Viewpoint/Narrative Review
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# Pitfalls in Understanding and Handling of Covid-19 Vaccination ("Any Fool Can Know. The Point Is to Understand"[1])

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**Abstract**

The aim of this article is to critically review the managing of vaccination over the course of the present COVID-19 pandemic against the knowledge that had already been at hand and the scientific data that had yet to be learned. In the period before vaccines for COVID-19 became available, the startling similarity in epidemiologic behavior between COVID-19 and the Spanish flu could be observed. The development of vaccines against COVID-19 has evolved at an unprecedented speed resulting in highly immunogenic vaccines with incredible protective characteristics covering a relatively short follow-up time in clinical trials. The roll-out in the general population turned out to take significantly longer time than the duration of immunity conferred by a 2-dose vaccination schedule (about 3-4 months). Therefore, the SARS-CoV-2 was left with the opportunity for random mutations with each replication cycle, resulting in immune evasion, shortened incubation, shortened serial interval, and increased transmissibility. The short incubation period of COVID-19 requires a steady protective antibody titer to be maintained to avert infection, achieve herd immunity, and terminate the pandemic spread. The protective neutralization titer needed to avert symptomatic infection and infection altogether is about 3% and 20%, respectively, of the mean convalescent titer. The latter corresponds to an absolute titer of 1:10–1:30. The intensity and duration of protective vaccinal and hybrid humoral immunity are explored. From the present perspective, it was naive to believe that a 2-dose vaccination would suffice to counter COVID-19 primarily due to its short incubation and a roll-out that was not catching up with the waning protective vaccinal antibody levels. Besides, the spacing of doses and boosters with respect to previous infection or vaccination, and differences in natural immunity and vaccine-induced immunity (adenovirus-vectored and mRNA) are discussed. The issue of vaccination and multisystem inflammatory syndrome in children is briefly presented. Finally, ethical points are discussed as some vaccine production platforms and neutralization tests use human cell lines derived from aborted fetuses. **Conclusion** – If the COVID-19 vaccines had been licensed as 3-dose vaccines, with more generous spacing, e.g. 0-2-6 months, providing for quantitatively larger and temporally more durable humoral immunity, that would have enabled attaining a steadier herd immunity and probably a paradoxical earlier effect on stopping the transmission.

**Key Words:** COVID-19 ▪ Incubation Period ▪ Vaccine Schedule ▪ Duration of Immunity ▪ Multisystem Inflammatory Disease in Children.

## Introduction

The ribonucleic acid (RNA) sequencing of SARS-CoV-2 was completed on 5 Jan 2020 by Yong-Zhen Zhang at Fudan University, Shanghai, and immediately recognized as a novel coronavirus. On the same day it was reported to the Shanghai municipal authority and uploaded to the United States National Center for Biotechnology Information (NCBI). The work was published on 3 Feb 2020 in Nature (1).

The primary viral strain, later dubbed *Wuhan-Hu-1*, was used as a template to create the first mRNA and adenovirus-vectored vaccines by Pfizer,

[1] Words pronounced by Albert Einstein in the TV play "Doctor Einstein Before Lunch" by Ernest Kinoy, first aired on US NBC television on 20 May 1973. https://falschzitate.blogspot.com/2021/10/jeder-dummkopf-kann-es-wissen-der-punkt.html.

Moderna, AstraZeneca and Gamaleia Institute Moscow. The strain that was first identified in Europe carried a D614G mutation and was called B1 (2). The following text will cover the most important facts, observations and questions linked to the protective immunity against SARS-CoV-2 and its interplay with other factors influencing the COVID-19 pandemic.

We shall analyze the the missed opportunity to better manage the vaccination campaign relying on the knowledge that was at hand before the flood of litterature on COVID-19 pandemic and immunization against SARS-CoV-2 started flowing in.

## Mathematics: from RNA to Incubation

SARS-CoV-2 possesses a positive-sense single-stranded RNA of some 30.000 nucleotides. In comparison, the influenza A virus has a negative-strand RNA of about 10.000 nucleotides. The positive-sense RNA is immediately translated into proteins. The negative-sense RNA must first undergo transcription into a positive-sense strand. SARS-CoV-2 possesses a primitive RNA proof-reading apparatus enabling it to correct errors in newly replicated RNA. The frequency of mutations found in the influenza A virus is 1 in 10.000 nucleotides per replication cycle, while it is about 1 in 3.000.000 nucleotides in the case of SARS-CoV-2. Each new influenza virus carries 1 point mutation, but only 1 in 100 newly replicated SARS-CoV-2 does so. Taken together, the SARS-CoV-2 mutates at a significantly slower rate than the influenza A virus (3).

The useful descriptors of an epidemic are the basic reproduction number ($R_0$) and the incubation time. $R_0$ tells how many secondary cases arise from an index person within a population immunologically naïve to the causative microbe. At first, the $R_0$ was estimated at 1.5 – 2.5 (influenza A 1.5 – 1.8), but subsequently, it kept rising. The conservative estimates are as follows: the Delta – 5.2 (close to chickenpox or poliomyelitis) and the Omicron variant 8.2 –9.5 (approaching the transmissibility of measles: 12–14) (4). $R_0$ enables the theroetical prediction of the level of herd immunity (natural infection + vaccination) necessary to stop the epidemic spread (5): level of herd immunity = $1 – (1/R_0)$.

