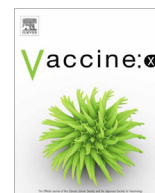


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A rapid evidence appraisal of influenza vaccination in health workers: An important policy in an area of imperfect evidence

Dawn C. Jenkin^{a,1}, Hamid Mahgoub^b, Kathleen F. Morales^c, Philipp Lambach^{d,*},
Jonathan S. Nguyen-Van-Tam^a^a Health Protection and Influenza Research Group (WHO Collaborating Centre), University of Nottingham School of Medicine, United Kingdom^b East of England Health Protection Team, Public Health England, United Kingdom^c Sierra Strategy Group, Evian les Baines, France^d World Health Organization, Geneva, Switzerland

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ABSTRACT

Introduction: The World Health Organization recommends vaccination of health workers (HWs) against influenza, but low uptake is intransigent.**We conducted a Rapid Evidence Appraisal on:** the risk of influenza in HWs, transmission risk from HWs to patients, the benefit of HW vaccination, and strategies for improving uptake. We aimed to capture a 'whole-of-system' perspective to consider possible benefits for HWs, employers and patients.**Methods:** We executed a comprehensive search of the available literature published from 2006 to 2018 in the English language. We developed search terms for seven separate questions following the PICO framework (population, intervention, comparators, outcomes) and queried nine databases.**Results:** Of 3784 publications identified, 52 met inclusion criteria. Seven addressed HW influenza risk, of which four found increased risk; 15 addressed influenza vaccine benefit to HWs or their employers, of which 10 found benefit; 11 addressed influenza transmission from HWs to patients, of which 6 found evidence for transmission; 12 unique studies addressed whether vaccinating HWs produced patient benefit, of which 9 concluded benefits accrued. Regarding the number of HWs needed to vaccinate (NNV) to deliver patient benefit, NNV estimates ranged from 3 to 36,000 but were in significant disagreement. Fourteen studies provided insights on strategies to improve uptake; the strongest evidence was for mandatory vaccination.**Conclusions:** The evidence on most questions related to influenza vaccination in HWs is mixed and often of low-quality. Substantial heterogeneity exists in terms of study designs and settings, making comparison between studies difficult. Notwithstanding these limitations, a majority of studies suggests that influenza vaccination benefit HWs and their employers; and HWs are implicated in transmission events. The effects of vaccinating HWs on patient morbidity and mortality may include reductions in all-cause mortality and influenza-like illness (ILI). Taken together, the evidence suggests that HW vaccination is an important policy for HWs themselves, their employers, and their patients.© 2019 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Abbreviations: HW, health workers; WHO, World Health organization; ILI, influenza like illness; NNV, number needed to vaccinate; LTCF, long-term care facility(ies); OR, odds ratio; GAVI, the global alliance for vaccines and immunization; RCTs, randomised controlled trials; RR, relative risk; cRCTs, clustered randomised controlled trials.

* Corresponding author.

E-mail address: lambachp@who.int (P. Lambach).¹ Present Address: Nottinghamshire County Council, United Kingdom.<https://doi.org/10.1016/j.jvacx.2019.100036>

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1. Introduction

1.1. Background

In 2012, the World Health Organization (WHO) updated its recommendation on influenza vaccination of health workers (HWs) concluding that “HWs are an important priority group for influenza vaccination, not only to protect the individual and maintain health-care services during influenza epidemics, but also to reduce spread of influenza to vulnerable patient groups” [1,2]. The *WHO Global Influenza Strategy (2019–2030)* reinforces this position by supporting countries to “develop and implement national, seasonal immunization policies for HWs and other high-risk groups” [3].

In 2017, 96 of the 194 WHO Member States reported having policies in place for influenza vaccination of HWs [4]. However, the Member States with such policies are unevenly distributed across WHO regions. Aside from mitigating seasonal influenza, influenza vaccine is considered the primary intervention to reduce mortality and morbidity in a severe pandemic. An efficient pandemic response depends largely on how well seasonal vaccine response to annual epidemics is embedded and implemented [5].

The *Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009* concluded that experience with comprehensive seasonal influenza programmes would provide valuable preparation in advance of a major pandemic [6]. In November 2018, the Global Alliance for Vaccines and Immunization (GAVI) Board requested that the GAVI secretariat in collaboration with WHO assess the feasibility and impact of routine influenza immunization of HWs to support epidemic and pandemic influenza preparedness [7].

To support these global considerations and considering the poor uptake of influenza vaccination in HWs despite the multiple reasons advocated for it as a policy, we conducted a *Rapid Evidence Appraisal* [8]. We aimed to capture the breadth of available evidence on influenza in health care settings and the wider health impacts of influenza vaccination in HWs. We critically appraised the literature relating to: influenza risk to HWs and the risk they pose to their patients; the benefit of influenza vaccination in HWs; and influenza vaccine uptake in HWs. By including evidence relevant to multiple stakeholders collectively - HWs, patients, and

their employers - we holistically evaluated the evidence in the most policy-relevant framework as possible.

2. Methods

2.1. Systematic literature search

General Search Approach: The search objective was to examine the evidence under three topics using a Rapid Evidence Appraisal approach. Each topic gave rise to 2 or 3 questions for query (see Table 1). Evidence was queried from MEDLINE, EMBASE, CINAHL, Cochrane CENTRAL, Cochrane Reviews, WHO Global Index Medicus, National Health Service (NHS) Evidence, NHS HTA database, and multiple international clinical trials’ registries. We executed three independent searches by topic with distinct search terms to capture literature for all topic questions. *Search terms* followed the PICO framework (population, intervention, comparators, outcomes) and studies were selected based on pre-determined criteria.

Study Types varied by review topic and question but generally included experimental or observational studies, systematic reviews, controlled observational studies, and randomized controlled trials (RCTs). Due to the volume of evidence for *Topic 3 (HW vaccine uptake)*, literature was restricted to systematic reviews, RCTs, and evidence-based policy guidelines or toolkits. *Study Outcomes* were limited to laboratory-confirmed influenza as a primary outcome measure, when relevant to the queried question. Other outcomes included sickness absence incidence and/or duration, economic or productivity costs due to illness, influenza-like- illness (ILI) or respiratory illness, the number needed to vaccinate (NNV), and vaccination uptake in HWs.

Study Selection, exclusion and inclusion: Studies were selected and extracted onto a standardized template by 3 reviewers (DJ, HM, KM \ominus) independently, defaulting to a third party (JSN-V-T) as needed. Study selection followed the following process: remove duplicates and unrelated content by title; review abstracts - remove unrelated content, descriptive studies, commentaries, or studies that clearly do not meet the inclusion/exclusion criteria defined for each question; review full text - exclude based on exclusion/inclusion criteria or remove studies that lack a clear

Table 1
Rapid Evidence Appraisal topics, queried questions, number of studies selected, and their associated references.

Topic	Description	Questions	Total Studies cited/ question	Refs.
1	The Impact of HW Influenza Vaccination on HWs and their employers	1. What is the evidence that HWs are at an increased risk of influenza infection compared to the general population?	7	[11–17]
		2. What is the evidence that vaccinating staff in healthcare settings against influenza reduces influenza in HWs, absenteeism and/or the wider economic impact of influenza in the healthcare workforce?	14	[11,18–30]
2	The Impact of HW Influenza Vaccination on their patients	1. What is the evidence that HWs transmit influenza (asymptomatic or symptomatic) to inpatients in healthcare settings?	11	[31–41]
		2. Does influenza vaccination of HWs provide a protective effect for inpatients in healthcare settings?	6	[11,25,42–45]
		3. If so, what number or proportion of HWs needs to be vaccinated to provide this effect?	8	[11,42,46–51]
3	Influenza Vaccine Uptake in HWs—hurdles and solutions	1. What is the evidence for successful practical interventions to increase HW vaccine uptake of influenza vaccine?	11	[11,25,52–60]
		2. What is the state of knowledge in sociological, behavioural, and public health policy research on influenza vaccine uptake in HWs?	3	[11,61,62]

study design, methodology, or results section. Studies were then ranked according to the Maryland Scientific Methods (SMS) Quality Scale [9] with 1 being the lowest and 5 being the highest [10]. We limited the inclusion of studies to those scoring 2–5 on the quality scale published from 2006 to 2018 in whole or in summary in the English language.²

2.2. Data handling

Data Extraction: Two reviewers (DJ, KM) executed the search strategy and results were independently screened by three reviewers (DJ, HM, KM) for eligibility using a three-stage sifting approach of title, abstract and full-text. The two reviewers for 2006–2016 (DJ, HM) literature reached consensus on which search hits met the criteria for inclusion at each stage (including exclusion at the full-text stage). Any disagreements were resolved by discussion or involvement of an additional reviewer.

Data analysis: Detailed characteristics of included studies were captured and descriptively summarized in tables and figures identifying study design, population, setting, measured outcomes, results, and limitations (See Tables 2–5).

