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REVIEW

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Influenza vaccination in healthcare workers: A comprehensive critical appraisal of the literature

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ABSTRACT

Influenza imposes a significant burden worldwide from the healthcare and socio-economic standpoints. This is also due to suboptimal vaccination coverage among the target population, even though immunization is recommended since many years and still remains the fundamental tool for its prevention. Healthcare workers (HCWs) are at increased risk of exposure to respiratory pathogens compared with the general population, including flu, with potential threat for their health and for patients' safety. Nevertheless, despite recommendation for immunization of this work-category in most of Western Countries, inadequate flu vaccine uptake is reported during the last decade in the European area. According to recent systematic reviews on this topic, the main determinants of vaccine acceptance among HCWs have been largely investigated and include desire for self-protection and to protect family rather than absolute disease risk or desire to protect patients, among the main drivers. On the other hand, concerns regarding safety of the vaccines resulted in decreased vaccine uptake. Moreover, influenza vaccine hesitancy among HCWs was also associated with several issues such as low risk perception, denial of the social benefit of influenza vaccination, low social pressure, lack of perceived behavioral control, negative attitude toward vaccines, not having been previously vaccinated against influenza, not having previously had influenza, lack of adequate influenza-specific knowledge, lack of access to vaccination facilities, and socio-demographic variables. The topic of influenza vaccination among HCWs is challenging, full of ethical issues. Systematic reviews of randomized controlled trials (RCTs) investigating the effectiveness of interventions for improving vaccine uptake among HCWs found that combined strategies were more effective than isolate approaches. Mandatory policies are currently under debate in several countries. High quality studies would help policy-makers and stake-holders to shape evidence-based initiatives and programs to improve the control of influenza.

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Introduction

Influenza and its prevention

Influenza is a contagious acute viral infection, with a short incubation period, spreading mainly by droplets, and characterized by fever or feeling feverish/chills associated with respiratory as well as systemic symptoms such as muscle or body aches, headache and fatigue. Flu is caused by influenza viruses, which are negative-sense, single-stranded RNA viruses belonging to the *Orthomyxoviridae* family. Three types of influenza viruses, namely influenza A, B and C, exist and types A and B are able to cause seasonal epidemics in humans: in particular, influenza A is the most commonly circulating type and, being prone to antigenic shifts, represents the most likely type to cause severe illness.[1-3]

The course of influenza can be mild or severe depending on several factors and conditions (i.e. age, immune status, co-morbidity, seasonal flu strain). However, the overall burden of influenza is heavy, both in clinical, epidemiological and societal terms. Indeed, the World Health Organization (WHO) has estimated that annual epidemics may affect from 5% to 15% of the population worldwide, causing up to 4–5 million severe cases and from 250,000 to 500,000 deaths, with a mortality rate of 4–8% among adults hospitalized and greater than 10–15%, during pandemics, and among the immunocompromised subjects.[4,5]

Despite the availability of antiviral drugs that can be administered both for therapeutic and preventive purposes against influenza, including neuraminidase (NA) inhibitors (NAIs), vaccines remain the most effective tool for preventing flu.[1-3] A variety of vaccines exists against seasonal influenza: they can be basically divided into inactivated influenza vaccines and live, attenuated influenza vaccines (called LAIVs). The category of inactivated flu vaccines includes: subunit vaccines made up of purified hemagglutinin (HA) and NA proteins, and split-virion vaccines. Conventional non-adjuvanted trivalent influenza vaccines have been recognized as having some deficiencies, such as suboptimal immunogenicity particularly in the elderly, in patients with severe chronic diseases

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Table 1. List of excluded studies with reasons.

Excluded study (with reasons)	Reasons for exclusion
Brien et al.[12]	Did not perform a comprehensive search (only 1 database, namely PubMed, was consulted)
Collange et al.[13]	Did not perform a comprehensive search (only 1 database, namely PubMed, was consulted)
Hollmeyer et al.[14]	Did not perform a comprehensive search (only 1 database, namely PubMed, was consulted)
Hollmeyer et al.[15]	Did not perform a comprehensive search (only 1 database, namely PubMed, was consulted)
Thomas et al.[16]	Old systematic review and meta-analysis, updated by Thomas et al.[17]
Thomas et al.[18]	Old systematic review and meta-analysis, updated by Thomas et al.[17]
Thomas et al.[19]	Old systematic review and meta-analysis, updated by Thomas et al.[17]
Thomas et al.[20]	Old systematic review and meta-analysis, updated by Thomas et al.[17]
Thomas et al.[21]	Old systematic review and meta-analysis, updated by Thomas et al.[17]

and immunocompromised. Moreover, the protection offered by conventional vaccines may be reduced by periodic antigenic drifts, resulting in a mismatch between the circulating and vaccinal viral strains. New technologies used in vaccine composition, administration and manufacture have led to major advances during the last few years:[6] many efforts have been spent to provide different vaccine options in such a way to improve the performance of flu vaccines, in terms of tolerability, simplicity, ease-of-use and, particularly, clinical protection.[7-9] These novel approaches have been developed to increase the uptake among patients and individuals at risk, including healthcare workers (HCWs).[6-11]

In the current paper, we systematically review and appraise published systematic reviews and/or meta-analyses performed among HCWs concerning the incidence or prevalence rate of influenza, the impact of influenza vaccination both on HCWs and on patients, HCWs' adherence to vaccination coverage, including their knowledge, attitudes and beliefs (KABs), the determinants of influenza vaccine uptake and the economic burden of influenza vaccination in this risk category.

Results

The initial search yielded 407,824 items. After removing duplicate studies, 247,636 items remained and were screened for