In practice, this means that with $R_0$ around 1.8 the targeted herd immunity would be 0.45, i.e. 45%, and with the current Omicron wave ($R_0 \approx 9$) it is at 89%. Until the end od 2021, the ratio of symptomatic to asymptomatic cases, within the positively testing persons, has been around 60% : 40% (6). During the current Omicron wave it is about 15% : 85% (7). In February 2022 the seropravalence of natural SARS-CoV-2 infection in U.S.A. was 58%. It was derived from the prevalence of nucleocapsid antibodies during the previous 6 months. Seroprevalence in children was higher – 75% (8). This reminds of influenza which infects children at a higher rate, but the clinical course is often asymptomatic or mild.

At first, the incubation was said to be 4–6 days, but was calculated to have been 6.5 days on average during 2020 (9). The serial interval, i.e. the number of days needed for the first secondary case to appear following an index case was 5.2 days, indicating that presymptomatic and possibly asymptomatic transmission was in place (9). Incubation was accelerated with ensuing variants: for Delta 4.3 days (10), and for Omicron 2.5–4.3 days, with serial interval of just 2.9 days indicating very rapid spread (11). The incubation period is commonly thought of as an important characteristic of subclinical infectiousness and necessary quarantine in case of exposure. However, the incubation time is an important factor influencing the vaccination strategy, as will be laid out in Section 5.

## Is This the First Pandemic in the History of Mankind?

A Swiss study compared the epidemic of „Spanish flu“ in 1918 with the present COVID-19 epidemic in the Canton of Bern. The „Spanish flu“ was a larger epidemic, but otherwise, the curves representing the weekly incidence rates from March 1918/2020 to Jan 1919/2021 followed a very similar course. The maximum in both epidemics was in October/November: 1300 per 100.000 weekly incidence in

1918, and 700 in 2020 (12). Restriction of mass gatherings to < 5 persons, and closure of schools and restaurants had the most impact on harnessing the spread of both epidemics, but in 1918. it resulted in a general strike and gradual relaxation of the lock-down. Masks were worn only during the COVID-19 era, but interestingly, their use was evenly imposed during the quiet and active epidemic phases without obvious merit regarding the COVID-19 transmission. It has recently been shown that besides droplets (diameter ≥ 100 μm), fine aerosols (diameter < 100 μm) effectively spread the SARS-CoV-2 to persons > 2 m away from index case in indoor settings, especially if continuous ventilation is lacking, despite masking and distancing measures (13).

The tactics of those responsible for managing the present COVID-19 pandemic were sometimes based on the use of fear to control the behavior of the population because it was thought that people wouldn't be compliant with distancing, masking, and lock-down measures (14). The disclosure and subsequent apology for this approach came during the vaccine implementation upsurge and the vaccine uptake was not compromised. Insisting on public dangers based on individual examples of young and healthy persons succumbing to COVID-19 was used across several countries, including Croatia, and frequently garnished with statements that there was not sufficient scientific data about all sorts of „unknowns" surrounding the pandemic. The fear-inspiring tactics were, however, fraught with embarrassing misinterpretations of examples presented to terrify the public. No apology was ever offered (in Croatia), and the public and political opposition mounted an atmosphere of distrust, which was also reflected in vaccine hesitancy. To date, only 59% of the total Croatian population has received 2 doses of COVID-19 vaccines (15).

## Is This the First Epidemic in Our (50+ Years) Lives?

The case of the smallpox epidemic in the former Yugoslavia in 1972 was quite informatory. Smallpox $R_0$ = 5, similar to the Delta variant. Unlike today, a blitz-style vaccination campaign was carried out in the whole country, although all the cases (175, of whom 35 died) had been concentrated in Serbia with only one case i in Montenegro: in just 20 days 18.000.000 people (i.e. 86% of the then population of 21.000.000) had been vaccinated (16). The lifelong president Josip Broz Tito[2] took refuge on the isles of Brioni, and never appeared in the public during the epidemic. The medical profession had free hands and the only foreign expert who came to take part in managing the epidemic was Donald Henderson, the very WHO head of the campaign that a little later, in 1977, eradicated smallpox in Somalia.

During the 18 months of the vaccination campaign against COVID-19 in Croatia, the uptake of the full primary series has been mere 59%. In countering an epidemic by vaccination, it is the speed of attaining the necessary coverage (herd immunity) that will guarantee the interruption of disease transmission. The herd immunity needed to stop the COVID-19 epidemic until April 2021 would have been 45%, but with the Delta wave starting in May of 2021 it rose to 80% and since the advent of Omicron in November 2021 it increased to almost 90%. These theoretical projections work on the assumption of the ideal 100% vaccine effectiveness.

