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Note

Vaccination strategy for epidemic viral diseases in healthcare workers: Cut-off for optimal immunization

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ABSTRACT

Healthcare workers (HCWs) are at an increased risk of being exposed to epidemic viral diseases (EVDs), such as measles, rubella, mumps, and varicella-zoster. Currently, in case of the absence of written records on previous immunizations, the Japanese Society for Infection Prevention and Control guidelines require HCWs to have antibody titers higher than laboratory thresholds, possibly leading to over-immunization. We report our vaccination strategy and the consequent incidences of EVDs at the Osaka University Hospital between 2000 and 2016. In 2001, we initiated an annual serology check of antibody titers against EVDs and immunization for newly employed HCWs. As an additional vaccination program, all HCWs with low antibody titers were vaccinated in 2005 and 2010. Antibody titers were determined by an enzyme immunoassay (EIA), with a positive range of >2.0 cut-off index. After implementing the vaccination strategy to keep the laboratory threshold, there were only sporadic cases of EVDs among HCWs. More than 99% of individuals who had positive titers in 2005 remained the positive antibody titers in 2010, indicating that a minimum interval of 5 years is enough to measure immunity. Unprotected workers can, even silently, transmit the contagious viruses to patients and coworkers, possibly resulting in a nosocomial outbreak. However, over-vaccination may yield adverse effects and financial burdens. Our observational data indicate that the laboratory cut-off index of >2.0 by EIA may provide a sufficient herd immunity to prevent EVDs among HCWs.

Epidemic viral diseases (EVDs), including measles, mumps, rubella, and varicella-zoster, are highly contagious, leading to nosocomial transmission. Healthcare workers (HCWs) are at high risk of contracting these occupational infections through daily patient care. They can also spread the diseases to vulnerable patients and colleagues, resulting in nosocomial outbreaks, disruption in hospital functions, and financial burden to healthcare facilities [1]. Although there are effective vaccinations for these diseases [2], poor coverage of HCWs against these vaccine-preventable diseases (VPDs) is a global concern [3].

Indications of vaccinations for EVDs in HCWs have been provided by authorities. The U.S. Centers for Disease Control and Prevention (CDC) requires HCWs without laboratory evidence of immunity to be vaccinated, although the testing methods and reference cut-off values are not well defined [2]. The Japanese Society for Infection Prevention and Control (JSIPC) guidelines principally recommend to confirm two-dose immunizations for each of measles, mumps, rubella, and varicella-zoster with written records [4]. In the absence of previous vaccination data, a serological examination, followed by administration of booster dose(s), is endorsed. Although the guidelines approve several methodologies for antibody measurements, an enzyme-immunoassay (EIA) is commonly accepted for all viruses. Although the positive threshold for EIA is set at >2.0 cut-off index (COI), HCWs are required to have higher titers (≥16.0 COI for measles, ≥8.0 COI for rubella, and ≥4.0 COI for varicella-zoster) as per the JSIPC guidelines. While a lower cut-off may be insufficient in preventing the infections, a higher threshold should be avoided considering the risk of severe adverse reactions [5], as well as high costs, due to over-immunization. There is no established consensus on these criteria and evidence for the

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effectiveness of the higher titers in HCWs is still inadequate. Considering the high antibody titers required by the JSIPC guideline, we report our vaccination strategy and the consequent incidences of EVDs among HCWs at our facility.

This is a retrospective longitudinal observational study performed at the Osaka University Hospital between 2000 and 2016. We recorded consecutive incidences of measles, rubella, mumps, and varicella (or disseminated zoster) in the hospitalized patients and HCWs, which were reported to the Division of Infection Control and Prevention. To prevent nosocomial transmission of the diseases, starting from 2001, we have initiated an annual serology checkup of the EVDs for new employees and vaccinated those who tested negative. Additionally, in 2005 and 2010, we measured the serum titers of the four viruses in all HCWs and administered booster doses to those with low or no titers. Informed consent was waved since the data was obtained as a part of infection control activities in the hospital and personal information was anonymized.