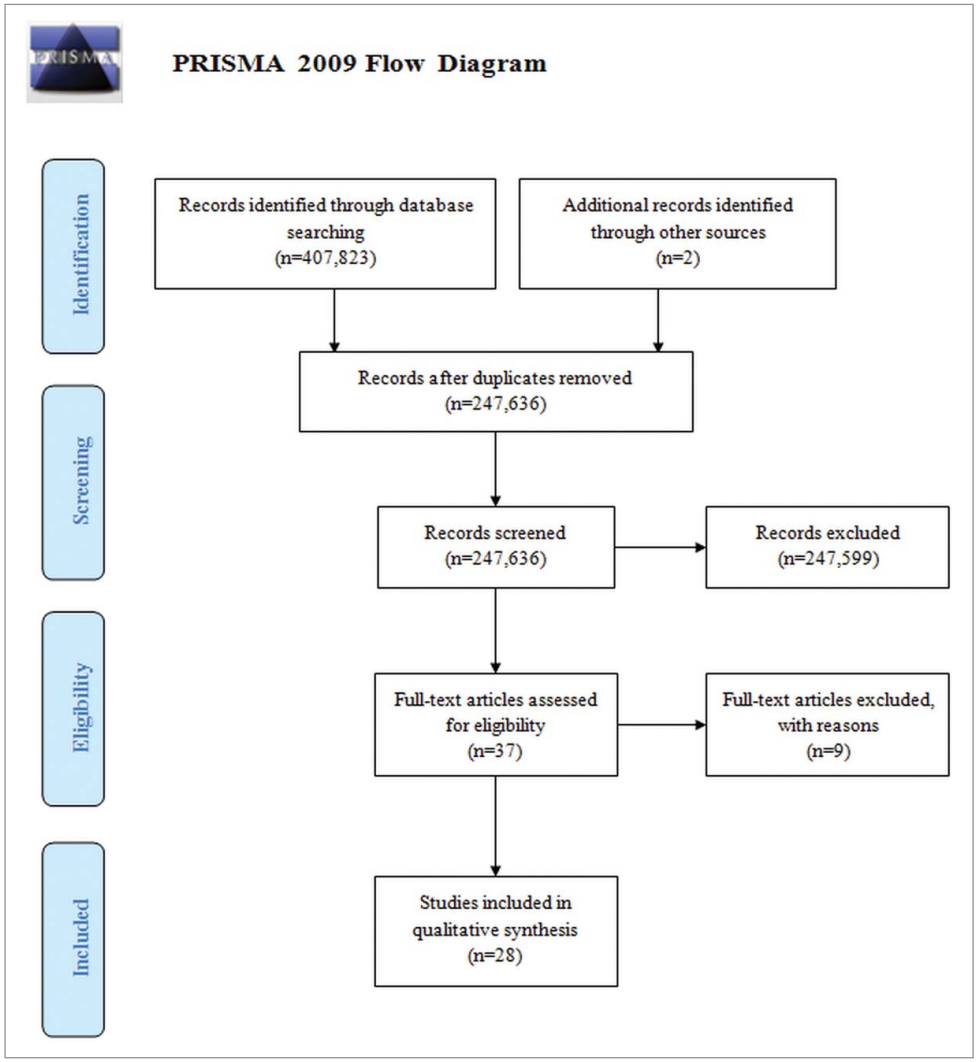

Figure 1. The "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) flow-chart for the selection and inclusion of studies in the present umbrella review.

eligibility. After excluding studies not meeting with inclusion criteria, 37 articles were assessed. 9 studies were subsequently excluded with reasons (Table 1).[12-16,18-21] 28 studies (12 systematic reviews, 13 meta-analyses and 3 appraisals of published reviews) were retained and included in the current study (Fig. 1).

They have been coded on the basis of the main research question(s) of each study and the following main themes have been found: 1) epidemiological data (incidence or prevalence) of influenza among HCWs (1 study); 2) influenza-related KABs among HCWs (2 studies); 3) influenza-related risk perceptions among HCWs (2 studies); 4) adherence of HCWs to influenza vaccination (4 studies); 5) determinants of influenza vaccine uptake among HCWs (8 studies); 6) effects of influenza vaccination among HCWs on HCWs themselves (5 studies); 7) effects of influenza vaccination among HCWs on patients (6 studies); 8) strategies for improving influenza vaccine uptake among HCWs (7 studies); and 9) economic impact of influenza vaccination among HCWs (1 study). For further details about the synthesized topics of the included studies, the reader is referred to Table 2.

After searching in the "International Prospective Register of Systematic Reviews" (PROSPERO), 4 relevant study protocols were found, only 3 of which corresponded to published systematic reviews and/or meta-analyses. Searching in the Cochrane Library and in the Joanna Briggs Institute (JBI) "Database of Systematic Reviews and Implementation Reports" yielded 2 relevant protocols, respectively, both corresponding to 2 published systematic reviews and/or meta-analyses.

The characteristics of each included study are outlined in Tables 3–5.

Table 2. List of coded topics and their respective references.

Topic synthesized	Number of studies	References
Prevalence/incidence of influenza among HCWs	1	Lietz et al.[22]
Influenza-related KABs	2	Gambhir et al.[23] Ng and Lai[24]
Influenza-related risk perceptions among HCWs	2	Koh et al.[25] Yiwen et al.[26]
Adherence of HCWs to influenza vaccination	4	Bish et al.[27] La Torre et al.[28] Maggiore et al.[29] Prematunge et al.[30]
Determinants of influenza vaccine uptake among HCWs	8	Bish et al.[27] La Torre et al.[28] Nowak et al.[31] Prematunge et al.[30] Riphagen-Dalhuisen et al.[32] Schmid et al.[33] Vasilevska et al.[34] Yiwen et al.[26]
Effect of influenza vaccination among HCWs on HCWs themselves	5	Kliner et al.[35] Kuster et al.[36] Michiels et al.[37] Ng and Lai[24] Restivo et al.[38]
Effect of influenza vaccination among HCWs on patients	6	Ahmed et al.[39] De Serres et al.[40] Dolan et al.[41] Kliner et al.[35] Michiels et al.[37] Thomas et al.[17]
Strategies for improving vaccination coverage among HCWs	7	Corace et al.[42] Lam et al.[43] Lytras et al.[44] Pitts et al.[45] Rashid et al.[46] Schmidt et al.[47] Siemieniuk et al.[48]
Economic impact of influenza vaccination among HCWs	1	Burls et al.[49]

Epidemiology of influenza among health-care workers

HCWs is an umbrella term which includes a variety of figures, such as medical doctors (like specialists, pediatricians, general practitioners), nurses, other health allied professionals, technicians, cleaners and porters, at increased risk of exposure to respiratory pathogens. HCWs may not only acquire but also transmit and spread infection to vulnerable patients[50]. It should be stressed that the definition of HCWs is highly variable among countries and may reflect discrepancies in their national history, cultural, juridical, and political factors that influence the precise way in which HCW' practices are coded. Economic variables should be taken into account as well. In low-resource contexts, since there is a shortage of HCWs, task shifting is usually applied and healthcare services are scaled up. As such, the role of HCWs varies among developed and developing countries.

This variability in HCW definition is reflected by the studies included in the current umbrella review. For example, Gambhir et al.[23] focused on clinical and pre-clinical dental students, Ahmed et al.,[39] De Serres et al.[40] and Thomas et al.[17] on HCWs working among residential institutions and La Torre et al.[28] on nurses, and ancillary workers.

Concerning the epidemiology of influenza among HCWs, Lietz et al.[22] performed a systematic review of 26 studies and a meta-analysis of 15 studies assessing the occupational risk of influenza A H1N1 infection among HCWs during the 2009 pandemic. The authors found an increased risk among HCWs, with a pooled prevalence rate of influenza of 6.3%.

Knowledge, attitudes and beliefs on flu among healthcare workers

Knowledge is generally higher among medical doctors compared with other HCWs. Gambhir et al.[23] found that among dentists knowledge concerning influenza and influenza vaccines was limited. Ng and Lai[24] found that knowledge and favorable beliefs have increased throughout time, but many misperceptions (such as the beliefs that HCWs are not susceptible to influenza or less susceptible than other subjects and that influenza is a threat only to frail and sick people) persist, varying according to the type or category of HCWs.

Risk perceptions among healthcare workers

Koh et al.[25] found that risk perceptions toward pandemic influenza among HCWs varied according to the working setting (working in tertiary hospitals *versus* community hospitals).