3. Literature search results

3.1. Identified literature

The collective literature search identified 3,784 publications, of which 52 individual publications met the inclusion criteria (see Fig. 1). Some publications addressed multiple questions resulting in a total of 60 references cited for all questions combined (see table 1). Of the 60 included studies, we identified 7 RCTs, 24 observational studies, 16 reviews (non-systematic or systematic), and 13 “other” study types (see Fig. 2A and B). Individual studies and systematic reviews were excluded from the final list of included studies (Tables 2–4) when they formed part of a more recent systematic review. These removed studies were still considered in the text if they are of moderate to high quality.

² See supplementary materials for full protocol with search criteria for each topic and exclusion and inclusion criteria by topic and question. KM executed search strategy/screened the literature for 2016–2018 and reevaluated inclusion/exclusion to total search 2006–2018.

3.2. Evidence by topic and question (Tables 2–4)

Topic 1 Question 1 - Are HWs at an increased risk of influenza infection?

We identified only 1 higher quality study (4 or higher score) for this question. The review by Dini et al. [11] included 28 studies (12 systematic reviews, 13 meta-analyses, 3 appraisals) and addressed several aspects relevant to influenza vaccination in HWs, including laboratory-confirmed incidence and risk compared to controls. The review included a higher level systematic review and meta-analysis on the occupational risk of pandemic H1N1 in HWs compared to the general population or across occupations. This meta-analysis [63] evaluated 15 studies (29,358 subjects), including 11 high quality studies of laboratory-confirmed influenza, and showed a significantly increased OR = 2.08 (95% CI, 1.73–2.51) in HWs with a higher risk in physicians {OR = 6.03 (95% CI, 2.11–17.8)}.

Kuster et al. [64], a systematic review also included in Dini et al, compared data on influenza infection rates in HWs and healthy adults from 29 surveys (n = 58,245) over 97 influenza seasons [11]. The review calculated a pooled annual incidence of 18.7% (95% CI, 15.80–22.11) per season in unvaccinated HWs versus 5.44% (95% CI, 3.01–9.84) per season in unvaccinated adults and 6.49% (95% CI, 4.63–9.09) for vaccinated HWs versus 1.20% (95% CI, 0.86–1.68) for vaccinated adults. However, this review [64] concluded the overall effect was driven by asymptomatic rather than symptomatic infections. A German study included as part of Dini et al evaluated ILI incidence combined with pre and post-season influenza serology in HWs and non-HWs [65] and concluded there was no difference in risk of symptomatic or asymptomatic influenza infection in HWs compared to non-HWs [11]. However, HWs were found to have an increased risk of clinically diagnosed acute respiratory infection (OR = 3.0, p = 0.04), and were more likely to have a pre-season antibody titre of ≥ 40 to influenza A/H3N2, indicating the possibility of asymptomatic or subclinical influenza infections.

Five additional studies of differing methodological approach and quality provided conflicting conclusions. Three studies pointed to a higher risk [12,13,16] including a pandemic simulation modelling study [13] which suggested a plausible attack rate as high as 60% greater in HWs and a moderate-low quality retrospective study in Hong Kong which suggested a higher H1N1 risk in HWs and an inconclusive result when applied to seasonal influenza [12]. Sartor et al. [16] found HWs at an increased risk of influenza infection in a geriatric hospital, although the study contained fewer than 50 subjects. A moderate quality case-control study in Canada

Table 2
Rapid Evidence Appraisal included studies and their characteristics for **Topic 1 - Questions 1&2.**

Study	Maryland Quality Score and classification	Study Design	Country	Setting	Included Studies/or Population type	# of participants	Intervention or Focus	Outcomes	Are HWs at a greater risk than the general population Yes/No
Dini [11]	4 High Moderate	Review	Mixed	Hospital	2 systematic reviews/ 28 included address this question	29,358 subjects	H1N1pdm09 vaccine	Lab-confirmed influenza infection	Yes for H1N1pdm09
Ip [12]	2 Low Moderate	OS- RC	Hong Kong	Hospital	Inpatient and outpatient health workers	~ 6000	H1N1pdm09 risk and impact	All cause or Acute Respiratory Illness Related Sickness Absenteeism during influenza epidemics	Yes during 2009 Inconclusive with seasonal influenza
Cooley [13]	No Score-Model Simulation	Pandemic Simulation Model	USA	Hospital	Simulation of influenza epidemic and the impact on hospital-based HWs	N/A	Seasonal vaccine	Secondary attack rate of pandemic influenza among unprotected HWs.	Yes, for pandemic influenza
Bellei [14]	2 Low Moderate	OS -PC	Brazil	- Outpatients - Community	Outpatient health workers, outpatients with acute respiratory infection, renal-transplant patients Medical professionals	203 HWs 140 community 69 renal-transplant	N/A	Lab-confirmed influenza rates by population, clinical symptoms, and risk factor.	Inconclusive, but vaccination may have confounded results
Yiannakoulias [15]	3 Moderate	OS- Retrospective CC	Canada	-Province-wide assessment using billing data			Exposure to ILI in a patient	Frequency of exposure to patient with ILI in 7 days prior to ILI diagnosis in case providers vs. matched control providers	Yes, but can't make a clear connection between exposure and ILI using billing data
Sartor [16]	2 Low Moderate	OS -PC	France	Internal Medicine Ward	Inpatients and health workers	23 patients and 22 HWs	N/A	Attack rate of influenza A among patients and HWs	Yes, but patients also at risk during an outbreak
Elder [17]	2 Low Moderate	OS - CS	Scotland	Acute care hospitals	Inpatient health workers with regular patient contact	518	N/A	Serologically-confirmed influenza. Proportion of asymptomatic infection (recall + serology)	Yes for asymptomatic infection
Imai [18]	5	SR and meta-analysis	Mixed		13 studies total 3 RCTs, 2PC, 8RC	N = 20,282; 5,083 vaccinated 15,199 not	Seasonal Vaccine only	Pooled n = RR, Lab-confirmed flu, ILI, absenteeism, mean difference, cost-effectiveness	Does vaccine benefit HWs or their employers? Yes/No Yes Yes
Dini [11]	4 High Moderate	Review	Mixed		6 systematic reviews relevant to this question/ 28 studies	Didn't pool	Influenza Vaccine	Lab-confirmed flu, ILI, absenteeism	Yes Yes
Gianino [20]	2 Low moderate	OS-RC	Italy	Hospital	Hospital health workers	~ 5000	Seasonal vaccine	Absenteeism during influenza epidemic periods	Yes
Pereira [21]	3 Moderate	OS- RC	England	223 health trusts each season	Hospital, primary care, inpatient, outpatient, specialist	~800,000	Seasonal vaccine	Sickness absence rate, Relationship between sickness absence rate and uptake	Yes
Frederick [25]	3 Moderate	OS-RC	USA	Hospitals & Outpatient	Health workers	~3000	Mandatory vaccine policy	Incidence/length of absenteeism mandatory vs. non-mandatory sites	Yes

Table 2 (continued)

Study	Maryland Quality Score and classification	Study Design	Country	Setting	Included Studies/or Population type	# of participants	Intervention or Focus	Outcomes	Does vaccine benefit HWs or their employers? Yes/No
Riphagen-Dalhuisen [28]	4 High Moderate	cRCT	The Netherlands	6 Tertiary Medical Centres	All hospital HWs during 2009–2011	HWs = all from	Multi-faceted uptake intervention for H1N1pdm09 and seasonal vaccine	Vaccine uptake; absenteeism rates among HWs in December of each year	No to absenteeism, actually saw an increase
Hui [30]	4 High Moderate	RCT	Malaysia	Faculty of Dentistry	Staff/students of the faculty of Dentistry Control	.Control = 176 Vaccinated = 179	Seasonal Vaccine	Follow up over a 4-month period from vaccination, via questionnaire to ascertain self-reported outcomes: ILI prevalence; Recurrence of ILI; Visits to doctor due to ILI; Family members or housemates reporting ILI, Days of absenteeism due to ILI, Fever days due to ILI	Yes, to all self-reported outcome measures
Nguyen-VanTam [23]	2 Low moderate	OS- RC-TS	England	Teaching Hospital, multiple wards	HWs – non-medical staff (nurses/ porters); nursing staff from admissions, intensive therapy and surgical; porters dealing with supplies and waste	N = 271	N/A	Individual sickness absence contrasted epidemic/ non-epidemic periods in season. Measured: Total time lost/person as % of rostered time.# weeks/ person which absence occurred '92-'93 season non-epidemic yr. comparison, since low flu activity	No
Atamna [26]	3 Moderate	OS-PC	Israel	Medical Centre	Health workers, vaccinated vs. non-vaccinated during flu seasons and not	733 vaccinated 908 not (199 in flu season)	Seasonal Vaccine	Rates of PCR confirmed influenza A infection in vaccinated vs. non vaccinated HWs	inconclusive
Njuguna [22]	2 Low moderate	OS-PC	Kenya	5 Hospitals with influenza surveillance	Health Workers who were offered free vaccine	3803	H1N1pdm09 vaccine	Vaccine effectiveness in vaccinated vs unvaccinated HCP: Incidence of acute respiratory illness, absenteeism from work due to respiratory illness laboratory-confirmed influenza (using PCR)	No, actually increased absenteeism
Saadeh-Navarro [27]	2 Low moderate	OS-RC	Mexico	Teaching Hospital	Vaccinated HWs (health care worker defined as all personnel with patient contact)	N = 3636	Seasonal influenza vaccine	A reduction in ILI, Absence due to ILI Total days of work lost	Yes
Fujita [24]	2 Low moderate	OS-RC	Japan	University hospital	Nursing Staff	1680	Seasonal vaccine	Vaccine effectiveness through self-reported fever and cold-like symptoms. Days absent.	Yes
Preaud [29]	No Score Economic Model	EM	8 European Countries	All health workers for those countries	Mixed HWs	N/A	Seasonal trivalent vaccine	Number of influenza-related events averted (cases, GP visits, hospitalisations, deaths and days of work lost) at current vaccination coverage rates.	Yes, to cases averted
Parlevliet [31]	No Score Cost-Benefit Analysis	CBA	The Netherlands	Hospitals	Health workers	6251	Seasonal vaccine	Retrospective cost-benefit model as employer's perspective to see costs and benefits. For vaccine programs as workplace absenteeism.	Yes, To cost benefit to employers

