Healthcare Workers' (HCWs) attitudes towards mandatory influenza vaccination: A systematic review and meta-analysis

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Abstract

Influenza is a disease responsible for thousands of deaths every year. Although healthcare workers (HCWs) represent a way of contagion for patients, vaccination coverage among them is low. Mandatory vaccination has been proposed, but controversies remain. This systematic review and meta-analysis aimed to assess the acceptance of mandatory vaccination by HCWs, and to investigate associated characteristics. MEDLINE, Scopus, Embase, PsycInfo, CINAHL and Web of Science were used to search for studies assessing the topic. PRISMA statements were followed. Of the 13457 univocal records found, 52 studies were included in the systematic review and 40 in the meta-analysis. The pooled proportion of HCWs accepting the policy was of 61% (95% CI: 53%-68%) but with great heterogeneity between continents (from 54% in Europe to 69% in Asia) and in different professionals (from 40% in nurses to 80% in students). Vaccinated HCWs agreed more frequently with mandatory vaccination than non-vaccinated ones. More studies that consider mandatory vaccination acceptance as the main outcome are needed, but the results of this study confirm that physicians and HCWs vaccinated against flu favour mandatory vaccination. This, combined with effects that a flu epidemic could have if overlapped to pandemics with similar symptoms, requires renewed considerations on mandatory vaccination.

Keywords

Influenza, Human; Vaccination; Immunization Programs; Health Personnel

Introduction

Influenza is a highly contagious acute respiratory illness characterized by fever, cough, headache, muscle and joint pain, severe malaise (feeling unwell), sore throat and runny nose. The symptoms range from mild to severe and can even cause death, due to complications.(*WHO Fact Sheet on Influenza*, n.d.) This condition affects approximately between 5% to 10% of the general population every year, predominantly during the winter season of each hemisphere, leading to 3 - 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths.(*WHO Fact Sheet on Influenza*, n.d.) The most effective way to prevent the infection is the seasonal vaccination.(Osterholm et al., 2012) WHO recommends annual vaccination for pregnant women at any stage of pregnancy, children aged between 6 months to 5 years, elderly individuals (aged more than 65 years), patients with chronic medical conditions and health-care workers (HCWs).(*WHO Fact Sheet on Influenza*, n.d.) In fact, different studies demonstrated that HCWs play a crucial role in the infection spreading to.(Ghendon, 1992; Potter et al., 1997) A review showed how vaccinating HCWs reduces influenza illness by 29%, medical consultations by 52%, and all-cause mortality by 55% in elderly people(Rivetti et al., 2006) and decreases the risk of illness-related absenteeism for themselves.(Gianino et al., 2019; Imai et al., 2018) Despite the strong recommendations provided, influenza vaccination rates among HCWs are globally well below targets set by WHO, proving how vaccine hesitancy is a phenomenon recorded even among health professionals.(Blank et al., 2009; Elawad et al., 2017; Ghandora et al., 2019; Jorgensen et al., 2018; Seale et al., 2011; To et al., 2016)

A review published in 2012 tried to assess different interventions used to increase vaccination uptake among HCWs.(Hollmeyer et al., 2013) Ten types of intervention measures were analysed: free vaccine, flexible worksite vaccine delivery, education material, education sessions, reminders, incentives, assignment of dedicated staff, feedback, signed declination statements and mandatory vaccination. The assessment revealed that programmes using more interventions achieved higher vaccine coverage. Among specific strategies reported to have higher success rates, free vaccination

seems to be crucial. The most effective intervention, however, appears to be a mandatory vaccination policy for healthcare workers.(Hollmeyer et al., 2013)

Even though mandatory vaccination strategies showed their efficacy, this type of intervention is still considered controversial.(Hollmeyer et al., 2013; Isaacs & Leask, 2008; Lorenc et al., 2017; Lugo, 2007) Opponents affirm that a similar policy would violate their personal autonomy and the right to take medical decisions concerning their body.(Isaacs & Leask, 2008; Lugo, 2007) On the other hand, supporters claim that a mandate meets the professional values to do no harm and to act in patients' best interests.(Anikeeva et al., 2009; Rea & Upshur, 2001)

Despite their subjective worthiness, some of these objections may shatter in the presence of the current global emergency due to the novel Coronavirus (Sars-CoV-2), causing upper and lower respiratory symptoms hardly distinguishable from influenza in the early stage.(MacDonald et al., 2015; Wu et al., 2020)

Influenza vaccine acceptability among healthcare professionals will be inevitably tested during the incoming winter season. Vaccination of all HCWs will play a key role during the next future, with the goal to avoid sickness from a preventable disease in a time of possible shortage of manpower.

