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# Vaccination of healthcare workers: A review

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**Abbreviations:** AEs, Adverse events; CDC, Centers for Disease Control and Prevention; DT, Diphtheria and tetanus; EEA, European economic area; EU, European Union; HBV, Hepatitis B virus; HBs, Hepatitis B virus surface antigen; HCW, Healthcare worker; ICUs, Intensive care units; MMR, Measles; mumps; rubella; RCT, Randomized controlled trial; Tdap, Combined tetanus; diphtheria and pertussis vaccine; VE, Vaccine effectiveness; VZV, Varicella zoster virus; WHO, World Health Organization

Vaccine-preventable diseases are a significant cause of morbidity and mortality. As new vaccines are proving to be effective and as the incidence of some infections decreases, vaccination practices are changing. Healthcare workers (HCWs) are particularly exposed to and play a role in nosocomial transmission, which makes them an important target group for vaccination. Most vaccine-preventable diseases still carry a significant risk of resurgence and have caused outbreaks in recent years. While many professional societies favor vaccination of HCWs as well as the general population, recommendations differ from country to country. In turn, vaccination coverage varies widely for each microorganism and for each country, making hospitals and clinics vulnerable to outbreaks. Vaccine mandates and non-mandatory strategies are the subject of ongoing research and controversies. Optimal approaches to increase coverage and turn the healthcare workforce into an efficient barrier against infectious diseases are still being debated.

## Introduction

Patients harbouring vaccine-preventable diseases are treated regularly by healthcare workers (HCWs), who may or may not have received corresponding vaccination. The relevance of immunization differs from one infection to another, depending on the epidemiology of each disease and the risks and benefits of each vaccine. Official recommendations about the best vaccine strategies have been issued for HCWs and management. All these factors participate in final vaccination coverage.

This review summarizes the recent literature on these topics, concerning the most common vaccines (**Table 1**), without discussing particular modalities of vaccine administration. Interventions to increase influenza vaccination coverage among HCWs have recently been the subject of significant research and are thus also covered. We mainly focus on articles published between 01/01/2011 and 01/02/2015, identified by PubMed search in English and French. Published national guidelines are also reviewed.

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## Influenza

### Background and epidemiology

Influenza is a viral respiratory disease that affects humans as well as animals, such as pigs and chickens. The virus mutates quickly, and its seasonal strains cause outbreaks every year, mostly during winter, affecting 5-10% of the population, killing up to 0.01%,[1] and even spreading in hospitals.[2-4] Major genetic rearrangements between viruses, usually from different species, can create pandemic strains that can infect much of the population. Vaccines against these strains are not the subject of this review. Influenza vaccine formulations are updated annually to match vaccine viruses with those predicted to circulate in the community. Two vaccine versions can be used, inactivated and live-attenuated. Inactivated vaccines seem to be more efficacious in adults aged 50 years or more, whereas the more recent live-attenuated version is more efficacious in children, less sensitive to mismatches with circulating strains and easier to administer (intranasally), but seems to be more likely to cause complications in recipients with underlying conditions.[5]

Seasonal influenza is usually a relatively benign illness in healthy adults, such as HCWs, but can be severe in other groups (children, the elderly, immunocompromised patients and patients with risk conditions). The symptoms include fever, sore throat and musculoskeletal pain typically lasting 3-7 days. Cough and malaise can persist for 2 weeks or more, with high intensity in the first week.[6] The disease facilitates infections by bacteria, e.g., *Streptococcus pneumoniae* or *Staphylococcus aureus*, which can be fatal. [7]

In healthy adults, incubation time is 1-3 days, viral shedding starts 0-2 days before the onset of symptoms and continues 4-14 days afterwards.[6,8,9] Pre- and asymptomatic shedding is common and can represent a significant proportion of infectiousness.[10] The reproduction number is around 2. Influenza transmission by HCWs has been observed during nosocomial outbreaks.[11] Cross-over immunity from infections in previous

**Table 1.** Summary of the key facts for each vaccine-preventable disease

| Disease | Patients most frequently/seriously affected | Nosocomial transmission | HCW vaccination / seroprevalence rates | Vaccination recommendations |
|---|---|---|---|---|
| Influenza | Children, elderly, obese, immunocompromised, affected by chronic neurological, hepatic, renal comorbidities | Frequent | 15-90% | Recommended for all HCWs in 26/31 EU/EEA countries, the USA and Japan |
| Hepatitis B | Stay in endemic regions, pregnant women, immunocompromised, disabled, dialyzed, intravenous drug users | Frequent | 63-95% | Recommended for all HCWs in high-income countries. Mandatory for medical students in France |
| Pertussis | Infants, affected by cardiac or respiratory comorbidities | Frequent | 14-73% | Recommended for all HCWs in high-income countries |
| Measles | Infants and children <5 years old, adults > 20, pregnant women, immunocompromised | Frequent | 87-97% | Recommended for all HCWs in high-income countries. Mandatory in Finland and for female workers in Slovenia |
| Mumps | Students, international travellers | Rare | | |
| Rubella | Pregnant women, children <5 years old | Exceptional | | |
| Varicella | Pregnant women, newborns, adults, immunocompromised | Rare | 90-100% | Recommended for the general population in the USA, Canada, Australia and 4 EU/EEA countries. Recommended for some or all HCWs in 10 EU/EEA countries |
| Tetanus | Elderly, affected by chronic conditions | Exceptional | 89-97% | Recommended for the general population in 14/30 EU/EEA countries and the USA |
| Diphtheria | Children <5 years old, adults >40 | Exceptional | | |

years is usually considered weak because of constant changes in the circulating virus genome.

### Benefits and risks in healthcare settings

Studying HCW influenza vaccination involves assessing benefits and risks in both HCWs and their patients, and balancing them against one another.

