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Humoral response to anti SARS-CoV2 vaccination at one and seven months is not different in shift workers and non-shift workers

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ABSTRACT

Since previous studies, mostly performed in healthy adults, show that sleep restriction around time of vaccination impairs antibody response and shift work affects sleep, aim of the study was to test the hypothesis that the antibody response to vaccination is impaired in shift workers, when compared to non-shift workers.

Employees (n = 445; mean age 44 ± 11 years; 35 % men) of the Centro Cardiologico Monzino, IRCCS (Milan, Italy) were vaccinated against SARS-CoV2 in February 2021 with an mRNA-based vaccine. Antibody titers were assayed 1 and 7 months later. Differences between groups were assessed using ANOVA, after log-transformation of variables with right-skewed distribution.

We report that the antibody titer was significantly higher in shift workers (33 % of employees) compared to non-shift workers at first assay [median (IQR): 2495 (1700; 4665) vs 2060 (1619; 2970) BAU/mL, p = 0.0123], as well as at the second one, and that this difference was abolished after adjustment for previous development of symptomatic COVID-19. Results were not affected by age or sex at birth.

These results show that shift workers were able to mount an unimpaired antibody response to vaccination. Since vaccinations were performed during the pandemic urgency, our retrospective study has several limitations, nevertheless it underlines the need for large prospective, controlled studies on the effects of acute and chronic sleep restriction on response to vaccination in the general population and on the impact of shift work on immune response.

1. Introduction

1.1. Sleep and immune response

Sleep and immune responses are reciprocally and closely linked. On the one hand, as shown by studies in animal models, in healthy volunteers and in patients, the immune response, activated for instance by an infection, alters sleep, with increased time spent asleep, increased and fragmented non-rapid eye movements (NREM) sleep and decreased or suppressed REM sleep (Besedovsky et al., 2019; Imeri and Opp, 2009; Lasselín et al., 2019; Mullington et al., 2000; Toth, 1995). On the other hand, impaired sleep dampens the immune response to vaccination, as shown by a recent systematic review (Rayatdoost et al., 2022) and an even more recent metanalysis (Spiegel et al., 2023).

It was shown that adequate sleep, at the correct circadian phase (i.e. during the night in diurnal animals, like humans), potentiates the

immune response, possibly because circadian rhythms and sleep, in coordination, produce during the night a pro-inflammatory, neuro-endocrine environment (as shown, for instance, by increased levels of pro-inflammatory cytokines, growth hormone and prolactin) which boosts a correct and effective immune response (Lange et al., 2010).

1.2. Shift work and sleep

The term “shift work” usually refers to a broad spectrum of non-standard work schedules, i.e., outside regular daytime hours. As such, different types of shift work exist (Sack et al., 2007). In industrialized countries, between 20 and 25% of the work force is involved in shift work (World Health Organisation, 2010). Shift work forcefully disrupts the normal sleep-wake cycle, leading to short sleep and excessive fatigue (Drake and Wright, 2017; Kecklund and Axelsson, 2016). A significant portion of shift workers, for instance 32.1% of night workers (Drake

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et al., 2004), develops a shift work disorder, characterized by insomnia and/or excessive sleepiness during wakefulness, typically accompanied by a reduction of total sleep time (American Academy of Sleep Medicine Medicine, 2005). Rotational shift workers, i.e., employees working on multiple shift types, have prevalence of sleep disorders comparable to that observed in night shift workers (Boersma et al., 2023).

1.3. Aim of the study

Studies on the association between sleep disruption and vaccine response are relevant not only to understanding the association of sleep and immune response, but mainly for health policy reasons. Unfortunately, such studies are very few and mostly performed in healthy volunteers. The recent COVID-19 pandemic provided a chance to study the effects of vaccination in adults from the general population. Based on previous work reviewed above, aim of this study was to test the hypothesis that antibody response to vaccination would be impaired in shift workers, when compared to non-shift workers. Here we present data that, by showing that the antibody titer induced by vaccination was not different in shift workers compared to non-shift workers, after correcting for previous COVID-19, refute the hypothesis tested by our study.

