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Viewpoint

Can integrated post-exposure vaccination against SARS-COV2 mitigate severe disease?

Claude P. Muller

Department of Infection and Immunity, Luxembourg Institute of Health, 29, rue Henri Koch, L-4354 Esch-sur-Alzette, Luxembourg

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Post-exposure vaccination is effective (>50%) against a number of infectious diseases with variable incubation times, including hepatitis A, B, measles, varicella, rabies and smallpox, if given early enough after infection [1]. While prophylactic vaccination against SARS-COV2 is highly efficacious and robust in protecting even against mild disease [2], the potential of interventional post-exposure vaccination to mitigate at least severe COVID19 disease has received little attention.

This is somewhat surprizing since in the published clinical phase III trial of the BNT162b2 vaccine (Pfizer-BioNTech) the authors already stated [2]: "that the cumulative incidence of Covid-19 cases over-time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incubation period of 5 days [3], indicating the early onset of a partially protective effect of immunization." In this trial 39 cases occurred in the vaccine group and 82 in the placebo group between the first and the second dose corresponding to a vaccine efficacy (VE) of 52% (29.5−68.4). However, almost half of the latter placebo cases occurred between day 12 and 21 (i.e. before the 2nd dose) and only 4 cases in the vaccine group, corresponding to a VE of more than 90% as early as 12 days after the first dose. A protection of more than 50% is already seen days earlier. Thus, BNT162b2 seems to provide already a significant level of VE within less than 10 days of the first dose or less than 7 days after the median incubation time of 5 days [4].

Only few studies have estimated the VE of the Pfizer vaccine after a single dose [5-8]. In a large-scale study from Israel, Chodick et al. [5] found a 51% effectiveness against PCR-positive SARS-COV2 infections (with or without symptoms) 13 to 24 days after vaccination with the first dose, compared to the first 1 to 12 days after the first dose as a reference. This comparison may give an underestimation of effectiveness because it ignores any effect caused by an early onset of the immune response. Hunter & Brainard [6] reanalysed the large original data set of Chodick [5], including 500.000 residents and more than 3000 cases under more realistic assumptions. As early as on day 8, daily incidence rates started to decline steadily from 0.06% to 0.01% on day 21 when it leveled off. From this, the authors attempted to calculate the daily change in VE from day 1 to 24 after the first dose. VE increased from about day 14, reaching 90% on day 21. As Chodick [5], Hunter & Brainard [6] assumed that there was no vaccine effect within the first 12 days of the first dose. The interpretation of VE during the first 2 weeks after the first dose was further complicated by an unexplained increase in incidence during this early period, possibly due to relaxed safety attitudes of vaccinees after the first injection. In another study from Israel, Dagan et al. [8] reported a VE of 46% against infection and 57% against symptomatic COVID19 between day 14 to 20 after the first dose. In an unpublished study in vaccinated and unvaccinated HCW, VE was 35% during day 1−14 after the first dose and reached 75% during day 13−24 after the first dose (reported in [7]).

Additional support for an early effect post-vaccination comes from the other mRNA vaccine (Moderna). Vaccine efficacy among those who received only one dose was 50.8% during the first 14 days (5/996, vaccine vs 11/1079 control group) and reached 92.1% (2/983 vs 28/1059) after day 14 [9].

In the elderly VE was measurable only 28 days after the first dose [7,10,11] and vaccine immunogenicity was mixed [12,13]. This suggests that with age the immune response may be delayed and less robust, although this did not show in the Pfizer-BioNTech trial after the 2nd dose [2].

In the Pfizer-BioNTech phase III study the primary endpoint was defined according to FDA criteria as the presence of at least one typical COVID-19 symptom concomitant with a positive PCR test [2]. The dataset of Chodik partially included also asymptomatic/oligosymptomatic cases [5,6]. These two large studies showed that the incidence of PCR-positive cases with mild disease started to decline by day 12 [2] or even by day 8 [6]. This can only be explained by an early immune response and partial protection at the time of the incipient infection several days earlier. This is fully compatible with our understanding of early induced innate effector mechanisms such as interferon induction [14].

