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REVIEW

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Sufficient Sleep, Time of Vaccination, and Vaccine Efficacy: A Systematic Review of the Current Evidence and a Proposal for COVID-19 Vaccination

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Introduction: The emergence of the novel Coronavirus Disease 2019 (COVID-19) sparked an unprecedented effort to develop effective vaccines against the disease. Some factors may boost the vaccine efficacy, including sufficient sleep and morning vaccination. We aimed to conduct a rapid systematic review to summarize data regarding the association between sleep and time of vaccination with immunity after vaccination. **Materials and Methods**: The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, and three databases (PubMed, Web of Science, and Scopus) were searched up to March 12, 2022. **Results**: Eight studies were included regarding the sleep and immune response after vaccination, of them, five studies were on influenza, two studies on hepatitis A (HAV), and one study on hepatitis B. Accordingly, six out of eight studies found a positive correlation between sleep and immune response after vaccination. Regarding the time of vaccination, seven studies were eligible to be included (two studies on influenza, one study on HAV and influenza, one study on BCG, one study on hexavalent vaccine, and two studies on SARS-CoV-2 vaccine). Among them, four out of seven studies (including a study on SARS-CoV-2 inactivated vaccine) reported the priorities of morning versus afternoon vaccination regarding antibody production and immune response after vaccination. **Conclusion**: Taken together, cumulative evidence suggests that sufficient sleep and vaccination in the morning could enhance the immune response after vaccination. Hence, modulating the time of vaccination and sufficient sleep could a be simple and applicable strategy for increasing vaccine efficacy. Future studies could be performed with SARS-CoV-2 vaccines to investigate the effects of time of vaccination and sufficient sleep on COVID-19 vaccine efficacy.

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Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; BCG, bacillus Calmette-Guérin; HAV, Hepatitis A; OSA, obstructive sleep apnea; Th, T helper; CER, cardiorespiratory event rate; HCWs, healthcare workers; Nab, neutralizing antibody; Tfh, follicular helper T; ASC, antibody-secreting cells; Ab, Antibody; HI, hemagglutination inhibition; PSQI, Pittsburgh Sleep Quality Index; PBMCs, Peripheral blood mononuclear cells; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; IFN-γ, Interferon gamma; Nabs, neutralizing antibodies; ASCs, antibody-secreting cells; GH, Growth hormone.

Keywords: COVID-19, SARS-CoV-2, vaccine, morning vaccination, sleep, circadian rhythm

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China in late 2019 and immediately spread throughout the world to become a pandemic [1]. The virus mainly spreads through respiratory droplets [2]; however, close contact with the contaminated surface may be responsible for COVID-19 transmission [2-5]. The disease affects people of all ages, nevertheless, elder people (>60 years old), males, and patients who have comorbidities or coinfections, have a higher risk of morbidity and mortality [6-11].

Respiratory symptoms, such as dyspnea, cough, sore throat, loss of smell and taste, as well as fever are the main clinical manifestations of COVID-19 [12]. Although, new variants of SARS-CoV-2, such as B.1.617.2 (Delta), can cause more severe diseases and their symptoms are different from the typical symptoms of COVID-19 [8]. Nevertheless, in addition to respiratory symptoms (eg, acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure), multiorgan involvement, such as gastrointestinal, neurologic, cardiac, hepatic, renal, endocrine, ocular, and dermatologic manifestations have occurred in severe COVID-19 cases [12,13].

Although such drugs (eg, Remdesivir, and Paxlovid) and monoclonal antibodies (eg, Bamlanivimab/Etesevimab and Casirivimab/Imdevimab) are approved by the Food and Drug Administration (FDA) for SARS-CoV-2 virus, strategies to reduce hyperinflammation and cytokine storm syndrome (CSS) is the best available therapy against COVID-19 [8].

Numerous factors can influence the immune response following vaccination [14], including intrinsic host factors (eg, age, sex, genetic background, and comorbidities), extrinsic factors (eg, coinfection), behavioral factors (eg, exercise, stress, sleep, smoking, and alcohol consumption), nutritional factors (eg, BMI (body mass index) and nutritional status), environmental factors (eg, rural versus urban environment, season, and geographic location), vaccine factors (eg, vaccine type, adjuvants, vaccine dose, and booster dose), and administration factors (eg, vaccination route and time of day) (reviewed in [14]). However, some factors are easily enacted to improve vaccine potency, including sufficient sleep and morning vaccination. Hence, we aimed to perform a rapid review regarding the association between sleep and time of vaccination with immunity after vaccination.