The individual benefits of HCW vaccination are the prevention of influenza and the reduction of influenza-related disability, measured mostly by HCW absenteeism. Major complications of influenza and influenza vaccines are rare among healthy adults; thus, their incidence variations are difficult to ascertain.

Vaccine effectiveness (VE) and efficacy vary significantly from season to season, mainly because of rapid virus evolution and mismatches between vaccines and seasonal strains. This will remain unchanged in the near future, although broader vaccines are the subject of ongoing research.[12] In randomized clinical trials (RCTs) among healthy adults, vaccine efficacy ranges from 16 to 76%, with a median of 50% (interquartile range: 42-68).[13,14] VE is similar in observational studies. The US Flu Vaccine Effectiveness Network estimates VE every year in the USA, in adults aged 18 to 49 years. Adjusted VE during the 2010-2015 seasons was 51%, 44%, 39%, 60% and 16%, respectively.[15-19] These figures are similar to what has been found elsewhere,[20] but somewhat lower than the 88% reported in a RCT conducted among HCWs in the 1990's,[21] which might have been due to HCW-specific characteristics or selection bias. Temporary disability, measured by influenza-like illness-related absenteeism, was reduced by 28% in a randomized, controlled, double-blind trial among HCWs.[22]

Guillain-Barré syndrome is the most severe, well-established adverse effect (AE) of influenza vaccines. An association has been observed for the 1976 pandemic swine flu vaccine, at a rate of 1 per 100,000 vaccinations,[23] with other studies reporting influenza vaccination as a risk factor. However, Guillain-Barré syndrome is also a rare complication of influenza itself, and investigations lasting several years have determined that vaccination has an overall protective effect against this neurological disorder.[24,25] Case-control studies of another auto-immune disease, narcolepsy, have shown increased risk among children who received ASO3 adjuvanted 2009 pandemic vaccine,[26,27] although the effect has not been consistent, and, like Guillain-Barré syndrome, the disease may be correlated with influenza itself.[28] Seasonal influenza vaccines do not contain squalene-based ASO3 adjuvant, which has been proposed to be the molecular trigger of this AE. It is consistent with studies of non-adjuvanted vaccine recipients in the USA who did not incur heightened risk,[29] but not with investigations into another squalene-based additive, MF59©, which did not discern any increase either,[30] making the cause of the complication less clear.

Other reported AEs, also mostly immunological in nature, have been researched to a lesser extent. They include, as reviewed in detail elsewhere:[31] 1) immune thrombocytopenic purpura, with conflicting studies,[32,33] and a possible association with influenza itself,[34] 2) oculo-respiratory syndrome, defined as bilateral conjunctivitis, facial edema and mild respiratory symptoms, with 2.9% attributable risk in 1 study,[35] 3) Bell's palsy, with highly varying effect sizes,[36-38] and a possible association with influenza itself,[39] 4) rheumatoid arthritis, with no association found,[36,40] 5) inflammatory bowel disease, with a hazard ratio of 1.25, only among early vaccination recipients in one study,[36] and 6) paresthesia, with an adjusted hazard ratio of 1.11, in the same study.[36] Overall, the evidence does not argue for the risk of severe complications among healthy recipients of the influenza vaccine.[41]

Several trials in long-term care facilities have demonstrated the benefits of HCW influenza vaccination for patient outcomes. The strongest effect was in all-cause mortality, with odds ratios of 0.56,[42] 0.70 (recalculated, unadjusted),[43] 0.61[44] and 0.80[45] for patients whose HCWs were allocated to the vaccination group. As discussed elsewhere,[46] the consistent effect on mortality contrasts with weaker results obtained with more specific outcomes, such as laboratory-confirmed influenza or respiratory diseases. Several factors could contribute, such as the worsening of underlying conditions by influenza infection, reduced herd immunity against co-infections, influenza-induced immunodepression and improper influenza diagnostics tools.

Prospective studies with robust designs are somewhat harder to undertake in the general acute-care population, since the much shorter exposure to risk in tertiary care would require very large cohorts. Case-control studies and open-label interventions to increase influenza vaccination have noted major reductions in the number of nosocomial respiratory illnesses when HCWs are vaccinated.[47-49]

### Recommendations

In light of this evidence, most official recommendations highly favor influenza vaccination of HCWs. All European countries but 1,[50] the Australian Communicable Diseases Network,[51] the US Centers for Disease Control and Prevention (CDC)[52] and the World Health Organization (WHO)[53] all recommend influenza vaccination of HCWs.

Despite a call by the Society for Healthcare Epidemiology of America,[54] and official coverage targets of 90% (USA)[55] and 75% (European Union (EU)),[56] no country has made it mandatory for now. Local regulations on mandatory HCW influenza immunization have been implemented, for example, in New York State and British Columbia province in Canada, but have run into legal challenges. Some states, such as California, require unvaccinated employees to sign a form declining vaccination.[57]

### Rates and determinants of HCW influenza vaccination

Despite these guidelines, vaccination rates remain low in most countries. **Table 2** reports HCW vaccination rates in different countries for the last 5 years. Vaccination coverage is higher in the USA and has been progressing for several years, perhaps because of more aggressive management policies with respect to influenza immunization.[58] In contrast, rates in Europe are lower and do not seem to have increased significantly over the years. Several factors influence the vaccination rate and single out target groups for vaccination campaigns. Men get vaccinated somewhat more often,[59] as do older workers.[59] Age can have other effects. For example, in a nation-wide Spanish survey,[60] among unvaccinated workers, being >35 years old was associated with an unwillingness to change one's mind and get vaccinated. Both the use of educational material and the presence of a vulnerable person at home had a lower association with decisions to change one's behavior after several years without vaccination. In European hospitals, physicians get vaccinated more often than nurses,[59,61,62] but the situation is different in the USA,[63] Korea[64-66] and Qatar.[67] The effect is also not found in primary care professionals.[60] Interestingly, the discrepancy is not seen with other vaccines, such as hepatitis B virus (HBV).[61] Vaccine uptake seems lower in long-term care facilities, [63] although most clinical trials have been conducted in them.