As stated by Yiwen et al.[26] relationship between HWCs' risk perceptions and risk-mitigating strategies is complex and multi-factorial, and, as such, needs to be further elucidated.

Table 3. Characteristics of the included systematic reviews.

Reference	Searched databases	Study protocol	Number of synthesized studies	Number of studied subjects	Outcome(s)	Main finding(s)	Quality assessment	Conflicts of interest	AMSTAR score
Bish et al.[27]	PubMed, WoS	Not available	19 studies	33,985 HCWs	Willingness to vaccinate themselves against pandemic influenza	Intention associated with higher perceived susceptibility to H1N1, higher perceived severity of H1N1, higher perceived benefits, lower perceived costs of vaccination, older age, male gender, not being a nurse, wish to protect oneself and others, beliefs in vaccine safety and effectiveness, past influenza vaccinations, adequate knowledge and information (received from official sources), having previously suffered from influenza, receiving recommendation from respected HCW	Not performed	Disclosed	3
					Intention to being vaccinated	22- 83%			
					Adherence to vaccination	13-53%			
Corace et al.[42]	MEDLINE, EMBASE, CINAHL, PsycINFO, The Joanna Briggs Institute, SocINDEX, and the Cochrane Database of Systematic Reviews	Not available	10 studies	7,312 HCWs	Impact of behavior change frameworks-based programs	It successfully predicted 85-95% of HCW influenza vaccination uptake	Performed		5
Gambhir et al.[23]	PubMed/MEDLINE, Embase	Not available	3 cross-sectional studies	1,017 HCWs	Swine influenza-related KABs	Socio-demographic variables, clinical *versus* pre-clinical students	Not performed		5
					Knowledge and awareness about swine influenza vaccine	31.5-82.3%			
Koh et al.[25]	CINAHL, Ovid, PubMed, ScienceDirect, Scopus and Wiley InterScience	Not available	14 quantitative studies and 2 qualitative studies, of which 3 focusing on influenza	1,762 HCWs	Risk perceptions towards pandemic influenza	Working in tertiary hospitals *versus* community hospitals	Not performed	Not available	4
Lam et al.[43]	MEDLINE, EMBASE, CINAHL, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Proquest (for dissertations and theses)	Not available	12 studies	55,605 HCWs, of which 34,834 cases	Determinants of the effectiveness of influenza vaccination campaigns	Interventions combining different strategies in LTCIs seem to be the most effective	Performed	Disclosed	6

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Table 3. (Continued)

Reference	Searched databases	Study protocol	Number of synthesized studies	Number of studied subjects	Outcome(s)	Main finding(s)	Quality assessment	Conflicts of interest	AMSTAR score
Maggiore et al.[29]	PubMed/MEDLINE and Scopus	Not available	Authors data + 17 studies, of which 3 focusing on influenza	At least 50,360 HCWs, of which at least 6,001 were evaluated with respect to influenza vaccination	Adherence to influenza vaccination Strategies for improving vaccination coverage	From <10% to 56% A complex, multifaceted intervention succeeded in increasing vaccination coverage	Performed	Not available	5
Pitts et al.[45]	MEDLINE, Embase, the Cochrane Library, CINAHL, SCIE, and Conference Proceedings Citations Index	Registered in PROSPERO CRD42012002913	12 observational studies	At least 113,239 HCWs	Impact of a program implementing mandatory influenza vaccination among HCWs	Vaccination rates increased, exceeding 94%.	Performed	Disclosed	6
Prematunge et al.[30]	MEDLINE, PubMed, EMBASE, PsycINFO, CINHAL, AMED, Cochrane Library, ProQuest, and grey literature sources	Not available	20 studies (1 focus group, 1 cohort study, 18 cross-sectional studies)	22,348 HCWs	Influenza vaccination coverage Determinants of influenza vaccination uptake	From 9% to 29% Believing that vaccine is safe and effective and that influenza is a serious disease	Not performed	Disclosed	5
Rashid et al.[46]	MEDLINE, Embase, the Cochrane Library, CINAHL, PsycINFO + grey literature	Not available	12 RCTs	193,924 HCWs	Interventions for increasing influenza vaccination rate among HCWs	Combined strategies seemed to be more effective than isolate approaches	Performed	Disclosed	7
Restivo et al.[38]	PubMed/MEDLINE, Scopus, Embase, ISI/WoS	Registered in PROSPERO CRD42017054854	2 studies (1 case-control study, 1 cohort study)	2,062 HCWs	Vaccine effectiveness among HCWs	From 70.5% to 90.5% [95%CI 73.5-97.3%]	Not performed	Nothing to disclose	5
Schmid et al.[33]	MEDLINE, LILACS, Embase, IBSS, PsychInfo, IMEMR (GIM), Cinahl, IMSEAR (GIM), the Cochrane Library, AIM (GIM), WoS, WPRIM (GIM)	Not available	470 studies, of which 117 specifically focusing on HCWs		Influenza vaccine hesitancy, and the main perceived barriers to vaccine uptake	A low risk perception, denial of the clinical/social benefit of vaccination practices, a low social pressure, lack of perceived behavioral control, not having been previously vaccinated, not having previously suffered from influenza, lack of influenza-specific knowledge, lack of access to vaccination facilities, and socio-demographic variables predicted low vaccine uptake	Not performed	Disclosed	4
Yiwen et al.[26]	CINAHL, PubMed, SCOPUS, ScienceDirect, Sociological Abstracts, PsycINFO, and WoS	Published	10 quantitative studies and 1 qualitative study, of which 5 focusing specifically on influenza	9,676 HCWs	HCW's risk perceptions and impact of risk perceptions on risk-mitigating strategies	Relationship between HWCs' risk perceptions and risk-mitigating strategies needs to be further elucidated	Performed	Disclosed	6

Table 4. Characteristics of the included meta-analyses.