2. Methods

2.1. Subjects, vaccination procedure and ethical approval

445 employees from the Centro Cardiologico Monzino, IRCCS (Milan, Italy), who were vaccinated against SARS-CoV2 in February 2021, were included in this retrospective observational study. Demographic data are shown in Table 1.

Shift workers were on a forward rotating shift schedule. Average nights worked were 47/year.

Employees were fully vaccinated with an mRNA-based vaccine (Comirnaty Pfizer/BioNTech) according to national protocols: two doses of vaccine 21 days apart. Specific antibodies were assayed (LIAISON SARS-CoV-2 TrimericS IgG; DiaSorin) 1 and 7 months after the second dose and reported as Binding Antibody Units BAU/mL. Vaccination was carried out by alphabetical order, based on the last name and was independent of shift. The study was approved by the Ethical Review Board (CCM 1795).

2.2. Statistical analysis

Based on available preliminary data, we assumed a mean vaccination-induced antibody titer (expressed as logarithm) of 3.3 ± 0.3 (at 1 month) and 2.6 ± 0.5 (at 7 months) in the control group; with a sample size of 500 subjects, one can detect as significant ($\alpha = 0.05$) a vaccination-induced reduction in antibody titer of 2.3% at 1 month and 4.85% at 7 months in the group in employees working in shifts, with a statistical power of 80%.

Post hoc power analysis was performed to evaluate whether our data had sufficient verification power, and an 80% statistical power was reached for antibody titer values at 1 month.

Continuous variables were reported as mean \pm standard deviation (SD) if normally distributed, otherwise as median, and interquartile range (IQR). Categorical variables were presented as frequencies and

Table 1
Demographic data of the study population by shift work status.

	n	Age (mean \pm SD)	Sex (M/W)
All	445	44 \pm 11	157/288
Shift workers	148	43 \pm 10	56/92
Non-shift workers	297	44 \pm 12	101/196
p		0.3431	0.4256

percentages. For continuous variables, comparisons between groups were assessed using ANOVA, after log-transformation of variables with right-skewed distribution (i.e., IgG levels). Comparisons for categorical variables were made using Chi-square test or Fisher's exact test, as appropriate. Analyses were also performed adjusting for age, sex at birth and previous COVID-19 disease. Potential interactions between group and age and group and sex at birth were evaluated by including the appropriate interaction terms in the models. All tests were two-sided and a P value < 0.05 was considered to indicate statistical significance. All analyses were performed with SAS software (version 9.4; SAS Institute Inc., Cary, NC).

3. Results

Shift workers had higher levels of antibodies against SARS-CoV2 than non-shift workers both at 1 month and at 7 months [BAU/mL (median and range)]: 2495 (1700; 4665) vs 2060 (1619; 2970), $p = 0.0123$ and 468 (217; 1295) vs 414 (198; 849), $p = 0.0483$, respectively (p was calculated on log transformed data, as specified in Methods). Fig. 1 shows the distribution of log transformed antibody titers in the two groups at 1 month.

Although mean age was not different between groups as reported in Table 1, age was distributed unevenly in shift workers compared to non-shift workers: more shift workers belonged to the younger age categories and more non-shift workers to the older age categories, as expected (Table 2). Age, however, and sex at birth did not influence antibody titers (not shown).

