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BRIEF REPORT

Decreased Antibody Response After Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination in Patients With Down Syndrome

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The risk of a severe course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults with Down syndrome is increased, resulting in an up to 10-fold increase in mortality, in particular in those >40 years of age. After primary SARS-CoV-2 vaccination, the higher risks remain. In this prospective observational cohort study, SARS-CoV-2 spike S1–specific antibody responses after routine SARS-CoV-2 vaccination (BNT162b2, messenger RNA [mRNA]–1273, or ChAdOx1) in adults with Down syndrome and healthy controls were compared. Adults with Down syndrome showed lower antibody concentrations after 2 mRNA vaccinations or after 2 ChAdOx1 vaccinations. After 2 mRNA vaccinations, lower antibody concentrations were seen with increasing age.

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Down syndrome (DS), also known as trisomy 21, is the most common chromosomal abnormality in the Netherlands. Individuals with DS show, at all ages, an increased incidence of respiratory morbidity and mortality. The risk of a severe course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with DS is substantially increased, resulting in hospitalization rates up to 56% [1–3]. Viral pneumonia, acute respiratory distress syndrome, and bacterial pneumonia are the most prevalent complications seen in individuals with DS during a SARS-CoV-2 infection [1]. The risk of death is 3- to 10-fold higher compared with individuals without DS [1, 2]. Aging is an additional risk factor, as is shown by higher mortality rates in people with DS >40 years of age [1].

Recent evidence shows a 12.7-fold increased risk for individuals with DS in coronavirus disease 2019 (COVID-19)–related mortality and hospital admissions, even after 1 or 2 SARS-CoV-2 vaccinations [4]. T-cell and B-cell responses in people with DS are impaired and previous, non–SARS-CoV-2, vaccine responses are known to be suboptimal [5, 6]. SARS-CoV-2 vaccines have been registered for adults and children ≥12 years of age, but none of them have been studied in people with DS. In this study, we investigated the antibody response after SARS-CoV-2 vaccination in individuals with DS and compared these with the antibody response in healthy controls (HCs).

METHODS

Study Design and Participants

The PRIDE study (Prospective Monitoring of Antibody Response Following COVID-19 Vaccination in Patients With Down Syndrome) is a prospective, observational cohort study. Adults (≥18 years of age) with Down syndrome (DS cohort) were compared with a healthy control cohort without Down syndrome (HC cohort). Participants with DS were recruited through patient networks and specialized DS outpatient clinics throughout the Netherlands. Household contacts of the DS participants and healthcare workers were asked to participate in the HC cohort. Exclusion criteria were receipt of organ transplant, active malignancy or completion of treatment for malignancy in the previous 3 months, or an infection with human immunodeficiency virus. For the HC cohort, additional exclusion criteria were any disease or condition for which regular visits to a healthcare provider were necessary. Participants received 2 doses of the following SARS-CoV-2 vaccines as part of the Dutch national immunization program: BNT162b2 (Pfizer/BioNTech, interval 3–6 weeks), mRNA-1273 (Moderna, interval 4–6 weeks), and ChAdOx1 (AstraZeneca, interval 10–14 weeks). Given the same general vaccine

mechanism and efficacy in other populations, BNT162b2 and mRNA-1273 were combined and referred to as messenger RNA (mRNA) vaccine. The study was approved by the University Medical Center Utrecht medical research ethics committee (NL76336.041.21). All participants and/or legal representatives provided written informed consent before inclusion.

Procedures

Blood samples were collected at baseline (<2 months before the first vaccination) (T = 1), 21–28 days after the first vaccination (T = 2), and 28 days (range, 21–42 days) after the second vaccination (T = 3). SARS-CoV-2 immunoglobulin G (IgG) antibodies against the spike protein (S), receptor-binding domain, and nucleocapsid protein (N) were measured by multiplex immunoassay and reported as binding antibody units (BAU)/mL as previously described [7], according to the first serum standard for COVID-19 (20/136), as provided by the National Institute for Biological Standards and Control and recommended by the World Health Organization to define specific serum antibody concentrations in an international perspective.