The aim of the present review and meta-analysis is to assess attitudes towards mandatory influenza vaccination programs among HCWs, to plan the best intervention to increase vaccination uptake.

Methods

The present review followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.(Liberati et al., 2009)

Search strategy and selection criteria

A systematic search of scientific literature was performed on MEDLINE (via PubMed), Scopus, Embase, PsycInfo (via EBSCO), CINAHL (Cumulative Index of Nursing and Allied Health

Literature) (via EBSCO), Web of Science. Research strings and inclusion/exclusion criteria were defined a priori.

The research string was obtained customizing for each research engine the following structure: {[Healthcare Workers (with synonyms and plurals)] OR [HCWs declinations (such as clinician, doctor, nurse, health students)] OR "Health Personnel"[mesh] OR "Students, Health Occupations"[mesh]} AND {"Vaccines"[mesh] OR [vaccine, vaccination, immunization synonyms and plurals] AND ["Influenza,Human"[mesh] OR [influenza, flu and variations]] OR "Influenza Vaccines"[mesh]} AND {"Mandatory Programs"[mesh] OR mandatory, requirement, required, obligatory, policy, law (various declinations with synonyms and plurals)}. More info on research strings used can be found in Supplementary Materials.

No filters were applied except for publication year ≥ 2000. Thus, search results span from the 1st Jan 2000 to the 12th Nov 2019. No language restrictions were set in this stage.

Studies investigating attitudes towards compulsory influenza vaccination of HCWs were considered. In the present study, all the individuals working in medical facilities, both in primary, secondary, and tertiary care settings were considered HCWs. In addition, students of health-related subjects were included, if they were carrying out an internship or training in a medical facility during their courses. Because of the recent cultural changes concerning compulsory vaccination and the increased attention to the issue of vaccine hesitancy,(MacDonald et al., 2015) only studies performed after the year 2000 were included. Due to the extensive alarm, attention and media coverage over H1N1 Pandemic Influenza during winter season 2009-2010, with a possible increase in perceived risk and attitudes toward mandatory vaccination, authors agreed to exclude papers focusing exclusively on H1N1 vaccine from the present review.

Studies were considered eligible for inclusion if: 1) They interviewed HCWs; 2) They consisted in structured or semi-structured surveys assessing attitudes towards compulsory influenza vaccination of HCWs; 3) They were full papers presenting original data, published with a peer-reviewed process

on scientific journals; 4) They were written in English, Italian, French, Spanish or German; 5) They were published after year 2000.

No restrictions were performed based on sample size or setting of the survey.

However, studies were excluded if: 1) They assessed vaccination coverage but not the attitudes towards compulsory vaccination; 2) They focused exclusively on H1N1 pandemic influenza; 3) They do not provide original data or do not present them in a full text fashion.

Finally, a meta-analysis was performed to investigate attitudes of HCWs about compulsory influenza vaccination. In addition to the inclusion and exclusion criteria previously mentioned, studies were considered eligible for the meta-analysis if: 1) The relevant question was proposing mandatory vaccination of the same group of HCWs who were answering to the question; 2) The question was clearly expressed, and the hypothetical mandate was not amended by specific conditions (e.g. "Only for those HCWs..."); 3) The outcome was clearly delivered as proportion/percentage of favourable HCWs directly by authors or plainly ascribable to this meaning from original data.

Studies were excluded if: 1) They assessed attitudes towards compulsory vaccination exclusively in health care facilities managers, administrators, or policy makers; 2) They did not clearly express the outcome.

If the study was providing them, data were collected also for specific HCWs categories, referred in the present work as "subsamples". In particular, specific data was collected by analysing influenza vaccination status (vaccinated, not vaccinated), occupation (physician, nurse, student, general practitioner) and category of occupation [clinic (physician, nurse…), non-clinic (administration personnel…)]. Each subsample that was reported in a sufficient number of studies was then furtherly analysed, as a single or in comparison with other subsamples, as described in the "Statistical analysis" section.

