Vaccination programs are essential for solving the SARS-COV2 pandemic
Unmasking misinformation

Willemstad, April 27 2021

Dear Dr. Vanden Bossche

Below please find our response to your letter dated April 19 2021.

We received your comments on the informative video we made (https://youtu.be/lzb3IOkJJfY). We deemed our video necessary as your personal opinion expressed on YouTube was causing unnecessary hesitancy in locals for participating in the vaccination program on our islands as well as creating unwarranted confusion among medical professionals in the Dutch Caribbean.
First of all it should be made clear that we adhere strictly to our scientific code of conduct based on rigor, respect (of each individual person) and responsibility (1). To this end, argumentation on issues should be based on sound data published in peer reviewed journals, not baseless opinion. Pursuing the truth is more than creating knowledge as it also entails fighting untruths in an ethical way (2). There should be no room for denigrating or condescending remarks and it would fit you well to adhere to this code and avoid future diatribe.

1. A code of ethics for scientists. Pang CL. Lancet. 2007 Mar 31; 369(9567): 1068.
2. A code of ethics to get scientists talking. Nature. 2018 Mar 1; 555(7694): 5., WEF Code of ethics 2018

Several arguments you brought forward in defense of you advocating natural infection as the only effective approach for a pandemic, and insisting on vaccination and public health interventions being high-risk procedures during a pandemic with grave effects, can certainly not be supported by scientific data (neither public health, immunological nor virological). The same holds true for several unjust fundamental immunological and virological mechanisms you describe in your comments.

From the start it should be clear that in an immune response both innate and adaptive pathways are intricately involved in a fine tuned and highly integrated system that, over the course of humankind, has proven itself to be extremely successful. Stratifying immune functions has its explanatory benefits but its effectivity is better understood in the cooperative functionality of different cells.

Public Health measures and vaccination are essential for curbing pandemics
Public health data and a myriad of scientific publications have unequivocally proven that vaccination is a fundamental step for eliminating viral threats during pandemics and for preventing ongoing viral mutation and immune escape variants (3,4). Pursuing herd immunity as you propose through infection should be rejected in view of the related high mortality and morbidity. The futility of such an approach in the SARS-CoV2 pandemic has for instance painfully been shown in the unmitigated outbreak in Manaus, Brazil (5) and the current disastrous COVID-19 outbreak in India. Furthermore recent reports have also shown substantial burden of health loss for COVID-19 survivors of up to 6 months after initial infection (6). Clearly, aquiring herd immunity by infection is not an option.
Achieving protective immunity through vaccination has proven safe and very effective (3,4). Also recent results of the SARS-CoV2 vaccination program in Israel using mRNA vaccines show an impressive reduction in SARS-CoV2 related mortality and

morbidity and further accentuate the necessity of combining Public Health Measures with effective vaccines in addressing the SARS-CoV2 pandemic (7,8).
The importance of combining both approaches for achieving protection and saving lives is further accentuated in the current dire public health situations faced in Sweden that is in stark contrast to its neighboring countries of Denmark, Norway and Finland (9). This as Sweden chose to minimally implement public health measures and let natural infection run its course (an approach you propose).
As a Caribbean island with direct Latin American connections we are certainly aware of the discrepancy of the ongoing SARS-CoV2 outbreak in Chile in spite of achieving a relatively high population vaccination percentage. Probable scientific explanations provided for these observations by Chilean scientist themselves include low adherence to public health measures (10) and primarily use of the less effective inactivated virus Coronavac SARS-CoV2 vaccine for their vaccination program. Studies performed by the University of Chile and the Chilean Department of Health show only 3% and 16% vaccine effectivity after priming and 54 and 67% respectively after a booster shot for documented infectivity (11,12). These results are much poorer than the ones observed in vaccine programs making use of the BNT162b2 mRNA vaccine (46% and 92% respectively)(13).