Reference	Searched databases	Study protocol	Number of synthesized studies	Number of studied subjects	Outcome(s)	Main finding(s)	Quality assessment	Conflicts of interest	AMSTAR score
Ahmed et al.[39]	MEDLINE, Embase, CINAHL, WoS, and the Cochrane Library	Not available	4 cluster RCTs and 4 observational studies (2 cohort and 2 case-control studies)	8,468 residents	Overall impact of the influenza vaccination	The overall quality of the evidence was moderate	Performed	Nothing to disclose	6
					Reduction in patient mortality	It may provide a protective effect (RR 0.71 [95%CI 0.59–0.85], RD −44 [95%CI from −23 to −62], ΔRR% 29% [95%CI 15-41%]), whose evidence quality is moderate			
					Reduction in laboratory-confirmed influenza cases	It may provide a protective effect (RR 0.80 [95%CI 0.31–2.08], RD −13 [95%CI from −44 to 69]), whose evidence quality is low			
					Reduction in ILI episodes	It may provide a protective effective (RR 0.58 [95%CI 0.46–0.73], RD −68 [95%CI from −44 to −87], ΔRR% 42% [95% CI 27–54%), whose evidence quality is low			
					Reduction in patient hospitalization rate	No effect (RR 0.91 [95%CI 0.69–1.19], RD −9 [95%CI from −29 to 18])			
De Serres et al.[40]	MEDLINE, US CDC, the Cochrane Library	Not available	4 RCTs	8,490 residents	Impact of influenza vaccination among HCWs	At least from 6,000 to 32,000 HCWs would need to be vaccinated in order to avert a single patient death	Performed	Disclosed	NA, being a critical review and appraisal of already published systematic reviews and meta-analyses
Kuster et al.[36]	OVID MEDLINE and EMBASE	Not available	29 studies (97 influenza seasons)	58,245 HCWs	All infections in unvaccinated HCWs per season	IR 18.7 (95% CI, 15.8 to 22.1)	Performed	Disclosed	7
					All infections in unvaccinated HCWs	IRR 3.4 (95% CI, 1.2 to 5.7)			
					All infections in vaccinated HCWs per season	IR 6.5 (95% CI, 4.6 to 9.1)			
					All infections in vaccinated HCWs	IRR 5.4 (95% CI, 2.8 to 8.0)			
					Symptomatic infections in unvaccinated HCWs per season	IR 7.5 (95% CI, 4.9 to 11.7)			
					Symptomatic infections in unvaccinated HCWs	IRR 1.5 (95% CI, 0.4 to 2.5)			
					Symptomatic infections in vaccinated HCWs per season	IR 4.8 (95% CI, 3.2 to 7.2)			
					Symptomatic infections in vaccinated HCWs	IRR 1.6 [95%CI 0.5-2.7]			

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Table 4. (Continued)

Reference	Searched databases	Study protocol	Number of synthesized studies	Number of studied subjects	Outcome(s)	Main finding(s)	Quality assessment	Conflicts of interest	AMSTAR score
La Torre et al.[28]	PubMed/MEDLINE, Scopus, Google Scholar, ISI/Web of Knowledge	Not available	15 studies (qualitatively synthesized) and 6 studies (quantitatively synthesized)	At least 20,296 HCWs (1 study did not report the number of total subjects studied)	Proportion of influenza vaccination rate among nurses	13.47% [95%CI 9.58-17.90%]	Performed	Not available	7
					Proportion of influenza vaccination rate among ancillary workers	12.52% [95%CI 9.97-15.31%]			
					Ideas/reasons encouraging vaccination such as self protection	70%–94.3%			
					family protection	24%–69%			
					patients protection	26%–57.8%			
					protection of other people	28.0%–58.2%			
					being an healthcare worker	9.31%			
					being elderly or affected by a chronic disease	21.33%			
					Ideas preventing vaccination such as not caring about influenza	35.2%–57.1%			
					doubts about vaccine efficacy	14.1%–43.8%			
					fear of adverse effects	14%–30.6%			
					being opposed to vaccination	2.3%–6.2%			
					forgetfulness	8.5%			
					believing that vaccines do not have a protective effect	12.1%			
					believing that influenza is a mild disease	9.5%			
Lietz et al.[22]	Embase, MEDLINE, PsycINFO, CINAHL (all via OVID), PubMed and Google Scholar	Available upon request	26 studies (qualitatively synthesized) and 15 studies (quantitatively synthesized)	109,815 subjects, of which 72,281 HCWs	Occupational risk of influenza A H1N1 infection among HCWs during the 2009 pandemic	OR of 2.08 [95%CI 1.732.51]	Performed	Disclosed	7
					Overall influenza prevalence rate among HCWs	6.3%			
Lytras et al.[44]	MEDLINE and Scopus	Not available	46 studies	All studies with all HCWs, except for 3 studies with all HCWs with direct patient contact, 1 with physicians and nurses, 1 with medical residents and students, 2 all HCWs except physicians	Impact of interventions for increasing seasonal influenza vaccine coverage such as mandatory vaccination	RR_{unvacc} 0.18 [95%CI 0.08-0.45]	Performed	Disclosed	7
					Declination statements	RR_{unvacc} 0.64 [95%CI 0.45-0.92]			
					Increased awareness	RR_{unvacc} 0.83 [95% CI 0.71-0.97]			
					Increased access	RR_{unvacc} 0.88 [95%CI 0.78-1.00]			
					Incentives	No significant difference			
					Education	No effect (RR_{unvacc} 0.96 [95%CI 0.84–1.10])			
Ng and Lai[24]	22 databases	Not available	3 RCTs	992 HCWs	Overall impact of vaccination	No definitive conclusions	Performed	Disclosed	8
					Reduction of laboratory-confirmed influenza cases and vaccine effectiveness	Significant protective effect; vaccine effectiveness of 88% [95%CI 59-96%]			
					Reduction of number of ILI episodes	1.07 [95%CI 0.62-1.85]			
					Reduction of days with ILI symptoms	Reduction by 0.12 days [95%CI 0.06-0.3]			
					Reduction in amount of sick leave	Reduction by 0.08 days [95%CI 0.02-0.19]			

Nowak et al.[31]	US CDC	Not available	29 unpublished, primarily qualitative CDC-sponsored studies	2,090 HCWs (132 nurses, 1,811 doctors, 14 HCP, 75 clinical staff, 35 hospital service workers, 23 allied health professionals)	Influenza-related KABs among HCWs	Knowledge and favorable beliefs have increased throughout time, but many misperceptions (HCWs are not susceptible to influenza; influenza is a threat only to frail and sick people) persist, varying according to the type or category of HCW	Not performed	Disclosed	Not applicable, being a qualitative meta-analysis
Siemieniuk et al.[48]	MEDLINE, Embase, CENTRAL, WoS, Scopus, and CINAHL + gray literature	Registered in PROSPERO	CRD42013006122	121 studies with 174 comparisons, (132 before/after studies, 23 randomized trials, 12 surveys, 7 cohort studies, and 1 case-control study)	From 120,670 HCWs to 764,570 HCWs, according to the synthesized strategy intervention	Strategies for improving influenza vaccination coverage among HCWs such as condition of service	93% reduction [95%CI 91-95%]	Performed	Disclosed
			8			Vaccine-or-mask	74% reduction [95%CI 61-88%]		
						Declination forms	41% reduction [95%CI 35–46%]		
						Audit-and-feedback	35% reduction [95%CI 29–40%]		
						Increased vaccine access	32% reduction [95%CI 27–36%]		
						Role models	30% [95%CI 24–36%]		
						Peer-vaccination	29% reduction [95%CI10–45%]		
						Incentives	28% reduction [95%CI21–33%]		
Education/ promotion only	11% reduction [95%CI 7–16%)]								
Riphagen-Dalhuisen et al.[32]	PubMed and Embase	Not available	13 studies	84,880 HCWs	Predictors of seasonal influenza vaccination such as knowing that the vaccine is effective	RR 2.22 [95%CI 1.93 to 2.54]	Not performed	Disclosed	5
					Being willing to prevent influenza transmission	RR 2.31 [95%CI 1.97 to 2.70]			
					Believing that influenza is highly contagious	RR 2.25 [95%CI 1.66 to 3.05]			
					Believing that influenza prevention is important	RR 3.63 [95%CI 2.87 to 4.59]			
					Having a family that is usually vaccinated	RR 2.32 [95%CI 1.64 to 3.28]			