LEGEND: CC– Case Controlled; OS- Observational Study; CS- Cross Sectional; PC- Prospective Cohort; RC- Retrospective Cohort; SR-Systematic Review; EM- Economic Model; CBA- Cost-Benefit Analysis; TS- Time Series; RCT- Randomised Controlled Trial; cRCT- Clustered Randomised Controlled Trial; UC- Unclear; Q1 – Question 1; Q2 – Question 2; RR-Risk Ratio.

found inconclusive results on the risk of ILI in exposed HWs as did a prospective cohort study in Brazil using lab-confirmed influenza [14,15].

Topic 1, Question 2 - Does influenza vaccination benefit HWs or their employers?

We identified several higher quality studies for this question. Two reviews compared lab-confirmed influenza in vaccinated HWs vs. controls and found a vaccine efficacy of ~50–90% and a significant protective effect {Relative Risk(RR) = 0.40 (95% CI, 0.23–0.69)} [18,66] for HWs. The high quality systematic review by Imai et al. [18] further found a reduced incidence of absenteeism due to ILI {RR = 0.62 (95%CI, 0.45–0.85)}, and a significantly shorter sick leave in the vaccinated group {RR = 0.46 (ILI + lab-confirmed), RR = 0.60 (lab-confirmed)}. The study concluded that vaccination provided a protective effect in HWs and deemed vaccination programs as cost-saving. The widely-cited studies by Klinder et al. [66] and Kuster et al. [64] were included in the appraisal by Dini et al who identified 6 reviews relevant to this question [64,66–70] and also concluded that vaccination was protective and potentially cost-saving in HWs [11].

Two contradictory RCTs included a Malaysian study that [28] found reduced absenteeism (12 days vs. 52 in the control group, $p = 0.002$) and ILI (reduced by 52.6%, $p = 0.002$) due to vaccination, using all self-reported outcomes. A Dutch RCT [25] actually found an increase in absenteeism in the vaccinated groups {2009/10 (4.6% vs 3.4%); 2010/11 (4.6% vs 3.9%)}, although they attributed the increase to more frequent testing for influenza in the intervention cluster and the study was performed during periods of H1N1pdm09 activity in 2009–2011.

We identified 8 observational studies of moderate to lower moderate quality [19–23,26,27,30], 5 of which found a vaccine benefit to HWs or employers and 3 which found no benefit or inconclusive results. A study in a large Italian hospital found an increase in absenteeism [19] from 2.99 days/person (outside of flu season) to 5.06 days/person (during flu season), which translated to 11,000 attributable absent days/year. The study also found that vaccinated HWs had fewer excess sick days compared to non-vaccinated HWs (1.45 days/person vs. 2.09). A retrospective study in the United States (4063 subjects) compared absenteeism in mandatory vs. non-mandatory vaccination sites [21] and found that vaccinated HWs had fewer symptomatic days absent {2012/2013, OR = 0.82 (95% CI, 0.72–0.93); 2014/2015, OR = 0.81 (95% CI, 0.69–0.95)} and concluded that mandatory vaccination would reduce symptomatic absenteeism.

Three studies suggested no benefit including a prospective cohort study in Israel [23] which found HWs less likely to develop lab-confirmed influenza, although this finding was not significant. A study in Kenya [26] found vaccinated participants were more likely to develop acute respiratory illness (ARI) and more likely to miss work after vaccination. A large retrospective ecological study [20] evaluated ~800,000 HWs per year over 4 flu seasons in England and found that a 10% increase in vaccine uptake would lead to a decrease in approximately 0.43 percentage points in the absolute sickness absence rate (from 4.5% to 4.07%), or a 10% relative decrease in the sickness rate. Studies looking at the cost-benefit of vaccination generally found HW vaccination to be cost-saving and of economic benefit from the perspective of the employer [18,24,28,29].

Topic 2, Question 1 – Do HWs transmit influenza to patients?

Evidence varied widely in methodological approach, yet some findings suggest HWs are at least one of the sources of transmission. We identified moderate to higher quality studies which implicated HWs in some transmission events, particularly in geriatric patients, in acute care settings during flu season [31–33] and during hospital outbreaks [36]. These studies utilized technologies such as wearable sensors [31,34], molecular-based subtyping

methods [32], or phylogenetic analyses combined with case studies or epidemiology [35,40]. One retrospective cohort study analyzed routes of transmission among HWs and geriatric patients using molecular-based subtyping methods. The study identified three nosocomial outbreak clusters within one ‘outbreak’ and found a higher influenza incidence in patients (24%) than in HWs (11%) [32]. A large nosocomial outbreak in a geriatric hospital [35] used detailed case studies combined with phylogenetic analysis to reveal 5 clusters of cases and multiple introductions of community strains into the hospital. Similarly, a study by Valley-Omar et al. [40] in South Africa combined epidemiological investigation with phylogenetic analysis to study influenza transmission chains and the extent of nosocomial transmission over a four-month period within a pediatric hospital. This analysis found that most potential nosocomial infections resulted from multiple introductions of Influenza A into the hospital and suggested transmission between asymptomatic patients, HWs, and visitors.

Topic 2, Question 2, Part A – Does influenza vaccination in HWs benefit patients?

We identified two higher quality studies relevant to this question [11,25], and several lower quality studies using ILI [43–45] as an outcome measure. The comprehensive review by Dini et al. [11] evaluated 6 systematic reviews [66,69,72–74,76] and found overall inconclusive results as studies were of moderate but mostly lower quality, evaluated the same 4 RCTs [77–80], and came to different conclusions. The review included the latest version of a Cochrane Systematic Review by Thomas et al. [74] which evaluated these 4 highly cited RCTs in long term care facilities (LTCFs) [77–80]. However, different from prior reviews by the same author, this time they excluded all-cause mortality as an outcome measure (only influenza-related outcomes) and found no conclusive evidence of the benefit of HW vaccination to LTCF residents. They also found a low quality of evidence with a high risk of bias. Another systematic review and meta-analysis [76] included in Dini et al pooled data from 4 RCTs and suggested a benefit to all-cause mortality {RR = 0.71 (95% CI, 0.59 – 0.85)} and ILI {0.58 (95% CI, 0.46 – 0.73)}, but all-cause hospitalization and laboratory-confirmed influenza were not statistically significantly altered [11].

Although we identified 5 higher quality clustered randomized controlled trials (cRCTs) [25,77–80] which address this question, only the Dutch trial [25] was not included in prior reviews (per our exclusion criteria), other than in de Serres et al. [73] in the next section, illustrating the need for updated cRCTs. This pragmatic cRCT [25] measured rates of nosocomial infection as a secondary outcome in 2 high risk departments – pediatrics and internal medicine. Within the higher vaccine coverage groups of the internal medicine departments, nosocomial influenza and/or pneumonia was recorded in 3.9% compared to 9.7% in the control hospitals, respectively ($p = 0.015$). An increase in vaccine coverage was associated with decreased inpatient morbidity from influenza and/or pneumonia in internal medicine settings, but not in pediatrics.

Topic 2, question 2, Part B – How many HWs need to be vaccinated (NNV) to ensure a benefit to patients?