As expected, believing the vaccine is effective[59] and unlikely to cause significant AEs[68-72] is correlated with higher uptake. The conviction that influenza is a serious disease,[60,63] the willingness to prevent influenza transmission,[59,60,63,71] to protect oneself[59,60,63,71] and one's patients[59,60,71] are also correlated with vaccine uptake. However, the wish to protect oneself seems to have a greater effect than the desire to protect patients,[59] suggesting that selfish motivations might provide more leverage than altruistic reasons. This is in line with a survey showing that 95% of unvaccinated HCWs in a geriatric ward knew that influenza could kill their patients.[71] Other similar factors associated with higher uptake include the belief that influenza prevention is important,[59,73] suffering from a chronic condition[60,62] or having a high-risk person in one's household.[60,62]

In addition, the strong effect of habit has been found to be somewhat independent of intent,[74] indicating that convincing HCWs might not be enough. In a pilot Dutch study over 1 season,[73] 26.1% of HCWs who intended to get vaccinated eventually did not (they represented 5.2% of the total). In addition, while 52% of participants did not want to be vaccinated, final vaccine coverage was only 19.7%, making the case for more convenient vaccination programmes. In this regard, relevant organizational factors include the distribution of free vaccines[59,63] and the ability to arrange immunization at convenient times.[68,75]

### Policies to increase influenza vaccination rates

Different strategies are being adopted in hospitals worldwide to increase influenza vaccination rates among HCWs. Free vaccines, on-site vaccinations, mobile vaccination carts, walk-in vaccinations, educational materials, communication campaigns and declination forms have had a limited effect of less than 10 points in vaccination coverage,[57,76,77] with 1 exception yielding a 18 percentage point increase,[78] possibly due to the distribution of vaccine kits in units for on-site vaccination of colleagues.

One strategy that seems to have a strong effect is the requirement that all unvaccinated staff wear a mask when in contact with patients, to prevent transmission. An intervention, conducted in 2009 in a US healthcare network employing 161,000 people, combined such a mandate with previous policies and reported increased coverage (from 58 to 95% in 1 year).[79] Similar interventions in different settings, with the addition of manager accountability for coverage rates in some cases, have yielded good results.[80-84] One post-intervention survey established that employees explicitly cited the inconvenience and stigma of having to wear a mask as the strongest motivator to get vaccinated.[81] These multifaceted, sometimes logistically-challenging interventions have nevertheless been ascertained to be relatively inexpensive in industrialized countries, around US$ 20-30 per vaccine

**Table 2.** Vaccination coverage against influenza

| Country | Year | Setting | Type of staff | Respondents | Rate | References |
|---|---|---|---|---|---|---|
| China | 2010 | — | — | 576 | 11% | 218 |
| | 2011 | — | — | 576 | 12% | 218 |
| China (HK) | 2010 | H | — | 1,556 | 30% | 70 |
| Croatia | 2013 | — | — | — | 19% | 219 |
| France | 2009 | H | Direct-care | 451 | 35% | 61 |
| | 2009 | PC | MD | 1,431 | 78% | 220 |
| | 2010 | PC | MD | 1,431 | 77% | 220 |
| | 2011 | — | — | — | 28% | 221 |
| Germany | 2008 | — | — | 738 | 22% | 222 |
| | 2009 | — | — | 578 | 20% | 222 |
| | 2011 | — | — | — | 26% | 221 |
| Greece | 2008 | H | N | 606 | 21% | 223 |
| Hungary | 2011 | — | — | — | 41% | 221 |
| | 2013 | — | — | — | 29% | 219 |
| Ireland | 2013 | — | — | — | 30% | 219 |
| Italy | 2005 | — | Mixed | 5,336 | 21% | 224 |
| | 1990-2003 | — | N, ancillary | 13,989 | 13% | 225 |
| Lithuania | 2013 | — | — | — | 37% | 219 |
| Ireland | 2012 | — | — | — | 18% | 226 |
| | 2013 | — | — | — | 30% | 219 |
| Norway | 2011 | — | — | — | 14% | 221 |
| Poland | 2012 | — | — | — | 6% | 226 |
| | 2013 | — | — | — | 10% | 219 |
| Portugal | 2012 | — | — | — | 32% | 226 |
| | 2013 | — | — | — | 28% | 219 |
| Qatar | 2012 | H (1) | N, MD, Tc | 209 | 62% | 67 |
| | 2013 | H (1) | N, MD, Tc | 325 | 71% | 67 |
| Romania | 2011 | — | — | — | 64% | 221 |
| | 2012 | — | — | — | 54% | 226 |
| | 2013 | — | — | — | 42% | 219 |
| Singapore | 2010 | H | — | 284 | 43% | 70 |
| South Korea | 2008 | H | — | 8,827 | 58% | 64 |
| | 2009 | H | — | 8,996 | 61% | 64 |
| Spain | 2006 | — | — | 497 | 22% | 227 |
| | 2007 | — | — | 435 | 27% | 227 |
| | 2009 | — | — | 325 | 29% | 227 |
| | 2010 | — | — | 312 | 31% | 227 |
| | 2009 | PC | — | 2,625 | 58% | 60 |
| | 2010 | PC | — | 2,625 | 57% | 60 |
| | 2011 | PC | — | 2,625 | 53% | 60 |
| | 2012 | PC | — | 2,625 | 49% | 60 |
| | 2011 | — | — | — | 21% | 221 |
| | 2012 | — | — | — | 25% | 226 |
| | 2013 | — | — | — | 23% | 219 |
| UK (ENG) | 2010 | — | N | 522 | 37% | 228 |
| | 2010 | PC | N, MD | 205 | 36% | 229 |
| | 2011 | PC | MW | 266 | 43% | 230 |
| | 2012 | — | — | — | 45% | 226 |
| | 2013 | — | — | — | 46% | 219 |
| UK (NIR) | 2013 | — | — | — | 15% | 219 |
| UK (SCO) | 2013 | — | — | — | 34% | 219 |
| UK (WAL) | 2013 | — | — | — | 36% | 219 |
| USA | 2010 | — | Mixed | 16,975 | 52% | 231 |
| | 2010 | — | — | 1,860 | 60% | 232 |
| | 2011 | — | Mixed | 1,937 | 64% | 233 |
| | 2011 | — | — | * | 61% | 234 |
| | 2012 | — | Mixed | 2,348 | 67% | 235 |
| | 2013 | — | Mixed | 2,005 | 72% | 236 |
| | 2014 | — | Mixed | 1,949 | 75% | 237 |
| | 2014 | H | — | ** | 82% | 238 |
| India | 2010 | H (3) | — | 1,421 | <5% | 75 |
| Slovenia | 2010 | — | MD | 1,718 | 51% | 72 |