Statistical Analysis

Antibody concentrations are presented as geometric mean antibody concentrations (GMCs). An S antibody concentration >10.08 BAU/mL was considered positive. Participants with a concentration below this value at T = 3 were defined as nonresponders. At the moment of analysis, no specific threshold in correlation to neutralization is known for individuals with DS. Participants with a positive anti-S IgG concentration at T = 1 (>10.08 BAU/mL) were considered to be previously infected with SARS-CoV-2 and excluded from primary analysis. In case no T = 1 sample was available, a positive anti-N IgG concentration at T = 2 or T = 3 (>14.3 BAU/mL) was also regarded as a possible previous infection and excluded from primary analysis [8]. Statistical analyses after log-transformation included a Student *t* test for comparison between the DS cohort and HC cohort and between the administered mRNA vaccines. For correlations, a Pearson test was used. Unfortunately, we were not powered to undertake a multivariable analysis. Statistical analyses were performed in IBM SPSS Statistics 26 software (IBM, Armonk, New York). A *P* value < .05 was considered statistically significant.

RESULTS

Population

Between February and September 2021, 318 participants were included, of whom 214 DS participants (51.8% male) and 93 HC participants (27.4% male) had results available at T = 3 at the time of preliminary analysis (Figure 1). Further baseline characteristics are presented in Supplementary Table 1.

Antibody Concentrations

None of the participants, HC or DS, were nonresponders. However, the DS cohort showed a significantly lower GMC after vaccination with an mRNA vaccine compared with the HC cohort (1055.2 BAU/mL [95% confidence interval {CI}, 889.4–1251.9] vs 2271.4 BAU/mL [95% CI, 1763.6–2925.4], respectively) ($P < .001$, Figure 2*A*). The significant difference in GMCs between the DS cohort and HC cohort was found in both subgroups <40 years of age (1429.8 BAU/mL [95% CI, 1199.3–1704.5] vs 2837.4 BAU/mL [95% CI, 2054.7–3918.2], respectively) ($P = 0.003$) and ≥40 years of age (614.0 BAU/mL [95% CI, 451.3–835.3] vs 1927.9 BAU/mL [95% CI, 1322.0–2811.6], respectively) ($P < .001$). After vaccination with ChAdOx1, the DS cohort also showed significantly lower GMCs compared with the HC cohort (343.1 BAU/mL [95% CI, 264.7–444.8] vs 592.1 BAU/mL [95% CI, 466.9–750.9], respectively) ($P = .002$, Figure 2*B*). In general, antibody concentrations after ChAdOx1 were lower compared with antibody concentrations after mRNA vaccines, showing values <100 BAU/mL in DS participants <30 years of age.

In the DS cohort, a negative correlation was found between age and log-transformed antibody concentration after mRNA vaccination, showing lower antibodies with increasing age (Pearson $r = -0.522$, $P < .001$; Figure 2*D*). No such correlation was found in the HC cohort (Pearson $r = -0.245$, $P = .170$). No correlation for antibody concentration in relation to age was found in the DS cohort after vaccination with ChAdOx1 (Pearson $r = -0.176$, $P = .247$), nor in the HC cohort (Pearson $r = -0.092$, $P = .544$).

For the DS cohort, the GMC after BNT162b2 (n = 100; 918.0 BAU/mL [95% CI, 748.2–1126.2]) was significantly lower than after mRNA-1273 (n = 28; 1679.9 BAU/mL [95% CI, 1332.5–2117.9]) ($P < .001$). The HC cohort also showed a lower GMC after BNT162b2 (n = 28; 2228.9 BAU/mL [95% CI, 1542.3–2669.4]) compared with mRNA-1273 (n = 6; 3774.8 BAU/mL [95% CI, 1975.3–7213.4]). The significant differences in GMCs observed between the DS and HC cohort remained when BNT162b2 and mRNA-1273 were analyzed separately.

The relation with age is also found after BNT162b2 vaccination but could not be determined after mRNA-1273 vaccination (only 4 participants were >40 years of age). The participants with evidence of past SARS-CoV-2 infection showed a significantly higher GMC after vaccination compared with SARS-COV-2–naive participants (Figure 2*A* and 2*B*).

DISCUSSION

Our results show that adults with DS have decreased antibody concentrations after SARS-CoV-2 vaccination with mRNA or ChAdOx1 vaccine compared with healthy controls. To our knowledge, this is the first report determining SARS-CoV-2 vaccine antibody responses in a large cohort of adults with