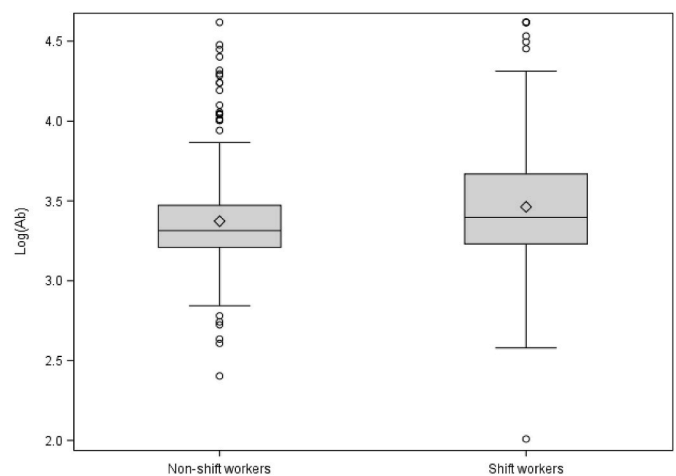
Previous COVID-19 was unevenly distributed between shift and non-shift workers (Table 3), with more symptomatic disease in shift workers compared to non-shift workers, though hospitalization prevalence was the same.

When antibody titers were adjusted for previous symptomatic COVID-19 before vaccination, no significant differences were observed anymore between shift workers and non-shift workers either at 1 or at 7 months ($p = 0.0841$ and $p = 0.2482$, respectively). Distribution of antibody titers at 1 month in either unaffected or symptomatic COVID-19 individuals are shown in Fig. 2.

4. Discussion

4.1. Summary and conclusions

Since sleep restriction impairs the response to vaccination (Opp, 2023; Rayatdoost et al., 2022; Spiegel et al., 2023) and shift work



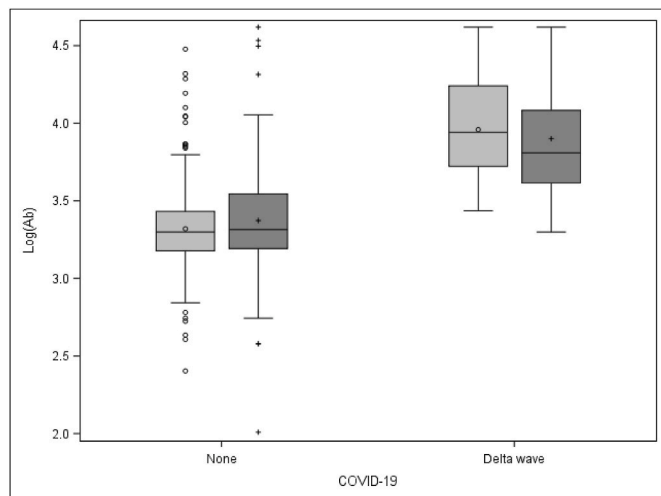
Legend to Fig. 1. Box plots of the distribution of antibody titers induced by vaccination against SARS-CoV2 at 1 month in shift and non-shift workers. Antibody titers are shown after log transformation (Log (Ab)).

Table 2
Distribution by age of non-shift and shift workers.

Age in years	Non-shift workers	Shift workers	p
	N (%)	N (%)	
<35	79 (26.6)	29 (19.6)	0.0051
35–45	71 (23.9)	47 (31.8)	
46–52	59 (19.9)	44 (29.7)	
>53	88 (29.6)	28 (18.9)	

Table 3
Distribution of COVID-19 in shift and non-shift workers.

	ALL	Non-shift workers	Shift workers	p
	N (%)	N (%)	N (%)	
No COVID-19	374 (84.0)	258 (86.9)	116 (78.4)	0.0051
COVID-19 symptomatic, no hospitalization, delta wave	29 (6.5)	11 (3.7)	18 (12.2)	
Hospitalized COVID-19, Delta wave	11(2.5)	8(2.7)	3(2.0)	
COVID-19 omicron wave	31(7.0)	20(6.7)	11(7.4)	



Legend to Fig. 2. Box plots of the distribution of the antibody titers (log transformed) in non-shift (pale grey) and shift (dark grey) workers with either no COVID-19 (none) or symptomatic (with or without hospitalization) COVID-19 (only delta wave was considered). Differences in antibody titers were not significant ($p = 0.6112$).

impairs sleep (Drake and Wright, 2017; Kecklund and Axelsson, 2016), we expected to find a reduced antibody response to vaccination in shift workers when compared to non-shift workers. Our results show that the antibody titer induced by vaccination was as high in shift workers as in non-shift workers. Moreover, our results show that the percentage of subjects developing symptomatic COVID-19 is higher in shift workers than in non-shift workers, but that the percentage of hospitalization is the same in the two groups, suggesting that the clinical response to infection is not dampened in shift workers in comparison to non-shift workers.