3. A guide to vaccinology: from basic principles to new developments.
Pollard AJ, Bijker EM.Nat Rev Immunol. 2021 Feb; 21(2): 83-100.
4. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Li X, Mukandavire C, Cucunubá ZM et al. Vaccine Impact Modelling Consortium.Lancet. 2021 Jan 30; 397(10272):398-408.
5. Three-quarters attack rate of SARS-CoV-2 in the Brazilian **Amazon** during a largely unmitigated epidemic. Buss LF, Prete CA Jr, Abrahim CMM et al. .Science. 2021 Jan 15; 371(6526): 288-292.
6. High-dimensional characterization of post-acute sequalae of COVID-19.
Al-Aly Z, Xie Y, Bowe B.Nature. 2021 Apr 22. doi: 10.1038/s41586-021-03553-9. Online ahead of print.
7. Signals of hope: gauging the impact of a rapid national vaccination campaign.
Shilo S, Rossman H, Segal E.Nat Rev Immunol. 2021 Apr; 21(4): 198-199.
8. COVID-19 dynamics after a national immunization program in Israel.
Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E.Nat Med. 2021 Apr 19. doi: 10.1038/s41591-021-01337-2. Online ahead of print.
9. The Swedish COVID-19 strategy revisited. Claeson M, Hanson S.Lancet. 2021 Apr 19:S0140-6736 (21) 00885-0.
10. Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile G. E. Mena *et al.*, *Science* 10.1126/science.abg5298 (2021).
11. Vacunas contra el SARS-CoV2 muestran 56,5 por ciento de efectividad en la prevención de contagios - Universidad de Chile, Martes 6 de abril 2021.
https://www.uchile.cl/noticias/174186/resultados-primer-estudio-de-efectividad-de-las-vacunas-en-chile
12. Ministerio de salud. Gobierno de Chile. 16 de abril 2021.
https://www.minsal.cl/wp-content/uploads/2021/04/20210416_ESTUDIO-EFECTIVIDAD-CORONAVAC.pdf
13. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting.
Dagan N, Barda N, Kepten E. et al. N Engl J Med. 2021 Apr 15;384(15):1412-1423.

Avoiding viral mutation and vaccine resistance by allowing natural infection
According to your opinion asymptomatic infected persons with suboptimal antibody titers are selected by stringent public health interventions facilitating viral mutation and vaccine resistance. You also state that "a natural pandemic of an acute viral

infection does not generate variants". As already mentioned, the published Manaus data clearly demonstrate the opposite to be true (5, 14). Mutations have arisen causing variants of concern (P.1) with increased transmissibility, higher morbidity and mortality in a population lacking implementation of public health measures and effective vaccination programs. To put this more clearly, most current detected variants have arisen prior to vaccination initiation.

14. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Faria NR, Mellan TA, Whittaker C. et al. Science. 2021 Apr 14:eabh2644. doi: 10.1126/science.abh2644. Online ahead of print.

An effective immune response

It should be clear that for an effective immune response both humoral (e.g. antibodies) and cellular (innate cells, T-cells and B-cells) pathways are of importance. Antibodies primarily protect against cells becoming infected by blocking viral entry whereas innate cells and T-cells are responsible for effective virus containment and removal after cellular infection (effectively preventing clinical complications; as correctly mentioned in our informative video at 14:56!). (15)

In contrary to your stated opinion, several recent publications show asymptomatic SARS-CoV-2–infected individuals to have strong antiviral immunity characterized by a highly functional virus-specific cellular immune response and stable antibody neutralization titers regardless of infection symptomatology (16,17). It is also consistent with the hypothesis that there may be ongoing affinity maturation in response to residual antigen after viral clearance, leading to improved quality of the antibody over time (17). Such a general antiviral mechanism is known to be important for protection against re-infection through the generation of long-lived antibody secreting plasma cells and memory B cells that can be quickly reactivated to secrete potent neutralizing antibodies. B cells undergo a process of somatic hypermutation (SHM) to generate the best virus-binding Abs. (18) (as mentioned in our informative video a powerful and effective way our immune system adapts and obtains more capability to address current and future mutated viruses). This fundamentally known process has now also been extensively described as occurring in natural SARS-CoV2 infections (19,20). Even small changes in SHM may be biologically relevant, as somatically mutated clones can exhibit higher degrees of cross-protection against different mutant strains of the virus (20). We would suggest for you to familiarize yourself with this mechanism for a better understanding of the viral-immune interaction.