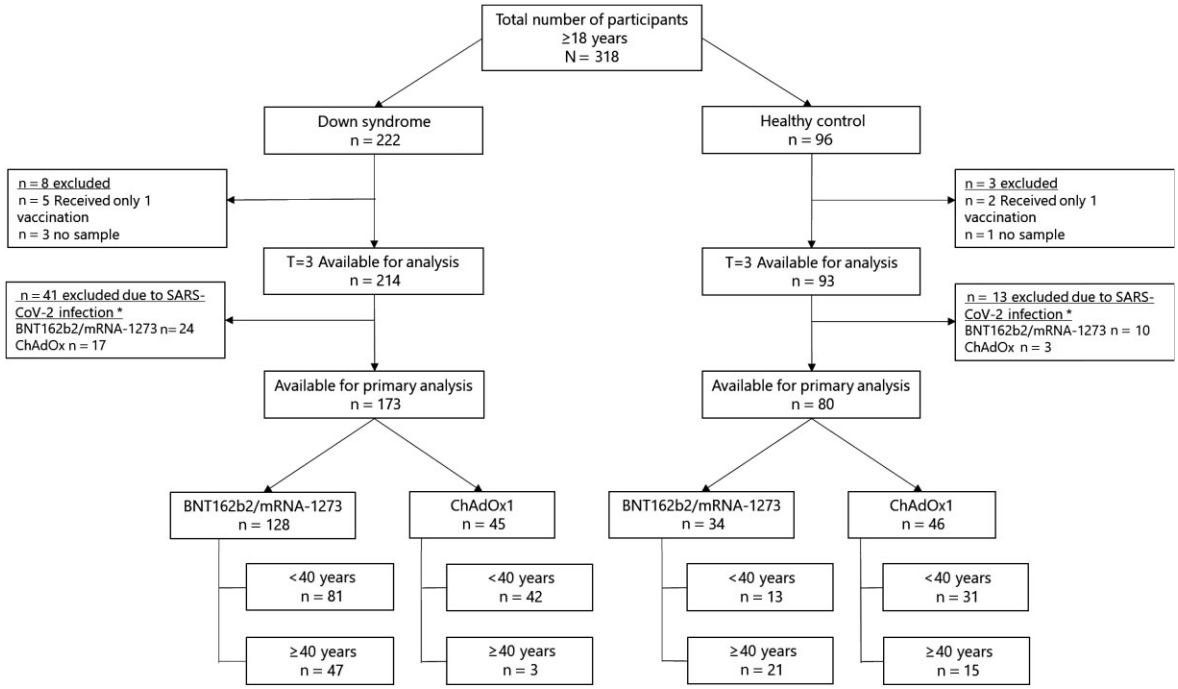

Figure 1. Flow diagram of included participants for analysis. *Participants with a positive anti-spike immunoglobulin G concentration at T = 1 or a positive anti-nucleocapsid IgG concentration at T = 2 or T = 3. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DS. Our findings are important since recent evidence shows that individuals with DS have a higher risk for COVID-19–related mortality and hospital admissions even after 1 or 2 vaccinations [4]. It is not fully clear how our results relate to protection. Currently, no validated cutoff values for either the mRNA or ChAdOx1 vaccines are validated; suggestions in literature differ based on testing technique and timing of measurement [9, 10].

Antibody concentrations were measured at peak levels and will decline over time [11]. It is conceivable that vaccine protection decreases more rapidly in adults with DS than in controls. The Dutch Health Council recently recommended an early booster vaccination for adults with DS, based on our preliminary results. Since vaccine efficacy is higher for mRNA vaccines and recent studies showed high antibody concentrations with a potent T-cell response and only limited side effects after heterologous vaccine schedules with a vector vaccine followed by an mRNA vaccine, a third vaccination with an mRNA vaccine is administered to adults with DS in the Netherlands [12].

A strength of our study is the large number of participants in our DS cohort. There was no loss to follow-up. Besides this, the control group is relatively large, which makes it possible to draw solid conclusions from the data.

Our study has limitations. First, the design is observational. Vaccines were given as part of the national immunization program and changed during the observation period. However, we recruited enough participants to draw conclusions for each vaccine type, and this enabled us to compare the antibody response in 2 vaccine types. Second, the HC cohort consists of a higher percentage of women and this could have affected the antibody response. Third, we only analyzed and compared binding antibodies and were not able to determine a threshold for adequate response, for which analysis of neutralizing antibodies is needed. By comparing antibody concentrations between DS and HC and with increasing age we were able to determine relative antibody responses between groups and with increasing age. Fourth, additional information on cellular responses after vaccination is not yet present, which is also important in the evaluation of vaccine immunogenicity, especially in people with DS, as previous studies have shown that individuals with DS have lower amounts of circulating B and T cells [13, 14]. Decreased thymic output results in low amounts of naive T cells [15]. Loss of memory against SARS-CoV-2 may further contribute to risk of severe COVID-19 disease over time in adults with DS. Fifth, long-term response in our cohort is not yet known, so we do not have information about waning immunity in this particular population.