MATERIALS AND METHODS

Search Strategy, Inclusion, and Exclusion Criteria

The data were selected according to the standard protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. Three databases (PubMed, Web of Science, and Scopus) were searched by two independent researchers (AA and ER) up to March 12, 2022. We searched in title and abstract by the search terms ("vaccine" OR "vaccination") AND ("sleep" OR "morning" OR "time"). The relevant documents were screened by title and abstract, then duplicates were removed, and the remaining records were evaluated by two investigators (AA and ER). Finally, full texts of the articles were evaluated for eligibility and inclusion criteria. The inclusion criteria were: (1) original articles; (2); articles with full-text or abstract in English without geographical restrictions; and (3) articles that provided the exact total sample size. Non-original articles (eg, reviews, editorials, and/or letters to the editor) and those with unclear analysis and sufficient data were excluded. The citations to the eligible articles were checked in Google Scholar to retrieve any missing references.

RESULTS

After performing the PRISMA protocol (Figure 1, Figure 2, and Appendix A), eight and six articles were eligible to be included for "sleep" and "time of vaccination," respectively (Table 1 and Table 2). The main characteristics of each study are summarized in Tables 1 and 2.

Sleep and Immune Response After Vaccination

Eight studies evaluated the relationship between sleep and vaccine efficacy, including five studies on influenza, two studies in hepatitis A (HAV), and one study in hepatitis B (Table 1). Regarding influenza vaccination, Spiegel et al. found that sleep deprivation at the time of influenza vaccination reduced the antibody response after vaccination [16]. However, Dopp et al. did not find a significant difference between moderate-to-severe obstructive sleep apnea (OSA) and influenza antibody responses after vaccination [17]. Benedict et al. did not find a significant difference between acute sleep deprivation on the antibody response to H1N1 (swine flu) virus vaccination [18]. Taylor et al. found that individuals with insomnia had a lower antibody response following influenza vaccination [19]. Prather et al. found that shorter sleep duration was associated with fewer antibodies to the flu vaccine 1- and 4-months after vaccination [20]. Regarding HAV vaccination, Lange et al. demonstrated that sleep on the night after HAV vaccination improves the antibody response compared with the sleep deprivation group [21]. Another study by the same group of researchers revealed that sleep after HAV vaccination increased the frequency of Ag-specific T helper1 (Th1) cytokine-producing cells compared with the sleep deprivation group. Indeed, sleep

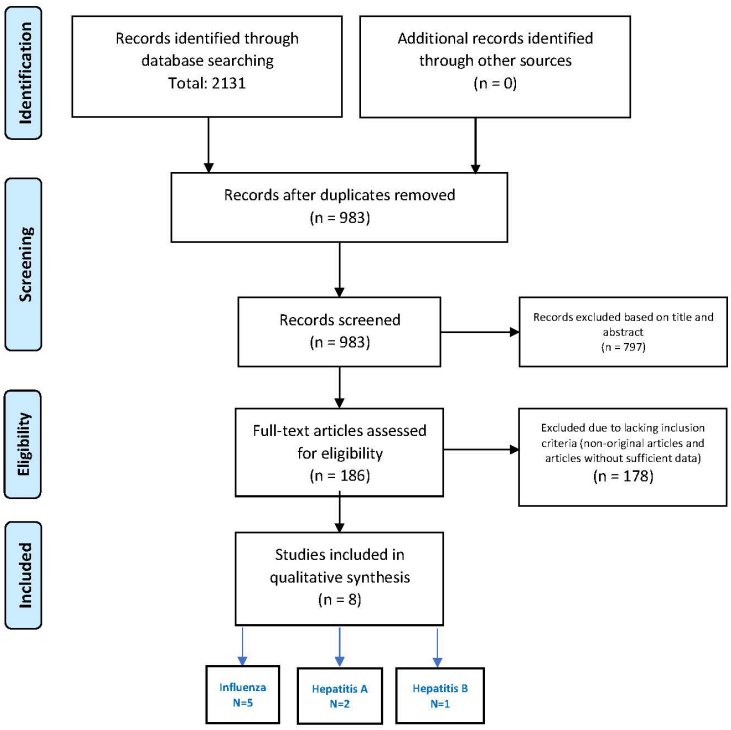

Figure 1. **PRISMA diagram through the different phases of the review regarding sleep and vaccination**

