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META-ANALYSIS

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Effectiveness of on-site influenza vaccination strategy in Italian healthcare workers: a systematic review and statistical analysis

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ARSTRACT

Introduction: One of the main determinants of non-adherence to influenza vaccination among healthcare workers (HCWs) is lack of time to attend vaccination services. Therefore, international Public Health Organizations have recommended on-site influenza vaccination in order to improve vaccination coverage among HCWs.

Areas covered: We conducted a systematic narrative review of the relevant literature to evaluate the effectiveness of this strategy among HCWs in Italy. Fifteen studies, selected among scientific articles available in MEDLINE/PubMed, ISI Web of Knowledge and Scopus and published from January 1st, 2018, to May 31st, 2022, were included. A significant relationship was evidenced between influenza vaccine uptake and adoption of an on-site outpatient clinic (OR = 2.06; 95%Cl = 1.43-2.95). The review highlighted a significant increase in VC when on-site vaccination was implemented (even exceeding +150% compared to the previous season), among other measures. Nevertheless, none of the reported experiences proved to meet the minimum target of 75% VC among HCWs.

Expert opinion: Despite strategies to achieve greater willingness to immunize in this category, mandatory vaccination appears to be the only one that can guarantee protection for HCWs and the patients they care for.

ARTICLE HISTORY

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KEYWORDS

Healthcare workers; vaccine compliance; influenza; nosocomial infection: mandatory vaccination

1. Introduction

Vaccination is an effective measure of individual and collective protection from disease and is especially important for healthcare workers (HCWs). It protects both HCWs from occupational infectious diseases and patients from the risk of infection in the nosocomial environment. High vaccination coverage (VC) among HCWs also prevents absenteeism and guarantees the quality of health care services offered [1]. Among the recommended vaccinations, the influenza vaccine should be administered once a year, shortly before the flu season. In fact, HCWs are constantly in contact with a number of people (family members, other HCWs, patients, ward visitors) and are at a greater risk of exposure to influenza viruses than the general population; moreover, if infected (ill o incubating) they are potential contagion spreaders [2].

In Italy, vaccination of HCWs is required by Law Decree n. 81 of April 9^{th} , 2008 [3]. Official recommendations for immunization of HCWs are also part of the National Immunization Plan [4] and yearly guidelines for seasonal influenza prevention provided by the Italian Ministry of Health. HCWs are among the high-risk subjects for whom influenza vaccination is strongly recommended. Promoting the active offering of influenza vaccination to health personnel each year is fundamental. Vaccination campaigns should be held shortly before the influenza season (October to December), and vaccination strategies should be managed by the hospital's facility director and occupational physician. The minimum VC target for this category has been set at 75% [4].

In Italy, current coverage data are not available because there is no national data collection system regarding VC by the Ministry of Health. According to a 2010 review by Prato R et al. [5] vaccination coverage among Italian HCWs ranged from 12% to 37% during 1999-2007.

The causes of low compliance to vaccination among HCWs have been investigated in various studies, according to which vaccine hesitancy is associated with lack or inadequacy of awareness campaigns, insufficient health literacy regarding vaccine efficacy and adverse reactions, perception of not being included in high-risk categories, not having been previously vaccinated against influenza, lack of past flu-like syndromes, lack of access to vaccination facilities, and sociodemographic variables [6-9]. In any case, one of the most important determinants of non-adherence is the lack of time to attend vaccination services [6-8]. To deal with this issue, international Public Health Organizations have recommended on-site influenza vaccination in order to improve VCs among HCWs. As described by the United States' Centers for Disease Control and Prevention (CDC), on-site vaccination is a cost-effective strategy that was demonstrated to increase productivity, reduce overall absenteeism, and lower direct



Article highlights

- HCWs are at a greater risk of exposition to influenza viruses than the general population.
- HCWs are among the at-risk categories for whom influenza vaccination is strongly recommended
- Public Health Organizations have recommended on-site influenza vaccination in order to improve vaccination coverage
- Our study evaluate the effectiveness of the on-site strategy among HCWs in Italy.
- A significant relationship was evidenced between vaccine uptake and the vaccination in an on-site clinic.
- The scenario of management strategies for hesitant individuals is very
- On-site vaccination is associated with better immunization attitude.
- None of the reported experiences proved to meet the minimum target of 75%
- Mandatory strategy seems to be necessary to deal with low uptake

health-care costs [10]. This strategy involves physicians with experience in vaccinology going to the Operational Units (OUs) of a hospital where there are HCWs who wish to join the vaccination campaign, on scheduled occasions and through mobile task forces.