## How Does the Immune System React to Vaccination?

Vaccination is bringing into contact the immune system with the antigen through which it is possible to neutralize the microbe, virus, or toxin. We shall first look at non-replicating vaccines. In the case of SARS-CoV-2, the target antigen is the spike protein (S1) which attaches to the ACE2 (angiotensin-converting enzyme 2) on the host cell. The primary immune response entails IgM and subsequent IgG synthesis that partially overlap (Fig. 1).

[2] Josip Broz Tito was a communist dictator and the lifelong head of state and communist party of the Socialist Federative Republic of Yoguslavia. He died in 1980. Yugolsavia fell apart in 1991.

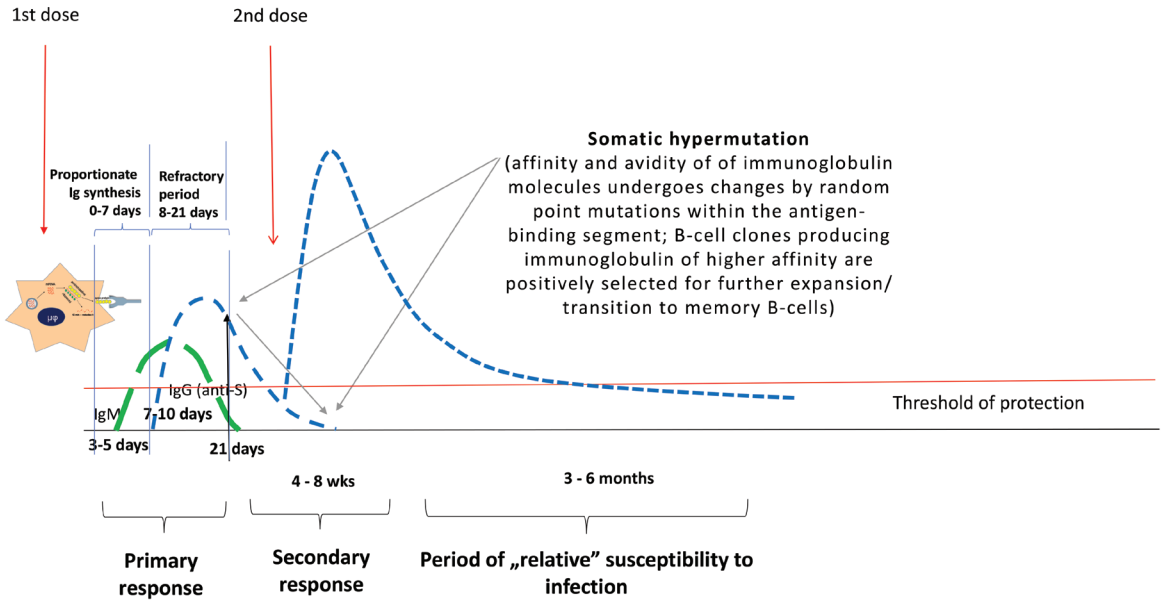


**Fig. 1.** *Primary humoral immune response to a nonreplicating vaccine. The vaccine here is mRNA vaccine that acts through an antigen presenting macrophage (μφ) expressing the spike protein to the immune system. See text.*

After the antigen is eliminated IgG starts to fall. This is usually seen around day 20, but not before day 18–19 after the initial contact. The waning phase is characterized by somatic hypermutation within the paratopic portion of the immunoglobulin. Numerous random point mutations affect the IgG affinity for the disappearing antigen, and only those B-cells that happen to produce IgG of higher affinity will be selected to enter the memory state. If at this phase the immune system receives another stimulus with the same antigen, the secondary response will be manifold stronger, i.e. quantitatively higher and affinity-wise more specific.

The somatic hypermutation is preceded by two phases: the initial phase of proportionate IgG response and the refractory phase. During the first 7 days, and not later than 8–9 days of the initial contact with the antigen, additional antigen doses may proportionately increase IgG synthesis to a certain plateau, but during the ensuing, refractory period (9–18 days), the addition of antigen has no effect. This is the theoretical basis for the selection of a vaccine dose that will, in the first 7 days, result in an optimal trade-off between immune stimulation and reactogenicity, while the earliest booster should never be given before 21 days. Longer periods are preferable: 6 weeks to 2 months or more because higher secondary titers can be obtained compared to the interval of 21–36 days (17).

Following the 2nd dose and the powerful secondary response, in the absence of further antigenic stimulation, the specific IgG wanes. What ensues is the time of relative susceptibility to infection. The „relativity" of susceptibility to infection is influenced by antibody titer and affinity, antigenic escape, distance in time from the latest vaccine dose, and natural exposure to infection (including the size of the inoculum and droplet/aerosol physical property). Besides these factors there may be other environmental and health factors that affect susceptibility to COVID-19, as demonstrated in two hypothesis generating papers by Habibzadeh et al. showing that locally (18) and worldwide (19) exposure to oral polio vaccine reduces the incidence of COVID-19 regardless of socioeconomic development index.

Regardless of age-related differences in the maximum antibody titers, there is a fall to low detectable levels in 3–4 months in all age groups (Fig. 2) (20).

