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Immunity against vaccine-preventable diseases in Finnish pediatric healthcare workers in 2015

Karoliina Koivisto [a,*], Laura Puhakka [a], Maija Lappalainen [b], Soile Blomqvist [c], Harri Saxén [a], Tea Nieminen [a]

[a] Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[b] Laboratory Services (HUSLAB), Department of Virology and Immunology, University of Helsinki and Helsinki University Hospital, Finland
[c] National Institute for Health and Welfare, The Viral Infections Unit, Finland

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ABSTRACT

Healthcare workers (HCWs) pose a risk to themselves and their patients if not protected against vaccine-preventable diseases. Alarmingly, lacking immunity has been reported in several studies. We assessed the immunity against vaccine-preventable diseases in 157 pediatric HCWs in Helsinki Children's Hospital. The HCWs enrolled answered a questionnaire and gave a serum sample. Antibodies were measured with EIA against MMR-diseases, tetanus and diphtheria toxins, Hepatitis B (HBV), Hepatitis A (HAV), varicella zoster and pertussis toxin. Neutralizing antibodies against poliovirus 1, 2 and 3 were measured. All of the HCWs had antibodies against tetanus and 89.8% against diphtheria. All had measurable levels of polio antibodies to all three polioviruses. 41% had suboptimal levels of antibodies against at least one of the antigens tested: MMR-viruses, diphtheria, HBV or polio. Measles, mumps and rubella antibodies were detectable in 81.5%, 89.2% and 93%, respectively. Only one HCW had no varicella-antibodies. Hepatitis B surface antibodies (HBsAb) were detected in 89.8% of the nurses. 67.5% had HAV-antibodies. A poor correlation between detected antibody levels and reported vaccination history was noticed, indicating a need for a universal record system for registering the vaccines given to each individual.

1. Introduction

Healthcare workers (HCWs) working in direct contact with patients are susceptible to transmittable diseases and may play a role in nosocomial transmission of infectious diseases. When not protected against vaccine-preventable diseases, they pose a risk to themselves and their patients, especially in an outbreak situation. Alarmingly, several studies have reported lacking immunity against vaccine-preventable diseases in HCWs [1–3].

Numerous measles outbreaks have recently occurred in Europe [4,5]. The proportion of HCWs with suboptimal levels of antibodies against measles has varied from 1.6% to 19% in European studies done in this century [6]. A study in the UK recently assessed the immunity of 3921 newly employed HCWs who did not have documentation of immunization for measles-mumps-rubella (MMR). Out of this cohort, 11.8% did not have antibodies against measles, 31.2% against mumps and 6.1% against rubella [7]. In an Italian study of 333 HCWs, antibodies against measles (98.2%) and rubella (97.6%) were seen in most of the studied HCWs, but mumps antibodies were somewhat less frequent (85.9%) [8]. In a study in Catalonia, anti-rubella IgG was measured in 642 HCWs. Even though most of them had sufficient anti-rubella IgG-levels, the lowest prevalence of rubella antibodies was seen in HCWs less than 30 years of age [9]. In another study of 537 HCWs in Catalonia, anti-tetanus and –diphtheria antibodies were shown to be at suboptimal levels or totally missing in the older HCWs [10].

Pertussis has been re-emerging in industrialized countries in the past decade. Antibodies are shown to wane quite rapidly in the years following vaccination with acellular pertussis vaccine [11,12]. A recent study in Spain showed that 51.7% (238) of the 460 HCWs tested had pertussis IgG, thus raising the question whether the remaining HCWs were susceptible to the disease [13].

Vaccine-preventable diseases are rare in Finland due to the high vaccination coverage achieved by the national vaccination program. As thousands of asylum seekers from countries with disrupted vaccination programs have entered Europe and Finland during the previous year, diseases that have been rare or nonexistent in Finland may reappear with this trend. Examples of this have already been seen in Europe as Germany and France have experienced measles epidemics among the asylum seekers [5,14], and polio cases have been reported during the war in Syria [15].

HCWs in clinical work have an increased risk of exposure to Hepatitis B (HBV) through contact with body fluids. In 2003 the

* Corresponding author.
E-mail address: karoliina.tirri@helsinki.fi (K. Koivisto).

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immunity against HBV was assessed in 702 HCWs in a study in Turkey. Close to 70% of the HCWs had vaccine derived immunity, which is in correlation with the level of HBV-immunity seen in the general Turkish population [16].

Although the Finnish vaccination program [17] is well organized, a national database on vaccination records has been lacking until 2009, and the database does not capture previously administered vaccines. Thus, individual vaccination history is based on each HCW's personal records and knowledge on vaccines received, and may therefore be unreliable.

The aim of this study was to assess the immunity against vaccine-preventable diseases in HCWs working in pediatric wards at Helsinki University Hospital. We studied antibodies against tetanus, diphtheria, polio, pertussis, HAV, HBV, MMR-diseases and varicella zoster.