We conducted a systematic narrative review of the relevant literature to evaluate the effectiveness of on-site vaccination strategies among HCWs in Italy. We assessed the association between vaccine uptake and active vaccine provision through an on-site vaccination strategy. Experience of on-site strategy in Italian hospitals reported in the literature and their effectiveness in achieving higher VC were also analyzed.

2. Methods

The protocol of the systematic review was prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [11]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with reference acknowledgment number [anonymized]. The population, intervention, comparison, and outcome (PICO) framework of a systematic review was used to formulate the review question; the resulting question was 'effectiveness of on-site influenza vaccination strategy for healthcare workers in Italy.'

2.1. Search strategy, selection criteria and data extraction

The Scopus, MEDLINE/PubMed and ISI web of knowledge were systematically searched. Research articles, brief reports, letters and editorials published between 1 January 2018 and 31 May 2022 were included in our search; the time window was chosen considering that from previous literature reviews there were no studies on the topic prior to 2018. The following terms were used for the search strategy: (on site OR mobile unit* OR mobile vaccination clinic) AND (influenza OR flu) AND (vaccin* OR immun*) AND (healthcare worker* OR health personnel OR physician* OR nurse* OR doctor* OR resident* OR student*) AND (ital*). Studies in English or Italian with full text were included. Abstracts without full-text, reviews and metaanalyses, papers not reporting epidemiological data, clinical trials, studies focusing on issues unrelated to the purpose of this review (vaccine knowledge, seroprevalence, etc.) and studies not set in Italy were excluded. When necessary, study authors were contacted to obtain additional information. The list of papers was screened by title and/or abstract independently by two reviewers who applied the predefined inclusion/exclusion criteria. Discrepancies were recorded and resolved by consensus.

Extracted data included year, professional category, Italian region and reported on-site vaccination experience.

2.2. Quality assessment

The methodological quality of selected studies was assessed via the Newcastle-Ottawa Scale (NOS), adapted for the evaluation of cross-sectional studies [12]. It is divided into nine categories checking three aspects of quality (selection, comparability and outcome/exposure) and scores range from 0 to 10. The quality of a study was considered high if the NOS score was between 7 and 10, intermediate if the NOS score was between 4 and 6, and low if it was between 0 and 3.

The risk of bias for each study was independently assessed by two researchers. Discrepancies were recorded and resolved by consensus.

2.3. Pooled analysis

The odds ratios (ORs) and 95% CIs were selected as general outcome variables for the relationship between influenza vaccine uptake and active vaccine offering through an on-site vaccination strategy. The data of ORs and standard errors (SEs) was calculated from the 95%CIs, and an additional logarithmic transformation was performed to stabilize the variance and normalize the distribution.

The OR in the analysis was calculated using the inverse variance and DerSimonian-Laird weights for random effects models, with the heterogeneity estimate obtained from the inverse-variance fixed-effects model. The OR and the associated 95% Wald confidence interval were plotted, and a forest plot was drawn. The I² statistic was calculated as a measure of the proportion of the overall variance attributable to heterogeneity between studies rather than chance. A p-value < 0.05 was considered an index of statistical significance of heterogeneity.

Due to the small number of studies included in the analyses, sensitivity and publication bias analyses were performed.

Statistical analysis was conducted using STATA MP17® software.

Strategies to increase vaccination compliance among HCWs through on-site vaccination were collected from all available studies, and the respective findings were compared, with particular attention to the evidence presented in several of the included papers.

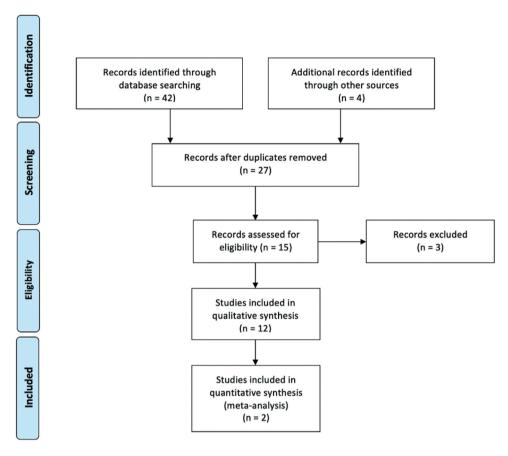


Figure 1. Flow-chart of the bibliographic research.

