Clinical Infectious Diseases

MAJOR ARTICLE

VPM1002 as Prophylaxis Against Severe Respiratory Tract Infections Including Coronavirus Disease 2019 in the Elderly: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Study

Alexandra M. Blossey,[1,a] Sina Brückner,[1,a] Marcus May,[1] Gerald P. Parzmair,[1] Hitt Sharma,[2] Umesh Shaligram,[2] Leander Grode,[1] Stefan H. E. Kaufmann,[3,4,5] Mihai G. Netea,[6,7,8] and Christoph Schindler[9,10]

[1]Vakzine Projekt Management GmbH, Hannover, Germany; [2]Serum Institute of India Private Limited, Pune, India; [3]Max Planck Institute for Infection Biology, Berlin, Germany; [4]Hagler Institute for Advanced Study, Texas A&M University, College Station, Texas, USA; [5]Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany; [6]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; [7]Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands; [8]Department for Immunology and Metabolism, Life and Medical Sciences Institute, University of Bonn, Bonn, Germany; [9]Clinical Research Center Core Facility, Hannover Medical School, Hannover, Germany; and [10]Center for Pharmacology and Toxicology, Hannover Medical School, Hannover, Germany

Background. Bacille Calmette-Guérin (BCG) vaccination can potentially reduce the rate of respiratory infections in vulnerable populations. This study evaluates the safety and efficacy of VPM1002 (a genetically modified BCG) as prophylaxis against severe respiratory tract infections including coronavirus disease 2019 (COVID-19) in an elderly population.

Methods. In this phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial, healthy elderly volunteers (N = 2064) were enrolled, randomized (1:1) to receive either VPM1002 or placebo, and followed up remotely for 240 days. The primary outcome was the mean number of days with severe respiratory infections at hospital and/or at home. Secondary endpoints included the incidence of self-reported fever, number of hospital and intensive care unit (ICU) admissions, and number of adverse events.

Results. A total of 31 participants in the VPM1002 group reported at least 1 day with severe respiratory disease and a mean number of days with severe respiratory disease of 9.39 ± 9.28 while in the placebo group; 38 participants reported a mean of 14.29 ± 16.25 days with severe respiratory disease. The incidence of self-reported fever was lower in the VPM1002 group (odds ratio, 0.46 [95% confidence interval, .28–.74]; $P = .001$), and consistent trends to fewer hospitalization and ICU admissions due to COVID-19 were observed after VPM1002 vaccination. Local reactions typical for BCG were observed in the VPM1002-vaccinated group, which were mostly of mild intensity.

Conclusions. Vaccination with VPM1002 is well tolerated and seems to have a prophylactic effect against severe respiratory disease in the elderly.

Clinical Trials Registration. NCT04435379.

Keywords. VPM1002; respiratory tract infections; COVID-19; SARS-CoV-2; trained immunity.

Elderly people have an increased risk to develop severe respiratory tract infections (RTIs) [1]. During the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic, elderly people are a major risk group for developing severe coronavirus disease 2019 (COVID-19) [2]. At the beginning of the pandemic, no specific intervention measures were available, emphasizing the need for innovative prophylactic approaches [3].

Bacille Calmette-Guérin (BCG) vaccine has been in use as tuberculosis (TB) vaccine since 1921 and is one of the most widely used vaccines with >4 billion doses administered worldwide [4–6]. Apart from protection against TB, the BCG vaccine also induces partial protection against other pathogens, reduces all-cause mortality [7–9], and ameliorates other conditions including diabetes and bladder cancer [10–12]. These effects are mediated via long-lasting changes of the innate immune system, a mechanism known as trained immunity [7].