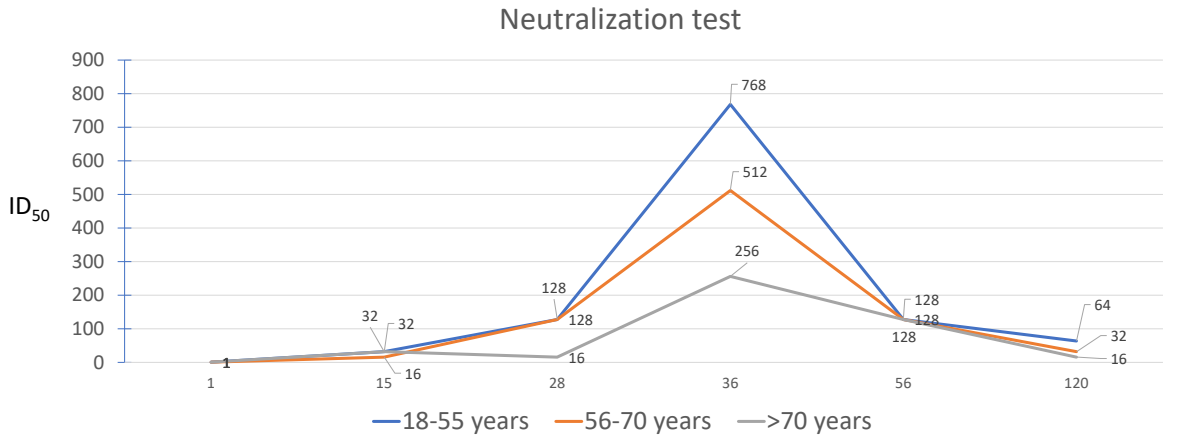


**Fig. 2.** *Temporal dynamics of neutralization titers after 2 doses of mRNA vaccine. (Plot based on data from Ref. 20). $ID_{50}$ = 50% inhibitory dilution titer, Abscissa shows days after vaccination.*

## Why Is the Incubation Time Important?

The incubation time is not there just to determine the length of quarantine or to model the spread of infection, but it is equally important for conceiving an effective immunization schedule. Infectious diseases with an incubation in excess of 8–9 days can be prevented by timely vaccination within a window of 48–96 h post exposure. Likewise, if the person had already been vaccinated, even in the absence of protective or detectable antibody titers at the moment of exposure, the incubation period of 8–9 days allows for activation of the secondary immune response and prevention of symptomatic infection. Examples are measles, chickenpox, hepatitis A and B, tetanus, rabies, human papilloma virus, etc.

On the contrary, an infectious disease with incubation shorter than 8–9 days can be prevented only if there is protective antibody titer present at the time of exposure. Examples include *Haemophilus influenzae* type B, meningococcus, influenza, poliomyelitis, rotavirus, etc. In such cases chemoprophylaxis or seroprophylaxis may help, provided drugs and antisera (specific immune globulin) are available. In conclusion, COVID-19 is a short incubation disease and an effective prevention by vaccination presupposes continuous maintenance of adequate titers of neutralizing antibody.

## Initial Immunization Schedules

Having this knowledge, it remains a mystery why the producers decided to register their vaccines as a 2-dose schedule. The same goes for regulatory agencies that went along. Perhaps they were in a hurry to finish off the 3rd phase of safety and efficacy trials and prove the immediate protectiveness within the shortest possible time, starting 7 days post-dose 2, and truncating the follow-up at about 4 months. It soon became obvious that a 3rd dose would be needed due to waning immunity and short incubation. This created a terminological hassle: instead of admitting that COVID-19 vaccines should have been labeled as 3- or multiple-dose vaccines, there was unnecessary and confusing language about the „booster“, „3rd dose“, or „revaccination“. This created further distrust against vaccination in the general public.

The added confusion about breakthrough infections, poor distinction between positive PCR, symptomatic COVID-19, and vaccine effect on transmissibility, and the popular expectations for vaccines to do away with the germ altogether resulted in further distrust of vaccine effectiveness and exaggeration of the significance of side effects.

If the vaccines had been marketed as 3-dose vaccines, e.g. 0–2–6 months, which would have been a slower schedule but would have provided for quantitatively larger and temporally longer humoral