Table 1. Characteristics of the selected studies included in meta-analysis and systematic review.

First author	Year	NOS score	Quality	Italian region	Flu season(s)	Population	Evaluation of on-site vaccination as determinant of better flu vaccine attitude
Quantitative study							
Bianchi FP	2022	8	high	Apulia	2018/19	HCWs	Multivariate logistic regression model of flu vaccine uptake; determinants: on- site clinic, sex, age, medical area, job mansion. Flu season 2018/19
Barbara A	2020	7	high	Latium	2016/17; 2017/18; 2018/19	HCWs	Multivariate logistic regression model of flu vaccine uptake; determinants: on- site clinic, sex, age class, job mansion. Flu seasons 2016/17 and 2017/18
Qualitative study							
Lecce M	2022	7	high	Lombardy	2019/20; 2020/21; 2021/22	HCWs	-
Dettori M	2021	7	high	Sardinia	2019/20; 2020/21	HCWs	-
Scardina G	2021	8	high	Tuscany	2018/19; 2019/20; 2020/21	HCWs	-
Bert F	2020	7	high	Piemonte	2017/18; 2018/19	HCWs	-
Brunelli L	2020	7	high	Friuli Venezia Giulia	2019/20	HCWs	-
Costantino C	2020	7	high	Sicily	2019/20	HCWs	<u>-</u>
Pelullo CP	2020	8	high	Campania	2018/19	HCWs	-
Tognetto A	2020	7	high	Latium	2017/18	HCWs	-
Vimercati L	2019	7	high	Apulia	2017/18	HCWs	-
Gilardi F	2018	7	high	Latium	2017/18	HCWs	-

HCW = healthcare worker

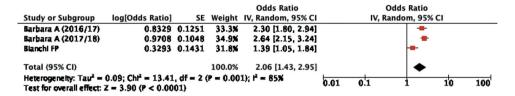


Figure 2. Forest plot of the association between vaccine uptake and on-site vaccination strategy.

3. Results

3.1. Identification of relevant studies

The flow-chart, constructed following the PRISMA guidance [11] (Figure 1), shows the process of article selection. According to the aforementioned inclusion criteria, 19 articles were identified in ISI Web of Knowledge, 3 in Scopus and 20 in MEDLINE/PubMed; 4 studies were identified through the bibliographic research. After exclusion of duplicate articles in the three databases, there were 15 eligible studies. Of these, two were excluded because the results were described in a more recent and comprehensive article already included in the systematic review and one because it did not fulfill the inclusion criteria. Thus, a total of 12 studies were eligible [13–24], of which two were quantitative [13,14] and ten were qualitative [15–24] (Table 1). Overall, 15 studies did not meet the inclusion criteria and were excluded.

3.2. Quality assessment

The NOS was applied appropriately to the included studies, and all were evaluated as being of high quality (Table 1).

3.3. Pooled analysis

A significant relationship was evidenced between influenza vaccine uptake and the opportunity to vaccinate in the context of an on-site clinic (OR = 2.06; 95%CI = 1.43-2.95; $I^2 = 85.0\%$; p < 0.0001; Figure 2).

3.4. Effectiveness of on-site vaccination strategy

Vimercati L and Bianchi FP [13,24] described the on-site vaccination strategy in the 2017/18 and 2018/19 influenza seasons at Bari Policlinico General University Hospital. In the 2017/18 season, the hospital's Department of Hygiene, in collaboration with the Department of Occupational Medicine, tested the onsite vaccination strategy in 8 OUs of Medical specialties identified in relation to the presence of patients at high risk of complications in case of influenza; the on-site clinic in each OU was manned by Public Health physicians. Moreover, an ad hoc outpatient clinic was set up in the Department of Hygiene operating for about 10 hours a day Mondays to Fridays. HCWs were able to access the clinic directly and without reservation, as they were during the 2016/17 flu season. Directors of each OU received a specific letter outlining vaccination strategies, which were also communicated through the hospital's website and internal informatic network. In the days leading up to the vaccination campaign, informative posters were displayed in