2. Methods

2.1. Study design

HCWs were eligible for the study if they were 18–65 years old and their job description included at least 50% clinical work with patients. HCWs who had received immunizations, blood products or immunoglobulins during the previous two months were excluded.

HCWs were recruited from pediatric wards in Helsinki University Hospital during October and November in 2014. Recruitment was done by e-mail and posting flyers in the wards. Participating was voluntary. HCWs willing to participate were advised to contact the research personnel and give their personal contact information. Enrollment was continued until each of the four designed age categories (<30 years, 30–40 years, 40–50 years, >50 years) had 38–40 participating nurses (Table 1).

The HCWs enrolled answered a questionnaire regarding their vaccination history based on recollection or by viewing their possible written vaccine records.

2.2. Laboratory methods

Blood samples were taken between December 2014 and March 2015 from 157 recruited HCWs. The sera were analyzed at HUSLAB with EIA techniques during fall 2015. Varicella IgG was measured using an inhouse VZV-IgG EIA test [18,19]. Measles and mumps IgG antibodies were measured using commercial ELISA-assay (Measles Virus, Human-ELISA-IgG-Antibody-Test, Human Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany and Mumps IgG: Mumps Virus, Human ELISA-IgG-Antibody-Test, Human Gesellschaft für Biochemica und Diagnostica mbH, Wiesbaden, Germany). Rubella, diphtheria and tetanus IgG antibodies were measured by an inhouse EIA test. The samples were tested for antibodies against HBV surface antigens (HBsAb) (Architect anti-HBs Reagent Kit, Abbott) and HBcAb as well as antibodies for HAV (Architect HAV-IgG Reagent Kit, Abbott) and Hepatitis C virus (HCV, Architect anti-HCV Reagent Kit, Abbot).

Varicella, measles and mumps antibodies were defined positive or negative according to the manufacturer's guidelines. Rubella antibodies were considered non-protective when titers less than 15 EIU were detected. Tetanus and diphtheria antibody titers less than 0.1 IU/ml were defined as not protective [20]. HBsAb over 10 mIU/ml was considered positive. HAV IgG was defined either positive or negative.

Neutralizing antibodies against polioviruses 1, 2 and 3 (PV1, PV2, PV3) were tested for at Finland's National Institute for Health and Welfare [21]. Titers less than 1:32 were considered inadequate.

IgA and IgG antibodies against pertussis toxin (PT) were tested at the national pertussis reference laboratory at the University of Turku (UTU). IgG and IgA antibodies were measured with EIA techniques (provided by GlaxoSmithKline, Belgium) [22].

2.3. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics version 22. Categorical variables were compared with Pearson chi square test or Fisher's exact test.

2.4. Ethics approval

The study protocol was approved by the Ethics committee of the Medical Faculty at Helsinki University hospital. A written consent was requested from every HCW participating in the study.

3. Results

A total of 157 out of 785 (20%) nurses employed by the Children's Hospital were included in the study. Most of the participants, 151/157 (96%), were female. The age-range of the participants was from 22 to 64 (Table 1). All of them answered a questionnaire on their personal vaccination history.

All 157 nurses had high anti-tetanus toxoid antibody-levels, and all of them could recall being vaccinated against tetanus and diphtheria. Altogether 141/157 (89.8%) of the nurses (95% CI 85.1–94.5) had diphtheria antibodies >0.1 IU/ml. There was no

Table 1
Age breakdown of study population, self-reported immunity and seropositivity to MMR-diseases.

Age	<30 years	30–40 years	40–50 years	>50 years
Nurses (n)	38	40	40	39
Female	38	38	37	38
Male	0	2	3	1
Immunity status				
MMR vaccination	**95% (36)**	**93% (37)**	**65% (26)**	**13% (5)**
Not known	5% (2)	8% (3)	15% (6)	23% (9)
No answer	–	–	20% (8)	64% (25)
History of infection				
Measles	–	–	38% (15)	69% (27)
Mumps	–	8% (3)	50% (20)	51% (20)
Rubella	–	5% (2)	20% (8)	41% (16)
Seropositivity				
Measles	**66%** (25)	**70%** (28)	**90%** (36)	**100%** (39)
Mumps	**82%** (31)	**95%** (38)	**93%** (37)	**87%** (34)
Rubella	**76%** (29)	**95%** (38)	**100%** (40)	**100%** (39)

statistically significant difference in diphtheria-antibody levels between the different age groups (Table 2).