The enzyme-linked immunosorbent assay (Enzygnost® Anti-Measles Virus/IgG, Siemens Healthcare Diagnostics Co. Ltd.) for each of the prophylactic antibodies was performed using the Behring ELISA Processor III (Siemens Healthcare Diagnostics Co. Ltd.). The positive cut-off levels were set at >2.0 COI, which was equivalent to >300 mIU/mL for measles, >8 mIU/mL for rubella, and >100 mIU/mL for varicella-zoster. There are no international reference standards for antibody titers against mumps. Booster doses were administered to individuals who tested negative for the tests.

From 2001 to 2016, all newly employed HCWs at our institute underwent an immunity checkup. The numbers and positivity rates of antibodies for each of the EVDs are summarized in Table 1. Of the 1047 HCWs who underwent the antibody checkup in 2005, 469 of them were tested for antibody titers in 2010 (Table 2). Of these 469 subjects, 170 were men (36.2%), and 299 were women (63.8%), with the median age of 37.3 years (interquartile range: 30, 44 and range: 21–57 years). The antibody positivity rates for measles, rubella, mumps, and varicella-zoster in 2005 were 95.6%, 88.3%, 78.6%, and 99.8%, respectively. Of 448 individuals who tested positive for measles antibodies in 2005, 444 (99.1%) were positive in 2010 as well. The positivity rates after 5 years were 99.8% (413/414) for rubella, 99.5% (367/369) for mumps, and 100% (468/468) for varicella-zoster. Notably, all the HCWs whose antibody titers were over twice the positive threshold (>4.0 COI) continued to test positive for 5 years for all the EVDs. In other words, individuals with antibody titers less than twice the positive threshold (2.1–4.0 COI) in 2005, tested negative 5 years later.

The annual incidences of EVDs are shown in Fig. 1. During the study period, there were 56 patients (6 measles, 2 rubella, 10 mumps, and 38 varicella) and 19 HCWs (6 measles, 1 rubella, 7 mumps, and 5 varicella). For the first two years (2000 and 2001), there were totally 10 EVDs involving HCWs (5 measles, 3 mumps, and 2 varicella). Subsequent to the annual serology checkup and vaccination for newly employed HCWs starting from 2001 and the additional vaccination programs for all HCWs in 2005 and 2010, HCWs suffering from EVDs have been sporadically reported. From 2002 to 2016, while 51 patients were hospitalized with EVDs, there were 9 cases of HCW-associated EVDs. Prior protective antibody titers of HCWs who suffered from EVDs were not recorded before 2010. All the 3 HCW cases reported after 2013 (1 rubella and 2 mumps) were confirmed to be sero-negative before the disease onset.

To facilitate infection control, we have enforced the annual serology checkup and vaccination for newly employed HCWs since 2001 and carried out two times of additional vaccination program targeting all the HCWs in 2005 and 2010. Subsequently, there have been only sporadic cases of EVDs among HCWs, suggesting that our vaccination strategy to keep >2.0 COI as determined by EIA seems to be effective in reducing the incidence of EVDs among HCWs. Additionally, more than 99% of the HCWs who had positive titers (>2.0 COI) remained the positive titers even after 5 years, indicating that a minimum interval of 5 years is enough to measure the immunity.

Vaccination is an essential measure to prevent nosocomial transmission of diseases, reinforce occupational safety, and maintain healthcare services even during outbreaks [6,7]. Under-immunization among HCWs is attributed to various factors including (a) lack of trust in the effectiveness and safety of vaccines, (b) religious beliefs, (c) lack of understanding of one's susceptibility to the infection, and (d) just an inconvenience. A recent cross-sectional study investigating compliance to vaccinations among HCWs revealed that a considerable number of them were unaware of their own protective status or their previous history of vaccination [8]. It is, therefore, not surprising that several nosocomial outbreaks of VPDs have occurred in various medical situations [9–12]. For the welfare of patients and the public, mandatory vaccination policies for HCWs have been adopted by healthcare authorities [13].