the OU to communicate the vaccination offer schedule [13,24]. Thus, a two-pronged strategy was designed, with vaccination being offered both on-site (directly in OUs) and in the outpatient vaccination clinic. VC increased from 8.7% in the 2016/17 flu season to 14.2% in the 2017/18 flu season (+63%), with nearly 80% of HCWs preferring to be vaccinated in their work setting rather than attending the vaccination clinic. The authors observed that the increase in VC between the two seasons in the OUs receiving the on-site offer (delta = +17%) was higher than in other OUs (delta = +1.5%) [24]. During the 2018/19 influenza season, the strategy described above was replicated, but the on-site strategy targeted 44 of the 50 (88.0%) OUs, with a total of 3,044 HCWs; the six OUs excluded from the on-site strategy were those with no beds and care activities; with this strategy, VC rose to 20.4% (+44%) [13].

Lecce M et al. [15] described the experience of a research and teaching hospital in Lombardy; from the 2019/20 flu season, an on-site outpatient clinic was organized, in addition to the ad hoc vaccination clinic already activated during previous flu seasons. The on-site vaccination service was carried out by a team of medical professionals visiting each building in the hospital. From the 2020/21 flu season, an educational communication campaign and a competition among the hospital departments (the so-called gaming strategy) were also deployed. In the 2021/22 flu season, due to the COVID-19 pandemic, most of the vaccination lines were located in a central hub, while the remaining lines were situated in four peripheral on-site clinics. Those clinics had shorter opening hours and initially had a scheduled period of operations of approximately 10 days; however, they closed after a few days due to decreased user flow, making the central hub the only active site, probably related to the inability to offer coadministration of both anti-SARS-CoV-2 and anti-flu vaccination in peripheral clinics. These combined strategies resulted in +48% more HCWs vaccinated during the 2019/20 season (VC: 21.5%) compared with the previous one, +82.4% more in the 2020/21 season (VC: 43.1%) compared with the previous one, and +20.6% more in the 2021/22 season (VC: 52.0%) compared with the previous one [15].

During the 2018/19 and 2019/20 flu seasons, a Sardinian University Hospital experimented the implementation of a pilot HCW influenza vaccination strategy administered directly in hospital wards, in addition to routine vaccination activities [16]. The on-site vaccination strategy was proposed again for the 2020/21 season with a more articulated organization structured around the needs of the operating units belonging to the medical, surgical, and service areas. Specifically, care departments with nursing activities (thus able to self-administer the vaccine) were given the option to

vaccinate staff directly in their own department, while for operating units and external companies that required medical or nursing staff to administer the jab, vaccination was offered in ad hoc vaccination clinics. During the 2019–2020 season, 400 vaccine doses were administered through routine vaccination activities, while an additional 229 doses were administered on-site for a total of 629 vaccinated HCWs (VC% = 27.7%; +94%); the 2020/21 flu season saw a further increase of +112.6% (CV: 58.9%).

Before the beginning of the 2015/16 flu season, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, a large Italian University Hospital located in Rome, created a multi-professional group focused on influenza vaccination. The group aimed to develop a 'long-term, step-by-step' project in order to increase flu vaccination coverage rates among HCWs [14]. The on-site vaccination intervention was implemented since the 2016-2017 campaign; this consisted of personal visits by 2 trained medical residents in Public Health and/or Occupational Medicine to the wards to conduct influenza immunization counseling and vaccinate free of charge HCWs who wished to be vaccinated. During the 2018-2019 season, in addition to medical residents, nursing students were also involved in performing on-site visits. For the 2016-2017 campaign, 12 out of 36 macro-areas (33%) were randomly selected. In the 2017-2018 season, the on-site intervention was extended to wards in physical proximity to those involved in the previous campaign. During the 2018/19 flu vaccination campaign, all wards in the hospital were involved. During the 2016/17 campaign, the overall VC was 9.3% (+55% compared with the previous season); the overall VC in HCWs working in wards targeted by the on-site intervention was 14.0% vs. 7.2% among HCWs who were not. During the 2017/18 campaign, VC was 14.0% (+51% since the previous season); VC in HCWs working in wards involved in the on-site intervention was 19.1% vs. 8.9% among HCWs not interested in the on-site intervention. During the 2018/19 campaign, VC was 22.0% (+57% compared with the previous season) [14].