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Table 4. (Continued)

Reference	Searched databases	Study protocol	Number of synthesized studies	Number of studied subjects	Outcome(s)	Main finding(s)	Quality assessment	Conflicts of interest	AMSTAR score
Schmidt et al.[47]	PubMed and Scopus	Not available	10 studies	13,322 subjects	Impact of strategies for improving influenza vaccination coverage among HCWs	Interventions combining educational and promotional components seem to be the most effective	Performed	Not available	7
					Impact of the quality of trials and year of publication	The quality of trials plays a major role			
Thomas et al.[17]	CENTRAL, MEDLINE, EMBAS, WoS, Biological Abstracts, SCIE	Available	4 cluster RCTs and 1 cohort study	12,742 HCWs (qualitatively synthesized) and 5,896 residents (quantitatively synthesized)	Impact of influenza vaccination among HCWs caring for individuals ≥60 years in LTCIs in terms of reduction of laboratory-proven infections	RD 0 [95% CI −0.03–0.03]	Performed	Disclosed	10
					Reduction of lower respiratory tract infection in residents	From 6% to 4% (RD −0.02 [95% CI −0.04–0.01			
					Reduced respiratory illness in residents	RD 0 [95% CI −0.02–0.02]			
Vasilevska et al.[34]	MEDLINE, Embase, and CINAHL	Not available	37 studies	67,384 HCWs	Determinants of vaccine acceptance such as desire for self-protection	OR 3.42 [95%CI) 2.42-4.82])	Performed	Disclosed	7
					Desire to protect family and friends	OR 3.28 [95% CI 1.10-9.75])			
					Concerns regarding safety and effectiveness	(OR 0.42 [95%CI 0.30-0.58])			

Table 5. Characteristics of the included systematic appraisals of published studies and economic evaluations.

Reference	Searched databases	Study protocol	Number of synthesized studies	Outcome(s)	Main finding(s)	Risk of bias assessment	Conflicts of interest	AMSTAR score
Burls et al.[49]	Cochrane library, CINAHL, NHSEED, HEED, DARE, MEDLINE and EMBASE	Not available	18 studies (3 RCTs, 3 cluster RCTs, 5 before/after studies, 7 surveys)	Reduction in mortality	Reduction from 17% to 10% (OR 0.56 [95%CI 0.4-0.8]) – OR 0.61, [95%CI 0.36-1.04]	Performed	Disclosed	5
				Vaccine effectiveness	88% [95%CI 47-97%]			
				Strategies for improving vaccine uptake	Increase by 5-45%			
				Economic analysis of influenza vaccination among HCWs	In the base case, vaccination was cost saving			
Dolan et al.[41]	22 databases + vaccine manufacturers, domain experts	Registered CRD420111092]	20 studies (4 RCTs, 10 observational studies; 6 reviews)	Overall impact of influenza vaccination among HCWs	It is likely to offer some protection, but further evidence is needed from acute care settings	Performed	Disclosed	6
				Reduction in cases of acute respiratory disease	Inconsistent effect			
				Reduction in clinically defined cases of ILI	It is likely to offer some protection			
				Reduction in GP consultations for ILI	Inconsistent effect across different influenza seasons			
				Reduction in outbreaks/clusters of ILI	It is likely to offer some protection			
				Reduction in laboratory confirmed cases of influenza	Small non significant effect			
				Reduction in laboratory confirmed outbreaks of influenza	No statistically significant effect			
				Reduction in respiratory mortality	Small non significant effect			
				Reduction of all-cause mortality	It is likely to offer some protection			
				Impact on hospitalization	No clear effect			
Kliner et al.[35]	MEDLINE, Embase, CINAHL, AMED and HMIC	Available	11 reviews	Impact of influenza vaccination among HCWs	No "straightforward evidence" of employer and patient safety benefits of influenza vaccination among HCWs	Performed	Disclosed	8
Michiels et al.[37]	PubMed, the Cochrane library	Not available	3 studies (2 randomized trials and 1 systematic review and meta-analysis)	Impact of vaccination on HCWs	Effectiveness of 53%	Performed	Disclosed	6
					Effectiveness in young physicians (30 years) aOR 0.35 [95%CI 0.13–0.96], efficacy 0.10 [95%CI 0.01–0.75]			
				Impact of vaccination on patients	Not significant			

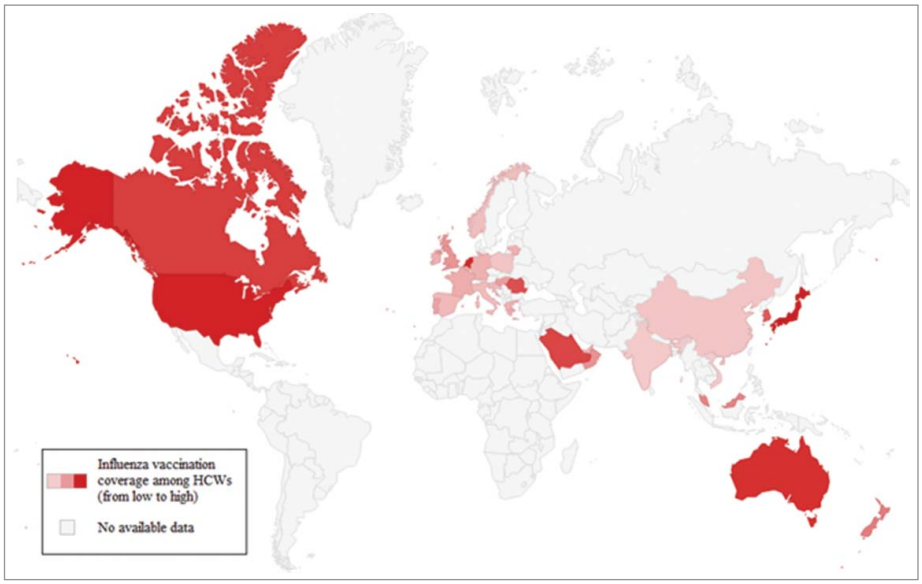

Figure 2. Influenza vaccination uptake among healthcare workers (HCWs) worldwide, between 2006 and 2015. Adapted from (To et *al*., 2016), reference 50.

Vaccine uptake among healthcare workers

Vaccination coverage among HCWs is low in Europe (generally less than 30%) despite several recommendations. A significant difference comparing data reported in the USA *vs*. Europe and other countries exists (Figures 2, 3).[51]

Concerning the available systematic reviews and meta-analyses, Bish and colleagues[27] found that adherence to influenza vaccination went from 13% to 53% (with an intention to vaccinate oneself in the range 22–83%). In Italy, La Torre et al.[28] performed a systematic review of 15 studies and a meta-analysis of 6 studies. They found a pooled proportion of influenza vaccination rate of 13.47% and 12.52%, respectively for nurses and ancillary workers. In other European countries, such as United Kingdom, Germany, France, the mean of influenza vaccination prevalence ranged from 15% to 29%.

