



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

- 10 Flament H, Rouland M, Beaudoin L, et al. Outcome of SARS-CoV-2 infection linked to MAIT cell activation and cytotoxicity: evidence for an IL-18 dependent mechanism. *medRxiv* 2020; published online Sept 2. <https://doi.org/10.1101/2020.08.31.20185082> (preprint).
- 11 Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor fedratinib. *J Microbiol Immunol Infect* 2020; **53**: 368–70.
- 12 Muir R, Osbourn M, Dubois AV, et al. Innate lymphoid cells are the predominant source of IL-17A during the early pathogenesis of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2016; **193**: 407–16.
- 13 Provine NM, Amini A, Garner LC, et al. MAIT cell activation augments adenovirus vector vaccine immunogenicity. *Science* 2021; **371**: 521–26.
- 14 Carolan E, Tobin LM, Mangan BA, et al. Altered distribution and increased IL-17 production by mucosal-associated invariant T cells in adult and childhood obesity. *J Immunol* 2015; **194**: 5775–80.
- 15 O'Brien A, Loftus RM, Pisarska MM, et al. Obesity reduces mTORC1 activity in mucosal-associated invariant T cells, driving defective metabolic and functional responses. *J Immunol* 2019; **202**: 3404–11.

## Could a good night's sleep improve COVID-19 vaccine efficacy?



More than 2 million people have died from COVID-19, caused by SARS-CoV-2.<sup>1</sup> In an unprecedented effort to develop vaccines to control the COVID-19 pandemic, mRNA, protein subunit, and viral vector-based vaccines have been developed within an extraordinarily swift timeframe. However, the efficacy of these vaccines (ie, their ability to reduce the incidence of severe disease and death from COVID-19) can vary considerably. For example, among 43 448 adults, the efficacy of the mRNA-based COVID-19 vaccine produced by Pfizer and BioNTech ranged between 29.5% and 68.4% against symptomatic COVID-19 after the first dose, and between 90.3 and 97.6% after the second dose.<sup>2</sup> By comparison, in an interim analysis of ongoing clinical trials (involving 23 484 participants), the corresponding efficacy of two standard doses of the ChAdOx1 nCoV-19 adenovirus vector vaccine produced by AstraZeneca ranged between 41.0% and 75.2%.<sup>3</sup>

Although data from phase 3 trials indicate that factors such as age and biological sex might not be as prominent in modulating the efficacy of certain COVID-19 vaccines (eg, in case of the mRNA-based COVID-19 vaccine produced by Pfizer and BioNTech),<sup>2</sup> the role of sleep in this context is unclear. As suggested by previous studies, sleep duration at the time of vaccination against viral infections can affect the immune response (figure). For instance, 10 days after vaccination against the seasonal influenza virus (1996–97), IgG antibody titres in individuals who were immunised after four consecutive nights of sleep restricted to 4 h were less than half of those measured in individuals without such sleep deficits.<sup>4</sup> Similarly, shorter actigraphy-based sleep duration was associated with a lower secondary antibody response to hepatitis B vaccination.<sup>5</sup> Sleep

might also boost aspects of virus-specific adaptive cellular immunity. Compared to wakefulness, sleep in the night following vaccination against hepatitis A doubled the relative proportion of virus-specific T helper cells, which are known to play a prominent role in host-protective immune responses.<sup>6</sup> Interestingly, in individuals who slept the night after the first vaccination, the increase in the fraction of interferon- $\gamma$  (IFN- $\gamma$ )-positive immune cells at weeks 0–8 was significantly more pronounced than in those who had stayed awake on that night.<sup>6</sup> IFN- $\gamma$  directly inhibits viral replication and activates immune responses to eliminate viruses, thus protecting the host against virus-induced pathogenesis and lethality.<sup>7</sup> Further emphasising the importance of sleep in the fight against viral pandemics, lack of sleep in the night after vaccination against the 2009 H1N1 influenza virus was found to reduce the early-phase production of H1N1-specific antibodies in men but not women.<sup>8</sup> Finally, nocturnal sleep has been shown to promote a cytokine milieu supporting adaptive cellular immune responses, such as decreased activity of the anti-inflammatory cytokine interleukin-10 and

Published Online  
 March 12, 2021  
[https://doi.org/10.1016/S2213-2600\(21\)00126-0](https://doi.org/10.1016/S2213-2600(21)00126-0)

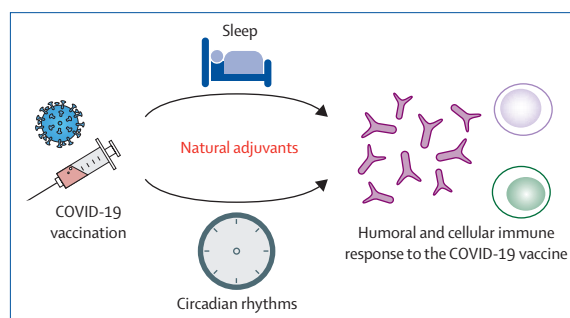


Figure: Post-vaccination sleep and morning timing of vaccination as possible immune adjuvants for COVID-19 vaccination

increased activity of the pro-inflammatory cytokine interleukin-12.<sup>9</sup> Although these data suggest that extending sleep duration at the time of vaccination can boost host immune responses, there is no evidence indicating that sleep quality and moderate-to-severe obstructive sleep apnoea are related to antibody responses to vaccination against viruses.<sup>5,10,11</sup>

