RESEARCH HIGHLIGHT

Timing vaccination against SARS-CoV-2

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Circadian rhythms play an important role in balancing innate and adaptive immune responses. In a recent study in *Cell Research*, Zhang et al. studied the immunological response in humans to an inactivated SARS-CoV-2 vaccine administered at two different times of the day and showed that vaccination in the morning induces a two-fold stronger immune response.

Since late 2019, the world is facing a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). An unprecedented scientific effort has led to the development of several vaccines against SARS-CoV-2 in an extraordinary short period. However, providing the world with vaccines at sufficient quantities is challenging given the difficulties in producing and delivering them to large populations, especially in developing countries and when multiple doses are required to gain complete immunity. Therefore, there is an urgent need to maximize the efficacy of vaccines to control this pandemic.

Virtually all physiological processes, including the immune system, are regulated by circadian rhythms, intrinsic cellular oscillations that exhibit a period length of ~24 h.[1] In the adaptive immune system, studies have demonstrated a time-of-day difference, such as seen in the trafficking of lymphocytes to lymph nodes[2] and their proliferation.[3] In addition to their role during homeostasis, circadian rhythms are also implicated in pathological conditions, including influenza infection[4] and autoimmune diseases,[2,5] during which they strongly modulate the response to inflammation. Such observations have led to the development of chronotherapies targeting the immune system, where time of day is used to enhance the treatment efficacy. In the context of vaccination, temporal oscillations in antibody production in response to the timed administration of specific antigens have been observed in both mice[6,7] and humans.[8,9]

A study by Zhang and colleagues in *Cell Research*,[10] has now investigated the immunological response to an inactivated SARS-CoV-2 vaccine administered to a cohort of healthcare workers either in the morning or in the afternoon. The authors found that volunteers who got vaccinated in the morning exhibited a significantly stronger immune response (Fig. 1). A total of 63 volunteer healthcare workers (aged 24–28) were administered the inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Sinopharm) at two times of day. The first cohort received the two vaccine doses on day 0 and day 28 in the morning between 9 am and 11 am, while the second cohort received both doses in the afternoon between 3 pm and 5 pm. The efficacy of morning or afternoon vaccine administration was evaluated by taking regular blood samples from the participants. Strikingly, the serological response to the vaccine was different between morning-vaccinated and afternoon-vaccinated cohorts with two-fold higher levels of

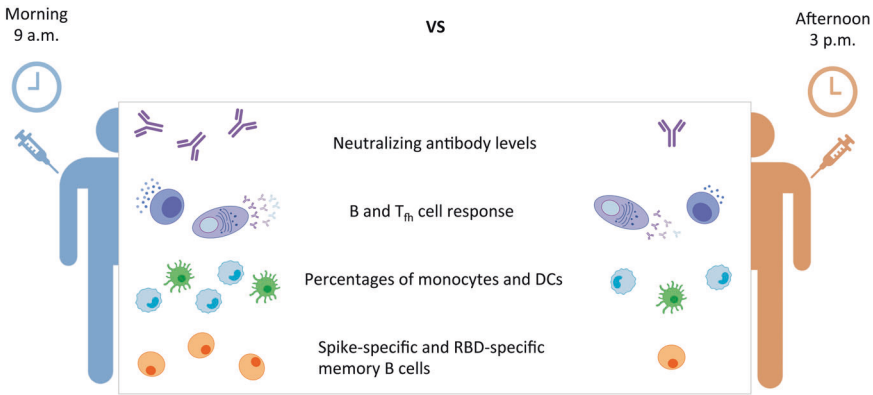

Fig. 1 Benefits of morning vaccination. Zhang et al. administered an inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Sinopharm) to 63 volunteer healthcare workers (aged 24–28) separated into two groups who received the vaccine at two different times of the day (morning 9–11 am or afternoon 3–5 pm). Participants who received the vaccine in the morning experienced a stronger immune response with higher neutralizing antibody levels, stronger B and T_{fh} cell response, and higher percentages of monocytes and DCs as well as spike-specific and RBD-specific memory B cells. T_{fh}, T follicular helper cells; DCs, dendritic cells; RBD, receptor binding domain.

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neutralizing antibodies in the morning-vaccinated cohort—an effect already observed after the first dose but with a more striking effect after two doses. Moreover, cellular responses to vaccination exhibited a time-of-day difference with stronger B cell and follicular T helper cell (T_{fh}) responses, as well as higher frequencies of monocytes and dendritic cells (DCs) in the morning cohort. In addition, the authors observed differences in memory B cells, indicating that vaccination in the morning could trigger a stronger long-term immunity than that in the afternoon. Thus, a simple change in time alters the vaccination response.

Findings uncovered by Zhang and colleagues will be key to the optimization of SARS-CoV-2 vaccination strategies. Similar higher morning effectiveness for an influenza vaccine[9] indicate that this concept should also be applicable to other vaccines. However, it is currently not known whether these observed time-of-day dependent changes in the vaccination response provide a real benefit, i.e., a better protection against the virus. Following differently time-treated patient cohorts over time will be essential to assess this. A second important remaining question is whether the occurrence and strength of adverse effects associated with different vaccines are also dependent on the time of the day. Nevertheless, these data provide fundamental evidence for circadian rhythms in vaccination responses in humans, which is surprising, given that these take weeks to develop. Understanding the precise mechanisms on how these rhythms are initially generated and how they are maintained over such a long time frame will be critical for the design of better treatments targeting this important regulatory aspect of any immune response.

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COMPETING INTERESTS

The authors declare no competing interests.

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