Setting: PC: primary care, H: hospitals, Tc: tertiary care. Numbers in parentheses represent number of hospitals in local surveys.
Type of staff: MD: medical doctors, N: nurses, MW: midwives.
Country: HK: Hong Kong, UK: United Kingdom, ENG: England, NIR: Northern Ireland, SCO: Scotland, WAL: Wales.
*Survey of 111 employers.
**4,254 employers, accounting for 8 million staff members.

administered,[85] which is cost-effective when accounting for reduced employee absenteeism.[20]

Mandatory influenza vaccination, with employment termination for unvaccinated employees without serious exemptions, is another frequently-used strategy endorsed in official recommendations.[54] This type of measure is mostly well-accepted.[86,87] In many instances, such mandates have been put in place after years of partially successful educational campaigns, and have resulted in coverage rates >95%,[88-91] even in 1 situation where it was low (<30%) before mandate implementation.[92] Terminations remained rare, around 1 per 1,000 employees at most.[88-92] However, low compliance can also occur, which makes enforcement difficult and fraught with legal challenges. This happened to a British Columbia province-wide mandate,[93] which, unlike the other examples discussed here, was enacted by a body not directly responsible for its local implementation.

## Measles, Mumps, Rubella

### Background and epidemiology

Measles, mumps, and rubella (MMR) are highly contagious viral infections that can result in severe complications, sequelae and congenital anomalies. The MMR vaccine, first licensed in 1971, is indicated for simultaneous vaccination in individuals ≥12 months of age. The Advisory Committee on Immunization Practices-recommended schedule of MMR vaccine is a 2-dose series at ages 12-15 months and 4-6 years.[94] With more than 575 million doses released in over 60 countries since its introduction, the MMR vaccine is the most widely-distributed combination vaccine world-wide.[95]

In the pre-vaccine era, MMR were considered as universal childhood diseases with peak incidence among 5-9-year-olds.[96] Reported cases of these 3 vaccine-preventable diseases declined considerably after the MMR vaccine was introduced in the late 1960s.[96] However, they can still be contracted, possibly because of suboptimal immunization levels.

*Measles*

Measles, one of the most transmissible of all human diseases, is caused by an RNA virus belonging to the *Paramyxoviridae* family. Humans are the only known reservoir of the virus. Measles is considered to be one of the most deadly vaccine-preventable diseases. Complications associated with measles include neurological (encephalitis), respiratory (pneumonia), ocular (keratoconjunctivitis) and gastrointestinal (diarrhea) manifestations as well as death. From 2000 to 2013, the world-wide annual incidence of measles was reduced by 72% (from 146 to 40 per million).[97] However, 92-95% vaccination coverage is required to achieve herd immunity and protect unvaccinated, susceptible individuals against measles.[98] Suboptimal vaccination rates can lead to regular outbreaks.

Europe is still far from a vaccine coverage rate of 95%.[99] It is probably the reason why this infectious disease has become more common since 2009, provoking several epidemic peaks throughout Europe. In 2011, measles outbreaks were reported by 36 of 56 European countries,[100] with France, Italy, Romania, Spain and Germany accounting for more than 90% of cases. From May 2014 to June 2015, 4,284 cases (74% unvaccinated) were reported by 30 EU/European economic area (EEA) states. One measles-related death and 9 encephalitis cases were noted during this period.[101]

The USA has documented the elimination of endemic measles with incidence rates of 1 case per 1,000,000 population reported since 2001.[102] The latest measles outbreak in the USA included 125 cases in California (n=110, 45% non-vaccinated) and neighboring states (n=15) after exposure in a Disney theme park.[103] Other outbreaks in the USA originated mainly from import-associated cases.[104] Increasing rates of vaccination refusal may be involved.[105]

*Mumps*

Mumps is a viral disease whose main target organ is the parotid salivary gland. Complications include encephalitis, meningitis, orchitis, oophoritis, deafness and pancreatitis.[106] The disease is no longer very common in the developed world, but outbreaks have struck both Europe and the USA. The latest mumps outbreaks in the USA occurred in Orthodox Jewish communities,[107] at university campuses in California[108] and in New York.[109] Similarly, several mumps outbreaks were reported in populations with vaccine coverage >80% in Europe,[110-112] stressing that the herd immunity threshold for mumps is about 90%.[98]

*Rubella*

Rubella is a rather mild infection in children but can become a serious concern in pregnant women due to the risk of congenital infection. In the WHO European region, rubella is still rather common with >11,000 cases and 17 congenital rubella syndrome infants.[113,114] During the first half of 2012, the number of rubella cases increased by 400% compared to the same period in 2011, with nearly all cases registered in Romania, Poland and the Russian Federation.[115] In contrast, rubella was considered eliminated in the USA in 2004, with a median of 11 rubella cases (range: 4-18) reported yearly from 2005 to 2011.[96] At least 85% of the population should be immune to rubella to prevent outbreaks.[104]

### Benefits and risks in healthcare settings

*Measles*

Nosocomial measles transmission is facilitated by its highly contagious nature (reproduction number ranging from 7 to 15),[116] and its ability to persist in aerosol suspension for at least 1 hour.[117] Compared to the general population, HCWs are estimated to be at 13- to 19-fold greater risk of acquiring measles.[117,118] Transmission from patients to unprotected HCWs can occur via infected individuals who seek medical care before developing clinically-recognizable disease, i.e., before rash onset. Thus, measles represents an occupational risk for HCWs. On the other hand, susceptible HCWs may expose their colleagues/patients to risk.