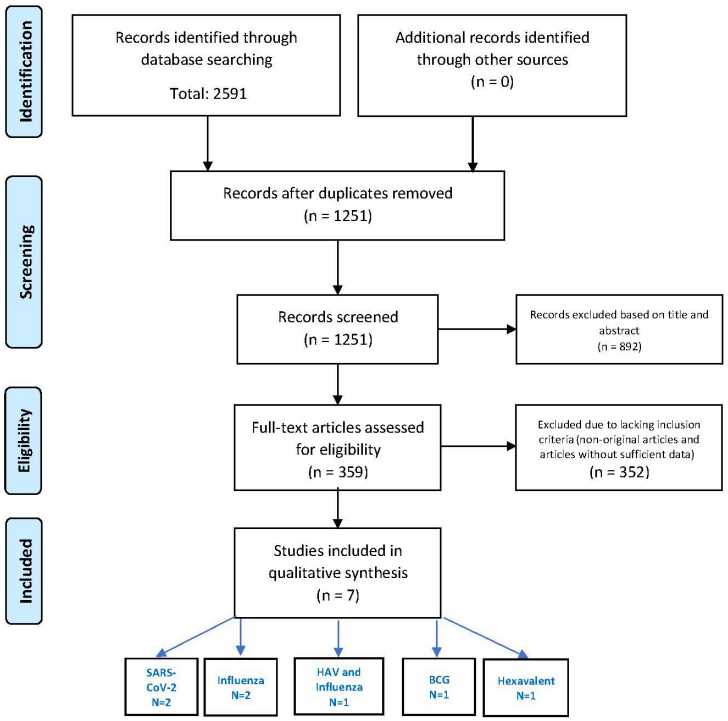

Figure 2. **PRISMA diagram through the different phases of the review regarding time of vaccination**

markedly increased Ag-specific IgG1 antibody response compared with the sleep deprivation group [22]. Regarding hepatitis B, Prather et al. found that shorter actigraphy-based sleep duration was associated with lower antibody response following immunization with hepatitis B vaccine [23] (Table 1).

Time of Vaccination

Seven studies eligible to be included regarding morning versus evening vaccination, including two studies on influenza, one study on HAV and influenza, one study on BCG, one study on hexavalent vaccine, and two studies on SARS-CoV-2 vaccine (Table 2). Phillips et al. compared the efficacy of influenza and HAV vaccines that injected in the morning versus afternoon [24]. They found that morning vaccination in men, but not women, enhanced the antibody response to both influenza and HAV [24]. Long et al. demonstrated that antibody response to influenza vaccine in older adults was mounted among those individuals who vaccinated in the morning than the afternoon [25]. The data by Kurupati et al. did not support that the time of vaccination could affect the immune response to influenza vaccine [26]. de Bree et al. investigated the time of Bacillus Calmette–Guérin (BCG) vaccination [27]. They found that morning vaccination induces stronger immune responses compared with evening vaccination [27]. Gottlob et al. did not identify a significant difference in antibody titers and cardiorespiratory event rate (CER) between morning and evening vaccination among infants who received their first hexavalent vaccine [28]. In a recent study, Zhang et al. investigated the dynamics of immune responses following administration of an inactivated SARS-CoV-2 vaccine among 63 healthcare workers (HCWs) who received vaccine in the morning (9 am–11 am) or afternoon (15 pm–17 pm) [29]. They found that participants vaccinated in the morning had significantly higher level of neutralizing antibodies (NAbs) in the serum as well as stronger B cells, monocytes, dendritic cells, and Tfh cells responses to vaccination. These data suggest the priority of morning than afternoon COVID-19 vaccination [29]. Wang et al. assessed the levels of anti-Spike antibody response following two types of SARS-CoV-2 vaccines (Pfizer, mRNA bnt162b2 or AstraZeneca, Adenoviral AZD1222) in three times of vaccination (**Time 1**, 7-10:59 h; **Time 2**, 11-14:59 h; **Time 3**, 15-21:59 h) among 2784 health care workers in UK [30]. The results revealed that anti-Spike antibody levels were significantly higher following the administration of two alternative SARS-CoV-2 vaccines (mRNA or adenovirus based). However, the results did not indicate an association between the time of day of vaccination ($p = .23$), day of sample collection ($p = 0.097$), and two time intervals (before or after 1 pm) with anti-Spike antibody response [30] (Table 2).