We found a limited number of moderate quality observational and modelling studies [46–51] which suggest that a proportionate effect of HW vaccination is likely, where nosocomial influenza infections decrease with increasing HW vaccination coverage. Salgado et al. [47] conducted a retrospective cross sectional study in a USA tertiary care hospital over 12 consecutive years. HW vaccination rates increased from 4% in 1987–1988 to 67% in 1999–2000 ($P < 0.0001$). Proportions of nosocomial influenza cases among employees or patients both declined significantly ($P < 0.0001$). Logistic regression analysis revealed a significant inverse association between HW compliance with vaccination and the rate of nosocomial influenza among patients ($P < 0.001$). The authors reported that surveillance of nosocomial spread and isolation poli-

Table 3
Rapid Evidence Appraisal included studies and their characteristics for **Topic 2 - Questions 1 – 3.**

Study	Maryland Quality Score and classification	Study Design	Country	Setting	Included Studies/ or Population type	Intervention or Focus	# of participants	Outcomes	Do HWs transmit influenza to patients? Yes/No
Voirin [31]	4 High Moderate	OS-PC	France	Geriatric Hospital	Geriatric patients Nurses, doctors, contacts in geriatric setting	Wearable sensors for 12 days	patients (n = 37) nurses (n = 32), doctors (n = 15) contacts (n = 18,765)	Sensor data combined with lab-confirmed Influenza A, B, phylogenetic analyses -track transmission	Yes
Eibach [32]	3 Moderate	OS-RC	France	Geriatric Ward -Acute Care	Geriatric patients and HWs tested for flu	Molecular-based subtyping	Patients (n = 66) HWs (n = 57)	Nosocomial influenza transmission confirmed with molecular and epidemiologic testing	Yes
Vanhems [33]	3 Moderate	OS-PC	France	Hospital in flu season – Acute Care	Patients and HWs	Exposure- contagious persons	Patients (n = 21,519) HWs (n = 2,153)	RR of hospital-acquired ILI based on source contacts, lab-confirmed influenza	Yes
Vanhems [34]	2 Low Moderate	OS-PC	France	Geriatric Ward – Short Stay	Geriatric Patients, HWs, contacts	Wearable sensors for 6 days	HWs (n = 46) Patients (n = 29) Contacts (n = 14,037) N = 155 suspected cases	Detection of close contact between HWs, patients, or contacts combined with time in contact to measure risk	Suggests yes, but unclear
Pagani [35]	3 Moderate	Outbreak	Switzerland	Geriatric Hospital	Suspected cases - Geriatric patients and HWs of nosocomial outbreak	Epidemiology/molecular typing	28 outbreaks	Respiratory virus molecular testing and sequencing to determine nosocomial transmission patterns	UC, HWs not directly cause
Voirin [36]	3 Moderate	Review	mixed	Hospital	28 nosocomial influenza outbreak reports	n/a; ORION checklist	28 outbreaks	Transmission of influenza by HWs to patients and as index cases	Yes in 10 studies
Ridgeway [37]	2 Low Moderate	OS-PC	USA	University Hospital	Different types of healthcare professionals	Temporary mandatory flu testing in HWs	HWs (n = 449)	% influenza positive HWs by vaccination status; % influenza positive symptomatic HWs vs. asymptomatic	UC, but 50% of flu positives were asymptomatic
Kay [38]	2 Low Moderate	Outbreak	USA	Hospital retreat facility	HWs attendees and facilitators of a retreat	Epidemiology/viral testing	HWs (n = 32) Facilitators (n = 14)	Viral load changes and returning to work, shedding and duration, the association with symptoms and fever	UC, but 75% of flu + HWs returned to work whilst ill
Rodriguez-Sanchez [39]	2 Low Moderate	Outbreak of H1N1	Spain	Clinical Microbiology/ infectious Diseases Unit	Hospitalized patients with confirmed H1N1 influenza (HIV + and non-HIV +)	n/a; genetic sequencing	HIV + patients (n = 49), Non-HIV + (n = 37)	Phylogenetic trees, outbreak-specific substitutions, and viral variants in infected patients	UC on the source of outbreak
Valley-Omar [40]	3 Moderate	OS-PC	South Africa	Hospital pediatric	Nosocomial outbreak of H1N1 and children admitted to pediatric ward over 4 months	Epidemiology/viral sequencing	14 cases	Nosocomial transmission chains and infection sources using phylogenetic analyses	Yes, transmission with HWs, asymptomatic patients, and visitors
Melchior [41]	2 Low Moderate	OS-PC	Brazil	University hospital	HIV + patients, children, contacts, and HWs	Flu testing in risk groups	N = 400	Prevalence of influenza infection by risk group; influenza + asymptomatic; influenza acquisition by contacts	UC
Dini [11]*	4 High Moderate	Review	Mixed		6 systematic reviews/ 28 studies	Influenza Vaccine	Not pooled	Lab-confirmed flu, ILI, absenteeism, NNV	Does vaccination in HWs benefit patients? Yes/No? UC benefit Yes
Riphagen-Dalhuisen [25]	4 High Moderate	cRCT	The Netherlands	Hospital ward	Internal medicine and pediatric department HWs of cRCT	Interventions to increase uptake		Rates of nosocomial transmission retrospectively as a secondary outcome by internal medicine or pediatric ward	Yes

(continued on next page)

Table 3 (continued)

Study	Maryland Quality Score and classification	Study Design	Country	Setting	Included Studies/ or Population type	Intervention or Focus	# of participants	Outcomes	Do HWs transmit influenza to patients? Yes/No
Seal [42]*	2 Low Moderate	Review	Mixed		1 systematic review of systematic reviews and 2 non-randomised studies	Influenza vaccine in HWs		All-cause mortality, clinically suspected influenza, vaccine efficacy, working days lost, others hospitalization of patients.	No
Amodio [43]	2 Low Moderate	CS-RC	Italy	Hospital	Acute care hospitalized patients	Influenza vaccine in HWs	N = 62,343 patients 185 nosocomial 700 patients	Influenza vaccine coverage, nosocomial ILI and the association between the two % reduction of hospitalized flu cases due to each intervention	Yes
Blanco [44]	Can't score	Model	USA	Hospital	Hypothetical hospital in Michigan	5 influenza preventions		Effect of resident and staff influenza immunization rates on the likelihood of ILI clusters.	Yes assumed
Shugarman [45]	2 Low Moderate	OB-survey	USA	Nursing Facilities	Nursing facilities (nurses = 301)	Influenza vaccine	301	Proportions of nosocomial cases among HWs and patients . Nosocomial influenza rate with lab-confirmed influenza confirmation	Yes (ILI)
Dionne [46]	2, Low Moderate	OS-RCS	USA	550 bed Hospital	Flu + Hospitalized patients over 5 flu seasons	Influenza vaccine in HWs	533 influenza + nosocomial cases over 5 years		How many HWs need to be vaccinated if there is a benefit? NNV or range No association; but some reduction in up to 50% vaccine coverage in HWs
Salgado [47]	3, Moderate	OS-RCS	USA	600 bed Hospital	Hospitalized patients in a 600-bed tertiary hospital over 12 years	Influenza vaccine in HWs	N/A	Association of HW vaccination and influenza infections prevented in patients	Yes , significant proportionate association between vaccine coverage in HWs and a reduction in nosocomial infections
Van den Dool '09 [48]	Can't score	Model	The Netherlands	Simulation of 24 bed ward hospital	Nursing home model applied to a general hospital ward patients and HWs	Influenza vaccine in HWs	N/A	Association of HW vaccination and influenza infections prevented in patients; herd immunity	Yes , 40% prevention when 100% of HWs vaccinated. NNV = 3
Van den Dool '08 [49]	Can't score	Model	The Netherlands	Simulation of Geriatric nursing home	Nursing home model with 30 beds	Influenza vaccination coverage HWs	N/A	Odds ratio of outbreak LTCFs by vaccination coverage of HWs - Lab-confirmed influenza or ILI symptoms	Yes , 60% prevention when 100% of HWs vaccinated. NNV = 7
Wendelboe 2011 [50]	3 Moderate	CS-PC	USA	Geriatric, long-term care facilities	Residents and HWs of 75 LTCFs with and w/o outbreaks over two flu seasons	Vaccination coverage in HWs	N = 21 lab confirmed residents N = 40 ILI residents	Herd immunity; HW vaccination and probability of influenza in LTCF residents	Yes , proportionate prevention of outbreaks with rising vaccination coverage
Wendelboe 2015 [51]	Can't score	Model	USA	Geriatric, long-term	Residents and HWs of 76 LTCFs over one flu season	Vaccination coverage in HWs	N/A		Yes , Inverse association

*Dini, et al and Seal et al relevant for questions 2&3.

