Supplement

Future MICROBIOLOGY

Risk of transmission of vaccine-preventable diseases in healthcare settings

Lara Tavoschi[1], Filippo Quattrone[1], Antonella Agodi[2] & Pier L Lopalco*,[1]
[1]Department of Translational Research & New Technologies in Medicine & Surgery, University of Pisa, Via Savi, 10, 56126, Pisa, Italy
[2]Department of Medical & Surgical Sciences & Advanced Technologies 'GF Ingrassia', University of Catania, via S. Sofia, 87, 95123, Catania, Italy
*Author for correspondence: pierluigi.lopalco@unipi.it

The transmission of infectious agents within healthcare settings is a priority public health problem. Although the main burden of healthcare-associated infections is commonly caused by Gram-negative bacteria and fungi, vaccine-preventable diseases represent an additional infectious risk for patients attending healthcare facilities. Hepatitis B, rotavirus gastroenteritis, influenza, measles, pertussis and pneumococcal and meningococcal invasive bacterial infections still represent a threat, notwithstanding the presence of universal vaccination programs. For this reason, healthcare worker immunization is an important strategy to limit the risk of vaccine-preventable diseases in such a fragile population.

First draft submitted: 21 August 2018; Accepted for publication: 22 March 2019; Published online: 18 June 2019

Keywords: healthcare-associated infection • outbreak • vaccine-preventable disease

The transmission of infectious agents within healthcare settings is a priority public health problem, largely linked to hospital-acquired infections with a number of Gram-negative (such as *Pseudomonas* spp., *Acinetobacter* spp., *Escherichia coli*, etc.) and Gram-positive bacteria (such as *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*), as well as fungi (such as *Candida* spp., *Aspergillus* spp., etc.) and viruses (such as *Norovirus*) [1,2]. In addition, the circulation of infectious agents within healthcare facilities represents one of the most important drivers of antimicrobial resistance [3].

The risk of acquiring a vaccine-preventable disease (VPD) following contact with healthcare settings is not perceived to be particularly high. This is probably due to the fact that VPDs are traditionally associated with childhood diseases that are primarily community spread. On the other hand, during the last few decades the list of VPDs has grown quickly, and immunization has become a life-long practice. For example, diseases such as rotavirus (RV) gastroenteritis – for which nosocomial spread represents a significant burden – recently became vaccine preventable [4].

Community-based immunization programs have greatly reduced the burden of VPDs, but the risk of acquiring a VPD can only be considered to be close to zero when disease eradication or elimination is achieved. For this reason, attending healthcare settings still represents an additional risk for susceptible individuals.

This paper is a narrative review of the evidence on risk of transmission of VPDs in healthcare settings.

Hepatitis B

Despite considerable improvements in blood supply safety and infection control, nosocomial and iatrogenic HBV transmission is still an issue, at least in some EU/EEA countries [5]. Such transmission accounts for 18.6% of all acute HBV cases, and for 40.4% of chronic cases reported in the EU/EEA in 2016, mostly in Italy and Romania [6], and can therefore result in outbreaks in healthcare settings [7–12]. Although the risk of developing chronic HBV infection decreases in older childhood and adulthood, acute hepatitis B and fulminant infection is of concern, especially among patients with co-infections, other co-existent diseases and concomitant medications [13]. Case fatalities were reported in a few outbreak investigation reports, underscoring the disease burden and the impact of such occurrences [7,8].

Future Medicine

The progressive introduction of HBV universal infant vaccination programs (UVPs) in Europe since the 1980s has proven to be successful [14]; however, data on coverage and impact of targeted vaccination for healthcare workers (HCWs) are limited. According to a recent review of published HCW–patient transmission incidents, cases have been relatively rare and have substantially decreased in frequency over the past four decades due to a combination of factors, including screening and vaccination of staff and better infection control practices [15].