DISCUSSION

The circadian rhythms have a pivotal role in the functions of our immune system; disruption of circadian rhythms leads to disruption of the immune response to pathogens [31,32]. Sleep disturbances and variable sleep patterns have been occurring in shift workers, which could disrupt the circadian rhythm, leading to an increased risk for developing viral infections [33]. Concerning COVID-19, it was observed that night shift workers have higher odds of COVID-19 severity [34-36]. Sleep deprivation has been linked to disturbance of innate and adaptive immune responses, resulting in chronic inflammatory conditions, and an increased risk for infectious diseases [37]. Human studies demonstrated that sufficient sleep was associated with a balance of T helper 1/T helper 2 cytokines [38]. Studies have found that vaccine efficacy may reduce in individuals suffering from chronic insomnia [19] and those subjected to sleep deprivation conditions [21]. Vaccines that were employed in human studies mainly induce Th1-dependent IgG responses, which were selectively improved by sleep compared with nocturnal wakefulness [39]. Sleep after vaccination could enhance immunological memory by promoting type I immune responses and antibody production [21,22]. Regarding sleep and vaccination, evidence has shown that anti-influenza IgG antibody titers among individuals with sleep deprivation at the time of vaccination with influenza vaccine declined compared with those with normal sleep times [16]. Another piece of evidence regarding the effects of sleep on immunity after influenza vaccination was revealed that individuals who had shorter sleep on the days before and after vaccination had a lesser immune response after the initial vaccination [20]. Regarding the HAV vaccine, an interventional study in humans demonstrated that sleep after vaccination increased Ag-specific IgG1 and Th cells compared with the wake condition group [22]. Another study among individuals who received the HAV vaccine revealed that subjects who had regular sleep had a nearly two-fold higher HAV antibody titers after 4 weeks than subjects who stayed awake that night [21]. Shorter sleep duration was also associated with lower antibody response after hepatitis B vaccination [23].

Melatonin is one of the main players in the physiology of sleep [40]. Melatonin is as an immunoregulatory hormone that could mitigate both severe inflammatory cascades and immunosuppression status [40]. It is proposed that melatonin could reduce the severity of COVID-19 via mitigating severe inflammation in response to SARS-CoV-2 [40].

In an expert review, Garbarino et al. reviewed the role of sleep deprivation in immune-related diseases [37]. They mentioned several beneficial effects of normal sleep

Table 1. A Snapshot of the Research in Sleep and Vaccination

Type of vaccine, year of publication, country	Setting/methods	Main findings	Conclusion	Ref
►Influenza 2002, USA	►**Setting:** Case-control (two groups were matched for age (mean age: 23 years), sex (all participants were males), and ethnicity. ►Case group: 11 young men with bedtime restricted to 4 hours for 6 nights and then extended to 12 hours per night for 7 nights to recover from sleep loss (as sleep deprivation group) were included for influenza vaccination. ►Control group: 25 healthy young men with bedtime 7.5-8.5 hours (as normal sleep group). ►Types of vaccine: Influenza Virus Vaccine, Trivalent types A and B, Fluogen. ►Types of vaccine administration: intramuscular injection. ►Anti-influenza IgG titers were measured at three times: before vaccination, 10 days after vaccination, and 21 to 30 days after vaccination.	►Antibody titers (IgG) were higher in normal sleep group compared with sleep deprivation group 10 days after vaccination.	►Sleep deprivation at the time of vaccination reduced antibody response to antigen after vaccination.	[16]
►Influenza 2007, USA	►**Setting:** Case-control ►Case group: 14 individuals (11 males and 3 females) with Obstructive Sleep Apnea (OSA); mean age of 44 ± 4 years. ►Control group: 17 healthy individuals (10 males and 7 females); mean age of 43 ± 2 years. ►Types of vaccine: Influenza Virus Vaccine (The (H1N1)-like and B/Shanghai/361/2002-like viral strains were used for vaccine design. ►Types of vaccine administration: intramuscular injection. ►All subjects were given the influenza vaccine for the years 2004–2005 or 2005–2006. ►Antibody titers were measured before and 2–4 weeks after vaccination using the hemagglutination inhibition (HI) assay.	►No significant differences were observed in antibody concentration, frequencies of seroconversion, or rates of seroprotection between subjects with OSA and control subjects.	►Moderate-to-severe OSA did not impair humoral responses to the influenza vaccine in these subjects.	[17]
►Influenza 2012, Sweden	►**Setting:** Case-control ►Case (sleep deprivation) group: 11 (5 males and 6 females); mean age of 20.4 ± 0.5 years. ►Control (normal sleep) group: 13 (5 males and 8 females); mean age of 20.6 ± 0.4 years. ►Types of vaccine: H1N1 (swine flu) virus vaccine. ►Types of vaccine administration: intramuscular injection. ►Effects of regular 24-hour sleep-wake cycle (8 hours of nocturnal sleep) were assessed in response to the H1N1 (swine flu) virus vaccination. ►The antibody titer was assayed by the HI test on the days 5, 10, 17, and 52 following vaccination.	►In comparison to the sleep group, sleep deprivation males but not females had reduced serum concentration of H1N1-specific antibodies five days after vaccination, whereas antibody titers at later time points did not differ between the conditions.	►The results do not support the view that acute sleep deprivation has lasting effects on the human antibody titer response to influenza vaccination.	[18]