The expected benefit of an early post-exposure vaccination would also depend on the COVID19 incubation time: Patients with longer incubation times would have a more time to develop an immune response before symptoms erupt. While the COVID19 incubation time is sometimes given as 5 days [3] it is worth looking at deviations

E-mail address: claude.muller@lih.lu

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from this mean value. In a meta-analysis of 99 studies mean incubation periods ranged from 2.3 to 17.6 days with an overall mean of 6.38 days and a range of 15.27 days, with no significant difference by age and gender [15]. Similar estimates (5.74, 95%CI 5.18−6.3; 5.7, 95%CI 5.1−6.4) were found in two other meta-analysis of 15 and 18 partially overlapping studies [16,17]. For the purpose of this discussion, patients with longer incubation times are of particular interest. In the meta-analyses of Elias et al. [15] the median incubation period was 5.41 days with a large heterogeneity between studies, indicating that overall, 50% of cases had incubations times longer than 5.41 days. Also 40% of the studies included had mean and median values above the 5.41 median average days [15]. During the early phase of the outbreak studies of incubation times could be established with more confidence than when the virus was more widespread, in particular when travellers arriving from a high incidence to a low incidence area [18]. McAloon et al. [18] calculated in their meta-analysis the cumulative distribution of aggregated incubation times. Their median was 5.1 days (95%CI 4.5−5.8). The 75th percentile had a median of 7.15 days (range 6.13 to 8.34); in the 90th and 95th percentile these values increased to 9.69 (8.06 to 11.6) and 11.7 days (9.49 to 14.2). Thus, essentially 15% and 10% of COVID19 patients have an incubation time greater than 8 days and even 10 days. In some studies, up to 30 and 20% of patients came down with symptoms only after day 8 and 10 [19,20,21]. Thus 10 to 30% of cases with an incubation time of more than 8 days could potentially benefit from the concomitant development of an immune response after post-exposure vaccination.

Several additional aspects may further enhance incumbent benefits of post-exposure vaccination:

(i) The primary endpoints in the above relevant studies are mild or even less strict case definitions. However, it is well known from clinical trials of vaccines in general and of SARS-COV2 in particular, that vaccination tends to protect better against severe disease than against mild disease [2,8,22,23]. Thus, the impact of early post-exposure vaccination on the incidence of severe complications, hospitalization and death may be even greater than estimated for mild disease. This was indeed confirmed by Dagan et al. [8] who reported VE of 46% against infection, 57% against symptomatic COVID19, but 74% against hospitalization, 62% against severe illness and 72% against death between day 14 to 20 after the first dose, demonstrating a higher VE against severe disease compared to mild disease.

(ii) Individuals with a weak immunity e.g. after prior asymptomatic disease, may respond with an accelerated immune response, protecting against reinfection after reexposure.

(iii) Since severe complications requiring hospital or ICU admission are usually delayed by a couple of weeks after onset of first symptoms, a considerable immune response may already have developed by then and mitigate the course of the disease.

(iv) Several lines of evidence suggest that after first dose vaccination viral load and infectivity are already reduced [10].

(v) The quarantine is normally terminated according to standard recommendations (e.g. by day 10) often without retesting. In particular, individuals with long incubation times may not be virus-free by the end of the recommended quarantine. Vaccination at the beginning of the quarantine may reduce this risk.

(vi) In the case of high-risk contacts of institutionalized individuals, all residents of the institution should be vaccinated, and in particular secondary/tertiary infected cases would benefit from such a rapid interventional ring-vaccination.

(vii) In many countries the long turn-around time of laboratory-based PCR tests and contact tracing may preclude such a rapid post-exposure vaccination. However, with inexpensive rapid diagnostic tests (RDT) and proper logistics the turn-around time until vaccination could be dramatically reduced.

Of note, to demonstrate the efficacy of post-exposure vaccination in mitigating at least severe COVID19 disease would require a large randomized control trial. However, even in the absence of such a trial, my prejudice is that the approach would cause no harm and that recipients could only benefit.

This discussion ignored interactions between length of incubation time, severity of disease, age, and immune competence and logistics. It was focused on the BNT162b2 mRNA Covid19 vaccine by Pfizer-BioNTech. However, similar effects have also be observed with other Covid19 vaccines [9, 23].

One of the main public health interventions to contain the SARS-COV2 pandemic is tracing and quarantining of contacts after high-risk exposure. Considering the timeline of the incipient immune response after SARS-COV2 vaccination and COVID19 incubation times, a significant number of individuals may benefit from an immediate post-exposure vaccination. They would be vaccinated as soon as their index case is tested positive and before being send to quarantine. Integrated with a rapid and flexible testing strategy based on RTDs, post-exposure vaccination may be a realistic perspective to further reduce (at least) severe cases in previously unvaccinated individuals.

Author's contribution

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Declaration of Competing Interest

The author declares no competing interests.

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