However, HBV outbreak investigations in North America and Europe point toward failure of healthcare personnel to adhere to fundamental principles of infection control and aseptic technique. Blood glucose testing was identified as the main putative mechanism of person-to-person transmission in a range of healthcare settings, including community healthcare facilities, nursing homes and hemodialysis centers [8–10].

Influenza

Influenza poses a special hazard within healthcare facilities, and can cause outbreaks of illness. Person-to-person transmission of influenza-like illness (ILI) and influenza has been described extensively in the literature as occurring in long-term care facilities, especially among the frail and the elderly, as well as in acute hospital settings [16–18]. However, accurate estimates of the burden of nosocomial influenza or ILI are limited.

Although HCWs are at risk of acquiring influenza and may serve as a reservoir for the patients, multiple routes of nosocomial transmission are possible, as transmission links between single patients and HCW–patient show [16–18]. A prospective study assessed the risk of hospital-acquired ILI among patients hospitalized in several short-term units of one US hospital. The estimated risk ratio increased from 5.5 to 17.9, and to 34.7, if the patient had been exposed to one contagious HCW, one contagious patient or one HCW and one contagious patient, respectively [17]. A review of the occurrence of outbreaks of ILI in acute healthcare settings reports cases in a variety of different wards, including ICUs, with attack rates ranging from 25 to 50% [18]. Fatalities during nosocomial outbreaks have also been reported, although mortality rates vary according to the affected patient population and circulating strain [18].

Despite the availability of a number of infection control measures that may be applied in combination, such as treatment of infected patients and patient isolation, the preventive role of HCW vaccination on virus circulation and influenza incidence among patients may merit further consideration. According to recent studies, vaccine efficacy among vaccinated HCWs was estimated to be above 80%, much higher than that among hospitalized patients in the same setting [19], and was associated with a protective effect on hospitalized patients, at least in long-term care facilities [20,21]. However, the reported coverage of vaccination among healthcare professionals in Europe is low [22], and often perceived as a personal protection measure rather than a patient safety one [23]. Several interventions to increase vaccination uptake have been proposed [24], including compulsory vaccination for HCWs working with high-risk patients [23,24].

RV infection

RV is the leading cause of dehydrating gastroenteritis and is responsible worldwide for 40% of the hospitalizations for diarrhea in children under 5 years old [25,26]. RV is highly contagious due to its long survival in the environment, its resistance to antiseptic products and the low viral load necessary to sustain infection. Pediatric wards are at increased risk of nosocomial transmission because they are a hub for severe RV cases [25,26]. An accurate estimate of the incidence of nosocomial RV (nRV) infection is hard to obtain due to the lack of active surveillance and methodological divergences among studies. A recent meta-analysis, however, found that before UVPs, incidence of nRV in Europe and North America was 0.4 cases per 100 hospitalizations, and 0.7 for children less than 5 years of age [25]. The availability of live-attenuated vaccines against RV and their inclusion in UVPs offers new opportunities to prevent nRV. UVPs are significantly affecting the burden of RV disease. A decline of 62–78% for hospitalizations and 57% for emergency department (ED) visits due to RV has been observed in the USA [26]. Two studies reporting data from an American and an Austrian single center found a significant decrease (67 and 92%, respectively) for nRV after the implementation of UVP [27,28].

Where RV vaccination levels are still low, another approach to prevent nRV could be the targeted immunization of eligible subjects at increased risk of severe disease (e.g., infants born prematurely, with low birth weight or with other high-risk medical conditions) [29]. Given the theoretical risk of nosocomial transmission of vaccine-type RV, vaccination is now recommended only at or after discharge from neonatal care settings. A recent study found no vaccine-type RV transmission among unvaccinated age-ineligible infants admitted to an urban academic ICU where eligible infants were vaccinated against RV [29]. This evidence could lead to new opportunities for RV vaccination and prevention of nRV in high-risk subjects.