These beneficial heterologous effects of BCG vaccination have been suggested to induce partial protection against the susceptibility to and/or severity of RTIs, including SARS-CoV-2 [3, 13, 14]. Furthermore, a recent study modeling the effects of heterologous vaccine interventions, such as BCG, during the COVID-19 pandemic, reported that even a modest effectiveness of 5%–15% could already relevantly reduce

Received 25 July 2022; editorial decision 07 November 2022; published online 11 November 2022

[a]A. M. B. and S. B. contributed equally to this work.

Correspondence: S. Brückner, Vakzine Projekt Management GmbH, Mellendorfer Strasse 9, Hannover D-30625, Germany (brueckner@vakzine-manager.de).

Clinical Infectious Diseases® 2023;76(7):1304–10

https://doi.org/10.1093/cid/ciac881

COVID-19 cases, hospitalizations, and mortality, and possibly reduce the burden of future pandemics [15].

VPM1002 is a genetically modified BCG vaccine derived from the BCG Prague strain named rBCGΔ*ureC:hly*. VPM1002 was generated by replacing the urease C-encoding gene with the listeriolysin-encoding gene from *Listeria monocytogenes* to improve the immunogenicity and safety profile. The modifications in VPM1002 enhance mycobacterial antigen translocation from the phagosome to the cytoplasm, thereby promoting efficient presentation to $CD8^+$ T cells and cross-priming of $CD4^+$ T cells. Preclinical and clinical studies have shown that VPM1002 is safer and at least equally immunogenic as existing BCG vaccines [16–20].

We hypothesized that VPM1002 induces trained immunity and protects against nonmycobacterial RTIs. The present phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated the potential beneficial effect of VPM1002 vaccination in reducing the number of days with RTIs, including COVID-19, in the elderly.

METHODS

Study Design and Participants

This phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted to investigate the efficacy and safety of VPM1002 in reducing hospital admissions and/or severe RTIs in the elderly during the SARS-CoV-2 pandemic. The study was conducted at 12 study sites in Germany and the study design was aligned to that of a parallel study conducted in the Netherlands using BCG vaccination [21]. Eligible participants were adults (age ≥60 years) who were contractually capable, able to understand study information, and had access to an internet-enabled electronic device. Key exclusion criteria included a known active or latent *Mycobacterium tuberculosis* infection or other viral/bacterial infections, fever, hypersensitivity or allergy to components of the study intervention or BCG, a history of malignancies, a positive SARS-CoV-2 test result, and a severely compromised immune system.

The clinical trial was performed according to regulatory requirements and after review and approval by independent ethics committees and the national regulatory authority. All participants provided written informed consent before undergoing any study-related activities. The study protocol is available in Supplementary Appendix 2.

Randomization and Masking

Eligible participants were randomized (1:1) to receive either VPM1002 ($2–8 \times 10^5$ colony-forming units) or placebo (saline solution) intradermally. The randomization was done in blocks using a block size of 4 and stratified by site and sex using an interactive web response system. The study participants and the study personnel responsible for the evaluation of any study endpoint were masked to treatment group assignment. The investigational medicinal product was prepared by designated unblinded personnel not involved in further study procedures, and the syringes were masked with a translucent wrapping before administration to maintain the blinding.

Trial Procedures

The study was conducted starting in 18 June 2020 during a phase of the SARS-CoV-2 pandemic with strict statutory hygienic measures and hence reduced overall RTI rates, including COVID-19 (Supplementary Figure 1) [22]. SARS-CoV-2–specific vaccinations were rolled out for people at risk starting in December 2020 (Supplementary Figure 2). Due to regulatory obligations during the pandemic, only 1 clinic visit was performed and personal contact reduced to a minimum. Participants were followed up remotely for 240 days using the web application of the electronic clinical outcome assessment system ViedocMe (version 4.69) and monthly telephone contacts with the site. Participants and caregivers were appropriately trained on the use of the web application and were informed regarding the questionnaires and the timelines for their completion. The questionnaires were designed to collect data regarding hospitalization, adverse events (AEs) and serious adverse events (SAEs), intensive care unit (ICU) admissions, and other secondary endpoints. In case the follow-up information had not been completed weekly, participants were reminded within the web application.