LEGEND: CC- Case Controlled; OS- Observational Study; CS- Cross Sectional; PC- Prospective Cohort; RC- Retrospective Cohort; RCS- Retrospective cross-sectional; SR-Systematic Review; EM- Economic Model; CBA- Cost-Benefit Analysis; TS- Time Series; RCT- Randomised Controlled Trial ; cRCT- Clustered Randomised Controlled Trial; UC- Unclear; Q1 – Question 1; Q2 – Question 2; Q3- Question 3;RR-Risk Ratio; NNV-number needed to vaccinate. Maryland Quality Score (2 – 5; Low Moderate – High).

cies remained constant during the study period, but concomitant increase in patient influenza vaccination rates may have contributed to the decrease in nosocomial infections. A nested-case control study [75] included in the review by Seal et al. [42] found that a vaccinated proportion of $\geq 35\%$ of HWs in short-stay units appeared to protect against nosocomial influenza among patients (OR = 0.07; 95% CI, 0.005–0.98) independent of patient age, influenza season and potential influenza source. The authors concluded that a minimum of 35% vaccination coverage in HWs would be required to have a potential protective impact on hospital-acquired influenza infection.

Dini et al. [11] also included a review by de Serres et al. [73] who used the mathematical principal of dilution as the basis for their re-examination of the main 4 cRCTs used as evidence for mandatory vaccine policies in HW [77–80]. They disputed the NNV (number needed to vaccinate) of 8 found by Hayward in 2006 in LTCF settings [79] and recalculated it to be 36,000, which was quickly disputed by Hayward [81]. Hayward stressed that results from their study in LTCFs were not necessarily applicable outside of the most frail and vulnerable patients.

In two modelling studies by van den Dool et al. [48,49], one model in LTCFs predicted “a robust linear relationship between the number of HWs vaccinated and the expected number of influenza infections in patients, preventing $\sim 60\%$ of influenza virus infections among patients” (NNV = 7). Comparing these results in LTCFs to a hospital or short stay setting, they found an equivalent or higher estimate of impact in hospital patients (NNV = 3) and that vaccination of 100% of HWs would potentially prevent 40% of inpatient nosocomially acquired influenza infections.

Topic 3, Question 1 – *What are the successful and practical interventions which increase HW influenza vaccine uptake?*

We identified several higher quality RCTs and systematic reviews addressing this question and there is consensus that no single intervention component has been found to rapidly and substantially raise influenza vaccination rates in HWs, aside from mandatory vaccination [82]. However, several systematic reviews [52,59,83] and tool kits [57,58] have highlighted that multifaceted approaches which sustain over time can see increases $> 90\%$ [47]. Dini et al. [11] evaluated 7 systematic reviews which together evaluated strategies to increase uptake in HWs in $> 200,000$ subjects. They found that some successful alternatives to mandatory vaccination included “soft-mandates”, such as masks, “opt-out”, or declinations statements, and multi-faceted programmes which take into consideration the local context, include incentives, education, advertising, and easy vaccine access as efforts to enhance behavior change.

Higher level systematic reviews had similar findings including a meta-regression analysis that [83] found that the single most successful strategies after mandatory vaccination were “soft” mandate strategies and a policy excluding non-vaccinated HWs from working with highly vulnerable patient groups. Another systematic review [52] found that successful interventions contained the following critical components: free and easy access to vaccine; knowledge and behavior change through educational activities; reminders and incentives; management/organizational approaches including personnel charged with implementing the programme; and a long-term strategy. An additional study of 121 publications also concluded that all interventions increased uptake to some extent with the most successful being those which required vaccination as a condition of being allowed to work [84].

Several randomised trials [85] have successfully used a pre-intervention survey as a basis for subsequent intervention mapping [25,86] in the development of multi-faceted interventions. This is particularly important as the reasons for vaccine hesitancy are complex and heterogeneous [52], making local, social, cultural,

institutional and logistical factors all relevant to the development of educational or knowledge-based interventions. Other RCTs failed to dramatically raise uptake using educational tools or manuals and a decision aide intervention which changed views but not actions [54–56].

Topic 3, Question 2 – *What are the sociological, behavioural, and public health policy aspects of influenza vaccine uptake in HWs?*

We identified 3 higher moderate studies on this topic, including two reviews [11,61]. One review [11] evaluated 16 systematic reviews on vaccination determinants in HWs, adherence to vaccination, and risk perceptions or beliefs about vaccination. The study broadly found the following: knowledge about influenza varied by occupation, not necessarily occupational level (doctors vs. dentists for example); many misconceptions about influenza persist, even though influenza knowledge has improved over time; the relationship between HWs' perception and mitigation of risk is complex and multi-factorial and needs to be better understood. Included as part of this review was a large systematic review by Schmid [86] which included 470 studies, of which 117 looked at HW barriers to influenza vaccine uptake. Their review found that micro-level determinants included age, gender, additional risk factors, and past behavior as the most reported factors to influence uptake. They further evaluated the determinants based on the 4C model for vaccine hesitancy (complacency, confidence, convenience, and calculation) and found that the strongest barrier to uptake was a HWs lack of confidence about disease severity or vaccine effectiveness and “a lack of professional or ethical obligation to get vaccinated”. This was in line with the systematic review by Hollmeyer which found that HWs are motivated to be immunized against influenza more often for their own benefit than for the benefit of their patients [52].

Lorenc et al. [61] conducted a systematic review of 25 studies on HWs' beliefs and perceptions about vaccination within different contexts and found that many participants are unsure of the real value of vaccination programs. This study highlighted that the success of a vaccination program may be influenced by the complex relationship between HWs and the organization and management of the health care system within which they work. Ofstead and colleagues [62] executed a three-part evidence-based intervention study in LTCFs which compared a multi-faceted ecological model and the health belief model. They raised uptake from 50% to 85%, decreased respiratory illness-related absenteeism by 12% and concluded that an ecological model was more effective than the health belief model at increasing uptake as it includes broader policy or organizational aspects relevant to program implementation.

4. Discussion

We executed a *Rapid Evidence Appraisal* [8] of the literature from 2006 to 2018 to evaluate the evidence relevant to the ongoing discussions about seasonal influenza vaccination in HWs. Influenza infection and vaccination in HWs poses a complex policy challenge due to the general lack of high quality evidence, the inherent complexity of influenza, and the number of potential benefactors: HWs themselves by avoiding influenza infection, their patients by virtue of reduced influenza transmission in health facilities, their employers in terms of business continuity, and potentially their families and wider community contacts.

4.1. Influenza risk to health workers

The evidence on whether HWs are at increased risk of influenza infection (symptomatic and asymptomatic) in HWs is mixed. Recent studies suggest a higher risk with pH1N1 [11–13,63], a high attack rate, and variations in risk which are connected to occupa-

Table 4
Rapid Evidence Appraisal included studies and their characteristics for **Topic 3 - Questions 1 & 2.**

Study	Quality	Design	# of participants or # of included studies	Country	Population	Intervention	Question 1 Results What are the successful and practical interventions which increase HW influenza vaccine uptake?
Dini 2013 [11]	4 Moderate High	Review	7 systematic reviews	Mixed	7 systematic reviews evaluating > 200,000 subjects	Interventions to increase uptake in HWs	Mandatory vaccination is most effective; soft mandates also effective; multi-faceted, complex/integrated programmes effective
Riphagen-Dalhuisen 2013 [25]	5 High	cRCT	N = 13,830	The Netherlands	All employees working in 6 University medical centres over two influenza seasons	Pre-intervention survey and model to develop intervention	Influenza vaccine coverage significantly higher in intervention groups (seasonal 32.3% vs. 20.4%; pandemic vaccine 61.7% vs. 38%)
Hollmeyer 2013 [52]	5 High	Systematic review	24 included studies	mixed	HWs from acute care hospitals between January 1990-December 2011	Interventions to increase uptake in HWs	Increases in vaccine uptake due to free and easy access to vaccine; education and behavior modification (education, incentives or reminders); must create culturally-relevant interventions
Abramson 2010 [53]	5 High	cRCT	13 clinics, 163 HCWs	Israel	Staff with direct patient contact in primary care community clinics in Jerusalem over 2007–2008 influenza season	HMO recommendation for vaccination of HWs	Immunisation rate 52.8% in the intervention group vs. 26.5% in the control group. Absolute increase since previous year was 25.8% in intervention clinics vs. 6.6% in the control clinics
Chambers 2015 [54]	4 Moderate High	RCT	Intervention group = 13, controls = 13	Canada	26 healthcare organizations across 6 provinces over two flu seasons	A successful influenza guide vs. nothing new	Intervention improved HW vaccination rates, but these rates continued to be sub-optimal and below rates achievable in programs requiring personnel to be immunised
Chambers 2012 [55]	4 Moderate High	RCT	N = 151	Canada	Non-vaccinated HWs at 6 weeks of influenza campaign in a healthcare centre (hospital, long-term, mental health)	Ottawa Influenza Decision Aid (OIDA)	It appears that the OIDA increases confidence in vaccination decision but does not increase odds of intending to be immunised
ECDC 2013 [56]	3 Moderate	Review	5 included studies	European region	Studies on the drivers and barriers to influenza vaccination/coverage in Europe	Interventions to increase uptake in HWs	Non-hospital settings: campaigns w/ more components, education/promotion and improved vaccine access increased uptake. Only mandatory vaccine could raise uptake above 90%
Europe WHO 2015 [57]	Policy toolkit	Evidence-based policy guide/toolkit	36 included studies	Mixed	Guidance on increasing HW influenza uptake; literature review	Studies of the determinants of vaccine uptake	Development of practical guide- <i>Tailoring Immunization Programmes for Seasonal Influenza</i> (TIP FLU)- categorizes vaccination decision making by behavioural determinants (personal, social/community, environmental, contact with HWs)
Europe WHO 2015 [58]	3 Moderate	Review	35 included studies	Mixed	Review to provide examples to countries of successful and replicable interventions to increase uptake in HWs	Interventions to increase uptake in HWs	Most successful interventions include multiple components; important to increase demand through changes in policy, legislation, and legislation; HWs need burden and risk data
Macdonald 2013 [59]	4 High Moderate	Systematic literature review	22 included evaluations	European region	Review of 22 evaluation studies in Europe of promotional communication interventions	Promotional communications for flu in Europe	They found that all forms of communication can stimulate HW vaccine uptake; promotional communications that target HWs can also improve uptake among patients
Stuart 2012 [60]	4 High Moderate	Review	11 included studies	Australia	11 studies on seasonal influenza uptake rates of Australian HWs , determinants and strategies to increase uptake	Interventions to increase uptake in HWs/ determinants	Factors contributing to immunisation in Australia show only minor variations from international samples. Not enough quality evidence on effective strategies in Australian and globally

