mRNA SARS-CoV-2 vaccination (mRNA-1273, Moderna). Their response was assessed by measuring IgM/IgG S antibodies and ELISpot against the nucleocapsid (N) and the S protein at baseline and 2 weeks after the second dose. Factors associated with vaccine unresponsiveness were diabetes and treatment with anti-thymocyte globulins [30]. Data based on the measurement of SARS-CoV-2 IgG antibodies after the second dose of the vaccine showed that only 22% of renal transplant recipients had a positive response to BNT162b2 (Pfizer-BioNTech, Kronach, Germany) compared to healthcare workers who had a 100% positive antibody response [31].

Finally, only 6.2% of 145 kidney transplant recipients had detectable antibody response following the administration of a single dose of an mRNA COVID-19 vaccine [32].

While in the immunocompetent population a third dose of SARS-CoV-2 vaccines has been authorized and rolled out over the past months, since their antibody titers tend to diminish with time [33], in immunosuppressed patients, who in multiple studies showed minimal response to two doses of SARS-CoV-2 vaccines (i.e., they never achieved a good humoral response), a third or even a fourth dose should be made mandatory given that it can increase their antibody titers up to those of immunocompetent individuals. This renders making the administration of a third or even a fourth dose an immediate priority for these non-responders, multiple recently published reports supporting this concept. Indeed, the patients with solid organ transplants receiving a third dose of vaccine directed against SARS-CoV-2 showed an elevation of antibodies; this is evident in a third of the patients who had no previous antibody response and in all the patients who had low-positive antibody titers [34]. In another study, a third dose of BNT162b2 mRNA COVID-19 vaccine enhanced humoral response in almost all the dialysis patients, but especially in those with low antibody titers after two doses of the vaccines [35]. In kidney transplant recipients who had a weak humoral response after the second dose of mRNA SARS-CoV-2 vaccines, a third dose amplified their response, although those on triple immunosuppression (i.e., glucocorticoids, tacrolimus, and mycophenolate) did not [36]. In a large study of 396 solid organ transplant recipients, a third dose of the mRNA-based vaccine (BNT162b2 vaccine [Pfizer-BioNTech]) was administered 2 months later, i.e., when the third dose was recommended by the French National Authority for Health. The mean titers of the anti-SARS-COV-2 S protein antibodies were assessed before the first and the second dose, and 4 weeks after the third dose. Among the 232 patients who were negative following the second dose of vaccine, 105 turned positive 4 weeks following the third dose [37]. In cancer patients, a third dose of Pfizer/BioNTech mRNA vaccine elevated their antibody response to levels comparable to those that immunocompetent individuals achieved after the second dose. The report, which involved patients with solid tumors on active cytotoxic anti-cancer therapy, compared their responses with those of a control cohort who also received the Pfizer/BioNTech vaccine. Using live SARS-CoV-2 assays, neutralizing antibodies were detected in 67 and 80% of cancer patients after the first and second immunizations, respectively, with a threefold increase in median titers following the third dose [37]. RBD- and Spike S1-specific memory B cell subsets were also measured as predictors of anamnestic responses to viral exposures or additional immunizations. After the second vaccination, Spike-specific plasma cell-biased memory

B cells were observed in most cancer patients at levels similar to those of the control cohort after their first dose [38].

In conclusion, a large percentage of immunosuppressed patients exhibit low or no response following two doses of mRNA SARS-CoV-2 vaccines. Most non-responders are on treatment with glucocorticoids, mycophenolate-mofetil (MMF), the anti-CD20 monoclonal antibody rituximab, tacrolimus, sirolimus, everolimus, azathioprine, or methotrexate for a variety of diseases, including autoimmune disorders, hematological malignancies, and solid cancers, or are recipients of solid organ transplants. Several published research papers suggest that a third dose of these vaccines induces an antibody response against the SARS-CoV-2 S protein in immunosuppressed patients comparable to that seen in immunocompetent individuals.