In conclusion, antibody responses after SARS-CoV-2 vaccination in adults with DS are significantly decreased compared with those of healthy adults. In older adults with DS, the decreased antibody responses were even more pronounced, which, combined with the highest mortality rates,

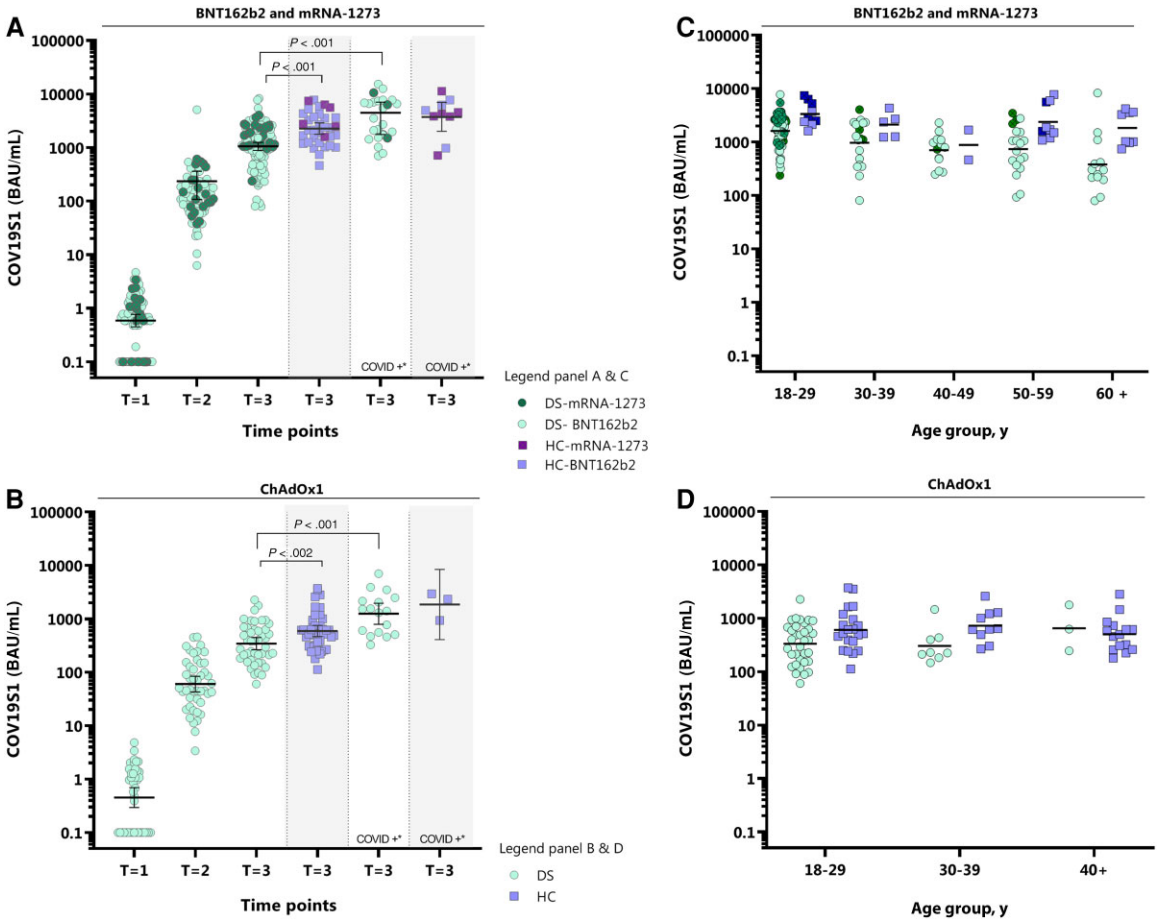

Figure 2. Overview of anti-spike (S1) immunoglobulin G (IgG) concentrations (COV19S1) after different severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. Antibody concentration at T = 1, T = 2, and T = 3 for the Down syndrome (DS) cohort. Each data point represents an individual's response. The black solid line represents the geometric mean concentration (GMC) and its 95% confidence interval (CI). *COVID$^+$ indicates evidence of past SARS-CoV-2 infection based on a positive anti-S IgG concentration at T = 1 or a positive anti-nucleocapsid IgG concentration at T = 2 or T = 3. *A*, A significantly lower antibody response is seen in the DS cohort after messenger RNA (mRNA) vaccination in comparison with the healthy control cohort (HC). Participants with evidence of past SARS-CoV-2 infection in the DS cohort show a significant higher antibody response with a GMC of 3583.2 binding antibody units (BAU)/mL (95% CI, 2436.2–5270.1) compared with SARS-CoV-2–naive participants (GMC, 1055.2 BAU/mL [95% CI, 899.4–1251.9]). *B*, After ChAdOx1 vaccination, a significant lower antibody response is found in the DS cohort compared to HCs. The participants of the DS cohort with evidence of SARS-CoV-2 infection receiving the ChAdOx1 vaccine also show a higher antibody response compared with naive participants (GMC, 1245.3 BAU/mL [95% CI, 791.3–1959.6] vs 343.1 BAU/mL [95% CI, 264.7–444.8]). *C*, Antibodies at T = 3 (±28 days after second vaccination) after mRNA vaccine per decade. In the DS cohort, a negative correlation between age and antibody concentration was found. *D*, Antibodies at T = 3 (±28 days after second vaccination) after ChAdOx1 per decade. No correlation between age and antibody concentration was found.