Table 4 (continued)

Study	Quality	Design	# of participants or # of included studies	Country	Population	Intervention	Question 2 Results What are the sociological, behavioural, and public health policy aspects of influenza vaccine uptake in HWs?
Dini 2018 [11]	4 High Moderate	Review	16 included systematic reviews	Mixed	Evaluating vaccination determinants, vaccine adherence or knowledge or beliefs about vaccine in HWs	mixed	Topic has been extensively studied under different categories; higher knowledge among medical doctors/more favorable perception; Risk perception influences uptake; variations in uptake by HW
Lorenc 2017 [61]	4 High Moderate	Systematic review	25 included studies	Mixed	Evaluating studies of qualitative evidence on HW vaccine uptake	mixed	Many beliefs are barriers to vaccine uptake- risk beliefs about influenza, vaccine effectiveness, concern about side-effects. Uptake influenced by HWs relationship to employer and feeling autonomous
Ofstead 2017 [62]	4 High Moderate	Intervention study and survey	N = 726	USA	Vaccinated and unvaccinated LTCFs' nursing staff from 4 LTCFs in the Midwest	Ecological model vs. health/belief model to increase uptake	Vaccination rates among LTCF HWs and their family members increased significantly, and absenteeism decreased after the implementation of a multifaceted ecological model

LEGEND: CC- Case Controlled; OS- Observational Study; CS- Cross Sectional; PC- Prospective Cohort; RC- Retrospective Cohort; RCS- Retrospective cross-sectional; SR- Systematic Review; EM- Economic Model; CBA- Cost-Benefit Analysis; TS- Time Series; RCT- Randomised Controlled Trial; cRCT- Clustered Randomised Controlled Trial; UC- Unclear; Q2 - Question 2.

tional exposure. Other studies find a risk to patients and HWs during an outbreak [16] and following contact with ILI patients [15]. Additional studies suggest only a risk of asymptomatic infection [17,64]. Taken together, these studies highlight that setting [88], occupation [89] or patient contact level, risk procedure [90], circulating virus, and existing immunity in the population (i.e. H1N1) can all vary risk [63]. However, respiratory illness has been reported as one of the main causes of sickness absence in HWs [92,91], pandemics and epidemics can be associated with concurrent increased rates of HW absenteeism [12,92,93], and HWs do overall appear to be at risk of contracting influenza.

4.2. Vaccine benefit to health workers or their employers

Recent higher level evidence [11,18] evaluating RCTs, cohort studies, and systematic reviews does suggest a vaccine benefit to HWs and their employers including a protective effect against laboratory-confirmed influenza, shortened sick leave, and a reduced incidence of absenteeism (due to ILI). However, vaccine benefit studies during the years of pH1N1, including an RCT in the Netherlands, found the opposite effect, an increase in absenteeism in the vaccination arms. Different authors draw contradictory conclusions from the use of the same RCTs [94-96], indicating a need for updated, large scale studies of higher quality. Observational studies also draw different conclusions and are constrained by poor study design, non-specific outcomes, a high risk of bias, and failure to adjust for confounding factors. Absence due to ILI is frequently used as an outcome measure when ILI itself has relatively poor predictive value for influenza infection [97,98]. Although studies may provide contradictory conclusions, vaccine efficacy in HWs has been shown to be as high as 90% for well-matched seasonal influenza vaccines [66,68], and high for pandemic vaccine [99]. Therefore, it seems reasonable that vaccinating HWs against influenza will reduce influenza burden in HWs, related work absenteeism, and possibly influence subclinical infection and/or "presenteeism" - attending work whilst ill.

4.3. Influenza risk to patients

The expanding volume of studies combining epidemiological and phylogenetic analysis, among other new technologies [71,72], suggest that HWs are implicated in at least some transmission during nosocomial outbreaks of influenza. However, the complexity of transmission in health facilities is also driven by various factors including patient to patient and visitor to patient contact, varying levels of possible infectiousness with asymptomatic vs. symptomatic transmission, and high patient turnover, particularly in acute care settings [37,38,40]. Nevertheless, Pagani et al. [35] identified multiple introductions of strains into the hospital from the community during an outbreak and noted that unvaccinated HWs may have played an important role in sustaining the outbreak. Other factors which may increase or decrease the extent to which HWs are implicated in transmission are individual (immune status, severity of disease, viral shedding), pathogen (virulence, infective dose), and environmental factors (infection control practices, ward layout, frequency of patient, staff and visitor contacts), including contact with HWs of varying degrees of risk exposure themselves. Notwithstanding, the evidence does suggest that HWs can clearly pose a transmission risk to patients, at least some of the time.

4.4. Vaccine benefit to patients

The benefit of HW influenza vaccination to patients is not clear or consistent in the literature and continues to be debated as numerous systematic reviews using mostly the same RCTs [77-

Table 5
Rapid Evidence Appraisal summary of findings table for all questions.

Review Question	# of individual studies included by question	# of Higher Quality studies (Maryland Quality Score \geq 4)	Settings Populations or# of studies included	Main findings	Limitations of included studies	Future Considerations
Topic 1 Question 1 <i>Are HWs at an increased risk of influenza infection?</i>	7	1 study A Comprehensive review which evaluates systematic reviews addressing this question.	-Hospital settings with different occupations such as physicians, nurses, close patient contact or less patient -H1N1 risk and Seasonal influenza risk -Patients and HWs during outbreaks	-Yes, in some cases, HWs are at an increased risk, but not always -H1N1pdm09 risk to HWs is clearer than seasonal influenza -Risk can vary by occupation with H1N1pdm09 but unclear for seasonal influenza -Influenza risk appears to vary year to year depending on virus circulation -Difficult to look across multiple studies to draw conclusions unless controlling for study year, circulating virus, patient populations, health worker type or occupation	-Pooled data may lead to inaccurate conclusions -Publication and selection Bias -Use of indirect measures of influenza -Use of seasonal influenza elements for pandemic models	-Research to validate variability in risk with influenza by year, virus, occupation, setting, patient populations - Consideration of this variability in risk as an inherent part of research or policy development
Topic 1 Question 2 <i>Does influenza vaccination benefit HWs or their employers?</i>	14	4 studies 2 reviews, 2 RCTs	-Hospital settings -University medical centres -Staff and students of Dental Faculty -Trivalent vaccine -H1N1pdm09 vaccine	-Yes, vaccine can be cost-saving and reduce influenza burden, but it isn't entirely consistent -Several higher-level studies suggest vaccine efficacy in health workers and cost-savings to employers through reduced absenteeism -We identified a total of 5 RCTs to answer this question, 2 not part of recent systematic reviews and had conflicting results -One RCT during 2009–2011 found vaccination to increase absenteeism -One RCT only used ILI as an outcome measure -Vaccine benefit may be greater when considering asymptomatic influenza and the possible impact on transmission	-Applying vaccine effectiveness, efficacy, or attack rate of healthy adults to HWs. -Self-reported outcomes -Non-specific outcomes -low circulation of virus confounds vaccine effectiveness	-A need for updated high quality RCTs assessing vaccine benefit over time in multiple settings. -Develop research standards for influenza vaccine benefit -Vaccine type may vary findings
Topic 2 Question 1 <i>Do HWs transmit influenza to patients?</i>	11	1 study Using high resolution contact data detected with sensors	-Patients and HWs in Elderly care Hospital Wards -In HIV + patients, -In children During Nosocomial outbreaks	-Yes, HWs have been implicated in some transmission events, most frequently among elderly patients -Transmission and introduction can be directly linked to HWs, patients, and community/visitors-	-Small sample size in many studies -Most studies of moderate quality	-Need to better understand the role of asymptomatic infections in transmission -Transmission reduction measures need to consider HWs, patients, and outside contacts as a continuum -Need larger studies over a longer duration using high-resolution contact data
Topic 2 Question 2 Part A <i>Does influenza vaccination in HWs benefit patients</i>	6	2	-Long-term care facilities in patients -Acute Care facilities -Internal Medicine -Pediatrics	-Maybe - evidence continues to suggest a benefit on protection against all-cause mortality to LTCF patients -Evidence is mixed in other populations, but one RCT in the Netherlands suggests a reduction in nosocomial infection in internal medicine wards, not pediatrics -Very few newer RCTs evaluating patient benefit -Several studies evaluate ILI rather than lab-confirmed as a measure of benefit	-Decisions based on 4 highly biased RCTs in long-term care facilities due to attrition rate, no blinding, contamination in control groups, low rates of vaccination coverage	-Need updated cRCTs which span years -Need standardized approaches/ population to answering this question -Patient benefit variations need to be understood and appreciated (more benefit to more vulnerable patients)

