Title Page: What if vaccines do not prevent infection?

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Acknowledgements:

Iñigo de Miguel Beriain's work received funding from the EU Commission, H2020 SWAFS Programme, PANELFIT Project, research grant number 788039 and the Basque Government, Ayudas a Grupos de Investigación, IT-1066-16

Jose Alcamí's work is supported by Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (Grants MPY 499/19, MPY 222/20 and COV 20/00072)

Both authors declare no conflicts of interest

What if vaccines do not prevent infection?

Abstract

Aims of the study

Vaccines are considered to be our greatest hope of defeating SARS-CoV-2. However, before we claim victory, there are some important questions that are in need of an urgent answer. In this paper we address a particularly relevant one, which unfortunately has not attracted much attention: whether approved vaccines provide us with sterilizing immunity (or to what concrete level).

Methods used to conduct the study

This study was based on the revision of the existing academic literature.

Results of the study

The capacity of approved vaccines to provide sterilizing immunity is key to designing our vaccination policies in an optimal way. We propose ways to obtain this knowledge and we assess the consequences that a lack of sufficient immunity would bring to publc health policies.

Conclusions drawn from the study and clinical implications

If further evidence proves that vaccines do not provide sterilizing immunity, prioritization strategies should introduce changes by providing preferential access to vulnerable populations instead of health care professionals or caregivers working in nursing homes. Policies aimed at promoting adherence to vaccination should consider that altruistic incentives would clearly diminish. In addition, policy makers should be aware that, in general, reaching herd immunity could take much longer than expected.

Introduction

The Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) is a novel RNA beta-coronavirus that is currently causing the first pandemic in a century. The first wave provoked thousands of deaths all over the world and impressive economic loss during the spring of 2020. As the second wave of COVID-19 in northern hemisphere countries grows, vaccines are becoming an urgent requirement. Fortunately, at the present moment three of them have already been approved for emergency use in Western Countries: Pfizer/BioNTech, Moderna and Oxford University/AstraZeneca. Consequently, vaccination has already started, first in the UK and soon afterwards all over the world.

However, some relevant issues regarding these tools are still a riddle. For instance, duration of protection will probably remain uncertain for a number of years post licensure of COVID-19 vaccines. This information is undoubtedly important, since it is often considered that for any licensed vaccine, efficacy and duration of protection are key issues to assessing vaccination policies (1). Their capacity to prevent infectiousness might also be essential to such purposes, but, surprisingly, this key issue has received minor attention. In this paper, we analyze the importance of the idea of sterilizing immunity in terms of vaccination policy design and informed consent issues. For this purpose, we start by defining the concept of sterilizing immunity. Then we analyze the possibility that the approved vaccines do not produce immunity at a significant level. Finally, we introduce some considerations about the ethical and policy issues involved.

Sterilizing immunity: where we are

Sterilizing immunity can be defined as "a unique immune status, which prevents effective virus infection in the host" (2). A vaccine confers sterilizing immunity when it prevents infection by the virus (or bacterium) in the vaccinated subjects, thus making it impossible for them to have a viral load sufficient to infect others. In contrast, vaccines that elicit "non-sterile" immunity protect the host against the disease, but do not impede infection. Consequently, whoever gets the virus has the capacity to spread it, even if they have been vaccinated. Most vaccines are somewhere in between both poles: they do not confer absolute sterility, but they do substantially reduce our capacity to transmit the virus. All approved vaccines reduce symptomatic infections and there are substantial

reasons to believe that at least some of them, and others that are yet to be approved, will reduce infectiousness substantially. In particular, a partial viral load decrease has been described in upper respiratory tract load after viral challenge in Rhesus macaques 3) with the Moderna vaccine, and complete protection with other vaccine prototypes 4). However, there are also some good reasons to think the opposite. This is based on "immune arguments "that obtaining secretory IgA antibodies is key to prevent infectiousness to SARS-CoV-2, since the virus enters the human body mainly through the ACE2 + TMPRSS2+ nasal epithelial cells (5). The initial host response to this pathogen occurs in a peculiar immune microenvironment, starting from the Nasopharynx-Associated Lymphoid Tissue (NALT) system. NALT represents the first lymphoepithelial barrier exerting a "gate control" to airborne antigens including respiratory viruses such as SARS-CoV-2 (6). In such a scenario, we can hardly defend against local infection if we do not have secretory IgA, a duplicate of two IgA-type antibody molecules assembled by a secretory "S" protein that enables it to be released into the mucous membranes. Without it, sterilization does not seem possible in a virus with the characteristics of SARS-CoV-2. Unfortunately, Pfizer/BioNTech, Moderna and Oxford University/AstraZeneca vaccines mostly generate "systemic" immunity in the organs, thanks to the creation of IgG, IgM and IgA type antibodies. This does not ensure the creation of secretory IgA (11).