After duplicates removal, five researchers (MC, EO, GV, AC and DC) screened results by title and abstract. Every study was evaluated by 2 reviewers independently. Irrelevant or duplicated papers were excluded. Studies regarding the attitude towards influenza vaccination in HCWs not explicitly

mentioning questions about mandate were provisionally allowed to proceed the selection process to prevent the rejection of suitable studies due to incomplete abstract compilation.

In case a selected publication consisted in abstract alone, Researchers attempted to search for a full publication from the authors. If no full text version of the study was found, abstract was discarded in accordance with exclusion criteria.

Selection conflicts were resolved reaching consensus or by a third reviewer's advice. This method was adopted during both selection phases: the first one based on title and abstract, and the second one based on full text, resulting in the final inclusion of papers in the systematic review results.

Reasons for exclusion are displayed in PRISMA flow diagram (Figure 1): wrong outcome (intervention studies, vaccine coverage studies, surveys without an item about mandatory vaccination or not explicitly referred to influenza vaccination), wrong literature (studies consisting in an abstract alone, letters to the editor, secondary literature or book chapters), wrong context (studies considering different vaccines or diseases such as mumps, measles, or H1N1 influenza), true or false duplicates, wrong population (such as hospital managers, patients, parents or stakeholders), language limitations.

Data extraction and quality assessment

The researchers independently extracted data from the full-text version of the selected studies, collecting information about the country in which the study was performed, the characteristics of the sample, the questionnaire used, the relevant question and the results of the study.

Quality assessment of the selected evidence, as stated by expert groups such as The Cochrane Collaboration,(Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, 2019) consists in interpreting the results highlighting methodological quality and risk of bias, in order to detect if study design befits the research question. On this occasion, a piece of information such as the attitude toward mandatory vaccination was only occasionally the main outcome of the questionnaires administered, and thus it was difficult to assess if the variable of interest was properly collected.

Statistical analysis

Microsoft Office suite software (Microsoft Corp., Redmond, WA) was employed to manage duplicates removal of extracted data, selection process and data extraction. The R software,(R Core Team (2020), n.d.) and in particular meta(Balduzzi et al., 2019) and metafor(Viechtbauer, 2010) packages were used to perform meta-analyses.

Fixed effects models require the assumption that a common, underlying effect across studies is present. However, this work analysed the attitude towards mandatory influenza vaccination policies in studies conducted worldwide, with different populations and different sampling methods.

Given that the assumption of common effect across studies was not able to be made, random effects models were used.(Higgins et al., 2009)

A generalised linear mixed model (Logit transformation, Maximum-likelihood estimator for τ^2) was performed for the meta-analyses of full sample proportions(Schwarzer et al., 2019; Stijnen et al., 2010) in all the studies yielding comparable outcomes. Specific, similar meta-analyses were performed for every subsample of HCWs if data was sufficient (e.g. vaccinated and not vaccinated HCWs).

In the case of full sample proportions, a by continent subgroup random-effects model was also utilized. Subgroup differences were assessed with a random-effects model.(Borenstein & Higgins, 2013)

Moreover, relative risks between subsamples within each study were calculated if the number of studies reporting stratified figures was sufficient to perform a subsequent meta-analysis (>4) and if subsample analysis reported proportions different among them, so that the proportion of a subsample was not included in 95% CI of the other subgroup.

Then, a meta-analysis of relative risks was performed and, if possible, stratified by continent (Mantel-Haenszel method, Paule-Mandel estimator for τ^2, Hartung-Knapp adjustment for random effects model).(Veroniki et al., 2016) In case of subgroup differences or significant heterogeneity, a meta-regression model of relative risks was performed (Paule-Mandel estimator for τ^2, Hartung-Knapp

adjustment for random effects model). Potential moderators investigated were continent and year of publication.

A funnel plot was drawn, and an Egger's test was performed in order to check publication bias and small-study effect, although the use of these methods in meta-analysis of proportions are under debate(Maulik et al., 2011) and results must be treated with caution. However, not standard error but size of the study was used in funnel plot drawing, as suggested by Hunter et al.(Hunter et al., 2014) Additionally, subsample funnel plots were drawn to investigate differences between continents.

The Cochran Q, $\tau 2$, and the I^2 were used to evaluate heterogeneity of studies.

Results

A total of 13457 univocal articles were retrieved from the scientific databases analysed (MEDLINE, Embase, Scopus, CINAHL, PsycInfo, Web of Science). After duplicates removal (7115 results), the remaining papers were screened by title and abstract, and 6864 were excluded because not relevant, resulting in 251 studies eligible for the full text review. Of the eligible studies, 199 were subsequently excluded because they did not respect the inclusion criteria (Figure 1). In particular, 72 studies were excluded for wrong outcome, 64 came from wrong literature, 24 considered a different context, 21 were found to be true or false duplicates, 17 studies selected a different population, and finally 1 study was excluded due to language limitations (Polish).