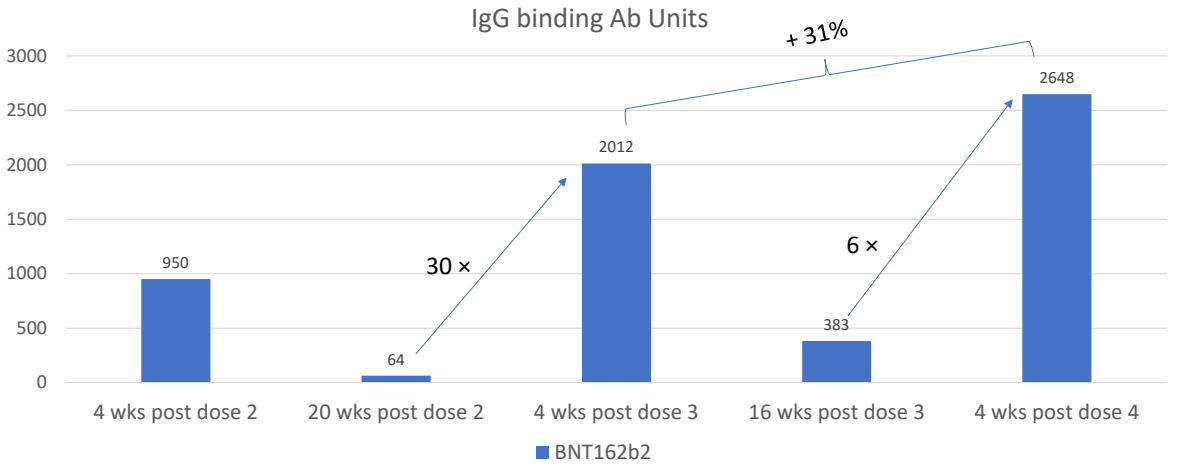


**Fig. 3.** *Increase in specific IgG after the 4th dose of mRNA vaccine. (Plot based on data from Ref. 23).*

immunity, that would have enabled attaining more durable herd immunity and very probably a paradoxical earlier effect on stopping the transmission. This has eventually been grasped and changes to the vaccine schedules were made (24 June 2022): both mRNA vaccines are now offered in a series of 3 doses with longer intervals: dose 1 to 2 at least 3–8 weeks (BNT162b2) or 4–8 weeks (mRNA-1273), dose 2 to 3 at least 5 months. Dose 4 is indicated for ages ≥ 50 years at least 4 months after dose 3 (21). There are some age-specific adjustments for the mRNA-1273: a 2-dose regimen is kept for children 6 months to 12 years but spacing is increased to 4–8 weeks.

As mentioned above (Section 2) the formal 2-dose coverage in Croatia has not yet surpassed 59%. Besides, most of the vaccinated are now beyond the 4–6 months of reasonable protectiveness of the 2-dose schedule. The numboer of those who had the 3rd dose is not officially reported but it seems to be modest. The case fatality rate is quite high – so far 1,4% of diseased have died of COVID-19 (world statistics: 1,1%) (data as of 1 July 2022; check current data on website (15). The third dose of mRNA vaccine demonstrates > 90% protectiveness against severe COVID-19, and about 50% against symptomatic disease caused by initial subvariants of Omicron BA.1 and BA.2 for up to 6 months following the 3rd dose (22).

As regards the 4th dose (Fig. 3), the difference in the magnitude of serologic response between doses 2 and 3 is +100% (950 to 2012 units), and between doses 3 and 4, it is +30% (2012 to 2648 units). This is termed the phenomenon of leveling of the immune response (plateau).

However, within this moderately leveled general IgG response, there is a more significant surge in neutralization titer (+1000%, i.e. 10× up) to the wild virus and both presently prevalent variants (Delta and Omicron) (Fig. 4) (23). The 4th dose is currently recommended for those 50 years and older and immunocompromised persons 12 years and older (24). Since April 2022 Pfizer and Moderna have started testing the safety and efficacy of vaccines against Beta, Delta, and Omicron variants (25). Interim results show that Moderna's bivalent mRNA-1273.214, coding for the original S1 antigen plus Omicron subvariant BA.4 and BA.5 common domain induces a potent neutralizing antibody response in previously vaccinated and boosted persons (i.e. 3 dose received) to all antigens in the vaccine, regardless of natural infection (26). Pfizer is equally studying two potential vaccines for 3-dose vaccine recipients: a monovalent shot that targets only Omicron, and a bivalent combination booster that adds Omicron to the original vaccine strain. The interim results show powerful antibody responses to the Omicron variant with both

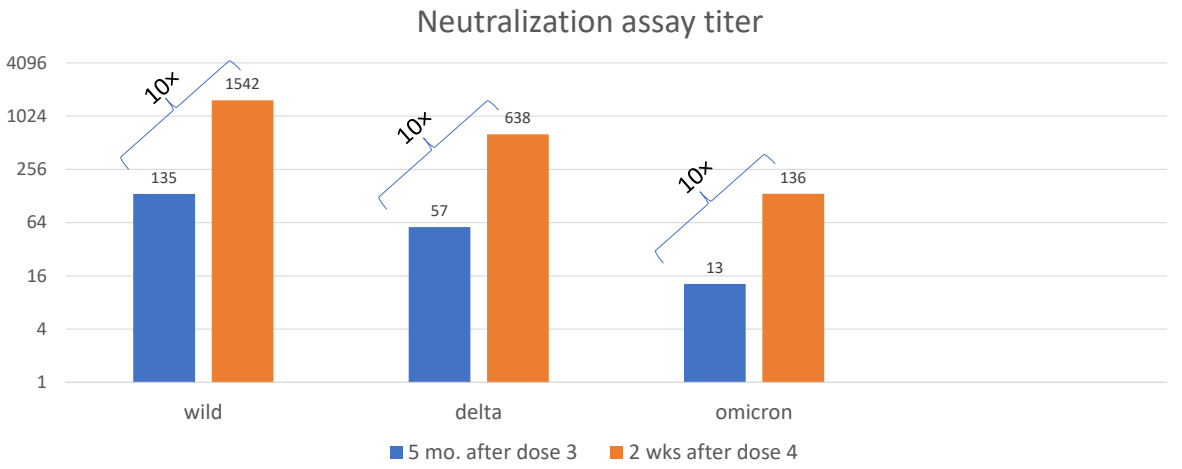


**Fig. 4.** *Increase in neutralization titer after dose 4 of mRNA vaccine. (Plot based on data from Ref. 23)*

vaccines (9- to 19-fold). The bivalent one induced a 9-fold increase in neutralizing titer to Omicron, which, in comparison to boosting with the original vaccine, was at least 1.5-fold greater (27).