Whether reduced antibody production due to sleep loss can impact vaccine efficacy remains largely undetermined. In one study investigating the impact of acute sleep loss in the night following vaccination against hepatitis A in healthy young adults, a small subsample of individuals failed to reach the clinically significant antibody level at week 20—the threshold for an additional vaccination.<sup>6</sup> For most healthy people, sleep loss in the night after vaccination might be of minor concern with respect to the vaccine's efficacy. However, among those whose immune systems' ability to fight infectious diseases is compromised or absent (eg, immunosuppressed individuals), extending sleep duration during the night after the vaccination might help ensure an adequate response to vaccines and potentially contribute to reducing the incidence of severe disease. Furthermore, emerging variants of SARS-CoV-2 might modulate vaccine efficacy against COVID-19. In particular, mutations found in the variant B.1.351 might reduce vaccine-derived neutralisation of SARS-CoV-2 by the mRNA vaccines by about threefold to sixfold.<sup>12</sup> In this context, the difference in antibody levels, due to differences in sleep duration in the night after vaccination, might become clinically more significant. Encouragingly, for some individuals, sleep duration might even have increased during the COVID-19 pandemic, possibly as a result of greater work flexibility that enables improved daily activities with individual sleep-wake preferences.<sup>13</sup>

Since the immune system exhibits marked circadian rhythmicity,<sup>14</sup> the timing of vaccination might also affect the immune response to COVID-19 vaccines. For instance, one study found that administering hepatitis A and influenza vaccines in the morning instead of the afternoon results in an almost twofold higher antibody titre 4 weeks later, an effect only seen in men.<sup>15</sup> Thus, it is possible that administering COVID-19 vaccines in the morning might result in higher antibody titres. However, several uncertainties remain, such as how to determine the appropriate time of vaccination for night-shift workers. This group often has chronic circadian disruption

and exhibits a markedly greater risk of COVID-19 diagnosis.<sup>16</sup>

Given the urgency of achieving effective global COVID-19 vaccination, we strongly advocate gathering information about individuals' sleep patterns preceding and following vaccination, as well as information about vaccination timing. Combined with data such as baseline serostatus, possible re-infections, work schedules, and comorbidities, monitoring of sleep and the timing of vaccination could provide more conclusive information for public health agencies, health-care providers, patients, and vaccine developers about the importance of these factors for optimising vaccine efficacy.

We declare no competing interests.

*Christian Benedict, \*Jonathan Cedernaes*  
jonathan.cedernaes@medsci.uu.se

Department of Neuroscience (CB), and Department of Medical Sciences (JC), Uppsala University, Sweden

- 1 Wu A, Peng Y, Huang B, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 2020; **27**: 325–28.
- 2 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**: 2603–15.
- 3 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**: 99–111.
- 4 Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *JAMA* 2002; **288**: 1471–72.
- 5 Prather AA, Hall M, Fury JM, et al. Sleep and antibody response to hepatitis B vaccination. *Sleep* 2012; **35**: 1063–69.
- 6 Lange T, Dimitrov S, Bollinger T, Diekelmann S, Born J. Sleep after vaccination boosts immunological memory. *J Immunol* 2011; **187**: 283–90.
- 7 Presti RM, Pollock JL, Dal Canto AJ, O'Guin AK, Virgin HW 4th. Interferon gamma regulates acute and latent murine cytomegalovirus infection and chronic disease of the great vessels. *J Exp Med* 1998; **188**: 577–88.
- 8 Benedict C, Brytting M, Marksström A, Broman JE, Schiöth HB. Acute sleep deprivation has no lasting effects on the human antibody titer response following a novel influenza A H1N1 virus vaccination. *BMC Immunol* 2012; **13**: 1.
- 9 Lange T, Dimitrov S, Fehm HL, Westermann J, Born J. Shift of monocyte function toward cellular immunity during sleep. *Arch Intern Med* 2006; **166**: 1695–700.
- 10 Dopp JM, Wiegert NA, Moran JJ, Muller D, Weber S, Hayney MS. Humoral immune responses to influenza vaccination in patients with obstructive sleep apnea. *Pharmacotherapy* 2007; **27**: 1483–89.
- 11 Prather AA, Pressman SD, Miller GE, Cohen S. Temporal links between self-reported sleep and antibody responses to the influenza vaccine. *Int J Behav Med* 2021; **28**: 151–58.
- 12 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum—preliminary report. *N Engl J Med* 2021; published online Feb 17. <https://doi.org/10.1056/nejmc2102017>.
- 13 Blume C, Schmidt MH, Cajochen C. Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms. *Curr Biol* 2020; **30**: R795–97.
- 14 Druzd D, Matveeva O, Ince L, et al. Lymphocyte circadian clocks control lymph node trafficking and adaptive immune responses. *Immunity* 2017; **46**: 120–32.
- 15 Phillips AC, Gallagher S, Carroll D, Drayson M. Preliminary evidence that morning vaccination is associated with an enhanced antibody response in men. *Psychophysiology* 2008; **45**: 663–66.
- 16 Rizza S, Coppeta L, Grelli S, et al. High body mass index and night shift work are associated with COVID-19 in health care workers. *J Endocrinol Invest* 2020; published online Aug 27. <https://doi.org/10.1007/s40618-020-01397-0>.