To sum up, there is a reasonable scientific hypothesis that holds that vaccinated people only become fully sterile for a short term (in between both doses of vaccination), or perhaps never. Unfortunately, this riddle is hard to solve since we are suffering from an exasperating lack of data about the concrete features of the approved vaccines in terms of infectiousness. Primate studies are not conclusive. As previously mentioned, some of them show that vaccines do not sterilize takers, but some others provide reasons to believe that they do. Data obtained from clinical trials do not clarify this issue. Thus, the only possible conclusion we can arrive at is that currently we do not know whether the approved vaccines provide protection against infectiousness. What are the implications of this lack of knowledge? We will discuss this issue and its consequences ~~provide~~ in answer to this question in the next sections.

Understanding risk, introducing the issues at stake

According to what we have already stated, there is a certain risk that the approved vaccines do not sterilize us from an immunological perspective. In these circumstances, one should keep in mind that the extent of the security threat from a particular factor is defined by an equation similar to the following:

Safety risk = likelihood of undesirable event * severity of the harm caused

In our case, the likelihood that vaccinated people present a lack of sterilizing immunity is probably low. However, the severity of its undesirable consequences is remarkably high. If many vaccinated people who do not obtain sterilizing immunity become infected by the virus, they will behave as asymptomatic carriers. In other words, vaccination could lead to more asymptomatic infections, which are transmissible. This scenario could have terrible consequences in terms of public health and overload of medical services. One of the reasons that has made SARS-CoV-2 particularly fearful has been its ability to spread before patients show symptoms. We are certainly aware that most people try hard to avoid contagion, but this is not always possible. Usually, infection is detected by the fact that we develop symptoms. If symptoms are masked by vaccination, particularly in the absence of other preventive measures, the chances for spread increase exponentially. Keeping in mind that health care workers (HCWs) will be some of the first people to be offered vaccination, and given the fact that they have close contact with vulnerable populations, it might happen that vaccination, at least in its first steps, could lead to an enhanced risk of accidental silent spreading of COVID-19.

On this basis, we consider that knowing whether approved vaccines provide sterilizing immunity is an urgent matter that must be immediately addressed. Unless we opt for promoting human challenge studies that infect vaccinated people to know if they are infectious or not, there are two main strategies to reach this aim. The first is a careful review of the data of the clinical trials already available and the new materials that might be added in the next weeks. Phase III studies were designed to check efficacy in the prevention of symptomatic infection, but it is still possible to assess their impact on prevention of asymptomatic cases. For this purpose, it would be of great interest to test seroconversion against infection as defined by detection of nucleocapsid antibodies, not included in current vaccines, in both placebo and vaccinated groups. If in the vaccinated group a significant decrease in seroconversion against nucleocapsid is found, this strongly suggests that sterilizing immunity has probably been achieved because the

viral load in the upper respiratory tract has not reached the threshold required to trigger systemic immune responses. The generation of antibodies against nucleocapsid does not rule out the possibility of some degree of sterilizing immunity. But if similar asymptomatic infection rates occur in both groups then the efficacy of the vaccine to provide protection from infection would not be confirmed.

An alternative approach to the issues at stake is to introduce control measures aimed at monitoring the infectiousness of the first vaccinated persons, especially health care workers and caregivers. This will not only help them avoid involuntary infection, but will also allow us to collect important data such as viral load detection levels or seroconversion to viral proteins, as we have proposed for participants in phase III studies. This will provide us with better knowledge about infectiousness. Continuous testing of these groups, particularly of health care workers, seems to be the optimal measure for this purpose, even though this option involves impressive challenges in terms of logistic and costs. Needless to say, other preventive measures, such as mask use and social distance, also for vaccinated people, should be kept until the sterilizing immunity question is answered and/or herd immunity achieved.