makes this group particularly vulnerable. A third or early booster vaccination should be considered in all adults with DS, given their risk for severe disease after SARS-CoV-2 infection.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. B. M. M. S., M. B., A. M. W. C., M. E. W., R. L., L. J. B., and J. G. W. contributed to conceptualization and design of the study. B. M. M. S., R. S. B., G. S., G. d. H., L. J. B., and J. G. W. were involved in laboratory experiments and/or analysis and interpretation of collected data. All authors contributed to writing, review, and editing of the manuscript. The corresponding author had full access to all data and takes final responsibility to submit for publication.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hüls A, Costa ACS, Dierssen M, et al. An international survey on the impact of COVID-19 in individuals with Down syndrome. medRxiv [Preprint]. Posted online 5 November **2020**. doi:10.1101/2020.11.03.20225359.
2. Clift AK, Coupland CAC, Keogh RH, Hemingway H, Hippisley-Cox J. COVID-19 Mortality risk in Down syndrome: results from a cohort study of 8 million adults. Ann Intern Med **2021**; 174:572–76.
3. Malle L, Gao C, Hur C, et al. Individuals with Down syndrome hospitalized with COVID-19 have more severe disease. Genet Med **2021**; 23:576–80.
4. Hippisley-cox J, Coupland CAC, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. BMJ Open **2021**; 374:n2244.
5. Meier S, Bel M, L'Huillier A, et al. Antibody responses to natural influenza A/H1N1/09 disease or following immunization with adjuvanted vaccines, in immunocompetent and immunocompromised children. Vaccine **2011**; 29: 3548–57.
6. Kusters MA, Bok VLA, Bolz WEA, Huijskens EGW, Peeters MF, De Vries E. Influenza A/H1N1 vaccination response is inadequate in Down syndrome children when the latest cut-off values are used. Pediatr Infect Dis J **2012**; 31: 1284–5.
7. Hartog G D, Schepp RM, Kuijer M, et al. SARS-CoV-2-Specific antibody detection for seroepidemiology: a multiplex analysis approach accounting for accurate seroprevalence. J Infect Dis **2020**; 222:1452–61.
8. van den Hoogen LL, Smits G, van Hagen CCE, et al. Seropositivity to nucleoprotein to detect SARS-CoV-2 infections: a tool to detect breakthrough infections after COVID-19 vaccination? Vaccine **2022**; 40:2251–7.
9. Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol **2021**; 2045:1–11.
10. Zitt E, Davidovic T, Schimpf J, et al. The safety and immunogenicity of the mRNA-BNT162b2 SARS-CoV-2 vaccine in hemodialysis patients. Front Immunol **2021**; 12:704773.
11. Ward H, Cooke G, Atchison C, et al. Declining prevalence of antibody positivity to SARS-CoV-2: a community study of 36 500 adults. medRxiv [Preprint]. Posted online 27 October 2020. doi:10.1101/2020.10.26.20219725.
12. Chiu N-C, Chi H, Tu Y-K, et al. To mix or not to mix? A rapid systematic review of heterologous prime–boost covid-19 vaccination. Expert Rev Vaccines **2021**; 20: 1211–20.
13. De Hingh YCM, Van Der Vossen PW, Gemen EFA, et al. Intrinsic abnormalities of lymphocyte counts in children with Down syndrome. J Pediatr **2005**; 147:744–7.
14. Bloemers BLP, van Bleek GM, Kimpen JLL, Bont L. Distinct abnormalities in the innate immune system of children with Down syndrome. J Pediatr **2010**; 156: 804–9.e5.
15. Bloemers BLP, Bont L, de Weger RA, Otto SA, Borghans JA, Tesselaar K. Decreased thymic output accounts for decreased naive T cell numbers in children with Down syndrome. J Immunol **2011**; 186:4500–7.