## Declarations

**Conflict of interest** The author declares no competing interests.

## References

- Jackson LA, Anderson EJ, Roupael 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 (2020) An mRNA vaccine against SARS-CoV-2 - preliminary report. *N Engl J Med* 383:1920–1931
- Bianchi FP, Germinario CA, Migliore G, Vimercati L, Martinelli A, Lobifaro A, Tafuri S, Stefanizzi P, Control Room Working Group (2021) BNT162b2 mRNA COVID-19 vaccine effectiveness in the prevention of SARS-CoV-2 Infection: a preliminary report. *J Infect Dis* 224:431–434
- Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S, Lörks V, Sikorski J, Hilker R, Becker D, Eller AK, Grützner J, Boesler C, Rosenbaum C, Kühnle MC, Luxemburger U, Kemmer-Brück A, Langer D, Bexon M, Bolte S, Karikó K, Palanche T, Fischer B, Schultz A, Shi PY, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J, Scully IL, Cutler M, Kalina W, Kyratsous CA, Cooper D, Dormitzer PR, Jansen KU, Türeci Ö (2020) COVID-19 vaccine BNT162b1 elicits human antibody and T<sub>H</sub>1 T cell responses. *Nature* 586(7830):594–599
- Wheeler SE, Shurin GV, Yost M, Anderson A, Pinto L, Wells A, Shurin MR (2021) Differential antibody response to mRNA COVID-19 vaccines in healthy subjects. *Microbiol Spectr* 4:e00341–e421
- Havlin J, Svorcova M, Dvorackova E, Lastovicka J, Lischke R, Kalina T, Hubacek P (2021) Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients *J Heart Lung Transplant* 21:S1053–2498(21)02318–4.
- Lineburg KE, Neller MA, Ambalathingal GR, Le Texier L, Raju J, Swaminathan S, Lekieffre L, Smith C, Rehan S, Crooks P, Panikkar A, Srihari S, Khanna R, Smith C (2021) Rapid whole-blood assay to detect SARS-CoV-2-specific memory T-cell immunity following a single dose of AstraZeneca ChAdOx1-S COVID-19 vaccine. *Clin Transl Immunology* 10(8):e1326
- San Segundo D, Comins-Boo A, Irure-Ventura J, Renuncio-García M, Roa-Bautista A, González-López E, Merino-Fernández D, Lamadrid-Perojo P, Alonso-Peña M, Gonzalo Oejo-Vinyals J, Gutiérrez-Larrañaga M, Guiral-Foz S, López-Hoyos M (2021) Immune assessment of BNT162b2 m-RNA-spike based vaccine response in adults. *Biomedicine* 9:868
- Comins-Boo A, Gutiérrez-Larrañaga M, Roa-Bautista A, Guiral-Foz S, Renuncio-García M, González-López E, Irure-Ventura J, Fariñas-Álvarez MC, SanSegundo D, López-Hoyos M (2021) Validation of a quick flow cytometry-based assay for acute infection based on CD64 and CD169 expression new tools for early diagnosis in COVID-19 pandemic. *Front Med (Lausanne)* 8:655785
- Malipiero G, Moratto A, Infantino M, D'Agaro P, Piscianz E, Manfredi M, Grossi V, Benvenuti E, Bulgaresi M, Benucci M, Villalta D (2021) Assessment of humoral and cellular immunity induced by the BNT162b2 SARS-CoV-2 vaccine in healthcare workers, elderly people, and immunosuppressed patients with autoimmune disease. *Immunol Res* 69(6):576–583
- Schoot TS, Kerckhoffs APM, Hilbrands LB, van Marum RJ (2020) Immunosuppressive drugs and COVID-19: a review. *Front Pharmacol* 28(11):1333
- Zhang ZL, Zhong H, Liu YX, Le KJ, Cui M, Yu YT, Gu ZC, Gao Y, Lin HW (2020) Current therapeutic options for coronavirus disease 2019 (COVID-19)-lessons learned from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) therapy: a systematic review protocol. *Ann Transl Med* 8(22):1527
- Liu C, von Brunn A, Zhu D (2020) Cyclophilin A and CD147: novel therapeutic targets for the treatment of COVID-19. *Med Drug Discov* 7:100056
- Boyarsky BJ, Ruddy JA, Connolly CM, Ou MT, Werbel WA, Garonzik-Wang JM, Segev DL, Paik JJ (2021) Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*, 21–220289.
- Mahil SK, Bechman K, Raharja A, Domingo-Vila C, Baudry D, Brown MA, Cope AP, Dasandi T, Graham C, Lechmere T, Malim MH, Meynell F, Pollock E, Seow J, Sychowska K, Barker JN, Norton S, Galloway JB, Doores KJ, Tree TIM, Smith CH (2021) The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. *Lancet Rheumatol* 3(9):e627–e637
- Park JK, Lee EB, Shin K, Sung YK, Kim TH, Kwon SR, Lee MS, Hong SJ, Choi BY, Lee SS, Korean College of Rheumatology Task Force for COVID-19 vaccine guidance for patients with autoimmune inflammatory rheumatic diseases (2021) COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases clinical guidance of the Korean College of Rheumatology. *J Korean Med Sci* 36(12):95
- Maneikis K, Šablauskas K, Ringelevičiūtė U, Vaitekėnaitė V, Čekauskienė R, Kryžauskaitė L, Naumovas D, Banys V, Pečeliūnas V, Beinortas T, Griškevičius L (2021) Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. *Lancet Haematol* 8:e583–e592
- Re D, Barrière J, Chamorey E, Delforge M, Gastaud L, Petit E, Chaminade A, Verrière B, Peyrade F (2021) Low rate of seroconversion after mRNA anti-SARS-CoV-2 vaccination in patients with hematological malignancies. *Leuk Lymphoma* 26:1–3
- Agha ME, Blake M, Chilleo C, Wells A, Haidar G (2021) Sub-optimal response to coronavirus disease 2019 messenger RNA