15. Adaptive immunity to SARS-CoV-2 and COVID-19.
Sette A, Crotty S.Cell. 2021 Feb 18; 184(4): 861-880.
16. Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection Nina Le Bert, Hannah E. Clapham, Anthony T. Tan. Et al. J. Exp. Med. 2021 Vol. 218 No. 5 e20202617
17.Down but far from out: The durability of SARS-CoV-2 immunity after asymptomatic infection. Kedl RM.J Exp Med. 2021 May 3; 218(5): e20210359. doi: 10.1084/jem.20210359.
18. Dual Nature of Type I Interferons in SARS-CoV-2-Induced Inflammation.
King C, Sprent J.Trends Immunol. 2021 Apr; 42(4): 312-322.
19. Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination.
Goel RR, Apostolidis SA, Painter MM, et al. Sci Immunol. 2021 Apr 15; 6(58): eabi6950. doi: 10.1126/sciimmunol.abi6950.
20. Evolution of antibody immunity to SARS-CoV-2.

Gaebler C, Wang Z, Lorenzi JCC, et al. Nature. 2021 Mar; 591(7851): 639-644.

Effectivity mRNA vaccines

From a practical perspective, several studies have shown the effectivity of mRNA vaccines for several mutated strains. This is based on the presence of neutralizing antibodies, memory B cells and T cell activity. This is again contradictory to your opinion that vaccine-induced responses are antigen-specific and hence, not properly recognizing mutated S protein, "especially not when originating from highly infectious variants". Both mRNA vaccines (Pfizer, Moderna) generate significant neutralizing antibody titers, B cell memory and virus-specific T cell responses (19, 21).
To further elaborate on the mechanism, vaccines require a pathogen-specific immunogen as well as an adjuvant —the latter stimulates the innate immune system and provides the necessary second signal for T cell activation.
An optimal adjuvant stimulates innate immunity without inducing systemic inflammation that could elicit severe side effects (hence simulating infection without systemic inflammation; a possible culprit for natural infection sequalae). For mRNA vaccines, the mRNA can serve as both immunogen (encoding the viral protein) and adjuvant, owing to intrinsic immunostimulatory properties of RNA (21).

21. COVID-19 vaccines: modes of immune activation and future challenges.
Teijaro JR, Farber DL.Nat Rev Immunol. 2021 Apr; 21(4): 195-197.

Next you vehemently present as a fact that there can be no pressure on the virus after natural infection, as "the protection is not provided by adaptive immunity but solely by natural immunity. Being non-specific, it cannot put selective immune pressure on the virus!" This opinion stands corrected by several studies demonstrating an important role for adaptive immunity in natural infection and vaccine generated protection. Saine et al. (22) show COVID-19 disease to drive substantial T cell activation, with T cell recognition of a large number of SARS-CoV-2-derived peptides. Of interest is the observation by the authors that considerable T cell recognition of such peptides exists in healthy donors, arguing for cross-recognition, potentially from T cells raised against other coronaviruses (considered by you as "nonsense" (sic)), likely influencing immune response to SARS-CoV2. Regarding B cells, convincing published data present an important role in natural infection. Ogega et al (23) show most SARS-CoV-2-infected individuals to develop S-RBD–specific, class-switched resting memory B cells that resemble germinal center–derived B cells induced by effective vaccination against other pathogens, providing evidence for durable B cell–mediated immunity (antibodies and memory B cells) against SARS-CoV-2 after mild or even severe disease (19).

Continuing on the topic of T cells in SARS-CoV2 infection, you are mistaken again for referring as a fact that "vaccines do not induce cytotoxic T cells". Several studies clearly show mRNA vaccines to induce virus-specific helper T cells and cytotoxic T cells, both of which might be involved in protection against challenge. (22,24)

22. SARS-CoV-2 genome-wide T cell epitope mapping reveals immunodominance and substantial $CD8^+$ T cell activation in COVID-19 patients. Saini SK, Hersby DS, Tamhane T, et al. .Sci Immunol. 2021 Apr 14; 6(58): eabf7550. doi: 10.1126/sciimmunol.abf7550.
23. Durable SARS-CoV-2 B cell immunity after mild or severe disease.
Ogega CO, Skinner NE, Blair PW, et al. J Clin Invest. 2021 Apr 1; 131(7): e145516. doi: 10.1172/JCI145516.
24. SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants.