Outcomes

The primary outcome of the study was the mean number of days with severe RTI at hospital and/or at home reported by either the participants or the investigator. For self-reporting, severe RTI was defined as "bedridden due to an RTI." The assessment by investigators complied with the Common Terminology Criteria for Adverse Events [23], where a "severe" course is defined as limitation of self-care activities of daily living. Secondary outcomes are defined in the study protocol (Supplementary Appendix 2) and included the incidence of self-reported fever, hospital, and ICU admissions. Treatment-emergent adverse events (TEAEs), serious TEAEs, related TEAEs, and the severity of TEAEs were assessed as safety variables. All self-reported events were captured by ViedocMe (version 4.69).

Statistical Analysis

Detailed information on the statistical analysis is included in the Supplementary Appendix. In brief, the primary efficacy endpoint, number of days with a severe RTI at the hospital and/or at home, was analyzed using a negative binomial regression widely used for count data. In addition, the primary endpoint was analyzed post hoc using a zero-inflated negative binomial model (data not shown).

To detect potential sex-specific differences in treatment, a mixed model including an interaction term between sex and treatment (treat*sex) was explored. Additional prespecified analyses were conducted for the primary endpoint including a complete case analysis, a subgroup analysis of participants not receiving a specific COVID-19 vaccination until the last diary entry, a subgroup analysis of participants receiving a specific COVID-19 vaccination before the last diary entry, and an analysis with data censored at the timepoint of specific COVID-19 vaccination. Adjustments for multiple testing of these sensitivity analyses were not performed.

Similar negative binomial regression models were used to analyze the secondary efficacy endpoints of number of days with self-reported fever and acute respiratory symptoms. For secondary efficacy endpoints such as hospital admissions, documented SARS-CoV-2 infections, or self-reported acute respiratory symptoms, the cumulative incidences were calculated by treatment group using the life table method with exposure time intervals of 30 days. Cochran-Mantel-Haenszel tests stratified by study site and sex were used throughout to analyze the event frequency of the secondary endpoints and to provide common odds ratios (ORs). For this purpose, events were counted when reported once in the by-week information. Descriptive statistical analysis was conducted on safety variables.

RESULTS

Between 18 June 2020 and 26 January 2021, a total of 2064 participants were enrolled in the study, randomized (n = 2037) to vaccination either with VPM1002 (n = 1013) or placebo (n = 1012), and included in the as-treated population, that is, full and safety analysis sets. Twelve participants were not treated because they either withdrew consent (n = 3) or became ineligible prior to dosing (n = 9). A total of 24 participants in the VPM1002 group and 15 in the placebo group discontinued the study prematurely (Figure 1). The treatment groups were generally well balanced with respect to baseline demographics and other baseline characteristics (Table 1, Supplementary Tables 1 and 2). The median age of the study population was 66 years with an overall range of 60–91 years (Table 1). A total of 953 (47.1%) participants were women and 1072 (52.9%) were men. A specific COVID-19 vaccination was administered to 667 (66%) participants in the VPM1002 group and 680 (67%) participants in the placebo group (Table 2).

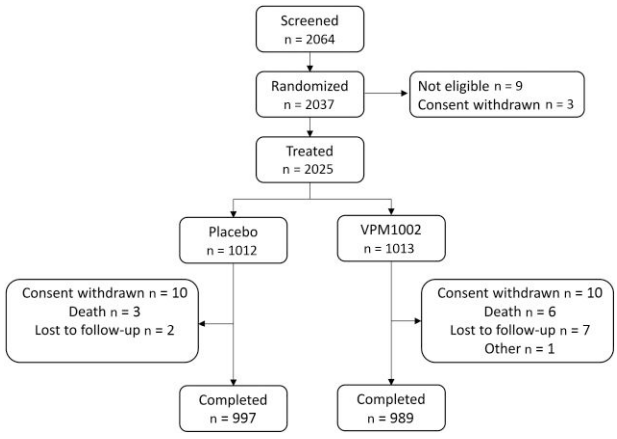

Figure 1. Trial enrollment. Consolidated Standards of Reporting Trials (CONSORT) flow chart of trial enrollment.