A different kind of vaccine has recently been registered: Nuvaxovid® of Novavax, containing recombinant spike protein nanoparticle vaccine with Matrix-M1 adjuvant which appears to be as safe and effective (>90%) as mRNA vaccines at 35 days follow-up (28). It, too, is now licensed as a 2-dose vaccine (0-21 days). It remains to be seen how soon the 3rd and 4th dose will become necessary because this is, as discussed above, predictably inevitable. The durability of protection depends on booster doses, natural boosting, antigenic escape, and immunoglobulin catabolism, and not on the production platform of the vaccinal antigen.

## What is Common to COVID-19 and Rabies?

The common ground is Wuhan, Hubei province, China. This large city harbors Coronavirus and Rabies Reference Laboratories, and there is intense work running on rabies immune postexposure prevention. Suspicious people may speculate on the intriguing topography of science, but here we are primarily interested in the proof of concept that there are indeed 3 phases to a primary immune response: the proportionate phase, the refractory phase, and the somatic hypermutation phase. In a recent article from Wuhan by Lei Zhang two protocols for postexposure rabies prevention were compared: the Essen and the Zagreb protocols (29). Rabies by definition is a long incubation disease, usually 2–8 weeks, although it can be just 10 days. The Essen regimen has been the time-honored standard approved by the World Health Organization (WHO) for postexposure rabies prevention. The Zagreb regimen was first published in 1982 (30) and recommended by WHO in 1992 (31). The Essen regimen comprises 5 doses and 5 visits (0 – 3 – 7 – 14 – 21 day). The Zagreb regimen comprises 4 doses in 3 visits (the first two doses are given at visit 1: 2 – 1 – 1; spacing 0 – 7 – 21 day). The immunogenicity and effectiveness results are identical (29). How is it explained? The Essen regimen contains one dose on day 14, amid the refractory phase, which results in zero increase in IgG. The Essen scheme spaces the first 2 doses on days 0 and 3, and the Zagreb scheme prescribes 2 doses at once on day 0. Both regimens add the 3rd dose on day 7. They concur in the phase of proportionate immune response (the first 7 days) by giving the same quantity of vaccine and achieving the same early immunogenicity result. A dose at day 21 is the first booster in both protocols and results, again, in identical serologic response.

The simple observation of the results of different empirical practices in postexposure rabies prevention demonstrates the principles of primary immune response that are true of any non-replicating vaccine.

## What Does the Immune Response to Infection Look Like?

The increasing quantity of antigens due to viral replication in the proportionate phase (0–7 days) brings about a strong primary response directed at a multitude of viral antigens. The somatic hypermutation phase ensues with the clearing of the virus against the background of excess antibody (Fig. 5)

Therefore, the humoral response is initially significantly larger and broader (although not faster) than with the initial dose(s) of a vaccine. It is not exclusively anti-S and neutralizing but consists of a mixture of IgM and IgG specific to many viral antigens. Thus, the serology to nucleocapsid antigen of SARS-CoV-2 is frequently used to detect past natural infection (7, 32). The response is higher in children than adults and provides detectable and protective titers for at least 10 months post-recovery (Figure 6) (33). The correlation of spike receptor binding domain (S-RBD) antibody titers to neutralization titers is tight (33).

Adding a second dose in 2–6 months produces a strong anamnestic response which tends to level off with further boosting. The humoral immune response is similar for asymptomatic and severe clinical infections alike. The combination of natural and vaccine-enhanced humoral immunity employing a single dose of vaccine following natural infection produces a strong anamnestic response. The size of the response is independent of the clinical severity of the preceding infection as is characteristic of hybrid immunity (34).

The theory has been validated in practice: a single dose of mRNA or adenovirus-vectored vaccine following recovery from COVID-19 produced a much stronger and more durable antibody response than two doses of vaccine in previously healthy individuals. The duration of detectable serology extended to >1 year (35).