Maggiore et al.,[29] pooling their own data with data from the extant literature, found that adherence to influenza vaccination ranged from <10% to 56%. Lower figures were found by Prematunge et al.,[30] with a range of 9–29%.

Determinants of influenza vaccine uptake among healthcare workers

Bish et al.[27] found that willingness and intention to vaccinate oneself against influenza were associated with higher perceived susceptibility to H1N1 influenza virus, higher perceived severity of the disease, higher perceived benefits (both clinical and societal), and lower perceived costs of vaccination. Furthermore, HCWs likely to protect themselves against influenza were characterized by older age, and male gender. Being a nurse

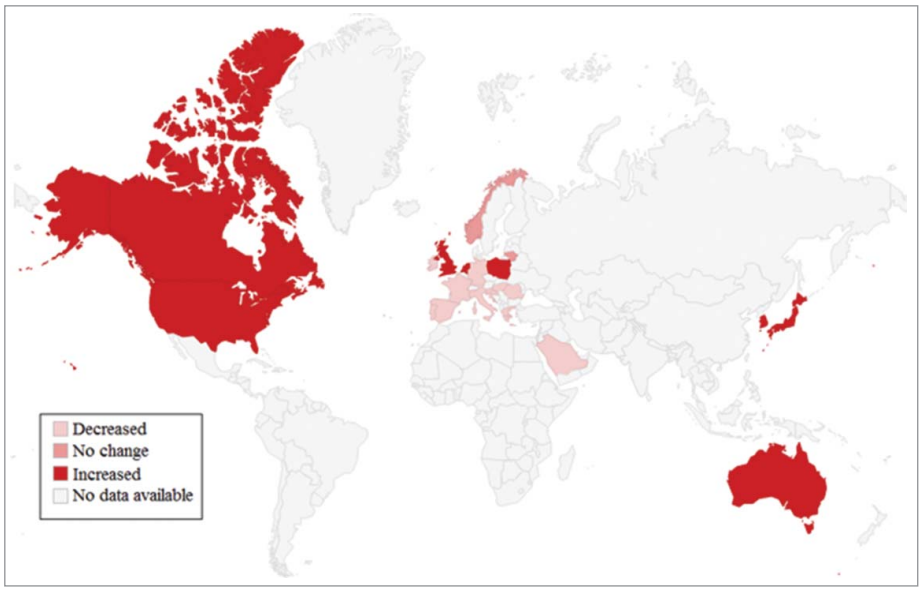

Figure 3. Temporal trend of influenza vaccination uptake among healthcare workers (HCWs) worldwide, between 2006 and 2015. Adapted from (To et *al*., 2016), reference 50.

correlated with a negative intention toward influenza vaccine uptake, while wish to protect oneself and others, beliefs in vaccine safety and effectiveness, as well as having previously had influenza and past influenza vaccinations were predictors of adherence to influenza immunization. Moreover, receiving adequate knowledge and information delivered from official sources, and receiving recommendation from respected HCWs played a major role.

Durando et al.[52] performed a cross-sectional study based on anonymous self-administered web questionnaires between October 2013 and February 2014, recruiting 830 HCWs. They found that being a medical doctor, not having concern about vaccine safety, having the perception of an increased risk of developing influenza among HCWs were statistically associated with flu vaccination uptake in the 2013/2014 season, while the idea that pharmaceutical companies could influence decision about vaccination programs was negatively associated with vaccine uptake.

Vasilevska et al.[34] performed a systematic review and meta-analysis of the studies assessing the determinants of vaccine acceptance (including influenza vaccination) among HCWs. They found 37 studies. Desire for self-protection, and desire to protect family and friends rather than absolute disease risk or protection for patients resulted predictor of vaccination acceptance. Concerns regarding safety and effectiveness of the vaccine resulted into decreased vaccine acceptance. Also cultural issues played a major role, shaping and influencing vaccine behaviors among Asian physicians and nurses *vs*. non Asian HCWs.

Llupià and colleagues[53] performed a cross-sectional study recruiting 235 HCWs interviewed after the 2010/2011 influenza vaccination campaign, investigating the impact of social network and the influence of peers on influenza vaccine acceptance among HCWs. They found that links were more likely to occur between HCWs sharing the same professional category, sex, age, and ward/department, but not the same vaccination behavior.

Riphagen-Dalhuisen et al.,[32] performing a systematic review, found that knowing that the vaccine is effective, being willing to prevent influenza transmission, believing that influenza is highly contagious and believing that influenza prevention is important and having a family that is usually vaccinated predicted seasonal influenza vaccination among HCWs.

La Torre et al.[28] found that desire of self protection as well as protection of family, patients and of other people encouraged influenza vaccination among HCWs. Being elderly or affected by a chronic disease was another predictor of influenza vaccine uptake. On the contrary, not caring about influenza, doubts about vaccine efficacy/effectiveness, fear of adverse effects, being opposed to vaccination in general, forgetfulness, believing that vaccines do not have a protective effect or believing that influenza is a mild disease represented ideas and beliefs preventing vaccination among HCWs.

Schmid et al.[33] performed a systematic review of influenza vaccine hesitancy, investigating the main perceived barriers to vaccine uptake. Synthesizing 470 articles, they found that a low risk perception, denial of the social benefit of influenza vaccination, a low social pressure (either real or perceived), lack of perceived behavioral control, a negative attitudes toward vaccination in general, not having been vaccinated in the previous influenza vaccination campaigns, not having had influenza in the previous years, lack of adequate influenza-specific knowledge, lack of access to vaccination facilities, and socio-demographic variables (including age, gender, additional risk factors such as unhealthy life-style factors) were negative predictors of vaccine uptake.

Effectiveness of influenza vaccination among healthcare workers

Kuster et al.[36] performed a meta-analysis of 29 studies covering 97 influenza seasons with 58,245 study participants and found that influenza vaccination is effective in protecting HCWs, reducing infections, both symptomatic and asymptomatic.

Wilde and colleagues[54] conducted a prospective, double-blind randomized controlled trial (RCT) recruiting 264 HCWs, over 3 consecutive years, from 1992–1993 to 1994–1995, to investigate the effectiveness of trivalent influenza vaccine, in reducing infection, illness, and absence from work in young, healthy health care professionals. Authors found a vaccine efficacy of 88% for influenza A and 89% for influenza B. Moreover, the vaccine contributed to decrease cumulative days of febrile respiratory illness and days of absence among vaccinated HCWs.

Ng and Lai[24] performed a systematic review and meta-analysis of published studies and found a vaccine effectiveness of 88% against laboratory-confirmed influenza cases, even though the overall impact of vaccination among HCWs on HCWs themselves did not allow the authors to make definitive conclusions in terms of reduction of influenza-like illness (ILI) episodes, of days with ILI symptoms and in amount of sick leave.

Restivo[38] and colleagues performed a systematic review of the extant literature and found a vaccine effectiveness ranging from 70.5% to 90.5%.

Recent controversial issues concerning flu immunization in healthcare workers: has influenza vaccination an impact on patients' health?