In the VPM1002 group, 31 participants reported at least 1 day with a severe RTI with a mean duration of severe disease of 9.39 ± 9.28 days, compared to 38 participants in the placebo group with a mean duration of 14.29 ± 16.25 days. For all participants, the mean number of days with severe RTI was 0.29 ± 2.28 days in the VPM1002 group and 0.54 ± 4.13 days in the placebo group. This resulted in a rate ratio of 0.60 (95.2% confidence interval [CI], .20–1.77; $P = .350$) (Figure 2*A*, Table 2). Although the rate ratio did not reach statistical significance, the mean and the total number of days with severe RTI were numerically nearly halved in the VPM1002 group compared to the placebo group (0.29 and 291 days versus 0.54 and 543 days, respectively). In participants who did not additionally receive a SARS-CoV-2–specific vaccination, the effect of VPM1002 was considerably more pronounced, with 11 participants in the VPM1002 group reporting at least 1 day with severe disease and a mean disease duration of 7.27 ± 4.96 days compared to 19 participants in the placebo group and a mean duration of 18.95 ± 19.72 days. In this subgroup, the mean number of days was 0.23 ± 1.54 and 1.09 ± 6.40, resulting in a rate ratio of 0.12 (95.2% CI, .01–1.34; $P = .08$) (Table 2).

For all participants, there was only a minor difference between the cumulative incidence of severe RTIs at hospital and/or home between the active group (0.032) and placebo group (0.039). This was more pronounced in participants not receiving a COVID-19 vaccination (0.035 and 0.061) (Figure 2*B*, Table 3). This finding is reflected by the stratified analysis leading to an overall OR of 0.81 (95% CI, .50–1.32; $P = .397$) for all participants and 0.51 (95% CI, .23–1.08; $P = .074$) for participants not vaccinated for COVID-19 (Supplementary Table 3).

The proportion of participants with self-reported fever was significantly lower in the VPM1002 group compared to the placebo group (2.5% vs 5.3%; OR, 0.46 [95% CI, .28–.74]; $P = .001$) and likewise the mean number of days with fever was significantly lower in the VPM1002 group compared to the placebo group (0.05 vs 0.14 days; rate ratio, 0.31 [95% CI, .16–.63]; $P = .001$). The subgroup of participants who reported at least 1 day with fever (25 participants in the VPM1002 group vs 53 participants in the placebo group) reported a mean number of 1.88 ± 0.97 days with fever in the VPM1002 group and a mean of 2.75 ± 3.18 days in the placebo group (Supplementary

Table 1. Participant Demographics—Safety Analysis Set (N = 2025)

Characteristic	Placebo (n = 1012)	VPM1002 (n = 1013)	Total (N = 2025)
Sex, No. (%)			
Male	534 (52.8)	538 (53.1)	1072 (52.9)
Female	478 (47.2)	475 (46.9)	953 (47.1)
Age, y			
Mean (SD)	67.5 (5.5)	67.2 (5.5)	67.3 (5.5)
Median (range)	67.0 (60–88)	66.0 (60–91)	66.0 (60–91)
Weight, kg			
Mean (SD)	83.97 (18.26)	83.74 (18.04)	83.86 (18.15)
Median (range)	82.60 (44.5–158.2)	82.00 (36.5–160.8)	82.40 (36.5–160.8)
Height, cm			
Mean (SD)	171.3 (9.5)	171.1 (9.2)	171.2 (9.3)
Median (range)	170.5 (140–205)	171.0 (140–202)	171.0 (140–205)

Abbreviation: SD, standard deviation.