We think these results (obtained in a population of 445 subjects), apparently at odds with previous work on the effects of sleep restriction around time of vaccination, have some possible explanations, and prompt future (and in our opinion much needed) studies on the effects of sleep on vaccination and exposure to infectious agents in the general population and in different kinds of conditions. Such studies would not only add to science but be important also for their possible consequences

for public health and the related public policies, considering, for instance, that vast part of the world is moving toward a 24/7 functioning (Crary, 2014).

4.2. Healthy volunteers vs general population, acute vs chronic sleep restriction, type of vaccine

We think that possible, although partial, explanations of the difference between the findings of the present study and the findings of previous studies on the effects of sleep restriction on the response to vaccination could be related to i) the characteristics of the vaccinated population (healthy young volunteers *versus* middle aged subjects from the general population), ii) acute *versus* chronic sleep restriction, and iii) the type of vaccine (mRNA based), which is different from the vaccines used in the previous studies.

First, the few previous studies on the effects of sleep restriction on vaccination were almost all performed in healthy volunteers. A recent systematic review (Rayatdoost et al., 2022) and a recent metaanalysis (Spiegel et al., 2023), were able to include nine studies, as the only ones in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (Page et al., 2021). All, but three, of these studies were performed in healthy volunteers with no baseline sleep disorders or other diseases, which were actively checked for. Since the annual prevalence of insomnia symptoms in the general adult population ranges from 35% to 50% (Walsh et al., 2011) and the prevalence of insomnia disorder ranges from 12% to 20% (Buysse, 2013; Roth et al., 2011), it is likely that the effect of vaccination could be different in a young, healthy cohort *versus* the middle aged shift workers from the general population included in the present study.

Moreover, whereas the general population, in everyday life is continuously exposed to any kind of immune challenge and infectious agents, in three studies on the effects of sleep restriction on response to hepatitis vaccination, prior infection or vaccination were excluded (Lange et al., 2003, 2011; Prather et al., 2012).

Second, adequate sleep, at the correct circadian phase, was shown to potentiate the immune response, maybe because circadian rhythms and sleep, in coordination, produce during the night a pro-inflammatory, neuro-endocrine environment which boosts a correct and effective immune response (Lange et al., 2010). Sleep, a phase of lowered metabolic demand, would allow to use precious resources to mount the highly energetically demanding host defense, which would be ready for the immune challenges in the subsequent hours of wakefulness (Irwin, 2019; Westermann et al., 2015). If night sleep is acutely disrupted or reduced for a few days, the nocturnal pro-inflammatory peak cannot occur and antibody response to vaccination is compromised. This could explain the impaired response to vaccination in healthy volunteers, who did not have a sleep disorder and who were not allowed to sleep only around the time of vaccination.

Our study subjects were different. When sleep cannot occur chronically during the night, due to shift work (or any disorder which compromises sleep), it leaks into the day, with excessive daytime sleepiness (EDS). Together with sleep, also the circadian and sleep-related pro-inflammatory, neuro-endocrine milieu slips into the day. It was shown that sleep disturbances shift the pro-inflammatory peak from the night to the day, with generalized excessive levels of inflammation (Irwin, 2019). Chronic exposure to nightshift work, as well as recent night-shift work, influence the immune status of healthcare workers, with higher levels of monocytes in shift workers than non-shift workers (Loef et al., 2019). In the day time, shift-workers have higher levels of pro-inflammatory cytokines TNF- α and IL-6, than non-shift workers (Ruiz et al., 2020). We suggest that the immune system of chronically sleep-deprived shift-workers might be better prepared to respond to an immune challenge than the immune system of a naïve, never sleep-deprived person. Shift-work is associated with several health problems (Kecklund and Axelsson, 2016; Knutsson, 2003) and alterations in the immune function play a role in several of these disorders