Then, 52 studies (shown in Table 1) were selected for the systematic review.(Akan et al., 2016; Alsuhaibani, 2020; Awali et al., 2014; Bali et al., 2013; Banach et al., 2013; Bazán et al., 2017; Boey et al., 2018; Chor et al., 2011; DeSante et al., 2010; Douville et al., 2010; Durando et al., 2016; Feemster et al., 2011; Ghandora et al., 2019; Gianfredi et al., 2019; Goldstein et al., 2004; Hakim et al., 2011; Halpin & Reid, 2019; Haridi et al., 2017; Hubble et al., 2011; Hudu et al., 2016; Karageorgou et al., 2014; Kent et al., 2010; Kyaw et al., 2019; La Torre et al., 2017; LaVela et al., 2015; Leask et al., 2010; Lester et al., 2003; Looper et al., 2017; Maltezou et al., 2013; Maltezou, Gargalianos, et al., 2012; Maltezou, Lourida, et al., 2012; Maurer et al., 2012; Naleway et al., 2014;

Nicolay et al., 2008; Pichon et al., 2019; Pless et al., 2017; Poland et al., 2008; Polgreen et al., 2010; Quintyne et al., 2018; Rebmann et al., 2012a, 2012b, 2016; Saluja et al., 2005; Sánchez & García-Fragoso, 2013; Seale et al., 2011; Shrikrishna et al., 2015; Thompson et al., 2013; Walker et al., 2016; S. Wicker et al., 2011; Sabine Wicker et al., 2010; Willis & Wortley, 2007; Yue et al., 2019)

Finally, 40 of the previous studies were selected for the quantitative synthesis of evidence (meta-analysis).

Main findings

The 52 studies included in the systematic review were published between 2003(Lester et al., 2003) and September 2019.(Alsuhaibani, 2020; Gianfredi et al., 2019) In regards to the continent where the studies took place, 26 were conducted in Northern or Central America, 16 were conducted in Europe, 3 in Oceania, 6 in Asia, and 1 study collected data both from Europe and Asia.(Chor et al., 2011) Most represented country was the USA, with 21 studies included. The sample size for the studies ranged from 18(Pless et al., 2017) to over 5141 subjects interviewed,(Boey et al., 2018) with a median of 572.5 and an IQR of 1129.25. Population samples were very different, but most of the studies enrolled physicians, nurses, or both. Almost all the studies collected data with anonymous self-administered questionnaires of various types (web-based, mailed, paper-based, telephone-based). Finally, one study reported results of focus group,(Willis & Wortley, 2007) while another described.(Pless et al., 2017)

Regarding the 40 studies included in meta-analysis, 19 were conducted in Northern or Central America, 5 in Asia, 12 in Europe, 3 in Oceania, and 1 collected data from both Europe and Asia.(Chor et al., 2011) Among these studies, fifteen reported the relevant data stratified for vaccination status both for vaccinated and unvaccinated HCWs,(Akan et al., 2016; Awali et al., 2014; Banach et al., 2013; Douville et al., 2010; Hakim et al., 2011; Haridi et al., 2017; Kyaw et al., 2019; Lester et al., 2003; Maurer et al., 2012; Poland et al., 2008; Quintyne et al., 2018; Rebmann et al., 2012a, 2012b;