Table 2. Number of Days With Severe Respiratory Disease at Hospital and/or Home and Sensitivity Analyses—Full Analysis Set (N = 2025)

	Placebo (n = 1012)			VPM1002 (n = 1013)				
Population	No.	Mean	(SD)	No.	Mean	(SD)	Rate Ratio (95.2% CI)	*P* Value
All participants	1009	0.54	(4.13)	1008	0.29	(2.28)	0.60 (.20–1.77)	.35
Participants with No. of days >0	38	14.29	(16.25)	31	9.39	(9.28)	NC	NC
Sensitivity analysis								
Participants not receiving a COVID-19 vaccination	329	1.09	(6.40)	341	0.23	(1.54)	0.12 (.01–1.34)	.08
Participants with No. of days >0	19	18.95	(19.72)	11	7.27	(4.96)	NC	NC
Participants receiving a COVID-19 vaccination	680	0.27	(2.32)	667	0.32	(1.96)	1.12 (.23–5.44)	.89
Participants with No. of days >0	19	9.63	(10.38)	20	10.55	(10.90)	NC	NC

No. indicates number of participants analyzed.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NC, not calculated; SD, standard deviation.

Table 4). No statistically significant differences were observed for the remaining secondary endpoints. However, the data showed consistent trends toward a favorable effect of VPM1002 vaccination compared to placebo for hospital (0.2% VPM1002 vs 0.8% placebo; OR, 0.25 [95% CI, .05–1.16]; P = .05) and ICU admissions (0.1% VPM1002 vs 0.5% placebo; OR, 0.20 [95% CI, .02–1.70]; P = .1) due to documented SARS-CoV-2 infection (Table 3).

Overall, the incidence of AEs was higher in the VPM1002 group (744 of 1013 participants [73.4%]) than in the placebo group (543 of 1012 participants [53.7%]), predominantly due to an expected increased number of almost exclusively mild injection site reactions, the most frequent being erythema (367 of 1013 participants [36.2%] in the VPM1002 group vs 8 of 1012 participants [0.8%] in the placebo group) and swelling (209 of 1013 participants [20.6%] in the VPM1002 group vs 4 of 1012 [0.4%] participants in the placebo group) (Table 4, Supplementary Tables 5 and 6). Reported SAEs were more frequent in the placebo group (94 of 1012 participants [9.3%]) than in the VPM1002 group (79 of 1013 participants [7.8%]) (Supplementary Table 7). Six participants in the VPM1002 group died during study follow-up, compared with 3 participants in the placebo group. All deaths had a natural cause and occurred due to diseases unrelated to vaccination (Supplementary Table 8).

DISCUSSION

In the current study, we investigated the impact of VPM1002 vaccination on the incidence and duration of RTIs, including COVID-19, in the elderly. The mean number of days with severe RTI at hospital and/or at home was numerically less than 40% in the VPM1002 group compared to placebo (0.54 vs 0.29; 95% CI, .20–1.77), although the cumulative incidence did not reach statistical significance. Furthermore, within the subgroup of participants not receiving a specific COVID-19 vaccination, the difference was even more pronounced with 78% less mean number of days with severe RTIs in the VPM1002 group compared to placebo (1.09 vs 0.23; 95% CI, .01–1.34). Notably, almost 70% of participants received a specific COVID-19 vaccination during study conduct and the sample size of the subgroup analysis is limited (n = 341/1013 for VPM1002; n = 329/1012 for placebo). The incidence of