Adenovirus-vectored vaccines behave similarly to natural infection. Although the adenoviral vector

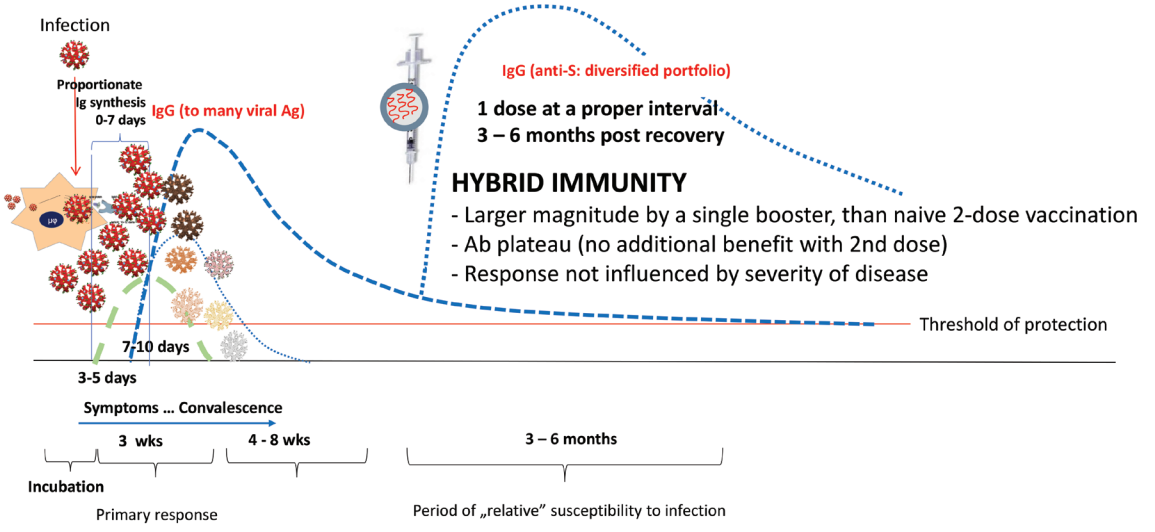


**Fig. 5.** *Primay humoral immune response to infection. Red globules with white spikes represent live replicating virus, while the pale shades indicate the elimination of the live virus. IgM and IgG of the primary response to a nonreplicating antigen are shown in pale green and blue dotted curves to contrast with blue dotted lines of cumulative immunoglobulin (M and G, and later only G) concentration. The syringe represents the vaccine given in the wake of a natural infection.*

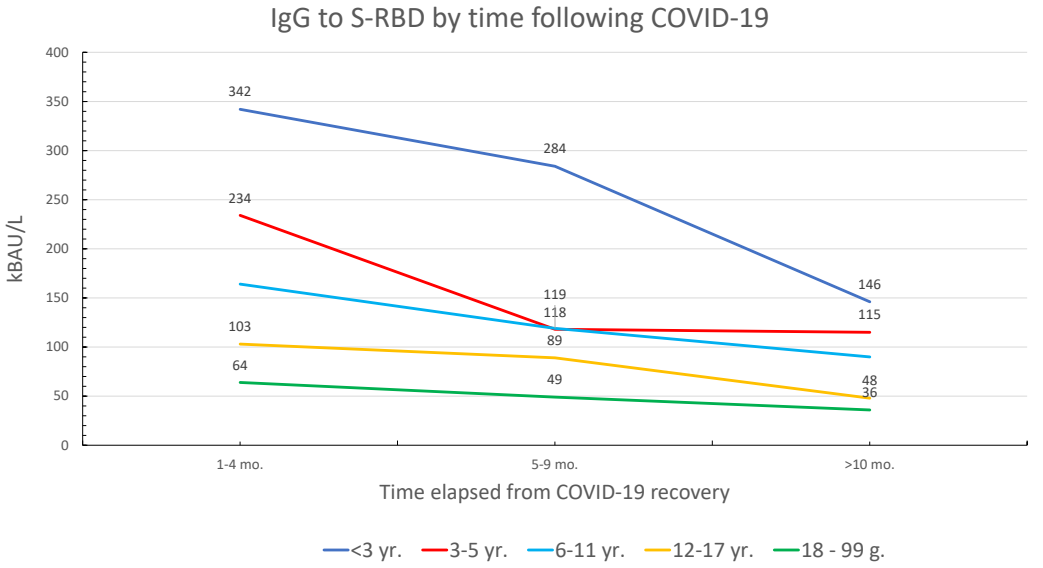


**Fig. 6.** *Duration of immunity to SARS-CoV-2 following recovery measured in kilo-binding antibody units/liter. S-RBD = spike receptor binding domain. (Plot based on data from Ref. 33).*

does not replicate, it is integrated into host cell DNA, and unlike mRNA that gets degraded within minutes to hours (36), continues to locally produce antigen for about 9 days and in remote lymphatic sites (lymph nodes, spleen) the adenoviral vector can persist for up to 3 months (37). More generous spacing between the 1st and 2nd dose provides a significantly greater immunogenicity and protection. This has been noted with the AstraZeneca ChAdOx1-S vaccine (*Vaxzevria*®): 55% protection with 1 month separating the first 2 doses, and 81% with 3 months (38). The antibody concentration between the two doses did not show a significant drop. Heterologous boosting is recommended with a dose of mRNA vaccine not earlier than 4 months after completion of the primary 2-dose series (39).