The impact of HCWs vaccination in terms of reduced risk of influenza and increased benefit among patients is a controversial topic. This is because of the scarcity of scientific evidences and the poor quality of primary studies.

A systematic review conducted by the Cochrane group[17] has identified 4 cluster RCTs and one cohort study of influenza vaccination for HCWs caring for individuals $\geq$ 60 y in long-term care institutions (LTCIs). The systematic review pooled data concerning 12,742 HCWs, however only the 4 cluster RCTs could be meta-synthesized (data concerning 5,896 residents) in that study populations, type of intervention and outcomes were comparable. On the other hand, because of several biases (including the attrition rate, the lack of blinding, the contamination in the control groups and the relatively low rates of vaccination coverage) the quality of the studies was poor. The authors found that vaccinating HCWs may have little or no effect for residents in terms of reduction of laboratory-proven infections (pooled risk difference or RD 0). HCW vaccination may probably reduce lower respiratory tract infection in residents from 6% to 4% (RD −0.02), while having very little or no

effect for residents in terms of reduced upper respiratory illness (RD 0). The authors stressed the need of high quality RCTs to avoid the risks of bias in methodology. Further, vaccination interventions should be tested in combination with others such as hand-washing, face masks, early detection of laboratory-proven influenza, quarantine, avoiding admissions, antiviral drugs or asking HCWs with influenza or ILI not to work.

Further, De Serres et al.[40] critically reviewing the 4 cluster RCTs found mathematical discrepancies and implausibility. They re-calculated that at least from 6,000 to 32,000 HCWs would need to be vaccinated to avert a single patient death.

On the other hand, Ahmed et al.[39] computed that influenza vaccination among HCWs contributed to a 42% reduction in ILI episodes and a 29% reduction in patient mortality. However, assessing the evidence quality of the studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, they found that the quality of the evidence for the impact of vaccination among HCWs on mortality was low, while the effect on influenza cases in patients and patient hospitalization was moderate and low, respectively, with a moderate overall evidence quality.

Strategies for improving vaccine coverage among healthcare workers: is it time for mandatory vaccination?

Pitts et al.[45] performed a systematic review of 12 observational studies, investigating the impact of a program implementing mandatory influenza vaccination among HCWs: the authors found that vaccination rates increased, exceeding 94%. Only 2 single-institution studies reported mixed findings. Requests of medical and religious exemptions and terminations or voluntary resignations were rare.

Corace et al.[42] performed a systematic review of 10 studies assessing the impact of behavior change frameworks-based programs (namely, health belief model, theory of planned behavior, risk perception attitude theory, and Triandis model of interpersonal behavior) for improving influenza vaccine coverage among HCWs. Synthesizing the studies, the authors found that the main predictors of influenza vaccine uptake were positive attitudes regarding the efficacy and safety of influenza vaccination, perceptions of risk and benefit to self and others, self-efficacy, cues to action, and social-professional norms. The behavior change frameworks successfully predicted 85–95% of HCW influenza vaccination uptake.

Rashid et al.[46] performed a systematic review of RCTs investigating the effectiveness of different interventions aimed at improving influenza vaccine coverage among HCWs. They identified 12 RCTs that, collectively, assessed 6 major categories of interventions (namely, educational materials and training sessions, improved access to the vaccine, rewards following vaccination, organized efforts to raise vaccine awareness, reminders to get vaccinated, and the use of advocacy) involving 193,924 HCWs in high-income countries. Combined strategies seemed to be more effective than isolate approaches, however the poor quality of the studies hindered the generalization of the results and warranted further research.

Lytras and colleagues[44] performed a systematic review of the extant literature and found that "soft mandate"-based alternatives to "hard mandate" (such as compulsory influenza vaccination) exist. Declination statements, increased awareness, increased access to vaccination facilities, incentives and education represent effective approaches for increasing influenza vaccine uptake among HCWs.

In particular, Siemieniuk et al.,[48] performing a comprehensive systematic review and meta-analysis of 121 publications, found that all interventions assessed successfully increased HCW influenza vaccine uptake, with condition of service policies resulting in sustained HCW vaccination rates of > 95%.

Discussion

Despite almost a decade of efforts and wide recommendation for the immunization of HCWs across most of European countries, vaccination coverage is still low in this group. During the season 2010/11, the mean vaccination rates registered in 11 European countries resulted less than 30%.[55]

Vaccination coverage declined in the post pandemic season in Europe; in Germany, seasonal influenza vaccine uptake among HCWs decreased from 30.5% in the pre-pandemic 2008/09 season to 25.8% in the first post-pandemic 2010/11 season.[56] The decrease was consistent also in Italy[57] and a similar reduction was observed in France, Hungary, Portugal and Spain.[55]

Table 6. Narrative meta-synthesis reporting the main outcomes of the current umbrella review concerning influenza vaccination among healthcare workers. Abbreviations: HCWs (healthcare workers); KABs (knowledge, attitudes and beliefs).

Topic synthesized	Main outcome(s)
Prevalence/incidence of influenza among HCWs	HCWs are a risk group
Influenza-related KABs	Higher and more favourable among medical doctors
	Positive KABs have increased throughout the years, even though misconceptions persist
Influenza-related risk perceptions among HCWs	Variable according to type or category of HCWs
Adherence of HCWs to influenza vaccination	Low coverage, despite recommendations
	In some countries have increased throughout the years
	Higher among medical doctors
Determinants of influenza vaccine uptake among HCWs	Extensively studied
	Different categories including KABs, past experiences and socio-demographic variables
Effects of influenza vaccination among HCWs on HCWs themselves	Influenza vaccination has a protective effect for HCWs
Effects of influenza vaccination among HCWs on patients	Controversial effects
Strategies for improving vaccination coverage among HCWs	Mandatory vaccination is effective in increasing vaccination coverage among HCWs
	Soft mandate-based programs are effective as well
	Multi-faceted, complex and integrated programs seem to be the most effective approaches
Economic impact of influenza vaccination among HCWs	Potentially cost saving

Table 7. Search strategy of the present umbrella review.