Nosocomial infections may be associated with a high risk of poor outcomes in hospitalized patients with chronic conditions, who are prone to complications from infectious diseases.[119,120] Many nosocomial measles cases have been reported in the literature during the last 2 decades.[117] As with other highly contagious diseases, nosocomial measles transmission may involve a large number of potential contacts that should be traced quickly for implementation of appropriate isolation measures to stop the within-hospital spread of the virus. In 2 studies, 84 and 110 subjects were respectively identified as having been exposed to index HCWs.[121,122]

*Mumps*

Mumps is no longer a common disease in most high-income countries. Nosocomial mumps outbreaks have been infrequent.[123] Transmission from one HCW to another occurred in a neonatal intensive care unit (ICU) in Syracuse, New York.[124] No nosocomial transmission of mumps has been documented in Europe in recent years.[125]

*Rubella*

There have been no cases of noscomial rubella transmission in Europe[125] and in the USA, where the disease's elimination was announced in 2004.[126]

*Vaccine-associated risks*

More than 25 AEs have been proposed to be linked with the MMR vaccine.[41] Those for which there is supporting evidence in adults include encephalitis in immunocompromised patients, anaphylaxis, and transient arthralgia.[41] The available evidence argues against widely-publicized side-effects, such as autism and type 1 diabetes.[41]

**Recommendations**

MMR vaccination is recommended for HCWs in some European countries,[125] the USA,[96] Canada,[127] Australia[128] and the Caribbean[129] while it is mandated in Finland[130] and for female HCWs in Slovenia.[131] The WHO has not provided any specific recommendations or evidence of measles immunity in HCWs.[132]

Currently-accepted proof of immunity includes documented administration of 2 MMR vaccine doses, laboratory evidence of immunity and laboratory confirmation of disease. Being born before 1957 is considered acceptable evidence of immunity.[126] In the USA, during nosocomial outbreaks, 1 or 2 doses of MMR vaccine are recommended for all unvaccinated HCWs without laboratory-confirmed disease or immunity against rubella and measles/mumps, respectively.[96]

**Vaccination coverage**

In 2013, world-wide coverage with measles-containing vaccine has been estimated to be 84%, ranging from 97% in the WHO Western Pacific region to 74% in India.[97] Few studies have reported MMR vaccine coverage in HCWs. In the Puglia region of southern Italy, MMR vaccine coverage among HCWs was 9.7%.[133] Self-reported vaccination rates of 23.3%, 23.3% and 29.8% were attributed to measles, rubella and mumps, respectively, among HCWs in Greece.[134] In a review by the European Center for Disease Control, coverage rates for 2 measles doses among HCWs were 43.6% and 62.3% in France and Denmark, respectively.[125] A measles coverage rate of 33.3% was reported at Edouard Herriot Hospital in Lyon, France.[135] Initiatives for improving vaccination coverage among HCWs in Europe include serological screening, pre-employment screening, and mandatory vaccination.[125]

Demonstrated susceptibility to measles among HCWs comes mainly from seroprevalence studies that have been the subject of a recent systematic review.[132] Overall, 6% of HCWs in Europe were seronegative for measles. This proportion rose to 9.2% in the Middle East and 10% in Asia and the western Pacific but was lower (3.5%) in a South African study published in 1990.[132] These authors found differences in seroprevalence according to age, with older people being less likely to be seronegative. In a study from Catalonia, Spain, the overall prevalence of susceptibility to mumps was 12.5%, with the highest proportion of susceptible HCWs (23.6%) being those aged <27 years.[136] In Greece, 25% of HCWs from 152 primary healthcare centers turned out to be susceptible to mumps.[134] Earlier studies recorded mumps susceptibility rates of 8-13% in HCWs in the USA.[137,138] Seroprevalence investigations of rubella have confirmed antibodies in 97.2% of HCWs. Workers aged <30 years had a high susceptibility.[139]

## Hepatitis B

**Background and epidemiology**

The prevalence of chronic HBV infections varies widely between countries, with higher rates in developing nations. Global incidence has declined from 4.2% in 1990 to 3.7% in 2005.[140] Nosocomial exposure is an important risk factor for HBV infection. In 2012, 20.7% of notified acute HBV infections were related to nosocomial exposure.[141] HCWs are particularly exposed to HBV because of frequent contact with blood and other bodily fluids.

**Benefits and risks in healthcare settings**

In the USA, it has been estimated that the number of HBV infections among HCWs declined from 17,000 in 1983 to 263 in 2010,[142] owing to the introduction of routine hepatitis B vaccination and improvements in healthcare practices.[143] Several recent outbreaks involving patient-to-patient HBV transmission have been recorded.[144-146] Outbreaks mostly occurred in renal ward/hemodialysis patients and were frequently related to lack of infection control measures.[145,146] Transmission from HCWs to patients has also been observed.[147] The risk of HCWs acquiring HBV infection is related to the extent of percutaneous or mucosal exposure to blood and other bodily fluids.