## What Is the Protective Neutralization Titer against Covid-19?

If the average convalescent neutralization titer (mean±SD) is taken as a starting point it is possible to observe the protective effect of further dilutions and define the lowest titer that prevents infection. At least 3% of the mean convalescent titer is needed in order to prevent severe COVID-19. A level of 20% of the mean convalescent titer is necessary to prevent any infection. This fraction (20% of the mean convalescent titer) corresponds to an absolute titer of approximately 1:10–1:30 (40). The protective titer of neutralizing anti-hemagglutinin antibody in influenza A is accepted to be ≥1:40 (41).

## Vaccination and Multisystem Inflammatory Syndrome in Children (MIS-C)

The MIS-C is a serious postinfectious hyperinflammatory complication with an incidence of 1:3000-4000 children and adolescents who in the previous 2–6 weeks were infected with SARS-CoV-2 irrespective of wether it was clinically evident. Serology to SARS-SoV-2 is invariably positive. MIS-C is similar to Kawasaki disease but children are usually older (6–21 years) and have more pronounced cardiac and abdominal involvment (42). Therapy includes high-dose intravenous immune globulin and corticosteroids (43). The case fatality rate (2%) exceeds that of COVID-19 (0.5–1.5%).

Can a child develop MIS-C following vaccination? In the USA there have been 6 children who

developed MIS-C following mRNA vaccination without serologic evidence of natural infection (antibody to nucleocapsid antigen N negative). This makes an incidence 0.3 in 1 million vaccinated children (44). Conversly, among 15 children who received vaccine after they had recovered from MIS-C, none developed relapse during the 9-month follow-up (45).

## Ethical Aspects of Immunization against Covid-19

All adenovirus-vectored vaccines are produced on human cell lines. Science and modern secular ethics, depending on the author, place the beginning of human life in the window between conception and the end of week 8 of intrauterine development when organogenesis has been completed and the fetal stage has set in (46). The fact that all human cell strains/lines derive from fetuses is evident from the gestational age at which the abortions took place (≥12 and up to 18 weeks) and from the fact that the harvested cells are organ-specific: lung, kidney, retina, etc. Therefore, all human cell strains/lines used in vaccine development and production are derived from aborted human beings. The continuing hassle around this question has moved into the arena of the ideological rivalry of societal groups intending to impose a prevailing moral doctrine, regardless of scientific and philosophical arguments.

The mRNA vaccines are made on technology platforms that do not use live cells and appear not to present an immediate ethical or moral dilemma. However, neutralization tests used in evaluating immunogenicity in vaccine development and post-marketing follow-up are frequently performed with pseudoviruses, which, again, are engineered and produced on human cell lines.

The use of human cell lines in vaccine development and production is not inevitable. Several cell lines and expression systems for vaccine production that do not depend on human cell lines have been developed and used in vaccine production and testing (Vero cells from African green monkey kidney; human lung cell line Calu-3 and human colon cell line Caco-2, deriving from metastatic lung adenocarcinoma and colorectal adenocarcinoma, respectively). There is also ample experience with non-mammalian cell cultures in vaccine production and evaluation (e.g., yeast, bacterial, and insect cells). In the present case of COVID-19 vaccines, Nuvaxovid® by Novavax is a subunit recombinant vaccine produced by baculovirus grown on insect cells (ovarian cells of army moth, *Spodoptera frugiperda*), and virus-like particle vaccines produced on plant cell cultures are in advanced phases of clinical evaluation (47).

The Roman Catholic Church provides a strong articulate moral doctrine in the contemporary world. It dismisses any challenge to the fact that human life begins at conception. Accepting that some vaccines may pose moral problems, she strives to formulate the degree of moral responsibility of those who develop, produce, sell, prescribe, apply and receive vaccines bred on human fetal cell cultures. In the Vatican view, such behavior represents a kind of material cooperation in the evil act of abortion which is passive, mediate and remote in time. Therefore, it can be morally tolerated if there is a proportionate reason, i.e. an alternate ethically irreproachable vaccine does not exist. This tolerance, however, includes unequivocal rejection of abortion and demand to develop ethically acceptable platforms of vaccine production. For the sake of those who have a conscientious objection to the use of such vaccines, the biopharmaceutical companies, marketing companies, and health agencies should be required to declare on the packaging whether a vaccine was produced and/or tested using human fetal cell cultures (46).

## Conclusion

Those who know for sure that this is not the last pandemic should also answer the following question: why did the professional and scientific community behave as if COVID-19 was the first ever pandemic in the history of mankind? The lack of breaking scientific news was an ever-presented excuse for circumventing answers to specific issues

that could have been reasonably guessed from analogous events in the past. The dangers of modern pervasive scientific discussions at the detriment of all the existing knowledge and sound judgment consist in: 1. asking science to answer questions that have already been answered; 2. expecting science to answer questions it cannot answer. Science is not omnipotent and cannot be expected to solve everything, nor be an excuse for the lack of due knowledge accumulated in the past. Free, sound and critical observation of relevant phenomena should be fostered, time-honored and validated scientific facts kept in active knowledge, plus continually verified, explained, and refined to maintain the ability to expand the circles of knowledge relevant to the realities of the evolving history of mankind.

**Conflict of Interest:** The author declares that he has no conflict of interest.

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