Pertussis

Nosocomial pertussis is a potential threat, mostly in pediatric healthcare facilities [30]. HCWs, visitors, parents and patients with delayed diagnosis have been identified as sources of nosocomial outbreaks [30]. Several factors may combine to heighten the risk of pertussis transmission in this setting; for example, the high prevalence of susceptible subjects such as infants too young to be vaccinated or immunocompromised patients; behavioral activities of young children (e.g., sharing of toys) and the frequent visits of family members that may be a source of transmission, considering that colonization with *Bordetella pertussis* may be unrecognized among vaccinated adolescents and adults and may be present among individuals belonging to some religious or ideological groups that refuse vaccinations [30,31]. In addition, pediatric HCWs are at 1.7-fold greater risk for acquiring pertussis compared with the general population, due to occupational exposures and waning immunity [30]. Although effective prevention of pertussis in healthcare needs multiple concomitant actions (e.g., education of HCWs and visitors, limitation of contact among patients, correct respiratory hygiene, high suspicion in case of persistent whooping cough), immunization is considered the key preventive intervention. Due to the limited and waning effectiveness of the pertussis vaccine, the choice of the correct vaccination strategy is essential. Together with vaccination of close contacts of infants (cocoon strategy), vaccination of pregnant women and booster vaccinations in adolescents, vaccination of HCWs is emerging as an effective strategy to prevent pertussis in infants [30]. This has been confirmed by a recent meta-analysis that found moderate evidence that tetanus–diphtheria acellular pertussis vaccines for HCWs were effective in preventing pertussis in all age groups, and specifically in infants [32].

Measles (Rubeola virus)

Measles (Rubeola virus) is one the most contagious human diseases [33]. Despite the current global effort for its elimination, suboptimal immunization levels still lead to recurrent outbreaks even in industrialized countries [34]. Hospital outbreaks are common, and both cases of transmission from patients to HCWs, and from HCWs to patients have been described. Measles can, moreover, spread from a hospital setting to the community. A recent review reporting outbreaks involving hospitals found that 22% of total cases could be classified as nosocomial [35]. Nosocomial measles has high mortality and morbidity rates because of the underlying frailty of the subjects involved [35].

Healthcare settings are vulnerable for different reasons, including crowded and often inadequately ventilated places such as the ED, triage wards, waiting rooms and physicians' offices are an ideal setting for the spread of airborne diseases; measles can persist in aerosol suspension for at least 1 h, and infection is, therefore, possible even if the index case has left the hospital; measles is contagious before the onset of the characteristic rash and often requires access to the ED due to acute but aspecific symptoms, such as high fever, conjunctivitis and coryza. This can lead to delayed diagnosis and subsequent delayed adoption of isolation measures; and suboptimal immunization has increased the mean age of susceptible subjects, so that unvaccinated young adults (and, for the most part, HCWs are in this category), represent an at-risk population [35].

The active offer of two-dose vaccination, along with recording of the immune status of all workers within a hospital, including hospital personnel not in direct contact with patients [36], and notification of all suspected cases, represent the most efficacious preventive measures against measles. In the case of an outbreak, prompt implementation of respiratory isolation, the offer of postexposure prophylactic vaccination or immunoglobulins, and exclusion of susceptible HCWs from the workplace can help prevent further spread of the disease [35,37].

Nosocomial transmission represents a real public health threat that potentially contributes to the spread of the disease in endemic areas and to its reintroduction in regions where it had been previously eliminated [34,35]. It, therefore, deserves intensive monitoring and prevention efforts.

The use of combined vaccines against measles, mumps, rubella (German measles) and varicella (chickenpox) can help in preventing these diseases that can also cause nosocomial outbreaks and transmission from HCWs to patients [21,38–40].

Meningococcal & pneumococcal infections

The burden of nosocomial pneumococcal infections has not been described extensively. A study from Finland indicated a substantial proportion of reported cases of invasive pneumococcal diseases to be hospital acquired [41]. Likewise, reports of meningococcal disease spread in-hospital are very rare and risk is considered quite low [42].