►Influenza 2016, USA	►**Setting:** Case-control ►Case group: 65 healthy young adult students with Insomnia (26 males and 39 females); mean age of 20.35± 2.8 years. ►Control: 68 healthy young adult students without Insomnia (27 males and 41 females); mean age of 19.94 ± 2.2 years. ►Types of vaccine: In 2011–2012, the trivalent vaccine contained A/California/7/ 2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 viruses. In 2012–2013, the trivalent vaccine again contained A/California/7/09 (H1N1), as well as the new A/Victoria/361//2011(H3N2), and B/Wisconsin/1/2010 viruses. ►Types of vaccine administration: intramuscular injection. ►Case and control groups were compared for influenza serum antibody levels pre- and four weeks postvaccination using HI assay.	►Both groups had a significant increase in antibody levels pre- to post-vaccination, but Insomnia group had lower HI antibody levels overall. ►Exploratory analyses did find significant Pittsburgh Sleep Quality Index (PSQI) and Insomnia Status interaction effects.	►Insomnia may be a risk factor for decreased immunity to the influenza virus.	[19]
►Influenza 2021, USA	►**Setting:** Cohorts ►Types of vaccine: The trivalent vaccine consisted of three antigens: A/New Caledonia, A/Panama, and B/Yamanashi or B/Victoria. ►Types of vaccine administration: intramuscular injection. ►Eighty-three healthy young adults (aged 18–25 years, 44% male) completed 13 days of sleep diaries and received the trivalent influenza vaccine on day 3 of the study. ►Antibody levels were measured using HI assay at baseline and 1- and 4-months following vaccination.	►Shorter sleep duration was associated with fewer antibodies response 1- and 4-months after vaccination, independent of baseline antibodies, age, sex, and cohort year. ►Shorter sleep duration on the **two nights before** the vaccination predicted fewer antibodies 1- and 4-months after vaccination.	►The results support for an association between sleep duration and antibody responses to the influenza vaccine.	[20]
►Hepatitis A 2003, Germany	►**Setting:** Interventional ►Types of vaccine: Inactivated hepatitis A virus. ►Types of vaccine administration: intramuscular injection. ►Two groups of healthy humans (N=19; aged 20 to 35 years) were assessed. ►Ten subjects (5 women) participated in the **sleep condition** examined during two consecutive regular 24-hour sleep–wake cycles with nocturnal sleep between 23 and 7 hours. ►Nine subjects (4 women) were assigned to the **wake condition** had a regular sleep-wake cycle within the first 24-hour period, but were kept awake during the second night. ►On the night after vaccination, which took place at 9 hours, one group had regular sleep. The other group stayed awake, and did not sleep before 21 hours the following day. ►HAV antibody titers were measured repeatedly until 28 days after vaccination. ►Plasma hormone concentrations and white blood cell (WBC) subset counts were determined on the night and day after vaccination.	►A nearly two-fold higher HAV antibody titer was detected in subjects who had regular sleep after 4 weeks than subjects staying awake on this night (p=0.018). ►An increased release of growth hormone, prolactin, and dopamine (p=0.01) was detected among regular sleep subjects compared with wakefulness. ►Thyrotropin, norepinephrine, and epinephrine concentrations were lowered by sleep (p=0.02).	►Sleep on the night after vaccination improves formation of antigen-specific immune defense.	[21]