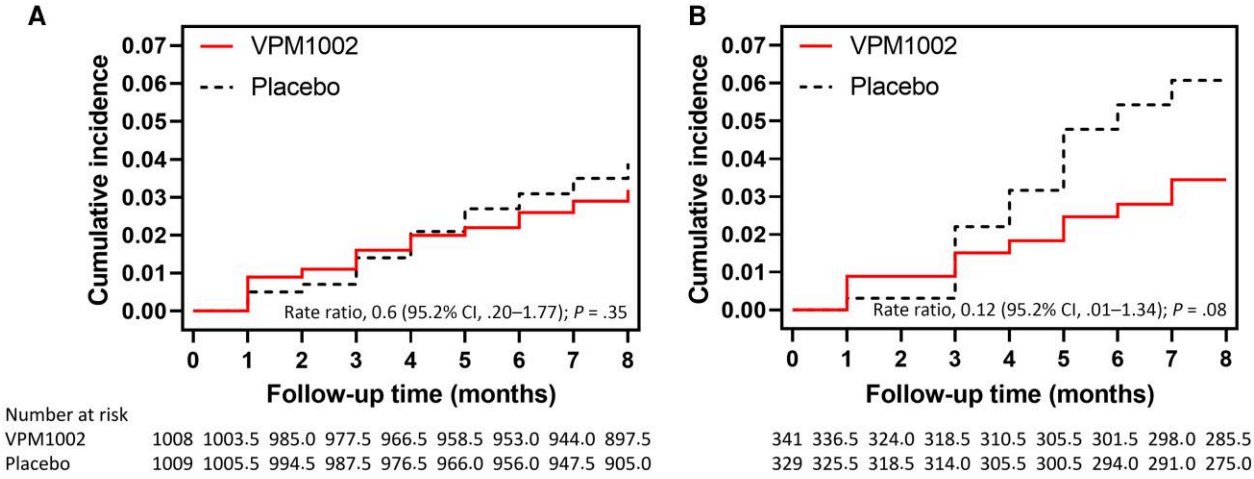

Figure 2. Cumulative incidence of days with severe respiratory disease at hospital and/or at home, calculated for all participants (VPM1002, n = 1013; placebo, n = 1012) (*A*) and for participants not receiving a specific coronavirus disease 2019 vaccination (VPM1002, n = 341; placebo, n = 329) (*B*) during the follow-up period of 8 months (240 days). Abbreviation: CI, confidence interval.

Table 3. Secondary Endpoints Assessed as Incidences During Follow-up—Full Analysis Set (N = 2025)

Event	Placebo (n = 1012)	VPM1002 (n = 1013)	OR (95% CI)	*P* Value
Severe respiratory disease at hospital and/or at home[a]	38 (3.8)	31 (3.1)	0.81 (.50–1.32)	.4
Cumulative incidence	0.0385	0.0315	…	
Self-reported fever[a]	53 (5.3)	25 (2.5)	0.46 (.28–.74)	.001
Cumulative incidence	0.0539	0.0257	…	
Self-reported acute respiratory symptoms	54 (5.4)	57 (5.7)	1.06 (.72–1.56)	.76
Cumulative incidence	0.0544	0.0581	…	
Hospital admission for any reason	116 (11.5)	106 (10.5)	0.90 (.68–1.19)	.47
Cumulative incidence	0.1173	0.1075	…	
Hospital admission due to documented SARS-CoV-2 infection	8 (0.8)	2 (0.2)	0.25 (.05–1.16)	.05
Cumulative incidence	0.0081	0.0020	…	
Documented SARS-CoV-2 infection	20 (2.0)	22 (2.2)	1.09 (.59–2.02)	.77
Cumulative incidence	0.0202	0.0226	…	
Death for any reason	3 (0.3)	6 (0.6)	2.01 (.50–8.12)	.32
Cumulative incidence	0.0030	0.0061	…	
Death due to documented SARS-CoV-2 infection	1 (0.1)	1 (0.1)	0.99 (.06–16.32)	1.0
Cumulative incidence	0.0010	0.0010	…	
ICU admission for any reason	14 (1.4)	10 (1.0)	0.71 (.32–1.60)	.41
Cumulative incidence	0.0142	0.0102	…	
ICU admission due to documented SARS-CoV-2 infection	5 (0.5)	1 (0.1)	0.20 (.02–1.70)	.1
Cumulative incidence	0.0051	0.0010	…	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Additional analyses not originally defined as endpoints.

self-reported fever was significantly lower in the VPM1002 group compared to placebo. No statistically significant treatment effect was observed for other secondary endpoints, but the data showed consistent trends toward a reduction of hospitalizations and ICU admissions due to COVID-19 in the VPM1002 group compared to placebo.