Data on coverage and effectiveness of pneumococcal and meningococcal vaccination for HCWs are limited in the scientific literature [43], as are policy options. In any case, the vaccination of HCWs has limited efficacy on

patient safety due to suboptimal effectiveness of vaccination on carriage [44,45]. Universal respiratory precautions are generally considered sufficient to prevent transmission in healthcare settings.

Future perspective

Both immunological and epidemiological factors make the risk of spread of VPDs in healthcare settings particularly high, and VPD outbreaks are not rare. UVPs limit the risk of healthcare-associated outbreaks of diseases such as HBV and RV, by reducing the spread of the infectious agent within the community. On the other hand, the spread of airborne diseases such as influenza, measles or pertussis is very difficult to prevent if a susceptible population is confined in a closed space like healthcare settings, and the infectious agent still circulates in the community. Immunization of HCWs is an important strategy to limit the risk of such VPDs and improving vaccination coverage among HCWs is a priority. The ongoing development of vaccines targeting other typical nosocomial pathogens such as *Clostridium difficile*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* are promising, and in the near future may become a valid support to limit infection risk in the ICU [46].

Executive summary

- The risk of acquiring a vaccine-preventable disease (VPD) within a healthcare setting is not commonly perceived to be particularly high.
- Epidemiological and demographic factors make VPDs an additional infectious threat in healthcare settings.
- Preventing VPDs in healthcare settings is important both to improve patients' safety and to prevent healthcare facilities become a hub of VPD diffusion.
- The immunization of healthcare workers is an important strategy to limit the risk of VPDs within fragile populations.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Weiner LM, Webb AK, Limbago B *et al.* Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect. Control Hosp. Epidemiol.* 37, 1288–1301 (2016).

• **Describes antimicrobial resistance patterns for healthcare-associated infections that occurred during the period of 2011–2014 in the USA.**

2. Cassini A, Plachouras D, Eckmanns T *et al.* Burden of six healthcare-associated infections on European population health: estimating incidence-based disability-adjusted life years through a population prevalence-based modelling study. *PLoS Med.* 13(10), e1002150 (2016).

3. Khan A, Miller WR, Arias CA. Mechanisms of antimicrobial resistance among hospital-associated pathogens. *Expert Rev. Anti Infect. Ther.* 16(4), 269–287 (2018).

4. World Health Organization. Rotavirus vaccines WHO position paper – January 2013. *Wkly Epidemiol. Rec.* 88, 49–64 (2013).

5. Stępień M, Zakrzewska K, Rosińska M. Significant proportion of acute hepatitis B in Poland in 2010–2014 attributed to hospital transmission: combining surveillance and public registries data. *BMC Infect. Dis.* 18(1), 164 (2018).

6. European Centre for Disease Prevention and Control. Hepatitis B – annual epidemiological report for 2015. https://ecdc.europa.eu/en/publications-data/hepatitis-b-annual-epidemiological-report-2015-0

7. Seiz PL, Slanina H, Ziebuhr J, Gerlich WH, Glebe D, Schüttler CG. Studies of nosocomial outbreaks of hepatitis B in nursing homes in Germany suggest a major role of hepatitis B e antigen expression in disease severity and progression. *Int. J. Med. Microbiol.* 305, 663–672 (2015).

8. Duffell EF, Milne LM, Seng C *et al.* Five hepatitis B outbreaks in care homes in the UK associated with deficiencies in infection control practice in blood glucose monitoring. *Epidemiol. Infect.* 139, 327–335 (2011).