248 Seale et al., 2011; Walker et al., 2016) while eight studies reported the figure for physicians,(Akan et
249 al., 2016; Alsuhaibani, 2020; Boey et al., 2018; DeSante et al., 2010; Douville et al., 2010; Lester et
250 al., 2003; Polgreen et al., 2010; Quintyne et al., 2018; S. Wicker et al., 2011) five for
251 nurses,(Alsuhaibani, 2020; Douville et al., 2010; Poland et al., 2008; Quintyne et al., 2018; Sabine
252 Wicker et al., 2010) five for students(Banach et al., 2013; Gianfredi et al., 2019; Looper et al., 2017;
253 Walker et al., 2016; S. Wicker et al., 2011) and two for general practitioners.(Akan et al., 2016;
254 Alsuhaibani, 2020) Of these, only four studies reported the relevant data for both physicians and
255 nurses.(Alsuhaibani, 2020; DeSante et al., 2010; Douville et al., 2010; Quintyne et al., 2018; Sabine
256 Wicker et al., 2010) Full summarized data about studies included is shown in Table 1.
257 Funnel plot (Figure 2) did not visually suggest publication bias, and this result was consistent with
258 Egger's regression test (p=0.337). Funnel plots stratified by continent suggested a publication bias
259 trend in Europe only (Figure 3). However, Egger's regression test showed no significant correlation
260 in this subsample (p=0.690).
261 The pooled proportion of agreement with mandatory vaccination policies in HCWs was 0.61 (95%
262 CI: 0.53-0.68). A very high heterogeneity was shown (I^2 = 99%). Figure 4 reports the proportion of
263 each subgroup by continent, which varied from 0.54 (Europe) to 0.69 (Asia). A statistically significant
264 difference between subgroups was not able to be found (p = 0.558).
265 Meta-analyses of subsamples results are summarized in Table 2. Since data of each subsample was
266 not independent regarding other subsamples, comparison between these subsamples was not
267 explored.
268 Because of the scarce number of studies reporting stratified subsample data, calculation of RRs and
269 subsequent meta-analysis was possible only regarding vaccination status. In particular, sixteen studies
270 were included.(Akan et al., 2016; Awali et al., 2014; Banach et al., 2013; Boey et al., 2018; Douville
271 et al., 2010; Hakim et al., 2011; Haridi et al., 2017; Kyaw et al., 2019; Lester et al., 2003; Maurer et
272 al., 2012; Poland et al., 2008; Quintyne et al., 2018; Rebmann et al., 2012a, 2012b; Seale et al., 2011;
273 Walker et al., 2016) Vaccinated HCWs had an increased "risk" to agree with mandatory vaccination

policies, and the difference between vaccinated and non-vaccinated HCWs was statistically significant (RR: 1.94; 95%C.I.:1.48-2.55, p<0.01), although in presence of high heterogeneity (I^2 = 97%). Then, a subgroup, by continent meta-analysis was performed. Due to issues in the number of studies, only studies from America and Asia were retained (Figure 5). The RR of vaccinated HCWs to agree with mandatory vaccination policies compared to non-vaccinated HCWs in American studies was of 2.13 (95%C.I.:1.48-3.07, p<0.01), while in Asian ones was of 1.19 (95%C.I.: 0.95-1.49, p=0.08). Since the difference between subgroups was statistically significant (p<0.01), a meta regression was performed. Results are summarized in Table 3. The estimate effect is expressed as the log of RR. Continent accounted for 29.96% of the heterogeneity observed in the sample, and moderators' effect was statistically significant (p = 0.0496).

Finally, 12 studies were included in the systematic review because they reported the outcome of interest but were excluded from the meta-analysis because the outcome was expressed in a way not suitable for a meta-analytic process (e.g. qualitative studies). Main findings are briefly reported. Goldstein and colleagues reported 40% of the HCWs interviewed supported mandatory vaccination as a state-wide law for workers with direct patient contact, and 49% as a facility-wide regulation.(Goldstein et al., 2004) A work describing data from Indian HCWs reported an 88% of support for mandatory vaccination of those workers employed in high-risk areas such as oncology.(Bali et al., 2013) Similar results but in a different population were reported by Karageorgou et al.: medical students were asked to imagine that their parents were hospitalized with a COPD diagnosis. With these assumptions, the 84.7% of the students stated that they supported mandatory vaccination for HCWs.(Karageorgou et al., 2014) Several qualitative studies as the one performed by Pless and colleagues(Pless et al., 2017) reported that nurses criticized mandatory mask because of fear of stigmatization, while declination form was considered a good approach; moreover, mandate for already employed HCWs was considered unacceptable, while it was considered acceptable as a requisition for hiring. Another study describing findings of focus groups reported that some nurses