Several neurological syndromes, including multiple sclerosis and other demyelinating affections, have been suspected to be linked with hepatitis B vaccination.[41] However, there is no evidence to confirm this relationship.[41,148]

**Recommendations**

As part of standard precautions and other mechanical control measures, vaccination is a major tool for preventing HBV infections in HCWs. HBV vaccination is recommended for all HCWs, whatever their specialty, in high-income countries. For unvaccinated HCWs, or if no proof of vaccination is available, a 3-dose series (on days 0, 30 and 180) of Hepatitis B vaccines should be administered. Testing for antibodies against HBV surface antigen (HBs) is recommended 1-2 months after the 3rd dose for HCWs at high risk of blood exposures, to evaluate the response to vaccination.[142] Re-vaccination with at least 1 dose of HBV vaccine should be considered for non-responders after the 3-dose series. In developing countries, due to the high prevalence of HBV infection, a universal vaccination strategy is probably not enough to control the occupational risk of HBV. Prevention of occupational blood exposures should be emphasized.[149] In addition, management of percutaneous or mucosal blood exposure should include the use of soaps, antiseptics and testing of patient HBs status. Depending on the immune status of HCWs, vaccination should be considered as soon as possible after exposure.[142]

**Vaccination coverage**

Notwithstanding these recommendations, vaccination coverage against HBV remains suboptimal, albeit higher than with other recommended vaccines. For example, in Italy, vaccination coverage was 24.8% for influenza compared to 70.1% for HBV;[133] vaccination coverage of HCWs against HBV in the USA was 63.4%. [150] The vaccination rate was higher in French healthcare students (91.8%), probably because of mandatory vaccination. [151]

## Pertussis

**Background and epidemiology**

Whooping cough, a highly-transmissible respiratory disease caused by *Bordetella pertussis*, is life-threatening for unvaccinated infants and remains a public health concern, even in countries with high vaccine coverage. Pertussis was first recognized as an epidemic disease in the 16th century. In the pre-vaccine era, the calculated attack rate was 872/100,000, and the majority of cases were children <5 years of age.[152,153] On average, 5,000-10,000 deaths occurred per year; the death rate began to decline before anti-microbial therapy and vaccination.[152,154] Although precise quantitative data are lacking, available clinical case reports indicate that re-infections in atypical forms are common in adults.[152] Incidence and mortality were reduced dramatically (>90%) in the industrialized world after large-scale vaccination during the 1950's and 1960's. However, the disease is still endemic nowadays, and pertussis cycles are witnessed every 3-5 years, even in regions with high vaccine coverage. Between-cycle intervals as well as disease intensity and incidence during cycles present variations that are not well-understood. Outbreak cycles may, therefore, result from the continued transmission of pertussis among adolescents and adults, with passage to susceptible infants (unimmunized or partially immunized).[155,156] In Western countries during the last few decades, there has been a shift of peak incidence from children to adolescents, adults and infants aged <1 year.[155-158] The number of pertussis cases has generally risen since the 1990s. Recent reports from around the world suggest that more pertussis cases are occurring in adolescents and adults than can be explained by better observation and better diagnostic methods, and experts differ on the role of several potential explanatory factors, including strain changes, clustering of susceptible individuals, and differences in efficacy profiles between acellular and whole-cell vaccines.[156,158,159] To date, no evidence of widespread pertussis resurgence exists. However, the SAGE Pertussis Working Group provided proof of resurgence in 5 of 19 countries reviewed.[158]

**Benefits and risks in healthcare settings**

Pertussis outbreaks in nosocomial settings are well-described in many countries with more than 30 reported nosocomial outbreaks.[160-162] The index cases were often found among healthcare staff, and *B. pertussis* transmission occurred more frequently among colleagues than between HCWs and their patients.[160-162] HCWs and patients may serve as pertussis sources in nosocomial outbreaks, which can result in substantial morbidity and constrain infection control measures.[160-162] Pertussis HCW immunization, testing and limitation of patient contact in case of prolonged cough could reduce the morbidity of pertussis outbreaks.[160-162] Currently, no RCT data support the effectiveness of pertussis vaccination in HCWs to prevent outbreaks and infant morbidity/mortality.[160-163] Furthermore, there are no approved protection correlates for pertussis vaccines.[164] However, recent modeling approaches are confirming that booster vaccination of pediatric HCWs is an effective intervention to reduce the risk of pertussis transmission[165] and is cost-effective or cost-saving, even at low coverage levels.[166]

Pertussis transmission from HCWs to their patients has been documented. A 2014 study found that between 2002 and 2011, in a large quaternary pediatric care network, a total of 1,193 confirmed exposures were linked to 219 index cases. Of these, 38% were infants <6 months old, and 7 were HCWs. Most exposures (77.5%) occurred in emergency departments or at ambulatory sites; 27.0% of exposures transpired after documented infection control intervention.[167] In a recent study among Spanish HCWs, the seroprevalence of anti-pertussis antibodies was 51.7%, and the incidence of recent infection, estimated by anti-pertussis toxin antibodies, was 15%. [168] This prevalence of recent infection concurs with previous investigations.[169,170]

No evidence has been documented on the effect of vaccination among HCWs in averting transmission to newborns and/or infants, but many case and outbreak reports have demonstrated their role in nosocomial pertussis transmission. Transmission has also been tracked from HCWs after tetanus, diphtheria, and pertussis (Tdap) administration in the previous 3 years,[159] showing that the vaccine is only partially effective.

Comparative data on AEs are sparse. Immuno-neurological manifestations, the most publicized type of serious vaccine-related AEs, are not increased by acellular pertussis vaccine,[171,172] and no other significant AEs have been found to be caused by it.[41]

### Recommendations

To control these risks, public health authorities have introduced vaccine recommendations for HCWs. HCW vaccination with pertussis-containing vaccine is recommended in many countries. [50,130,173] This may include either all HCWs or special groups of HCWs for whom close contact with pregnant women, newborns and infants is assumed, such as pediatricians or obstetricians.

