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Not Covid-19 vaccine-mediated but naturally acquired immunity enables herd immunity

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The single most important objective of mass vaccination with Covid-19 vaccines was to achieve herd immunity! Meanwhile, health authorities and their advising 'experts' have acknowledged that herd immunity is no longer within reach. They now tend to blame a number of factors for not achieving this goal. Amongst those, they like to cite disappointing vaccine coverage rates, essentially in the younger age groups, and reduced efficacy of the current vaccines towards emerging viral variants. They claim that instead we're now luckily heading towards a situation where the virus is becoming endemic and where vaccination will be key to ensure individual protection! Unless one is dealing with a pandemic or epidemic, only vulnerable people (the so-called 'target population') are getting vaccinated. As also younger people are now increasingly contracting Covid-19 disease, the need for all of us to get the shot remains unchanged and hence, mass vaccination campaigns are to be continued. That's at least the narrative that is currently used to convince youngsters and children to take the shot too.

From a scientific viewpoint, the above interpretation of the current situation is beyond shortsighted and is lacking every piece of scientific evidence. First, the weak link between the (rising) number of cases and the (declining) hospitalization and mortality rates, as now observed in a number of countries with high vaccine coverage rates, is not reflecting a transitioning of the virus into an endemic phase. Endemicity is not possible without herd immunity and herd immunity is the last thing that the ongoing mass vaccination campaigns will be able to achieve (see below). The weak link is much more likely to result from the fact that in many cases the vaccines still provide protection against severe disease whereas the infection rate is now dramatically increasing due to enhanced circulation of more infectious variants that flourish on a background of increasing spike (S)-directed immune pressure exerted by the (massively vaccinated) population. As already mentioned in multiple previous contributions, increased infectivity rates in the population will make it more likely that younger age groups get re-exposed to the virus at a point in time where they have become vulnerable (i.e. during a temporary window of suppression of their innate antibodies by short-lived, immature S-specific antibodies). As the vast majority of individuals in the younger age groups have either not been vaccinated at all or only received a single shot of a 2-dose vaccine, the level of their functional (i.e., non-suppressed) innate antibodies (Abs) may still be high enough to prevent severe disease. I presume that this situation is going to change for the worse when i) the virus becomes resistant to the current vaccines (which genomic

attenuated clinical symptoms are unlikely due to a shift of the pandemic towards endemicity or diminished virulence of circulating viral variants but merely reflect the impact of growing resistance of the virus to vaccinal Abs combined with a higher level of viral infectiousness. Growing resistance would still grant older age groups some remaining vaccine-mediated protection whereas younger age groups could still rely on some remaining innate immune protection. How otherwise could diminished hospitalization and mortality rates be reconciled with a steep incline in infection cases? This is certainly not a typical feature of a pandemic that is on the path of extinction!

It is, indeed, quite unbelievable that some advising experts pretend that although we won't achieve herd immunity, we will still be able to exchange the pandemic for an endemic situation. When does that happen? The answer is: never. Neither disappointing vaccine coverage rates nor diminished virus neutralization rates should be blamed for failure of these vaccines to enable herd immunity. *From their very first conceptualization, it should have been very clear that these 'S-based' Covid-19 vaccines are completely inadequate for generating herd immunity in a population, regardless of the magnitude of Ab titers induced or the rate of vaccine coverage*. Why is this? Let's first have a closer look at the definition of 'herd immunity'. Herd immunity occurs when most of a population is immune to an infectious disease and thereby provides indirect protection to those who are not immune to the disease. Mechanistically, indirect protection is due to absence or strong reduction of infectious transmission by those who have been immunized (i.e., the majority of the population). So who concluded all of a sudden that herd immunity would only depend on antigen (Ag)-specific (in this case, 'spike-specific') humoral (Ab) responses and nonantigen-specific innate immunity (i.e., operated through several different immune stimulatory and modulatory cytokines and chemokines secreted by immunocompetent cells, including noncytotoxic Ag-specific T cells)? If this were the case, a natural pandemic could never irreversibly evolve into an endemic infectious situation. Here is why S-specific Abs and nonAg-specific innate immunity could never force the Sars-CoV-2 pandemic into endemicity, let alone eradicate Sars-CoV-2:

In the course of a pandemic, the virus will eventually circulate in parts of the population that have previously been infected but see their Ab titers decline below a threshold that protects against infection. Although these people will no longer be able to control the infection, they are still capable of rapidly abrogating viral infection and transmission at the portal of entry thanks to their protective effector memory T cells. The latter will, indeed, be readily recalled as soon as pathogen-derived antigens are expressed on the surface of infected cells. Because of the rapid elimination of infected cells at the portal of entry, individuals with such subthreshold levels of functional anti-S Abs can still significantly reduce viral transmission in the host population. This is to say that even in the presence of suboptimal S-specific Abs, previously primed effector T cells will be recalled to eliminate Sars-CoV-2-infected cells and thereby curtail viral transmission at an early stage of re-infection. Elimination of those cells can take place regardless of the Sars-CoV-2 variant they are infected with as CoV-derived T cell epitopes are far more conserved than the S-derived B cell epitopes. This is in sharp contrast to the immune response induced by vaccination of naïve individuals. Although suboptimal titers of functional vaccinal Abs cannot prevent viral infection and transmission, they may still protect vaccinees from contracting (severe) disease. However, as none of the

infection with Sars-CoV-2. In addition, mass vaccination campaigns conducted in the heat of the pandemic simultaneously allow large cohorts of subjects with suboptimal Ab titers (e.g., as occurring after the first dose or between the 1st and 2nd dose of a 2-shot vaccine) to become exposed to the virus. This enables naturally selected immune escape variants to evade vaccinal (S-directed) Abs. Conclusively, the transmission-blocking potential of the immune status conferred to the population by mass vaccination is spike Ab-dependent and substantially lower than that conferred to a population that becomes infected by Sars-CoV-2 during a natural pandemic. This is to say that in the course of mass vaccination campaigns large parts of the population are left with suboptimal / incomplete immunity (e.g., Ab titers too low, Abs not fully mature/ functional, no priming of Ag-specific cytolytic T cells) and can, therefore, not control viral transmission upon exposure to the virus.

This, together with the propensity of viral variants to propagate on a background of S-directed immune pressure, prevents 'imperfect' vaccines from establishing herd immunity when used in mass vaccination campaigns at the height of a pandemic. As a result, vaccinees are prone to breed naturally selected immune escape variants and serve as asymptomatic spreaders. This is exactly the opposite of what herd immunity is defined as! It is important to note that coronaviruses have evolved a broad spectrum of strategies to also evade nonAg-specific innate immune responses. S-directed immune escape can, therefore, not be compensated by nonAg-specific innate immunity, even if the latter originates – at least to some extent – from stimulation of S-specific T cells (see references 12, 13 in previous critical opinion article: 'Why is the ongoing mass vaccination experiment driving a rapid evolutionary response of SARS-CoV-2?').

Overall conclusion: From the very beginning of the mass vaccination program, it should have been clear that because of the intrinsic limitations of S-based Covid-19 vaccines and their deployment in mass vaccination campaigns in the midst of a pandemic, herd immunity was simply the last thing this mass vaccination program could possibly achieve and that moving this program forward would fulfill all the conditions for driving S-directed viral immune escape to eventually result in full resistance of Sars-CoV-2 to the Covid-19 vaccines. Boosting vaccinal Abs with 2nd generation vaccines is not going to solve the issue of immune escape, even if the immunization with 'updated' vaccines would be repeated by 6-month intervals. This is because 2nd generation vaccines will primarily recall S-specific Abs elicited by the first generation vaccines (due to 'antigenic sin') and not be effective against recombinations of Sars-CoV-2 variants, which are highly likely to occur as a result of co-infection, especially in the most vulnerable (see previous critical opinion article: 'Why is the ongoing mass vaccination experiment driving a rapid evolutionary response of SARS-CoV-2?').

The more rational way to control infectious viral transmission in a pandemic of an acute, self-limiting viral infection and to achieve herd immunity is to use live attenuated vaccines. An even more effective approach to immune intervention in a pandemic is to use vaccines capable of conferring sterilizing immunity as those will rapidly and dramatically reduce (asymptomatic!) viral transmission, thereby providing herd immunity at a low vaccine coverage rate and eventually enable virus eradication.

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