• **Review reporting a series of hepatitis B outbreaks in healthcare facilities associated with malpractice in blood glucose monitoring.**

9. Thompson ND, Perz JF, Moorman AC, Holmberg SD. Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998–2008. *Ann. Intern. Med.* 150, 33–39 (2009).
10. Zheteyeva YA, Tosh P, Patel PR *et al.* Hepatitis B outbreak associated with a home health care agency serving multiple assisted living facilities in Texas, 2008–2010. *Am. J. Infect. Control* 42, 77–81 (2014).
11. Burns K, Heslin J, Crowley B *et al.* Nosocomial outbreak of hepatitis B virus infection involving two hospitals in the Republic of Ireland. *J. Hosp. Infect.* 78, 279–283 (2011).
12. Pourkarim MR, Verbeeck J, Rahman M *et al.* Phylogenetic analysis of hepatitis B virus full-length genomes reveals evidence for a large nosocomial outbreak in Belgium. *J. Clin. Virol.* 46, 61–68 (2009).
13. World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. *Wkly Epidemiol. Rec.* 92(27), 369–392 (2017).
14. Miglietta A, Quinten C, Lopalco PL, Duffell E. Impact of hepatitis B vaccination on acute hepatitis B epidemiology in European Union/European Economic Area countries, 2006 to 2014. *Euro. Surveill.* 23(6), doi:10.2807/1560-7917.ES.2018.23.6.17-00278 (2018) (Epub ahead of print).
15. Lewis JD, Enfield KB, Sifri CD. Hepatitis B in healthcare workers: transmission events and guidance for management. *World J. Hepatol.* 7, 488–497 (2015).
16. Vanhems P, Bénet T, Munier-Marion E. Nosocomial influenza. *Curr. Opin. Infect. Dis.* 29, 366–372 (2016).
17. Vanhems P, Voirin N, Roche S *et al.* Risk of influenza-like illness in an acute health care setting during community influenza epidemics in 2004–2005, 2005–2006, and 2006–2007. *Arch. Intern. Med.* 171, 151–157 (2011).
18. Salgado CD, Farr BM, Hall KK, Hayden FG. Influenza in the acute hospital setting. *Lancet Infect. Dis.* 2, 145–155 (2002).

• **Review of the risk of transmission of influenza in hospital settings.**

19. Vanhems P, Baghdadi Y, Roche S *et al.* Influenza vaccine effectiveness among healthcare workers in comparison to hospitalized patients: a 2004–2009 case–test, negative–control, prospective study. *Hum. Vaccin. Immunother.* 12, 485–490 (2016).
20. De Serres G, Skowronski DM, Ward BJ *et al.* Influenza vaccination of healthcare workers: critical analysis of the evidence for patient benefit underpinning policies of enforcement. *PLoS ONE* 12(1), e0163586 (2017).
21. Sydnor E, Perl TM. Healthcare providers as sources of vaccine-preventable diseases. *Vaccine* 32, 4814–4822 (2014).
22. Wicker S, Marckmann G. Vaccination of health care workers against influenza: is it time to think about a mandatory policy in Europe? *Vaccine* 32, 4844–4848 (2014).
23. Giannattasio A, Mariano M, Romano R *et al.* Sustained low influenza vaccination in health care workers after H1N1 pandemic: a cross sectional study in an Italian health care setting for at-risk patients. *BMC Infect. Dis.* 15, 329 (2015).
24. Hollmeyer H, Hayden F, Mounts A, Buchholz U. Review: interventions to increase influenza vaccination among healthcare workers in hospitals. *Influenza Other Respi. Viruses* 7, 604–621 (2013).
25. Bruijning-Verhagen P, Quach C, Bonten M. Nosocomial rotavirus infections: a meta-analysis. *Pediatrics* 129, e1011–e1019 (2012).

•• **Meta-analysis of the risk of outbreaks of rotavirus in healthcare settings.**

26. Gervasi G, Capanna A, Mita V, Zaratti L, Franco E. Nosocomial rotavirus infection: an up to date evaluation of European studies. *Hum. Vaccin. Immunother.* 12, 2413–2418 (2016).
27. Anderson EJ, Rupp A, Shulman ST, Wang D, Zheng X, Noskin GA. Impact of rotavirus vaccination on hospital-acquired rotavirus gastroenteritis in children. *Pediatrics* 127, e264–e270 (2011).
28. Zlamy M, Kofler S, Orth D *et al.* The impact of rotavirus mass vaccination on hospitalization rates, nosocomial rotavirus gastroenteritis and secondary blood stream infections. *BMC Infect. Dis.* 13, 112 (2013).