Table 1
The numbers and rates of immunity checkups and positivity rates of antibody titers for measles, rubella, mumps, and varicella-zoster among newly employed healthcare workers (HCWs) at the Osaka University Hospital from 2001 to 2016.

Year	The numbers of immunity checkups in newly employed HCWs	The numbers (rates) of antibody positivity			
		Measles	Rubella	Mumps	Varicella-zoster
2001	271	251 (92.6%)	238 (87.8%)	229 (84.5%)	260 (95.9%)
2002	264	239 (90.5%)	229 (86.7%)	189 (71.6%)	259 (98.1%)
2003	257	238 (92.6%)	219 (85.2%)	200 (77.8%)	252 (98.0%)
2004	182	156 (85.7%)	159 (87.4%)	123 (67.6%)	178 (97.8%)
2005	164	133 (81.1%)	150 (91.5%)	132 (80.4%)	161 (98.2%)
2006	198	178 (89.9%)	180 (90.9%)	171 (86.4%)	196 (99.0%)
2007	364	324 (89.0%)	340 (93.4%)	295 (81.1%)	357 (98.1%)
2008	205	188 (91.7%)	190 (92.7%)	161 (78.5%)	203 (99.0%)
2009	324	310 (95.7%)	306 (94.4%)	279 (86.1%)	319 (98.5%)
2010	342	326 (95.3%)	323 (94.4%)	302 (88.3%)	340 (99.4%)
2011	370	321 (86.8%)	341 (92.2%)	308 (83.2%)	368 (99.4%)
2012	493	454 (92.1%)	448(90.9%)	430 (87.2%)	488 (99.0%)
2013	488	444(91.0%)	456 (93.4%)	424 (86.9%)	478 (98.0%)
2014	438	384 (87.7%)	413 (94.3%)	395 (90.2%)	430 (98.2%)
2015	419	352 (84.0%)	388 (92.6%)	363 (86.6%)	405 (96.7%)
2016	441	385 (87.3%)	410 (93.0%)	371 (84.1%)	428 (97.0%)

The serological test was performed by an enzyme-linked immunosorbent assay, with a positive cut off index of >2.0.

Table 2
Positivity rates of antibodies titers for measles, rubella, mumps, and varicella-zoster among healthcare workers at the Osaka University Hospital in 2005, and their follow-up positivity rates after 5 years in 2010.

Antibody titers (cut-off index)	2005	2010	
	Positive (>2.0)	Negative (≤2.0)	Positive (>2.0)
Measles	95.6% (448/469)	0.9% (4/448)	99.1% (444/448)
Rubella	88.3% (414/469)	0.2% (1/414)	99.8% (413/414)
Mumps	78.6% (369/469)	0.5% (2/369)	99.5% (367/369)
Varicella-zoster	99.8% (468/469)	0% (0/468)	100% (468/468)

The serological test was performed by an enzyme-linked immunosorbent assay, with a positive cut off index of >2.0. More than 99% of individuals with positive titers in 2005 remained the positive antibody levels in 2010.