►Hepatitis A 2011, Germany	►**Setting:** Interventional ►Types of vaccine: Inactivated hepatitis A virus. ►Types of vaccine administration: intramuscular injection. ►Twenty-seven healthy men (mean age of 26.1 ± 0.7 years) were vaccinated against hepatitis A three times, at weeks 0, 8, and 16. ►Sleep conditions versus wakefulness in the following night were assessed. ►Sleep was recorded polysomnographically, and hormone levels were assessed throughout the night. ►Th cells and Ab responses were repeatedly monitored for 1 year after vaccination.	►Sleep after vaccination doubled the frequency of Ag-specific Th cells and increased the fraction of Th1 cytokine-producing cells compared with the wake condition. ►Sleep markedly increased Ag-specific IgG1.	►Sleep after vaccination improves Ag-specific antibody and Th cell responses.	[22]
►Hepatitis B 2012, USA	►**Setting:** Observational ►Types of vaccine: hepatitis B virus. ►Types of vaccine administration: intramuscular injection. ►Healthy midlife adults (n = 125; 70 females; age 40-60 years) received the standard 3-dose hepatitis B vaccination series. ►Sleep duration, sleep efficiency, and subjective sleep quality were assessed. ►Antibody titers were measured prior to the 2nd and 3rd vaccination. ►Anti-hepatitis B surface antigen immunoglobulin G was assessed 6 months after the final immunization.	►Shorter actigraphy-based sleep duration was associated with a lower secondary antibody response independent of age, sex, body mass index, and response to the initial immunization. ►Shorter sleep duration was also predicted a declining likelihood of protected from hepatitis B. ►Neither sleep quality nor sleep efficiency were significantly predicted antibody response.	►Short sleep duration may negatively affect antibody responses to novel antigens.	[23]

Ab: Antibody; Th: T helper; HAV: Hepatitis A vaccine; OSA: obstructive sleep apnea; HI: hemagglutination inhibition; PSQI: Pittsburgh Sleep Quality Index

on the vaccination response, including (1) sleep led to the accumulation of circulating immune cells into lymphatic tissues, which resulted in increasing the likelihood of encountering antigens and triggering the immune response; (2) sleep is associated activation of Th1 cytokines, which consequently may favor antigen presentation by antigen presenting cells (APCs), and T-cell and B-cell activation; (3) sufficient sleep has a pivotal influence on stress hormones, for instance, concentrations of cortisol mitigates hormones after sufficient sleep compared with night workers. Furthermore, sufficient sleep enhances the production of growth hormone (GH), prolactin, and aldosterone, which consequently support Th1 cell-mediated immunity, and may enhance an effective adaptive immune response to challenge with antigens and vaccines [37]. Hence, a good night's sleep may enhance vaccine efficacy by improving the immune response against vaccine antigens [41,42].

Regarding morning versus evening vaccinations, evidence has shown that morning vaccinations for HAV and influenza are associated with an enhanced antibody response in men [24]. Influenza vaccination in the morning enhances antibody response over afternoon vaccination among healthy adults [25]. Although, another study did not support this evidence following influenza vaccination among adults >65 years age [26]. A recent study revealed that BCG vaccination in the morning induces a stronger immune response and trained immunity compared with evening vaccination in healthy volunteers [27]. Two recent studies investigated the effects of vaccination time on the immune response following COVID-19 vaccination [29,30]. While a very recent study reported the priority of morning vaccination with an inactivated SARS-CoV-2 vaccine in China [29], another report [30] did not find a clear relationship between vaccination time of mRNA (Pfizer) and Adenoviral (AstraZeneca) COVID-19 vaccine and vaccine efficacy (Table 2). It seems that there is a good opportunity to investigate the time of vaccination, especially the COVID-19 vaccine, to evaluate the effects of morning or evening vaccination on vaccine efficacy as a simple and practical measure.

Limitations

Similar to other studies, our work had some limitations. The main limitations of this study were lots of heterogeneity among studies for types of vaccines, age of participants, outcome measures, sample size, location, and different setting of the studies. Hence, we could not perform meta-analysis due to high heterogenicity among the studies. Lack of registration in databases (eg, PROSPERO) was another limitation of this study, because the data were already extracted (we preextracted the data and were unable to register it according to PROSPERO). However, there were no similar studies in the PROSPERO database since the search was performed.

CONCLUSION AND FUTURE DIRECTIONS

Cumulative evidence suggests that sleep after vaccination and morning vaccination may enhance vaccine efficacy. Until now, several types of vaccines with various efficacies have been developed for COVID-19 [43,44], and vaccination led to a decline of severe infections, hospitalization, and death even after spread of the Delta variant [45-47]. It is plausible that sufficient sleep after vaccination and modulating the time of vaccination may improve COVID-19 vaccine efficacy. Some promising studies are ongoing regarding the time of COVID-19 vaccination [29,48], but future studies are needed to define the effects of sleep and time of vaccination on COVID-19 vaccine efficacy.