Search strategy item	Details
String of keywords used	(influenza OR flu) AND (vaccination OR vaccine OR vaccines OR immunization OR immunisation OR belief OR beliefs OR perception OR perceptions OR awareness OR knowledge) AND ("healthcare worker" OR "healthcare workers" OR "healthcare personnel" OR "healthcare staff" OR "health worker" OR "health workers" OR "health personnel" OR "health staff" OR physicians OR physician OR doctors OR doctor OR nurses OR nurse OR practitioners OR practitioner)
Databases searched	ProQuest Central, ABI/INFORM Complete, MEDLINE/PubMed (NLM), ScienceDirect Journals (Elsevier), Elsevier (CrossRef), Scopus (Elsevier), SpringerLink, PMC (PubMed Central), Springer (CrossRef), SAGE Journals, JSTOR Archival Journals, Taylor & Francis Online – Journals, Directory of Open Access Journals (DOAJ), Oxford University Press (CrossRef), Oxford Journals (Oxford University Press), BMJ Journals (BMJ Publishing Group), Wiley Online Library, Wiley (CrossRef), NARCIS (Royal Netherlands Academy of Arts and Sciences), Wolters Kluwer - Ovid - Lippincott Williams & Wilkins (CrossRef), Lippincott Williams & Wilkins Journals (Wolters Kluwer Health), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), the Cochrane Methodology Register (CMR), Health Technology Assessment Database (HTA) NHS Economic Evaluation Database
Inclusion criteria	P: HCWs I: strategies for improving vaccination coverage among HCWs C: vaccinated HCWs *versus* unvaccinated HCWs O: reduction in influenza cases, patient hospitalization and mortality Study design: systematic review and/or meta-analysis
Exclusion criteria	Study design: duplicated or not updated systematic review and/or meta-analysis
Time filter	None applied (from inception to 18th April 2017)
Language filter	None applied (any language)
Target journals	American Journal of Preventive Medicine; BMJ Open; Canadian Medical Association Journal; Clinical Infectious Diseases; Health Affairs; Human Vaccines; Human Vaccines & Immunotherapeutics; Influenza and Other Respiratory Viruses; Healthcare; JBI Library of Systematic Reviews; Journal of Clinical and Diagnostic Research; Occupational and Environmental Medicine; The Cochrane Database of Systematic Reviews; The Journal of Hospital Infection; Vaccine

The scarcity of knowledge among HCWs with respect to some topic issues such as the safety, and the efficacy profiles of the A(H1N1) 2009 pandemic influenza vaccines may have affected not only vaccine uptake in the pandemic season but also immunization rates against seasonal influenza and other vaccine preventable diseases (VPDs) in the post-pandemic scenario.[56,58]

Educational programs focused on the risks associated with influenza disease, benefits of vaccination and reinforcing reasons for vaccine acceptance should be improved.[59,60]

Ethical and legal issues of mandatory vaccination among healthcare workers

The topic of mandatory influenza vaccination among HCWs, besides being controversial, is full of ethical and legal implications. While some scholars maintain that, since it is an onus for hospitals and HCWs to protect their patients, influenza vaccination should be made compulsory for HCWs,[61] other researches claim that there are no scientific evidences for making vaccination mandatory. Further, there would be suspicions of unconstitutionality, and, as such, mandatory influenza vaccination among HCWs remains a challenging and open issue.[62-64]

Economic issues of influenza vaccination among healthcare workers

Economic issues of influenza vaccination among HCWs have been overlooked in the extant literature. Burls et al.[49] performed an economic analysis of influenza vaccination among HCWs. They found that in the base case, vaccination was cost saving (12 pounds per vaccinee). In the most pessimistic scenario it would cost 405 pounds per/life-year gained.

Strengths and limitations of the study

The present study meta-synthesizes available scientific evidences concerning influenza vaccination among HCWs. While it has some strengths, such as the systematic and rigorous methodological approach, its *a priori* design, the critical appraisal of extant systematic reviews and/or meta-analyses using a validated instrument, and the use of 2 independent data extractors, our investigation also presents shortcomings that should be properly acknowledged. First, the concept of HCWs is inconsistent and variable among countries and may depend on the degree of local economic prosperity. Further, most studies did not stratify their analyses according to the different HCWs subgroups (that is to say, medical doctors, nurses, technicians, etc.). Moreover, a significant variation in the quality of the systematic reviews/meta-analyses was noticed, with most studies included in the present manuscript being of moderate quality, on the basis of different parameters, such as the presence of "*a priori*" study design, the comprehensiveness of the search strategy and its reproducibility, the investigation of the scientific quality of primary studies and the declaration of conflict of interest.

Table 6 provides the reader with a narrative meta-synthesis of the main outcomes of the included studies.

Conclusions

The topic of influenza vaccination among HCWs is highly controversial and rather challenging.[65] For example, an appraisal of the scholarly literature and policy options available in the United Kingdom[35] showed that the evidence for both employer and patient safety benefits of influenza vaccination among HCWs is far from clear-cut and has given rise to different, contrasting interpretations. For these reasons, high quality studies are urgently required. These would also help policy-makers and stake-holders to shape evidence-based

initiatives and programs to optimize the prevention of influenza in this group.[66]

In the meantime, vaccination of HCWs continues to be a priority and vaccine uptake should be improved. Further efforts, including other preventive procedures, are also necessary to prevent nosocomial transmission. The main objective of increasing vaccination coverage rates against influenza among the healthcare personnel can be reached through well-designed long-term intervention programs that include a variety of coordinated managerial and organizational elements (i.e., including vaccination practice within Occupational Health Surveillance Programs). In this scenario, novel strategies such as mandatory vaccination of HCWs, at least starting from high risk wards, should be considered and debated to maximize the effects of flu immunization programs. This relevant point needs to be extended also to other VPDs such as Measles, Rubella, Varicella and Pertussis in this work category.

Material and methods

The current investigation was conceived and designed as an umbrella review,[67,68] and performed in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) guidelines.[69,70] The study protocol, developed according to the "PRISMA for systematic review protocols" (PRISMA-P) checklist,[71,72] was deposited in the PROSPERO database and registered as CRD42017064140.

Twenty-seven electronic databases/bibliographic *thesauri* were searched by 2 of the authors (NLB and GD), to ensure a broad and comprehensive search. The string used included keywords pertinent to the research question, such as "influenza," "vaccination," "immunization," "beliefs," "perceptions," "knowledge," "healthcare workers," and "healthcare personnel." The string was adapted for each database consulted. Medical subject headings (MeSH) terms and wild-card options were used where appropriate.

No time filter or language restrictions were applied. In addition, the reference lists of each relevant paper were searched to identify additional studies and target journals were hand-searched for potentially relevant articles. Conference abstracts, theses and dissertations, as well as other data not published in the peer-reviewed literature (that is to say, belonging to gray literature) were also considered. Data were extracted from included studies by 2 of the authors (NLB and GD). In case of disagreement, a third author (PD) was consulted. In particular, the following data were extracted: surname of the first author of the study, searched databases, availability of the study protocol, number of synthesized/pooled studies, number of studied subjects, outcome(s), main finding(s), risk of bias assessment and disclosure of potential conflicts of interest. Furthermore, the PROSPERO database was searched for eventual study protocols related to influenza vaccination among HCWs.

Concerning the critical appraisal of the included studies, 2 independent reviewers (NLB and GD) applied the AMSTAR ("A MeaSurement Tool to Assess systematic Reviews") checklist to each included study, and any disagreement was resolved by consensus. To avoid conflicts of interest, the paper by Maggiore et al.[29] was reviewed by 2 different independent reviewers (namely, NLB and LS), who were not authors of the study under scrutiny. AMSTAR is a validated, reliable tool and its scoring enables researchers to characterize study quality at 3 levels: from 8 to 11 (high quality), from 4 to 7 (medium/moderate quality), and 0 to 3 (low quality).[73,74]

For further details related to the search strategy, the reader is referred to Table 7.

To further enrich the presentation of results and the discussion, we supplemented our systematic search with works based on the experience of our group and with investigations focused on innovative and emerging aspects of the research field.

Disclosure of potential conflicts of interest

None to disclose.

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