Public health policy and vaccination strategy

If weak sterilizing immunity is finally confirmed, some policy advice might be worth considering. First, if we are not able to eliminate the infectiousness through vaccination, there is no point in implementing strategies that prioritize those who are the main vectors of virus transmission, unless they are also vulnerable persons themselves (that is, people who might probably develop serious symptoms because of their age, or have underlying medical conditions, etc.). Therefore, we should better prioritize the vaccination of vulnerable populations over health care professionals or caregivers working in nursing homes, in order to impede undetected asymptomatic carriers from mixing with unprotected patients. Indeed, an alternative strategy based on continuous testing of these professionals combined with the progressive vaccination of vulnerable populations would be much more recommendable in the short term. If vaccines do not fully prevent transmission, direct protection of vulnerable populations becomes much more reasonable than indirect protection (through vaccination of health care workers).

Further on, we could offer vaccination to health care workers and caregivers in nursing homes, prior to the rest of society, due to their greater exposure to the virus.

On the other hand, vaccinating children, as Giubilini *et al*. have recently proposed (7), would not be at all reasonable. Children do not usually develop serious symptoms when they are infected with COVID-19. If the vaccine does not eliminate their infectiousness, vaccination of children becomes completely futile, even though they are likely responsible for significant virus transmission.

Furthermore, it is also worth considering that herd immunity could hardly be obtained in the short term if sterilizing immunity is not acquired. Indeed, if vaccination creates a huge number of asymptomatic carriers, the R_0 will probably increase and, consequently, the theoretical coverage required for herd immunity will also increase. Even though some prospective models (8) consider the possibility that vaccines do not reduce infection or onwards transmission, they do not seem to include these circumstances in their recommendations. This is clearly a gap that should be filled as soon as possible. Moreover, considerations about sterilizing immunity should also be kept in mind if we promote a jump in the optimal allocation strategy from "direct protection of the vulnerable" to one of "herd impact", as those models have proposed (8) . Last but not least, if vaccines do not induce sterilization immunity, we should consider the possibility of implementing complementary actions to gain it. For instance, we could boost our common protection by providing vaccinated people additional doses of new vaccines able to trigger sterilizing immunity.

Informed consent issues

On the other hand, we must consider that information about infectiousness is also relevant in terms of decision-making on vaccination. If vaccines do not achieve sufficient sterilization of the population to impede transmission, it makes even more sense to vaccinate everybody since herd immunity will not be on target (even though 80% of people were unable to develop COVID-19, vaccinated persons would still spread the virus). Hence, the risk-benefit ratio will be even more strongly tilted in favor of vaccination , at least for those who seem to be the most vulnerable to the disease. However, we should also be aware that the lack of sterilizing immunity could discourage vaccination of those who a priori are not very likely to suffer from serious

symptoms of COVID-19 because the use of masks and social distance should be maintained despite vaccination. Indeed, altruistic incentives, the idea of protecting others through vaccination, would lose much of their consistence and vaccination rates could be reduced dramatically, especially among young people. Furthermore, anti-vaccination trends would probably benefit from these inconveniences to expand their influence on public opinion. These considerations, in our opinion, should be considered when planning the public vaccination and information campaign for the general population.

Vaccines, sterilizing immunity and public policy in the long term: the options

In the long term, there several possible scenarios can be drawn up. First, it might happen that the approved vaccines do provide sterilizing immunity. If this were the case (and hopefully it will be), this paper will have served to suggest some basic precautions while we corroborate this hypothesis. If this is not the case, we should probably focus on new vaccines. Currently, about 45 potential candidates for new COVID-19 vaccines are in phase 3 of clinical trials (4). At least a few (and hopefully most of them) will be approved by the corresponding bodies. It is certain that some of them will provide us with sterilizing immunity. If this were the case, we would have to combine all existing vaccines, profiting on the best features of each product.

In the worst possible scenario -if no vaccine provides sterilizing immunity- we should probably have to re-build all our strategy design, with several options in mind. First, we could try to vaccinate everybody to gain herd immunity, by introducing coercive vaccination policies. Second, we could try to support the use of certain adjuvants that is, substances that enhance the magnitude, induction, or durability of antigen-specific immune responses when used in combination with specific vaccine antigens, both at the level of B lymphocytes and T lymphocytes (9). Third, development of new vaccine prototypes providing sterilizing immunity should be a major objective of a second generation of SARS-CoV-2 vaccines. Finally, we could design a complex system based on continuous testing and certificates of non-infectiousness that allow people access to some specially protected areas (secure environments) (10).

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