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Table 2. A Snapshot of the Research in Time of Vaccination

Type of vaccine, Year of publication, country	Setting/methods	Main findings	Conclusion	Ref
►Hepatitis A vaccine ►Influenza vaccine 2008, UK	►**Setting:** Observational ►Types of vaccine: hepatitis A vaccine (HAVRIX; Glaxo Smith-Kline) and Influenza vaccine (the trivalent vaccine consisted of three antigens: A/New Caledonia/20/99; A/Panama/2007/99; and B/Shangdong/7/97). ►Types of vaccine administration: intramuscular injection. ►Data from two studies that examined morning versus afternoon vaccination. ►In the first study, 75 university students (34 men; mean age of 22.9 years) were randomly allocated to either a morning (10 a.m. to 12 p.m.; n=39) or early evening (4 p.m. to 6 p.m.; n=36) hepatitis A vaccination session. ►In the second study, influenza vaccine was administered to 89 (38 men) older (aged 65 years or older) community-based adults. Fifty-nine participants vaccinated in the morning between 8 a.m. and 11 a.m., and 30 in the afternoon between 1 p.m. and 4 p.m. Participants vaccinated between 11 a.m. and 1 p.m. were excluded. ►In both studies the anti-HAV and anti-influenza antibody titers were measured approximately 1 month after vaccination,	►Participants responded with a significant increase in antibody titer for all four antigens from baseline to 1 month. ►Vaccinated in the morning in men, but not women, mounted antibody response to both HAV and the influenza strains.	►Diurnal vaccination enhance hormonal immune response following vaccination.	[24]
►Influenza vaccine 2016, UK	►**Setting:** cluster-randomized trial ►Types of vaccine: Trivalent Influenza vaccine ►Types of vaccine administration: intramuscular injection. ►A cluster-randomized trial was designed to evaluate morning versus afternoon vaccination (either 9 and 11 am or 3 and 5 pm) among 276 adults (aged 65+ years) following influenza vaccination. ►One month after vaccination, the anti-influenza antibody titers, serum cytokines IL-6 and IL-10 and seven steroids in serum (cortisol, cortisone, corticosterone, 11-deoxycortisol, testosterone, dehydroepiandrosterone (DHEA) and androstenedione) were measured.	►Greater antibody response was detected in those individuals who vaccinated in the morning than afternoon vaccination. ►Cytokines and steroid hormones were not related to antibody responses.	►Morning vaccination in older adults may be beneficial for the influenza antibody response.	[25]
►Influenza vaccine 2017, USA	►**Setting:** Observational ►Types of vaccine: Trivalent Influenza vaccine ►Types of vaccine administration: intramuscular injection. ►A 5-year study to assess immune responses to the influenza A in 114 samples from younger (30–40-year-old) and 165 samples from aged (>65-year-old) individuals who vaccinated in the morning versus afternoon. ►Antibody responses, B cell subset distribution in blood and the blood transcriptome were analyzed before and after vaccination.	►Timing of vaccination did not affect immune response in younger and aged individuals. ►The time of sample collection effect on the numbers of some of the B cell subsets in blood and global gene expression of whole blood samples.	►The time of sample collection effect on the results of immunological factors following influenza vaccination.	[26]