stated mandatory vaccination could increase opportunities to take vaccination, but others opposed the policy, having concerns about disciplinary actions.(Willis & Wortley, 2007) Along the same line, 50% of unvaccinated HCWs declared that mandatory vaccination could influence their choice to be vaccinated,(Thompson et al., 2013) and in Naleway's study, 52% of enrolled HCWs declared they would have been vaccinated if it were mandatory.(Naleway et al., 2014) In a Canadian work, 60.9% of the medical, nursing and pharmacy students interviewed supported mandatory vaccination or mask policy.(Ghandora et al., 2019) Very low support was found among emergency medical technicians, with 9.1% of the sample supporting mandatory vaccination and 38.7% supporting it with decline option.(Hubble et al., 2011) Indeed, in a sample of 672 HCWs (physicians, nurses, midwives, administrative staff) only 1.04% declared that mandatory vaccination was the best strategy to improve vaccination rates.(Bazán et al., 2017) Finally, two studies investigated HCWs attitude with a Likert scale. The first reported a median of 5 in a scale with 1 as "not at all" and 10 as "absolutely yes" in agreement with mandatory vaccination with bimodal distribution towards the extreme scores (IQR 8).(Pichon et al., 2019) The other used a scale from 1 (strongly agree) to 5 (strongly disagree) and described results stratified for vaccination status: median of 2 for vaccinated HCWs and of 4 for unvaccinated ones.(Shrikrishna et al., 2015)

Discussion

The present systematic review and meta-analysis, conducted following the PRISMA Statements, investigated Healthcare Workers (HCW) attitudes towards mandatory influenza vaccination.(Liberati et al., 2009) An evident publication bias was not possible to be found; however, difference among continents exists, with Europe being currently the continent where a bias for publication seems more possible, and future researchers should keep this finding in mind.

Although compulsory vaccination has been presented as the most effective strategy to contrast vaccine hesitancy among this specific population at risk,(Hollmeyer et al., 2013) the HCWs attitudes cannot be defined unanimously.(Anikeeva et al., 2009; Hollmeyer et al., 2013; Isaacs & Leask, 2008;

Lugo, 2007; Rea & Upshur, 2001) In the present work, a great amount of heterogeneity between studies was found. Although part of this finding can be explained by differences in geographical areas, the most is due to differences in the sampling method of the HCWs population among selected studies. While some studies interviewed a single category of personnel, the majority pooled together different types of HCWs, basing sampling on opportunistic reasons. For this reason, researchers assessing attitudes in HCWs should focus on reporting subsample data as often as possible.

It is difficult to define if HCWs favour mandatory flu vaccination. On one hand, the majority of HCWs declared to be favourable to this policy, except in Europe. On the other hand, given that the measure would affect all HCWs and not only those that are in favour with it, it could be argued that greater percentages than the simple 50% majority are needed, before enforcing mandatory vaccination on the sole basis of its acceptance. However, other factors must be considered. Patient's safety, workdays lost, and the risk of flu being mistaken for more dangerous diseases such as COVID-19, should suffice in supporting policy makers who decide to take this route.

In addition, the incoming 2020 flu season and maybe subsequent ones will pose a challenge towards all healthcare systems, given that flu and COVID-19 contagion curves could well overlap. Furthermore, COVID-19 initial symptoms are often indistinguishable from flu ones: this could lead to massive quarantine measures, emptying hospital services; or, in order to prevent this scenario, policy makers could ease quarantine measures involving medical personnel, possibly leading to even more dramatic outcomes, with COVID-19 freely circulating among healthcare professionals.

Nonetheless, future researchers should focus on better understanding of factors that modify mandatory vaccination acceptance and overall flu vaccine acceptance, deepening cultural and national differences, and, no less important, differences among HCWs categories. Furthermore, after COVID-19 worldwide emergency, the attitude towards flu vaccination could have changed, and it will be interesting to compare data in the present study with post-pandemic data.

The meta-analysis returned that the pooled proportion of HCWs who favour a mandatory vaccination plan is 61% (95%C.I.: 53%-68%). This percentage ranged from 15.4% in a sample of emergency

medical technicians and paramedics from the USA(Rebmann et al., 2012a) to 93.1% among the Students from the University of Oklahoma Health Sciences Center.(Looper et al., 2017) Interestingly, when the subjects interviewed are not the ones personally involved in the vaccination the attitudes are generally more supportive towards compulsory vaccination. A study focused on interviewing parents and guardians of children hospitalized at Arkansas Children's Hospital, USA: 76% of the 372 respondents thought that HCWs should receive an annual influenza vaccination and that it should be mandatory.(Linam et al., 2014) The results are in line with the ones that emerged when assessing parents 'attitude towards mandatory vaccinations. In fact, a previous review outlined how the parents' support to this kind of policy ranged from 53% to 97% for different vaccination programs.(Gualano et al., 2019; Krok-Schoen et al., 2018; Perkins et al., 2010) Similarly, 93.1% of the faculty members of an American University agreed or strongly agreed that flu vaccination is appropriate for,(Looper et al., 2017) confirming the healthcare students' positive attitudes towards compulsory vaccination policies.(Ghandora et al., 2019; Karageorgou et al., 2014) However, previous studies assessed HCWs' attitudes towards mandatory childhood and adult vaccination, pointing out how the level of acceptance of this kind of policies is generally lower among this specific population compared to parents' attitudes.(Gualano et al., 2019)