Aside from personal protection, vaccination of HCWs is recommended in many countries to fulfil legal requirements minimizing potential exposure of patients to infectious agents. In countries where vaccination of adults is recommended for either universal or special groups, HCWs should be highly prioritized for vaccination. In countries where no adult programs exist, their implementation would be difficult logistically.[50,130]

Recommendations favor HCW pertussis vaccination in Belgium, Germany, Luxemburg, the Netherlands, and the UK. In Austria, Finland, and Norway, vaccination is recommended for pediatricians and HCWs in neonatal departments, whereas in France it is only recommended for HCWs involved in direct patient care. In other European countries, no recommendations are in place for pertussis vaccination of HCWs.[50]

### Vaccination coverage

Recent publications have provided data on vaccine coverage against pertussis among HCWs. Globally, the reported vaccine coverage varies from 14.4% to 72.7%.[135,151,174-178] In France, HCW vaccination coverage in published studies ranges from 12 to 66% in different settings: pediatric, obstetric, internal medicine and ICUs.[135,175,177,178] A French national survey of HCWs in 2009 reported 11.4% pertussis vaccine coverage.[61] Among healthcare students, coverage was high for compulsory vaccinations, but largely insufficient for recommended ones, such as pertussis, varying from 44 to 72%.[151,176]

### Policies to increase pertussis vaccination rates

Two recent publications ascertained the effect of active intervention in implementing mandatory vaccination against pertussis. A 1-year active campaign in a group of hospitals strongly increased coverage among HCWs in high-risk areas, from 50 to 98.6% (100% when accounting for legitimate exemptions). The final figure for all medical workers was 97.6% (100% with exemptions), while it was 88.3% (90%) among non-medical (volunteer) staff.[179] In the University of North Carolina Health Care Network, the Tdap vaccine was recommended for all healthcare personnel who provided direct patient care unless medically contraindicated. [180] Employment was made conditional upon Tdap vaccination. Implementation among newly-hired employees quickly resulted in complete compliance, but achieving adherence among previously-hired workers required setting a deadline for non-compliance.

## Tetanus, Diphtheria

### Background and epidemiology

Most tetanus cases are birth-associated and occur in developing countries among newborn babies or their mothers owing to poor peri- and post-natal hygiene. Tetanus in children and adults after injuries constitutes a considerable public health problem.

Tetanus, a sporadic and relatively uncommon infection in EU/EEA countries, as in other developed nations, is caused by the bacterium *Clostridium tetani*. Contamination of wounds with tetanus spores in unimmunized persons can evoke illness with muscular spasms and sometimes death. Tetanus is included in the primary vaccination schedule of all EU/EEA countries, and periodic boosters in adulthood are required to maintain immunity.[156]

Tetanus appears to be under control in all EU/EEA countries, thanks to good general hygiene and effective universal vaccination.[156] The total number of reported cases remains very low (0.03 per 100,000 population). The highest rate was documented in Italy (0.09 per 100,000), and elderly women (65 years or older) were affected the most. To prevent future outbreaks of diphtheria in Europe, efforts must continue to maintain national capacities for rapid case identification. Furthermore, immunisation programmes should be shielded from budgetary constraints to maintain high diphtheria routine and booster vaccination coverage, especially in adult and elderly populations.

Diphtheria is a very rare disease in the EU and in other developed countries. It is caused by *Corynebacterium diphtheriae* and *Corynebacterium ulcerans*. It usually produces respiratory symptoms, although some forms affect other organs, including the skin. Certain strains are toxin-producing and can be lethal. Diphtheria is largely under control in Europe.[156] In 2012, 27 diphtheria cases were reported across EU/EEA countries, with a notification rate of 0.01 per 100,000 population. The majority of *C. diphtheria* cases are 45-64-year-olds, while the majority of *C. ulcerans* cases are ≥65-year-olds. High vaccination coverage must be sustained, adult booster coverage increased, and epidemiological surveillance and laboratory capacity maintained.

More than 25 AEs have been proposed to be linked to the vaccine, anaphylaxis being the only one with supporting evidence.[41] A case of Guillain-Barré syndrome has been reported[181] but increased risk of this and other serious AEs has not been confirmed by small cohort studies[182,183] or larger scale data.[41,171,172,184,185] The vaccine could have a protective effect against multiple sclerosis. [148]

### Recommendations

Recommendations regarding tetanus-diphtheria vaccine vary across countries for HCWs and the general population.[50,130,173] 13 European countries recommend it, 16 do not, and 1 (France) has made it mandatory for the entire population. The USA also recommends it for HCWs with undocumented vaccination status.[186] In general, there are no specific recommendations for HCWs (compared to the general population).

## Vaccination Coverage

Recent publications report vaccine coverage among HCWs that varies from 35.7% to 66% in different settings: pediatric, obstetric, internal medicine and ICUs.[134,175,177,187,188] A French national survey of HCWs in 2009 recorded 95.5% coverage for the diphtheria-tetanus (DT) vaccine.[61] In the CDC's 2007 National Immunization Survey, 70.4% of HCWs received tetanus vaccination in the past 10 years.[189] In French healthcare students, vaccination coverage was high because of compulsory vaccinations, such as tetanus and diphtheria, varying from 96.7 to 96.9% for DT vaccination.[151,176]

Protective antibody titers have been defined and validated as a correlate of protection against tetanus and diphtheria,[164] so that seroprevalence data can provide reliable information on protection among HCWs. Protective antibody values against diphtheria were found in 89.2% (83.3%-91.5%) of 250 Thai HCWs, growing to 97.2% (95% CI: 95.1%-99.3%) after DT booster administration[190] and demonstrating the effectiveness of booster vaccination in maintaining protective antibody levels. A seroprevalence study of tetanus and diphtheria was carried out in 537 HCWs in Catalonia, Spain.[191] The prevalence of protective antibodies was 93.9% (95% CI: 91.5-95.7) against tetanus and 46.4% (95% CI: 42.1-50.7) against diphtheria, with lower rates found in people born before 1975.