• **Study showshow universal vaccination has impacted on the spread of rotavirus infection in healthcare settings and not only in the community.**

29. Hofstetter AM, Lacombe K, Klein EJ *et al.* Risk of rotavirus nosocomial spread after inpatient pentavalent rotavirus vaccination. *Pediatrics* 141, 1–10 (2017).
30. Calderón TA, Coffin SE, Sammons JS. Preventing the spread of pertussis in pediatric healthcare settings. *J. Pediatric Infect. Dis. Soc.* 4, 252–259 (2015).
31. Ruijs WLM, Hautvast JLA, van der Velden K, de Vos S, Knippenberg H, Hulscher MEJL. Religious subgroups influencing vaccination coverage in the Dutch Bible belt: an ecological study. *BMC Public Health* 11, 102 (2011).
32. van den Hoogen A, Duijn JM, Bode LGM, Vijlbrief DC, de Hooge L, Ockhuijsen HDL. Systematic review found that there was moderate evidence that vaccinating healthcare workers prevented pertussis in infants. *Acta Paediatr.* 107, 210–218 (2018).
33. Moss WJ. Measles. *Lancet* 390, 2490–2502 (2017).
34. Maltezou HC, Wicker S. Measles in health-care settings. *Am. J. Infect. Control* 41, 661–663 (2013).
35. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: an updated review. *Vaccine* 30, 3996–4001 (2012).

• **Review of nosocomial outbreaks of measles.**

36. Porretta A, Quattrone F, Aquino F *et al.* A nosocomial measles outbreak in Italy, February–April 2017. *Eurosurveillance* 22, 30597 (2017).
37. Biellik RJ, Clements CJ. Strategies for minimizing nosocomial measles transmission. *Bull. World Health Organ.* 75, 67–75 (1997).
38. Wharton M, Cochi SL, Hutcheson RH, Schaffner W. Mumps transmission in hospitals. *Arch. Intern. Med.* 150, 47 (1990).
39. Heseltine PN, Ripper M, Wohlford P. Nosocomial rubella–consequences of an outbreak and efficacy of a mandatory immunization program. *Infect. Control* 6, 371–374 (1985).
40. Depledge DP, Brown J, Macanovic J, Underhill G, Breuer J. Viral genome sequencing proves nosocomial transmission of fatal varicella. *J. Infect. Dis.* 214, 1399–1402 (2016).
41. Lyytikäinen O, Klemets P, Ruutu P *et al.* Defining the population-based burden of nosocomial pneumococcal bacteremia. *Arch. Intern. Med.* 167, 1635 (2007).
42. Elias J, Claus H, Frosch M, Vogel U, Vogel U. Evidence for indirect nosocomial transmission of *Neisseria meningitidis* resulting in two cases of invasive meningococcal disease. *J. Clin. Microbiol.* 44, 4276–4278 (2006).
43. Dolan GP, Harris RC, Clarkson M *et al.* Vaccination of healthcare workers to protect patients at increased risk of acute respiratory disease: summary of a systematic review. *Influenza Other Respi. Viruses* 7, 93–96 (2013).
44. van Hoek AJ, Sheppard CL, Andrews NJ *et al.* Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. *Vaccine* 32, 4349–4355 (2014).
45. Read RC, Baxter D, Chadwick DR *et al.* Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, Phase III randomised clinical trial. *Lancet* 384, 2123–2131 (2014).
46. Pletz MW, Uebele J, Götz K, Hagel S, Bekeredjian-Ding I. Vaccines against major ICU pathogens. *Curr. Opin. Crit. Care* 22, 470–476 (2016).