- vaccines in patients with hematologic malignancies a need for vigilance in the postmasking era. *Open Forum Infect Dis* 8:353
19. Barrière J, Re D, Peyrade F, Carles M (2021) Current perspectives for SARS-CoV-2 vaccination efficacy improvement in patients with active treatment against cancer. *Eur J Cancer* 154:66–72
  20. Palich R, Veyri M, Vozy A, Marot S, Gligorov J, Benderra MA, Maingon P, Morand-Joubert L, Adjoutah Z, Marcelin AG, Spano JP, Barrière J (2021) High seroconversion rate but low antibody titers after two injections of BNT162b2 (Pfizer-BioNTech) vaccine in patients treated with chemotherapy for solid cancers. *Ann Oncol* 22:S0923–7534(21)02075–5.
  21. Monin L, Laing AG, Muñoz-Ruiz M (2021) Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol* 22:765–778
  22. Jahn M, Korth J, Dorsch O, Anastasiou OE, Sorge-Hädicke B, Tyczynski B, Gäckler A, Witzke O, Dittmer U, Dolff S, Wilde B, Kribben A (2021) Humoral response to SARS-CoV-2-vaccination with BNT162b2 (Pfizer-BioNTech) in patients on hemodialysis. *Vaccines (Basel)* 9:360
  23. Stumpf J, Siepmann T, Lindner T, Karger C, Schwöbel J, Anders L, Faulhaber-Walter R, Schewe J, Martin H, Schirutschke H, Barnett K, Hüther J, Müller P, Langer T, Pluntke T, Anding-Rost K, Meistring F, Stehr T, Pietzonka A, Escher K, Cerny S, Rothe H, Pistrosch F, Seidel H, Paliege A, Beige J, Bast I, Steglich A, Gembarth F, Kessel F, Kröger H, Arndt P, Sradnick J, Frank K, Klimova A, Maurer R, Grähler X, Anft M, Blazquez-Navarro A, Westhoff TH, Stervbo U, Tonn T, Babel N, Hugo C (2021) Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur*. 100178
  24. Danthu C, Hantz S, Dahlem A, Duval M, Ba B, Guibbert M, El Ouafi Z, Ponsard S, Berrahal I, Achard JM, Bocquentin F, Allot V, Rerolle JP, Alain S, Toure F (2021) Humoral response after SARS-Cov-2 mRNA vaccine in a cohort of hemodialysis patients and kidney transplant recipients. *J Am Soc Nephrol* 16:ASN.2021040490.
  25. Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, Katchman E, Halperin T, Turner D, Goykhman Y, Shibolet O, Levy S, Houry I, Baruch R, Katchman H (2021) Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant* 21:2719–2726
  26. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM (2021) Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 325:1784–1786
  27. Havlin J, Svorcova M, Dvorackova E, Lastovicka J, Lischke R, Kalina T, Hubacek P (2021) Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients. *J Heart Lung Transplant* 21:S1053–2498(21)02318–4.
  28. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, Katchman E, Levi S, Houry I, Lubezky N, Shibolet O, Katchman H (2021) Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol* 75:435–438
  29. Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, Hebral AL, Izopet J, Kamar N (2021) Safety and immunogenicity of anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. *Ann Intern Med* M21–1341.
  30. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J, Cofan F, Moreno A, Rovira J, Banon-Maneus E, Ramirez-Bajo MJ, Ventura-Aguiar P, Pérez-Olmos A, Garcia-Pascual M, Pascal M, Vilella A, Trilla A, Ríos J, Palou E, Juan M, Bayés B, Diekmann F (2001) Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant* 21(8):2727–2739
  31. Korth J, Jahn M, Dorsch O, Anastasiou OE, Sorge-Hädicke B, Eisenberger U, Gäckler A, Dittmer U, Witzke O, Wilde B, Dolff S, Kribben A (2021) Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech). *Viruses* 13(5):756
  32. Yi SG, Knight RJ, Graviss EA, Moore LW, Nguyen DT, Ghobrial RM, Gaber AO, Huang HJ (2021) Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. *Transplantation* 105(7):e72–e73
  33. Mahase E (2021) Covid-19 booster vaccines: what we know and who's doing what. *BMJ* 374:n2082
  34. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, Segev DL (2021) Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med* L21–0282.
  35. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C (2021) Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int* 100:702–704
  36. Benotmane I, Gautier G, Perrin P, Olgagne J, Cognard N, Fafi-Kremer S, Caillard S (2021) Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. *JAMA*
  37. Del Bello A, Abravanel F, Marion O, Couat C, Esposito L, Lavayssière L, Izopet J, Kamar N. (2021) Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. *Am J Transplant*
  38. Shroff RT, Chalasani P, Wei R, Pennington D, Quirk G, Schoenle MV, Uhrlaub JL, Ripperger TJ, Jergović M, Dalgai S, Wolf A, Hammad H, Carrier A, Scott AJ, Nikolich-Zugich J, Worobey M, Sprissler R, Dake M, LaFleur BJ, Bhattacharya D. (2021) Immune responses to COVID-19 mRNA vaccines in patients with solid tumors on active, immunosuppressive cancer therapy medRxiv 14:2021.05.13.21257129.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.