Scardina G et al. [17] reported the experience of Azienda Ospedaliero-Universitaria Pisana, a large tertiary teaching hospital located in Pisa. In subsequent seasons, several strategies based on promoting and facilitating access to vaccination were progressively implemented. During the 2018/19 and 2019/20 flu vaccination campaigns, promotion materials (e.g. posters and flyers) were made available in the common areas of each unit, invitations to vaccinate were emailed to each employee, and access to vaccination was facilitated through the establishment of an on-site vaccination intervention, complementing the two vaccination clinics of Occupational Medicine with ad hoc vaccination services in different wards. In addition to these measures, the number of on-site clinics was increased in 2020/21, opening hours were extended, professionals delivering vaccination services were increased and education and training sessions were organized for healthcare-related personnel. At the end of the 2018/19 season, the VC rate against influenza among HCWs was 11.6%, which increased during the 2019/20 season (VC: 14.3%; +23.1% compared to the previous season) and during the 2020/21 season (VC: 39.6%; +177.6% compared to the previous season) [17].

Turin's Molinette Hospital organized a multifactorial strategy for offering influenza vaccination for the 2017/18 season, including a 3-months awareness campaign targeted at health personnel, active offering at the Occupational Medicine Service's vaccination clinic, and active on-site offering in the departments through four 'moving vaccination units,' each consisting of a medical doctor and a nurse. The VC change between the 2017/18 and 2016/17 vaccination seasons was +46.1%, while it was +84.7% when compared with the average of the previous 5-year period [18].

Tognetto L et al. [22] compared VC in 4 hospitals in Rome during the 2017/18 flu season; the highest coverage was recorded in the only hospital that implemented vaccination on-site (13%).

Bambino Gesù Children's Hospital, a large pediatric research hospital located in Rome, organized a multifactorial intervention for the 2017/18 flu season, including a new vaccination offer during occupational medicine surveillance visits, daily and prolonged availability of vaccination for HCWs at fixed locations at each hospital site, an expanded and integrated communication strategy, social promotion initiatives, and on-site vaccination offered to a wider number of Units and Departments and with the constant presence of an occupational physician. VC increased from 12.9% during the 2016/ 17 season to 17.3% during the 2017/18 season (+34.1%) [24].

All authors have suggested that an on-site vaccination clinic is an effective strategy to increase HCWs compliance; indeed, easy access to vaccination allows to overcome logistic barriers to HCWs' adherence to vaccine uptake, thus contributing to a better outcome in terms of vaccination coverage. In any case, only a combined approach, including actions of education, awareness raising, improved access to facilities, and active offers to workers, has the potential to increase compliance with influenza vaccination among HCWs [13,14,16,19,23]. Proactive one-by-one invitation to HCWs in the form of a personal e-mails, as well as an advertising campaign and competition among hospital departments (game strategy), seem to confer greater dissemination of campaign information.

On the other hand, the presence of a non-negligible number of opposed or undecided HCWs can undermine hospital health policies and jeopardize the safety of the frail patients with whom they come into contact, so several recent works have advocated for mandatory vaccination in response to a pressing social need for individual and public health protection, and especially as a defense of vulnerable individuals or patients [13,15,18-20,24]. Bert F et al. [18] proposed that declination statements should be included among the actions, in order to improve attitudes toward the vaccine.

4. Conclusion

Our statistical analysis revealed that on-site vaccination is associated with better immunization attitude (OR = 2.06; 1.43–2.95), and the systematic review of literature reported a significant VC increase during flu seasons when on-site vaccination was implemented (reaching over +150% compared to previous seasons), among other measures. Nevertheless, none of the reported experiences have been



shown to achieve the minimum VC goal of 75%. A 2021 review concluded that strategies based on on-site vaccination are effective in obtaining increased influenza immunization rates, although they rarely achieve high VC [25]. Moreover, the 2020/ 21 and 2021/22 influenza seasons were characterized by coexistence with the SARS-CoV-2 pandemic; the highest values of anti-flu vaccination coverage among Italian HCWs were recorded in this context. However, optimal vaccination coverage among HCWs was not achieved during these seasons either.