►BCG 2020, Western European countries	►**Setting:** Interventional and cohort ►Types of vaccine: BCG vaccine ►Types of vaccine administration: Intradermal injection. ►BCG vaccine was administered in at 6 pm and 6:30 pm (n=18; mean age of 25.8 SD=10.7 years; 61% females) compared with 36 age- and sex-matched volunteers with vaccinated between 8 am and 9 am. ►Peripheral blood mononuclear cells (PBMCs) were stimulated with *Staphylococcus aureus* and *Mycobacterium tuberculosis* before, as well as 2 weeks and 3 months after BCG vaccination and Cytokine production was measured in response to stimulation. ►Also, an independent cohort of 302 individuals vaccinated between 8 am and 12 pm with BCG in order to assess influence of vaccination time on induction of trained immunity.	►Morning vaccination elicited a stronger trained immunity and adaptive immune phenotype compared with evening vaccination (eg, specific *M. tuberculosis* IFN-γ responses were significantly higher in morning-vaccinated individuals 3 months after BCG vaccination compared with evening vaccination). ►In a large cohort of 302 volunteers, early morning vaccination resulted in a superior cytokine production capacity compared with later morning.	►BCG vaccination in the morning induces stronger trained immunity and adaptive responses compared with evening vaccination.	[27]
►Hexavalent vaccine 2019, Germany	►**Setting:** Randomized Controlled Trial ►Types of vaccine: Hexavalent vaccine ►Types of vaccine administration: Intramuscular injection. ►Twenty-six infants born at 26–30 weeks' gestation received their first routine hexavalent vaccination in the morning (7 and 10 a.m.) versus evening (7 and 10 p.m.). ►Pulse oximeter saturation, actigraphy, and rectal temperature were obtained for 24 h before and after vaccination. Antibody titers were measured before and 24 h after vaccination to determine inflammatory markers.	►Antibody titers for *Bordetella pertussis* were increased in both groups, but there was no difference in inflammatory markers 24 h after vaccination. ►Vaccination led to an increase body temperature and cardiorespiratory event rate (CER) in both groups, but there was no significant difference between the morning and evening groups.	►The study did not identify a difference in CER between morning and evening vaccination.	[28]
►SARS-CoV-2 inactivated vaccine 2021, China	►**Setting:** Prospective cohort study ►Types of vaccine: inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Sinopharm, Beijing). ►Types of vaccine administration: Intramuscular injection. ►The dynamics of immune responses were measured among 63 healthcare workers (HCWs) who received inactivated SARS-CoV-2 vaccine in the morning (9 am–11 am, n = 33) or afternoon (15 pm–17 pm, n = 30)	►Participants vaccinated in the morning showed significantly higher level of NAbs in the sera as well as stronger B cell and Tfh responses to the vaccination. ►The percentages of antibody-secreting cells (ASCs) cells, monocytes, and dendritic cells were significantly higher in the morning vaccination group.	►These data suggest that vaccination in the morning resulted in a stronger immune response to an inactivated SARS-CoV-2 vaccine than in the afternoon.	[29]

►SARS-CoV-2 mRNA (Pfizer) and Adenoviral (AstraZeneca) vaccine 2022, UK	►**Setting:** Randomized Controlled Trial ►Types of vaccine: SARS-CoV-2 mRNA (Pfizer) and Adenoviral (AstraZeneca) vaccine ►Types of vaccine administration: Intramuscular injection. ►Anti-Spike antibody levels were investigated in three times of vaccination (**Time 1**, 7-10:59 h; **Time 2**, 11-14:59 h; **Time 3**, 15-21:59 h), two type of vaccines (Pfizer, mRNA bnt162b2 or AstraZeneca, Adenoviral AZD1222), the age groups (16-29, 30-39, 40-49, or 50-74 years), sex, and the number of days post-vaccination. ►The anti-Spike responses were measured during the 2-10 weeks after vaccination.	►The anti-Spike responses were higher in those who were vaccinated later in the day (p = 0.013), in those who received the Pfizer mRNA vaccine (p<0.0001), in younger participants (p< 0.0001), and in women (p = 0.013). ►A significant association between days post-vaccination and vaccine type (p<0.0001) and age (p= 0.032), but not with vaccine time (p=0.238) were observed. ►The results did not show a significant effect of time of day of vaccination (p=.23), day of sample collection (p = 0.097) and two time intervals (before or after 1 pm). ►Analysis of 2784 health care workers revealed a significant effect of the time of vaccination on anti-Spike antibody levels following the administration of two alternative SARS-CoV-2 vaccines (mRNA or Adenovirus based).	►The results revealed that the magnitude of the anti-Spike antibody response is associated with the multiple variables, including time of day of vaccination, vaccine type, participant age, sex, and days postvaccination.	[30]

BCG: Bacillus Calmette–Guérin; CER: cardiorespiratory event ratel; HCWs: healthcare workers; Nab: neutralizing antibody; Tfh: follicular helper T; ASC: antibody-secreting cells; PBMCs: Peripheral blood mononuclear cells; TNF-α: tumor necrosis factor α; IL-1β: interleukin 1β; IFN-γ: Interferon gamma; NAbs: neutralizing antibodies; ASCs: antibody-secreting cells

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Appendix A: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	-
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

Appendix A: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P2-4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P2-4
Study characteristics	17	Cite each included study and present its characteristics.	P2-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	-
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P4
	23b	Discuss any limitations of the evidence included in the review.	P7
	23c	Discuss any limitations of the review processes used.	P7
	23d	Discuss implications of the results for practice, policy, and future research.	P7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P7
Competing interests	26	Declare any competing interests of review authors.	P7
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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