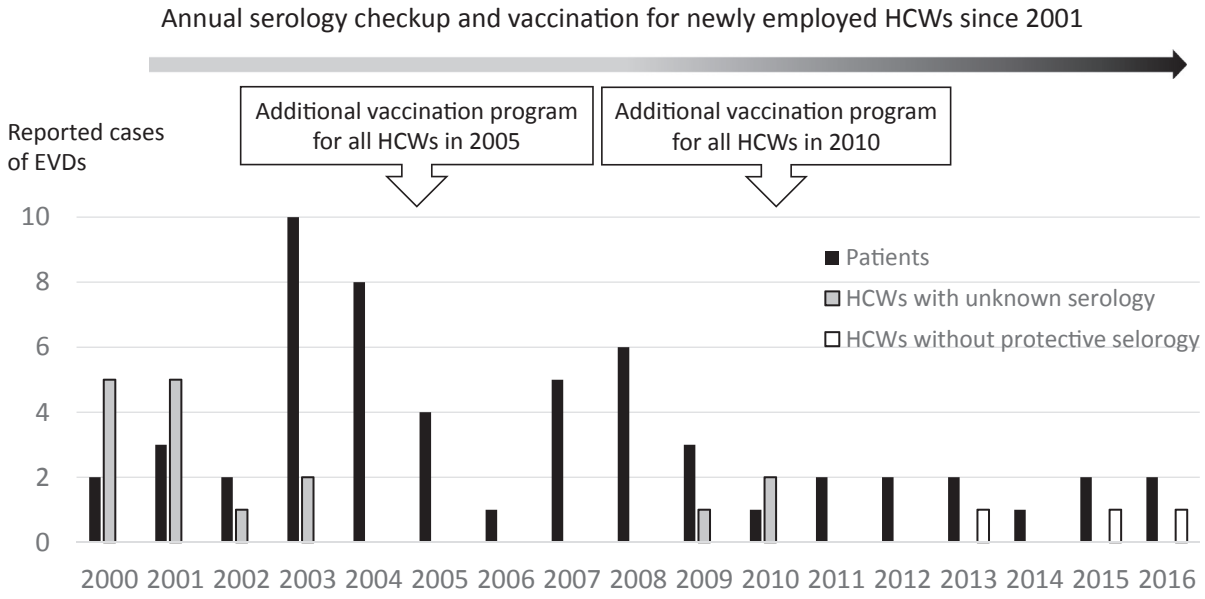

Fig. 1. Reported annual incidences of measles, rubella, mumps, and varicella-zoster in hospitalized patients and healthcare workers (HCWs) at the Osaka University Hospital, 2000–2016. There were no serological tests and immunizations for HCWs before 2001. Shown is the decrease in the number of HCWs infected with the viral diseases after implementing the annual serology checkup and vaccination for newly employed HCWs and additional vaccination program for all HCWs in 2005 and 2010.

The ethics of mandatory immunization policies for HCWs has been debated among international organizations [14]. A recent investigation on vaccination policies among European countries revealed significant differences in the vaccine types recommended for HCWs, recommendation grade (mandatory or voluntary), the occupation of the subjects, and the health-care settings [1]. Healthcare institutions are responsible for protecting both the patients and HCWs from EVDs by preventing the nosocomial spread of pathogens. Since vaccinations are associated with adverse reactions and economic burdens, they should not be administered excessively. The JSIPC guidelines recommend higher antibodies titers for EVDs in HCWs (≥720 mIU/mL for measles, ≥18.4 mIU/mL for rubella, and ≥200 mIU/mL for varicella-zoster). However, the benefits of achieving such high titers of antibodies for the purpose of preventing nosocomial outbreaks of the diseases are debatable. The present study indicated that a laboratory COI of >2.0 by EIA can be acceptable for the control of the nosocomial spread of EVDs.

Limitations of this study should also be mentioned. First, underreporting of the occurrence of EVDs can bias the results. Second, atypical cases may not have been diagnosed appropriately. Thirdly, exposures to viruses outside the hospital could have also influenced on the reported number of EVDs.

Collectively, our observational data suggest that maintaining a laboratory COI of >2.0 by EIA may provide a herd immunity to reduce the incidence of EVDs among HCWs. The JSIPC requirement for high antibody titers in HCWs may need to be reevaluated.

Authorship statement

All authors meet the ICMJE authorship criteria.

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Declaration of interest

The authors confirm that there are no conflicts of interests to declare.

Authors' contributions

Study conception, design, and acquisition and interpretation of data: N. Yoshioka, M. Deguchi, M. Kagita, H. Tsukamoto, and M. Takao. Drafting of the manuscript: H. Hagiya. Critical revision: K. Tomono.

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