Most of the studies assessed the attitudes towards compulsory vaccination policies addressed to HCWs in general, but some of them focused on HCWs in specific high-risk settings. In these cases the acceptance of mandatory vaccination was higher probably because of the increased perceived risk for the patient (such as in the oncology or paediatrics wards),(Bali et al., 2013; Little et al., 2015; Maltezou et al., 2013; Maltezou, Lourida, et al., 2012) or because of the increased risk for the professionals (such as in the emergency department).(Hubble et al., 2011; Little et al., 2015)

The relative risks meta-analysis performed found a statistically significant result, namely a positive association between vaccine acceptance and attitude towards mandatory vaccination for all HCWs. As previous studies did, the association between accepting the vaccination and accepting mandatory vaccination strategies must be underlined.(Gualano et al., 2018) However, the subgroup analysis

performed stratifying by continent showed different scenarios. In American studies, the association maintained its statistical significance, while in Asian ones the RR lowered to almost 1, with a p-value major than 0.05. This finding, together with overall higher percentages of vaccinated HCWs in Asian countries, could mean that in America the HCW who has negative attitudes towards mandatory flu vaccination successfully achieves to not be vaccinated, while personal attitude loses importance in Asian studies. On the other hand, a lower RR in Asian studies could mean that HCWs are in general not contrary towards mandatory flu vaccination; however, both favourable and unfavourable HCWs choose to vaccinate themselves because of other reasons, such as personal beliefs or opinion on side effects and efficacy. Nonetheless, this finding was drawn from a very limited number of studies, especially in the Asian subgroup (3 studies which took place in Turkey, Saudi Arabia, Singapore),(Akan et al., 2016; Haridi et al., 2017; Kyaw et al., 2019) and for this reason this evidence should be treated as a point of reflection for future studies rather than a finding generalizable to the Asian continent.

The meta regression findings were consistent with those of the subgroup's analysis and confirmed that continents' differences accounts for a good part of heterogeneity in this comparison between American and Asian studies (R^2 = 29.96%).

Our review has some limitations that should be reported. To be as comprehensive as possible, we did not exclude any study based on sample size, which varied considerably among studies. Additionally, great heterogeneity was present among studies. Major differences regarded the sample composition, with different kinds of HCWs, interviewed in different countries. However, this limitation was partially tackled with subgroup meta-analysis and meta regression. Finally, we limited the research including only studies published after 2000, and thus this work cannot give insight further back than that date.

Nevertheless, this work also has strengths. To our best knowledge, it is the first systematic review on HCWs attitude towards mandatory vaccination. In addition, the large sample of studies included gives

an overall view of the topic on a global scale, while subgroups analyses help deepen some findings and raise hypotheses on characteristics correlated with the outcome.

Conclusion

The aim of the study was to give a quantitative estimate of the acceptance of mandatory vaccination policies among HCWs. In fact, low coverage for the flu vaccine is a remarkable issue globally(Blank et al., 2009; Elawad et al., 2017; Ghandora et al., 2019; Jorgensen et al., 2018; Seale et al., 2011; To et al., 2016) and this kind of strategy resulted to be effective to reduce the impact of the influenza infection.(Hollmeyer et al., 2013) The results of this work could represent a strong tool to support evidence-based policy making, and the starting point for new works that will investigate acceptance of flu vaccination in HCWs.

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Conflicts of Interest

The authors declare no conflict of interest

Figure captions

Figure 1 – PRISMA flow diagram.

Figure 2 – Publication bias assessment, funnel plot – whole sample

Figure 3 – Publication bias assessment, funnel plot – whole sample, stratified by continent

Figure 4 – Pooled percentage of HCWs who agree with mandatory flu vaccination policies, forest plot – whole sample, stratified by continent

Figure 5 – Pooled relative risk for the association between vaccination status and agreement with mandatory flu vaccination policies, forest plot – subsample, stratified by continent

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