Table 5 (continued)

Review Question	# of individual studies included by question	# of Higher Quality studies (Maryland Quality Score \geq 4)	Settings Populations or# of studies included	Main findings	Limitations of included studies	Future Considerations
Topic 2 question 2 Part B <i>How many HWs need to be vaccinated (NNV) to ensure a benefit to patients?</i>	6	0	-Long term care facilities -Medical Centre hospital -Tertiary Hospital	-NNV range from 3 to 50 -Appears to be a benefit in LTCFs when 100% of HWs are vaccinated with the possible prevention of 60% of infections -Appears to be a proportional benefit with a greater reduction in nosocomial transmission with higher coverage -Appears to be a curvilinear relationship between rising coverage and reduction in nosocomial infections that can be impacted by visitors or other contact elements	-Vaccine effectiveness for HWs based on that for healthy adults -Other assumptions in models may lead to inaccurate conclusions -Outcome definitions in models significantly impacted whether herd immunity could be induced	-NNV estimates need to factor in differences in outcome measures used -Need to expand body of knowledge beyond geriatric populations which may skew the total findings -Need to develop HW vaccine efficacy and attack rate standards for models
Topic 3 Question 1 <i>What are the successful and practical interventions which increase HW influenza vaccine uptake?</i>	10	8	-Primary care community clinics -Acute care hospital staff -HWs in tertiary hospitals -HWs with and w/o patient contact -All personnel of a health institution	-Mandatory Vaccination to be able to work remains the most successful intervention to increase uptake -Other successful interventions are: <ul style="list-style-type: none"> • Multi-faceted including many elements together (the more the better) • Sustain over time • Provide free and easy access to vaccine • Use behavior change components (reminders, incentives, education) • Develop targeted multi-faceted interventions using baseline data collection to identify barriers in that population • Vaccine promotion from highest levels • Having a vaccine organizer from inside • Opt-out programs (declination statements, required mask use, flu-safe zones)-Appears that intervention success is linked in some respects to the number of interventions 	Publication bias considering studies that were not effective may not be published -Selection bias as some may not have reported baseline vaccine uptake before intervention -Lack of blinding in RCTs -Hard to separate the benefit of one intervention as distinct from the others when a part of multi-faceted interventions	-Clear guidance needed on vaccine program implementation in HWs which clarify the options of mandatory policy options vs. other. -Develop a standardized checklist of components critical for vaccine uptake success - Develop guidance on how to develop targeted interventions catering to the individual context for implementation
Topic 3 Question 2 <i>What are the sociological, behavioural, and public health policy aspects of influenza vaccine uptake in HWs?</i>	3	3	-Long-term care facilities - Mixed hospital settings of HWs -Mixed outpatient settings of HWs	-Strongest barriers to uptake were HW's lack of confidence about disease severity or vaccine effectiveness and a lack of professional or ethical obligation to get vaccinated. -Strongest reason to vaccinate was to protect oneself and not patients -Success of a vaccination program may be influenced by the complex relationship between HWs and the organization and management of the health care system within which they work. -Ecological model shows promise an alternate to the widely used health belief model	-Limited use of models other than Health Beliefs Model	-Greater diversity of study approaches to reframe issues through alternative lenses -Need to integrate HW influenza vaccine programs into existing programs to ensure long term -Need to expand discussion on the importance of top-down support for vaccine programs in HWs to develop a culture of vaccination -Need to have a better understanding of the influenza of management /organizational structures where implementation will take place

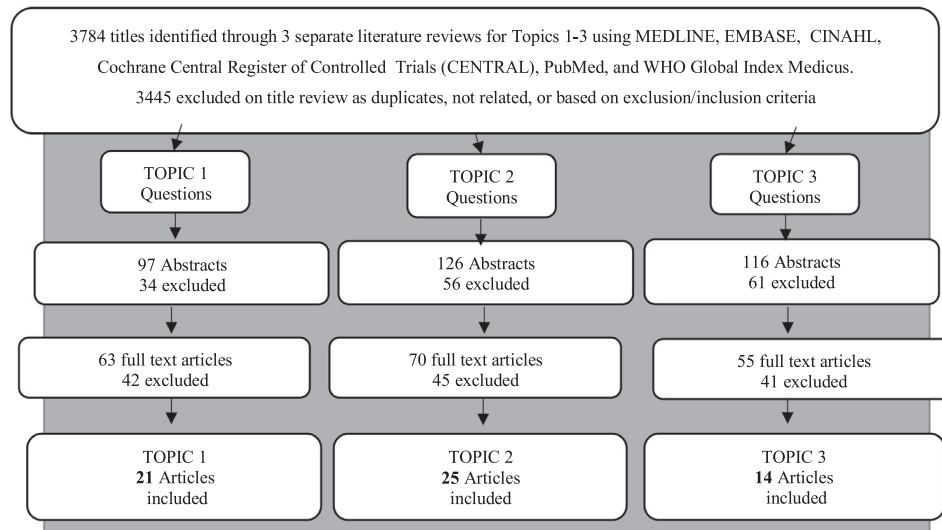


Fig. 1. Flow Diagram of the literature search strategy, study removal and selection by topic.

80] all draw different conclusions [11,66,73,76]. Research in LTCFs has consistently shown a benefit to patients, at least for all-cause mortality. Variations across study populations or studies, such as patient populations, level of HW to patient contact, patient vulnerability or susceptibility, or levels of risk exposure for HWs themselves, limit comparability between findings. This may explain why studies in LTCFs consistently find vaccination of HWs beneficial to elderly patients, where the stability of the setting, patient characteristics, and high level of contact between HWs and patients are all consistent factors. Whereas, a larger body of evidence suggests an unclear association between HW vaccination and patient benefit in hospital settings, which may be due to variations in study design, HW or patient characteristics, their individual risk or susceptibility, difference in vaccine type or diagnostic testing, or even the time of year. LTCF patients do however appear to benefit, at least regarding mortality, which demonstrates that vaccine benefit to patient warrants efforts to increase vaccination in HWs caring for the elderly [100].

4.5. Influenza vaccine uptake

The factors that feed into a HWs decision-making pathway for influenza vaccination are diverse and individually-driven [52]. Therefore, any efforts must be as equally diverse as the HWs they target. Mandatory vaccination is debated extensively from many perspectives including the reasons for [21] and against it [73]; however, no amount of debate can refute that mandatory vaccine policies do raise uptake quickly, usually to levels in excess of 94–96% [82]. Other successful interventions are multi-faceted, sustained over time [47], and evolve over time as data is collected on the target population [85]. These make vaccine easily accessible, maintain strong organizational support, develop education which varies by targeted groups, and may include “soft-mandate” policies, such as declination statements, or alternatives such as masks [52,83].

One area which deserves more consideration, is the use of different types of models in the development of interventions to improve uptake. Traditionally, the health belief model is most commonly used. However, studies exploring other possibilities [62,86] have shown promise with an ecological model, which takes into consideration the contextual, organizational, policy or background components which are relevant to a vaccine program and

henceforth to a HWs decision to take the vaccine. These models incorporate the growing understanding that HW vaccine uptake involves much more than individual knowledge, attitudes, and beliefs. The greater context of the HW and their relationship to the organization, other HWs, and broader cultural factors are all important to vaccine uptake.

4.6. Study limitations

Although we made every effort to execute an unbiased and systematic approach to our search and selection of included literature, our study was not without limitations. Due to resource and time constraints, we limited the search to English language abstract or full-text articles, did not include grey literature, and removed publications that were included as part of a more recent systematic review. This may have led to some selection bias and limited our exposure to all relevant articles. However, due to the breadth of questions included in the search and the execution of three distinct searches, we felt that this diversification may have added strength to the study design to compensate for this weakness.