An important lesson learned from the reported experience is that increasing VC among HCWs is not free of charge; it required several hours of work by highly trained physicians with expertise vaccinology. Although there are no specific studies on the costeffectiveness of on-site outpatient clinic, immunization programs among HCWs in hospital settings are recognized as effective in reducing disease-related costs, especially those associated with work absenteeism [13]. It should be considered that many studies in the literature report that HCWs can transmit influenza to patients, who may be particularly vulnerable to complications [26] and, with this in mind, for health personnel to use the influenza vaccine to prevent illness and transmission to others should be part of the 'duty of care' [27].

Educating HCWs to counter concerns about vaccine safety and efficacy, and to raise awareness of the importance of protecting vulnerable patients, as well as tackling fake news and misinformation to combat HCWs' vaccine hesitancy, were topics strongly advocated by the authors of the included studies and were reviewed in many papers in the literature [25,28-33]. In any case, most authors agreed that only a multifactorial approach, including a pro-active invitation, advertising campaign and competition among hospital departments, easy access to vaccination, and improved acceptance and information about the vaccine by HCWs, would be able to increase compliance with influenza vaccination among health personnel.

The main limitation of this statistical analysis was the small number of included studies and their high heterogeneity, as indicated by the I² values; the use of random-effects analysis in the statistical analysis minimized this bias; therefore, this does not appear to be a critical issue. Furthermore, due to the small number of studies, sensitivity and publication bias analyses could not be performed. However, a strength of our study was the estimation of the OR related to the association between influenza vaccine uptake and the on-site vaccination campaign, not previously reported in the literature. In addition, the systematic review reported the effectiveness of onsite vaccination in different flu seasons.

5. Expert opinion

Vaccination resistance by healthcare professionals is a globally studied phenomenon [34-37], although it may seem counterintuitive. Compulsory vaccination, which has already been proven to be effective among health personnel [38] and other population groups [39], seems to be the only one that can guarantee the protection of HCWs and the patients they care for. Indeed, the only study that reported a vaccination coverage value >75% was that of Di Lorenzo A et al. [40].

Apulian Regional Law 19 June 2018 n. 27 provided for influenza vaccination as mandatory for HCWs; this obligation is based on fitness for work assessed by occupational health physicians, with suspension of salary until immunization. The VC reached in health personnel after the mandatory policy was 77.8% (+179% compared with the previous season). Schumacher S et al. [25] reported that mandatory vaccination or mandatory declination policies were effective in achieving influenza vaccination coverage in HCWs above 90%.

In conclusion, vaccine hesitancy toward influenza vaccine among Italian health professionals is an existing and longlasting phenomenon. Many strategies have been adopted to improve HCWs' attitudes to achieve high vaccination coverage, but none of them has proven to be able to accomplish satisfactory VCs. Vaccination of HCWs, especially in a pandemic context, is a vital measure from a public health perspective; in fact, it ensures the protection of professionals and patients (especially the most fragile ones), allows the safety of nosocomial facilities, and reduces absenteeism due to illness, ensuring a smooth service to citizens. Also, HCWs are among the most trusted sources of vaccine information and have a direct influence on the vaccination decisions of their patients and social contacts [41]. A skeptical professional might change people's minds or reinforce the idea that vaccinations are unsafe, especially among those who already refuse vaccinations [42]. Indeed, the success of a vaccination campaign depends largely on the penetration of the message aimed at the general population.

Hence, mandatory vaccination should be deeply considered by policy makers in order to extend vaccination for influenza and also for other vaccine-preventable diseases to HCWs, especially those working in particularly high-risk departments. It should be considered that on 1 April 2021, the Italian Government issued Decree Law no. 44 establishing compulsory COVID-19 vaccination for HCWs, which has led to an increase in vaccination adherence with the achievement of very high vaccination coverage [38]. The effects of this mandatory strategy need to be evaluated in terms of costeffectiveness and considering the medical-legal aspects, but at the moment we believe that it is the quickest solution to solve the problem of poor vaccination attitudes among healthcare personnel. At the same time, in the medium to long term, complementary strategies to increase vaccination compliance should be put in place to reevaluate HCWs' attitudes toward vaccination and possibly revert to a nonmandatory strategy. Among these, on-site vaccination seems to be an effective strategy to achieve higher VC.

Author contributions

FPB and ST conceived the study. FPB and AM did the literature research. FPB did the systematic review. EC and PS participated in the design of the systematic review. ADL supervisioned the systematic review. FPB and ST codrafted the first version of the article.

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