Due to social distancing and statutory hygienic measures, the incidence of RTIs was low during the study conduct. The study was conducted during the second and third wave of the COVID-19 pandemic in Germany, when overall low incidences of RTIs including SARS-CoV-2 and influenza were reported [22, 24]. Furthermore, from December 2021 on, COVID-19–specific vaccines were rolled out, especially for elderly individuals, the population of interest for this study. Thus, a relatively low number of 22 participants in the VPM1002 group and 20 participants in the placebo group tested positive for

Table 4. Overview of Adverse Events—Safety Analysis Set (N = 2025)

	Placebo (n = 1012)			VPM1002 (n = 1013)		
Adverse Event	No. of Events	No. of Participants With Event	(%)	No. of Events	No. of Participants With Event	(%)
Any AE	1928	543	(53.7)	3030	744	(73.4)
Any TEAE	1926	543	(53.7)	3027	744	(73.4)
Any serious TEAE	128	94	(9.3)	108	79	(7.8)
Any related TEAE	136	90	(8.9)	1320	529	(52.2)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

SARS-CoV-2 in this study, which potentially limited the manifestation of beneficial effects of VPM1002. The protective impact of VPM1002 might be more pronounced when studying larger cohorts as well as populations with less developed medical facilities or increased infectious pressure. Furthermore, self-reporting of clinical events harbors the risk of recall bias. Although all participants and caregivers were trained in and reminded by the web application to collect their clinical data, which was then checked by qualified medical site staff for consistency, integrity could not be verified. Ideally, clinical monitoring would have been consistently performed by clinicians, which had not been possible due to COVID-19–related restrictions at the time of the study.

Various experimental studies analyzing the effect of BCG vaccination on the incidence and severity of RTIs were conducted worldwide, prior to, and during the COVID-19 pandemic. Whereas some studies assume a protective effect of BCG on RTIs, other studies could not demonstrate incidence reduction after BCG vaccination [9, 21, 25–29]. A recent clinical trial by Moorlag et al with a comparable study design did not observe an effect of BCG vaccination on the overall incidence of RTIs or SARS-CoV-2 infections in the elderly population [21], which is in line with the absence of an effect of VPM1002 on the total number of COVID-19 cases in our study. Discrepancies among the published studies were attributed to factors such as differences in vaccine doses and vaccination regimens, BCG strains, and genetic backgrounds of the study populations, as well as differences in the epidemiology of RTIs during lockdowns that were implemented during the pandemic [21].

Restimulation of peripheral blood mononuclear cells (PBMCs) from BCG-vaccinated individuals with either influenza A (IAV) or SARS-CoV-2 strains revealed enhanced cytokine production capacity, especially after IAV restimulation [21]. This is in line with previously published data in a mouse model, suspecting potentially stronger protection of BCG vaccination from IAV than SARS-CoV-2. This effect was attributed to the pulmonary vasculature damage induced by SARS-CoV-2 infection, which may allow the dissemination of the virus to the bone marrow, thereby preventing the ability of BCG to generate trained immunity [30]. VPM1002 vaccination is reported to result in increased multifunctional $CD4^+$ and $CD8^+$ cells comparable to BCG vaccination, accompanied by an increase in $CD8^+IL17^+$ cells [18, 19]. $CD8^+IL17^+$ cells are associated with vaccine-mediated protection in conditions such as influenza and human immunodeficiency virus (HIV) infection and have been detected in patients with active TB disease. This cell population is induced in response to inflammatory stimuli, particularly an interleukin 6 (IL-6)–rich environment. IL-6 has been associated with the beneficial effects of BCG on viral infections and plays a role in BCG-mediated humoral responses [18, 21]. Due to the pandemic situation, regulatory authorities requested to reduce the number of site visits to a minimum; thus, this study only included 1 on-site visit for the participants. Blood drawings to conduct restimulation analysis of PBMCs were therefore not possible and should be considered in future studies.