Moore JP, Offit PA.JAMA. 2021 Mar 2; 325(9): 821-822.

Finally on the topic of anti-S antibodies, one should consider the breadth of polyclonal antibody response against specific epitopes of the Spike protein. A mutation in the RBD does not imply that all polyclonal blocking/neutralizing antibodies directed against that specific epitope become ineffective. mRNA vaccines, in particular, induce such a strong neutralizing antibody response that there seems to be enough “spare capacity “to deal with reductions in the sensitivity of the variant viruses to neutralizing antibodies" (24). This is in stark contrast to your simplified representation of polyclonal antibody failure to effectively block viral activity. Your one-dimensional perspective on infection induced antibody response is only applicable when considering use of monoclonal antibodies for passive immunization and treatment of early COVID-19, which is not the addressed topic (25,26).

25. Neutralizing monoclonal antibodies for treatment of COVID-19.
Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL.Nat Rev Immunol. 2021 Apr 19:1-12.
26. FDA NEWS RELEASE 16-04-2021
Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab

As of today we have reached a grim milestone worldwide of more than 3 million direct COVID-19 deaths and the pandemic has set us back in many ways within healthcare and has resulted in devastating effects on the socio-economical level. Countries like India in which neither public health measures, nor vaccination, are adequately implemented are facing the catastrophic brunt of 'the virus running its course’ Furthermore it is becoming increasingly clear that post initial SARS-CoV2 infection long term sequelae will have high morbidity impact on a sizable group of persons (6) further increasing the necessity for vaccinations in preventing natural infections.

Conclusion

The internet and social media have changed the world as we know it. In their strength, they are now also a platform easily used for spreading misinformation sometimes with disastrous consequences.

Using social media to reach millions with inaccurate unfounded personal opinion and thereby causing distractions and vaccination hesitancy, potentially contributing to unnecessary loss of life, is condemnable. To end the pandemic as soon as possible, we must collectively continue to rigorously focus on essential public health interventions and aggressive and effective vaccination programs. These are based on sound science supported by published data in peer reviewed journals from the fields of public health, immunology and virology. Not baseless misinformation.

We report no conflict of interest

Sincerely,

Prof. Dr. AJ Duits, PhD, Medical Immunologist

I Gerstenbluth, MD, MSc
Public Health Physician & Epidemiologist

Take home messages for laymen

Is vaccination the solution for successfully addressing a pandemic?

Yes. All scientific evidence shows that a vaccination program combined with stringent public health measures will end the SARS-CoV2 pandemic.
It is very important to make use of a vaccine proven to be effective and adhere to public health measures. This approach is supported by the WHO and by studies done by scientists of different renowned institutes like University of Oxford, Imperial College of London, London School of Hygiene and Tropical Medicine, University of Singapore, University of Hong Kong.

Is letting the virus spread through natural infection to successfully address the SARS-CoV2 pandemic advisable?

No. This should be firmly rejected given the disastrous consequences; overwhelming health care capacity, loss of life. This is currently seen in for example Brazil and India. Furthermore, it is now known that persons recovered from the initial disease episode of COVID-19 can suffer from debilitating symptoms that persist for months (post covid syndrome), without effective treatment. The economic consequences are dire.

What examples do exist of successful vaccination and public health programs for addressing the COVID-19 pandemic?

Several well-documented examples have been published on institutional, regional and country level. We mention two:

Israel
Israel was one of the first countries to introduce a vaccine program (using mRNA vaccine from Pfizer) combined with stringent public health measures in December 2020. They have documented and published their data. These show an impressive reduction of persons getting infected, sick and/or dying. As they have reached about 70% of their population vaccinated, the country is now finally starting to relax its measures and allowing its citizens a more normal way of life.
Data reported among others by Clalit Research Institute, Innovation Division, Clalit Health Services, Tel Aviv, the School of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Be'er Sheva, Weizmann Institute of Science, Rehovot, Israel.