(Almeida and Malheiro, 2016), maybe because of a pro-inflammatory activity which is not contained into the night, but diffuses along the whole day. On the other hand, this prolonged, over the 24 h, pro-inflammatory status could be better suited to mount an effective response to an immune challenge.

Humankind, for different reasons (wars, migrations, floods, or earthquakes, for example), over the ages had sometimes (for shorter or longer stretches of time) no way to sleep during the night. Moreover, humankind not always sleeps a single, monomorphic, nocturnal chunk of sleep (Reiss, 2017): environmental reasons for instance, such as hours too hot in the middle of the day for at least a significant portion of the year, make it impossible to work outdoor. This determined moving part of the nocturnal sleep into the otherwise useless, hottest hours of the day. It could be speculated that being able to fight an infection under the circumstances mentioned above, would constitute a survival advantage. In other words, not sleeping during the night for any prolonged time has unavoidable health consequences, but the response to an immune challenge, as during an infection, is preserved, at any cost. We think that his hypothesis seems worth testing in large prospective studies.

Third, the anti-SARS CoV2 vaccine used in the study population was one of the first widely used vaccines based on mRNA technology. Whether these types of vaccines are more immunogenic and can elicit therefore an appropriate response also in sleep deprived persons compared to previous vaccines based on different technology is a possibility worth testing in large prospective studies.

At variance with our results, shift workers responded with a weaker response to meningococcal vaccination than non-shift workers in a small study that included 34 individuals from the general population, half of whom were shift workers and two thirds were women (Ruiz et al., 2020). We have no immediate explanation for the different results compared to the present study, except to underline that it was a smaller study compared to ours, with shorter follow-up time (less than two months), though it more completely analyzed immune response, both humoral and cell-mediated, to vaccination. No information, however, was available regarding protection from the natural pathogen.

4.3. Limitations of the study

We are aware of the several limitations of the present retrospective study. We have no information about the time of day the vaccinations were performed. Time of vaccination plays an important role in antibody response ((Hazan et al., 2023) and reviewed in (Rayatdoost et al., 2022) and (Wang et al., 2022)). Furthermore, no information was available on the cellular immune response to the SARS CoV-2 vaccination, which is known to be, as for other infectious diseases, an important aspect of the protection afforded by vaccination (Kingstad-Bakke et al., 2022). On the other hand, in our study, shift-workers developed more symptomatic COVID-19 than non-shift workers, but were not more hospitalized, indicating an overall adequate clinical response to infection. Finally, in the urgency of the vaccination campaign, there was no time to plan and design a study, controlling for sleep and medical history of the vaccinated population. We cannot therefore rule out that one or more confounding factors could affect our results. Notwithstanding such limitations, we believe our unexpected findings prompt further studies on the relationship between shift work, sleep, and immune response to vaccination in shift workers from the general population.

CRedit authorship contribution statement

Elena M. Faioni: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Luca Imeri:** Writing – review & editing, Writing – original draft, Conceptualization. **Alice Bonomi:** Writing – review & editing, Methodology, Formal analysis. **Arianna Galotta:** Methodology, Formal analysis. **Vanessa Guerra:** Methodology, Data curation. **Luca Pase:** Resources, Data curation. **Susanna Bianchi:** Visualization, Formal analysis, Data

curation. **Maria L. Biondi:** Methodology, Investigation, Data curation.

Declaration of competing interest

On the behalf of all the co-authors of the above-mentioned manuscript, I state that the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Data availability

Data will be made available on request.

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