## Varicella

### Background and epidemiology

Varicella-zoster virus (VZV) is one of the herpes viruses. It is responsible for chickenpox in primary infections (mostly in children, teenagers and young adults) and for herpes zoster (mostly in older people) when it reactivates, after a latent period in sensory nerve ganglia. Epidemiology varies between temperate/climate areas, where transmission is seasonal (winter-spring) and affects young children, and tropical areas, where infections occur later, resulting in higher rates of susceptible adults in tropical regions.

VZV is a highly-contagious, widespread virus. Infection during childhood induces long-lasting immunity; thus, seroprevalence of anti-VZV IgG antibodies in adults ranges from 90 to 100%, [192] although it may be lower in people living in or native to tropical countries. [193] Although still endemic, VZV prevalence is starting to decline because of varicella vaccine implementation in some countries. Consequently, increased varicella incidence in adults, including HCWs, is likely in these countries.

### Benefits and risks in healthcare settings

Varicella transmission in healthcare settings from HCWs to susceptible patients has been reported, mostly in tropical countries,[194] or in HCWs who received only 1 vaccine dose.[195]

HCW susceptibility is country-dependent, and ranges from 5%[196] to 50%.[197] Special attention should focus on medical students who represent the most susceptible population.

Infection control measures should be set up as soon as the first nosocomial case is diagnosed – to mitigate the risk of exposure and secondary cases.[198] Both varicella zoster intravenous immunoglobulin and varicella vaccine can be provided as post-exposure prophylaxis.

Varicella vaccine, a live-attenuated vaccine licensed since the mid-1990's, is available alone (monovalent) or associated with the MMR vaccine. Vaccine immunogenicity after 2 shots is above 95%. No booster doses are recommended so far. VE is estimated to be around 85%.[199] AEs for which there is evidence include: anaphylaxis, systemic infection by the live-attenuated vaccine Oka VZV strain with organ lesions in individuals with demonstrated immunodeficiencies, and vaccine strain viral reactivation with or without meningitis or encephalitis.[41,200,201] In addition, case reports of granulomatous dermatitis,[202] rash[203] and optic neuritis[204] have been published but the putative risk increase has not been confirmed by large scale comparative data.[41,200,201,205] At least 1 fatal systemic infection in an immunocompromised patient[206] has been observed. Less widespread types of VZV vaccines seem to have a good safety profile.[207,208]

### Recommendations

Recommendations vary from country to country: vaccination may be recommended for all HCWs (Belgium, Ireland, Spain, Sweden, Switzerland, USA), may prioritize HCWs in contact with high-risk patients (Austria, Finland, France, Germany, Italy, UK), or may not be recommended at all (Denmark, Netherlands, Portugal, Poland).[50] Some countries recommend universal varicella vaccination for children (USA, Australia, Canada, Costa Rica, Germany, Greece, Korea, Qatar, Saudi Arabia, Spain, Switzerland, United Arab Emirates, and Uruguay).

Some data suggest that varicella vaccine recommendations are not very well-known by HCWs,[209] partly because of unawareness of the vaccine itself or because of ignorance of their immune status relative to VZV.

### Vaccination coverage

Seroprevalence of anti-VZV IgG antibodies in adults ranges from 90 to 100% in Western countries,[192] but is probably lower among people who have lived in tropical countries during their childhood.[193]

Varicella vaccine coverage depends on vaccine recommendations for people entering the healthcare workforce. It is usually above 95% in countries where the vaccine is recommended for children (combined with the MMR vaccine). Vaccine coverage is low (<5%) in countries with recommendations for seronegative adults, because most people have already encountered the virus by the time they reach vaccination age. Nevertheless, healthcare students merit consideration, because they may be the most at-risk group of susceptible HCWs and because they may be neglected by healthcare-setting vaccination policies.[210]

## Ethical Issues Associated with HCW Vaccination

The role of institutions in terms of promoting or mandating vaccination is the subject of ongoing ethics debates. The main principles that have been invoked are autonomy, beneficence, non-maleficience, fairness and virtue ethics.[211] The main levels at which ethical decisions must be made are individual,[212] institutional[213] and governmental.[214]

Judging HCW vaccination by any ethical standard requires good assessment of empirical and theoretical evidence of each vaccine's benefits and risks, the lack of which is the most common cause of opposition to vaccination by individual HCWs. When benefits are low to moderate and risks are negligible, which is actually the case with most vaccines, all frameworks would recommend active educational campaigns and a mandate for alternative infection control measures for unvaccinated professionals. All frameworks could accomodate a mandatory vaccination policy with termination of employment for offenders,[211] but it should be preceded by a successful educational campaign for most of them, and a general consensus should be reached before the implementation of a mandate.[215,216] This is especially true when considering that a mandate without a consensus can lead to a serious backlash against vaccines in general.[217]

## Conclusion

Nosocomial transmission of vaccine-preventable diseases can be avoided thanks to immunization. The ideal coverage is dynamic for each disease, depending on the effective reproductive rate, which itself varies with the level of herd immunity in the population (from vaccination and infection), and the density of contacts. Improving vaccine coverage among HCWs is challenging, but benefits patients who might face contagious HCWs as well as HCWs who provide care to contagious patients.

In order to reach good immunization rates, we must acknowledge that vaccines have benefits and risks, about which misunderstanding or misinformation can occur among healthcare communities, as in the rest of the population. Education and academic leadership play a role here, but other interventions can be useful and must continue to be tried and implemented. Public education on vaccines may take a more operational approach in the future, perhaps translating to the general public some of the strategies that have proved successful in HCWs.

In addition to vaccination, traditional infection control measures also have a role to play; the adequate balance between them and their synergistic effects should be further investigated.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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