Whereas in some studies participants are revaccinated with BCG after initial vaccination in childhood [27, 31], others assess the effect of primary BCG vaccination [21]. In our study, we presume that most participants, being aged ≥60 years, had received a BCG vaccination in childhood.

Recent studies indicate that BCG may have an adjuvant effect to enhance heterologous adaptive immune responses induced by COVID-19 vaccines [32, 33]. This is in line with the observation that higher immunoglobulin G antibody titers were observed in BCG-vaccinated participants diagnosed with COVID-19 compared to those in the placebo group, suggesting that BCG may enhance the host's immune response against infection, thereby improving the duration of protection in older individuals [21]. Due to the restriction of participants' site visits, this was not evaluated in the present study.

VPM1002 was found to be safe for administration in the elderly. Generally mild to moderate local reactions at the injection site, mostly erythema and swelling, were reported. These findings are consistent with data from studies conducted in healthy volunteers as well as newborn infants including HIV-exposed infants [17–19].

In conclusion, the data presented here demonstrate that VPM1002 vaccination of individuals of older age is well tolerated and potentially protective against a broad spectrum of RTIs. Further studies are needed to investigate the effect of

VPM1002 on the severity of RTIs during a higher disease burden and its molecular mechanism.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the Serum Institute of India Pvt Ltd. S. H. E. K. reports support for this work from IMI JU BioVacSafe. L. G., A. M. B., S. B., M. M., and G. P. P. report employment with VPM, the sponsor of the trial (regular monthly payment according to the work contract without dependence to this specific study). M. G. N. was supported by a European Research Council Advanced Grant (number 833247) and a Spinoza Grant of the Netherlands Organization for Scientific Research.

Potential conflicts of interest. H. S. and U. S. are employed by SIIPL, which manufactures VPM1002. L. G., A. M. B., S. B., M. M., and G. P. P. are employed by VPM, which developed the vaccine. S. H. E. K. and L. G. are coinventors and named patent holders for VPM1002, which is licensed to Vakzine Projekt Management, Hannover, Germany, and sublicensed to Serum Institute of India Pvt Ltd. S. H. E. K. is also coholder of a patent licensed to Serum Institute of India Pvt Ltd; reports consulting fees (honorarium) from Memo Therapeutics AG, Switzerland, LTS Lohmann Therapie-Systeme AG, Germany, kENUP Foundation, Malta, and TUI AG, Germany; honorarium from IPSEN for speaker activities (information event for IPSEN employees) and from Gilead for speaker activity; and a role as Chair of Board for Schering Foundation. S. B. reports royalties or licenses related to a patent planned issued or pending (TB vaccine VPM1002) as an employee of VPM, the patent holder. M. G. N. is a scientific founder of TTxD and Lemba. M. G. N. also reports unrestricted research grants from GSK, ViiV Healthcare, Ono Pharma, and TTxD, all awarded to institution; patents for nanobiologics inducing or inhibiting trained immunity; participation on a scientific advisory board for TTxD; and stock in TTxD. G. P. P. reports royalties or licences and patents planned, issued, or pending for TB vaccine VPM1002, as an employee of VPM, the patent holder. H. S. reports license held by Serum Institute of India Pvt Ltd. L. G. reports royalties or licences and patents planned, issued, or pending related to employment with VPM, the patent holder of TB vaccine VPM1002. C. S. reports participation in the blinded part of the data and safety monitoring board as principal investigator of the present trial (no advisory board).

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.

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