The majority of included studies were observational studies, which limits the strength of our findings as observational studies are susceptible to bias and there is limited ability to infer causality. Additionally, many studies were executed in different types of settings, with different target populations, using different vaccines and with varying levels of risk or exposure to the populations being studied. This makes comparing across studies very difficult.

Our methodology lacks the robustness of a formal systematic review or meta-analysis and does not report on effect size. Systematic reviews have very defined limitations for study selection and inclusion and typically do not query so many questions. We executed a Rapid Evidence Appraisal - a time-limited effort of assessing the evidence to draw conclusions, a process similar to what might happen in a ‘real-life’ policy environment. To compensate, we approached the literature search in a systematic way to add robustness to our study design and the breadth of our included questions and consideration of multiple elements relevant to the decision-making process, offers a more realistic approach for policy makers. Finally, our study was adapted and updated from a white paper originally intended to advise and inform WHO when establishing the influenza vaccine research agenda. The objective was to support global policy recommendations.

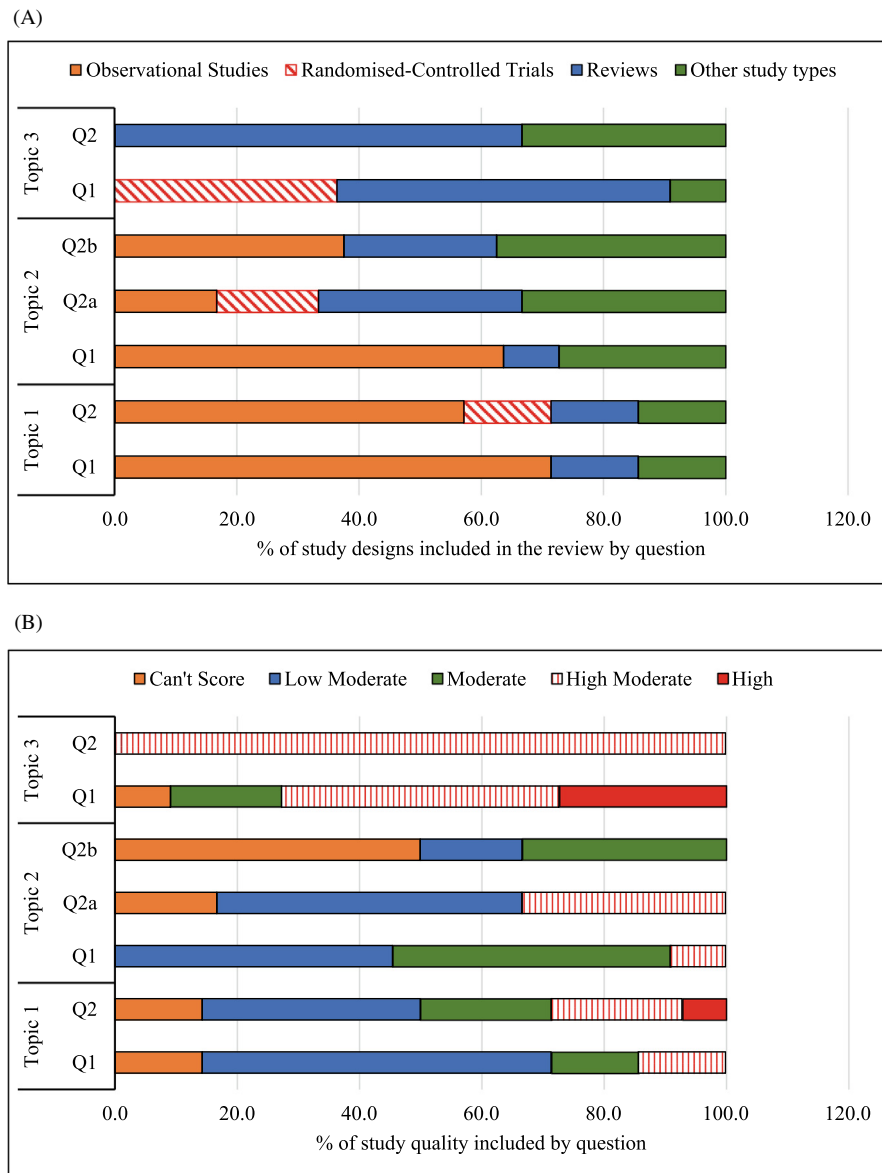


Fig. 2. (A and B). % Distribution of different study types included in our review and % distribution of included studies by Maryland Scientific Methods Quality Scale. (A) % Distribution of Included Study Types by Topic and Question illustrates the limited number of randomized-controlled trials. (B.) % Distribution of Included Studies by Maryland Scientific Methods Quality Scale illustrates the limited number of high-quality studies identified.

5. Conclusion (see summary of findings Table 5)

In recent years, several comprehensive reviews [11,18,42,61,64,66,67,73,74,76,83,86,87] have attempted to rigorously address different aspects of influenza vaccination in health workers. Paradoxically, the number of reviews far outweighs the number of studies that are of high quality or give definitive answers. Similarly, our review included only RCTs that have not already been evaluated as part of a more updated systematic review. It is therefore hardly surprising that it has proved difficult to draw universal and emphatic conclusions for policy makers, government leaders, and healthcare managers; and that implementation is poor and acceptance low.

Nevertheless:

- Nosocomial influenza is a recognized problem and it is clear there is a problem to solve or a case to answer.

- There is adequate evidence that HWs contract influenza and data suggests they are at risk of continuing to work whilst infected.
- There are sufficient data to conclude that influenza vaccines are as effective in HWs as in other adults of similar age.
- Data are emerging that capture the complexity of influenza transmission in health facilities and new molecular evidence implicates HWs in transmission events.
- Data on whether vaccinating HWs protects patients is of mixed quality and does not universally favor a positive (protective) outcome. However, there are strong signals from studies in LTCFs that HW vaccination protects patients, especially with regard to mortality.

The evidence base requires improvement and future research should aim to evaluate the impact of HW vaccination on clearly defined and standardized outcome measures in specific cohorts

of beneficiaries. A better understanding of transmission dynamics across a diversity of HW and patient risk groups is needed to facilitate a more nuanced and useful estimation of the wider benefits of HW influenza vaccination. The large body of knowledge on effective ways to increase vaccine uptake in HWs needs to be incorporated consistently within vaccination policies and practices. Programmes will need to consider the importance of organizational and contextual factors as drivers alongside the individual perceptions of HWs. The evidence demonstrating the effectiveness of mandation in improving uptake is however emphatic.

Influenza is likely to persist as a unique methodological challenge for researchers to produce reliable and robust results which lead to definitive conclusions about HW vaccination. Influenza burden, infectiousness, and severity vary yearly, seasonally, and spatially. Influenza risk also varies by setting, such as in proximity to young children or immune-compromised individuals, and by occupation or activity (such as performing respiratory procedures on infected patients). Additionally, influenza vaccine effectiveness is equally variable by season and subtype, making comparisons between years and populations challenging.

Due to the inherent complexity of influenza, waiting for the perfect results with influenza risks decision paralysis. When considering the evidence with a 'whole-of-system' approach, rather than considering specific evidence questions in isolation, we argue that the case for vaccinating HWs against influenza is maintained. Furthermore, to ensure the success and likelihood of expansion of seasonal influenza programs globally, guidance is needed for policy makers and implementers on how to best integrate influenza vaccination to HWs within existing vaccination and occupational health frameworks.

Declaration of Competing Interest

Author JSN-V-T declares no conflicts of interest in the last 5 years. Between 2000 and 2004 he was, at times, employed by SmithKline Beecham (now a part of Glaxo SmithKline) and Aventis Pasteur MSD, both of whom manufacture and/or distribute influenza vaccines; arising from this period he has no outstanding shares, share options, or accrued pension rights pertaining to either company.

Authors have no further conflict of interests to declare. All authors attest they meet the ICMJE criteria for authorship.

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Disclosure

All authors have approved the final article.

JSN-V-T is currently working on secondment at the Department of Health and Social Care, England (DHSC).

Philipp Lambach works for the World Health Organization (WHO). Hamid Mahgoub works for East of England Health Protection Team, Public Health England. Dawn C. Jenkin works for Nottinghamshire County Council.

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Contributors

- Dawn C. Jenkin: Literature search 2006-2016, interpretation of results, drafting of original report which served as the basis for this manuscript, editing final manuscript.
- Hamid Mahgoub: Literature search 2006-2016, interpretation of results, drafting of original report which served as the basis for this manuscript, editing final manuscript.
- Kathleen F. Morales: Main writer, editor, preparer of the manuscript; literature search 2016-2018, interpretation of results, development of all tables and figures in the manuscript.
- Jonathan S. Nguyen-Van-Tam: Study design, interpretation of results, drafting and finalizing the manuscript.
- Philipp Lambach: Study design, interpretation of results, drafting and finalizing the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jvacx.2019.100036>.

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