Curaçao
On the Caribbean island of Curaçao an immense COVID-19 outbreak (at a certain point the highest new cases per 100.000 inhabitants in the world) was successfully halted by stringent public health measures and then showed rapid decline after implementation of an aggressive mass vaccination program (using mRNA vaccines by Pfizer and Moderna) after 2 weeks (reaching almost 50% of the population vaccinated with minimally 1 shot).
Data reported by the Epidemiology and Research Unit, Government of Curaçao.

What doe we know of countries that have chosen for an approach based on natural infection?

The results have been devastating with a high number of patients with COVID-19 related complications and deaths. The hospitals and medical staff have been under extreme pressure to help each and every patient and in several countries the system has been completely overwhelmed. This also results in people suffering from other health issues not getting needed access to care.

India
On 24/04/2021 India reported 349,691 new cases of Covid-19 during the coronavirus pandemic (with 2627 deaths) according to official reports. Hospitals don't have sufficient intensive care units, oxygen, ventilators and supplies. The country has struggled with implementing public health measures and setting up a mass vaccination program (based on Covaxin (an Indian vaccine (inactivated virus based) and Covidshield (Astra-Zeneca vaccine produced locally)). On 24/04/2021 only 8.5% of the population had been vaccinated with minimally 1 shot. The country has also been facing the emergence of a SARS-CoV2 variant that seems more infective (B1.617 is however still only present in a relative small proportion of cases).
Data from the Johns Hopkins institute, University of Oxford, University of California

Manaus, Brazil
The effects of the SARS-CoV2 pandemic in Manaus, Brazil (population 2 million) has been well documented. Despite achieving at first a high percentage of persons naturally infected in October 2020 (76%), with no effective public health measures implemented and no effective vaccination program, uncontrolled resurgence of COVID-19 was subsequently observed with dire consequences. These results show that aquiring herd immunity by infection is not an option.
Data reported among others by Departamento de Molestias Infecciosas e Parasitarias and Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo , Imperial College London

Sweden
Sweden also supported a natural infection program based on voluntary public actions. This has resulted in a much higher patient infectivity, burden of hospitals and deaths in comparison to neighboring countries. Our World in Data COVID-19 statistics, with 606 new infections per million per day, with its neighbors Denmark, Finland, and Norway reporting 115, 62, and 112 new infections per million per day, respectively (April 15, 2021).
Data reported by Results for Development, Washington, DC 20036, USA (MC); Spånga Transkulturella Läkarmottagning, Spånga, Sweden (SH)

Chile
The recent data presented by Chilean scientists and the government show escalating COVID-19 infections, medical complications and deaths while implementing a mass vaccination program reaching a high percentage of the population vaccinated (41%). One of several possible explanations is the lack of

effectivity of the mainly used vaccine for the program (Sinovac; inactivated virus based vaccine). The data from Chile show only 3% or 16% effectivity after the first shot (in comparison Pfizer mRNA shows 46% effectivity after the first shot in Israel).
Data reported among others by Universidad de Chile, Santiago, Chile, , Ministerio de Salud, Gobierno de Chile., Clalit Research Institute, Innovation Division, Clalit Health Services, Tel Aviv

Does a program based on vaccination lead to viral mutations whereas a program based on natural immunization does not?

Studies show that the emergence of viral mutations is related to unbridled virus reproduction in a community; the earlier we stop availability of hosts for the virus the less chance the virus has to mutate. Obviously a program based on natural infection would prolong the period of virus reproduction in a population and lead to mutations (as shown for example in Manaus). As a fact most known SARS-CoV2 viral mutations of growing concern were described before the start of massive vaccination programs.

Are mRNA vaccines effective and safe?

Several studies and data garnered on millions of persons vaccinated with mRNA vaccines have shown a high grade of protection against infection and or disease with no safety issues of concern.
Data provided among others by Centers for Disease Control, USA.

Does mRNA vaccination give a higher degree of protection than natural infection?

Studies have shown convincingly that vaccinated persons have a higher degree of protection based on higher levels of protective antibodies and protective cells (T and B cells).
Furthermore in Manaus a high degree of naturally infected persons (70%) did not provide sufficient protection for COVID-19 resurgence. Thus,....
Data provided among others by Cedars-Sinai Medical Center, Los Angeles, CA, USA., Icahn School of Medicine at Mount Sinai New York, NY