Out of the 157 nurses tested, 118 (75%) had detectable antibodies against all three MMR-components – measles, mumps and rubella. A total of 128/157 (81.5%) (95% CI 75.4–87.6) of the nurses had measurable anti-measles (IgG) antibodies. All of the 29 nurses with non-measurable antibodies were under 50 years of age, and 25 nurses (86%), were less than 40 years old. Measles seroprevalence was higher in the older age groups and the difference was clearly significant ($p < 0.001$). Mumps antibodies were detectable in 140/157 (89.2%) (95% CI 84.3–94.1) of the HCWs and rubella IgG antibodies were positive (>15 EIU) in 146/157 (93.0%) (95% CI 89.0–97.0) of them. All eleven nurses with undetectable levels (<15 EIU) were less than 40-year-old females. Older HCWs (>40 year olds) had antibodies to rubella significantly more frequently than the younger HCWs ($p < 0.001$) (Chart 1).

Anti-varicella antibodies were detected in all but one of the HCWs (99.4%). She had received two doses of varicella vaccine according to the protocol for vaccinating HCWs in Helsinki University hospital and received a third dose after receiving the information of her negative response. A month later she was tested positive for varicella antibodies.

HBV surface antibodies indicating vaccine-derived immunity were found in 141/157 (89.8%) of the nurses (95% CI 85.1–94.5). Out of the sixteen nurses with no HBs-antibodies, four (25%) did not recall being vaccinated. Thus 92.2% of the nurses known to be vaccinated had HBs-antibodies. All of the subjects were negative for HBcAb. HAV-IgG was found in 106/157 (67.5%) of the nurses.

Table 2
Seropositivity to studied antigens by age group.

Measles	S-MorbAbG	Positive	Negative	RR (95% CI)	p
	Total	**128 (82%)**	**29 (18%)**		
	<30 years	25 (66%)	13 (34%)	6.8 (2.4–19.3)	<0.001
	30–39 years	28 (70%)	12 (30%)	5.9 (2.0–17.2)	0.001
	40–49 years	36 (90%)	4 (10%)	1 (reference group)	
	>50 years	39 (100%)	0 (0%)		
Mumps	S-ParoAbG	Positive	Negative	RR (95% CI)	p
	Total	**140 (89%)**	**17 (11%)**		
	<30 years	31 (82%)	7 (18%)	1.8 (0.7–4.6)	0.211
	30–39 years	38 (95%)	2 (5%)	0.5 (0.1–2.2)	0.357
	40–49 years	37 (93%)	3 (8%)	1 (reference group)	
	>50 years	34 (87%)	5 (13%)		
Rubella	S-RubeAbG	>15 EIU	<15 EIU	RR (95% CI)	p
	Total	**146 (93%)**	**11 (7%)**		
	<30 years	29 (76%)	9 (24%)	14.1 (3.2–62.4)	<0.001
	30–39 years	38 (95%)	2 (5%)	1 (reference group)	
	40–49 years	40 (100%)	0 (0%)		
	>50 years	39 (100%)	0 (0%)		
Tetanus	S-ClteAb	> 0.1 SPU/ml	<0.1 SPU/ml		
	Total	**157 (100%)**	**0 (0%)**		
	<30 years	38 (100%)	0 (0%)		
	30–39 years	40 (100%)	0 (0%)		
	40–49 years	40 (100%)	0 (0%)		
	>50 years	39 (100%)	0 (0%)		
Diphtheria	S-CodiAb	>0.1 SPU/ml	<0.1 SPU/ml	RR (95% CI)	p
	Total	**141 (90%)**	**16 (10%)**		
	<30 years	35 (92%)	3 (8%)	0.6 (0.2–1.9)	0.361
	30–39 years	38 (95%)	2 (5%)	0.4 (0.1–1.5)	0.169
	40–49 years	34 (85%)	6 (15%)	1 (reference group)	
	>50 years	34 (87%)	5 (13%)		
HBV	S-HBsAb	>10 mIU/ml	<10 mIU/ml	RR (95% CI)	p
	Total	**141 (90%)**	**16 (10%)**		
	<30 years	35 (92%)	3 (8%)	0.6 (0.2–2.1)	0.452
	30–39 years	37 (93%)	3 (8%)	0.6 (0.2–2.0)	0.405
	40–49 years	35 (88%)	5 (13%)	1 (reference group)	
	>50 years	34 (87%)	5 (13%)		
HAV	S-HAVAbG	Positive	Negative	RR (95% CI)	p
	Total	**106 (68%)**	**51 (32%)**		
	<30 years	30 (79%)	8 (21%)	0.5 (0.3–1.1)	0.07
	30–39 years	28 (70%)	12 (30%)	0.8 (0.4–1.3)	0.336
	40–49 years	24 (60%)	16 (40%)	1 (reference group)	
	>50 years	24 (62%)	15 (38%)		
Polio		Titer > 1:32	Titer < 1:32	RR (95% CI)	p
	Total	**150 (96%)**	**7 (4%)**		
	<30 years	34 (89%)	4 (11%)	4.2 (1.0–17.8)	0.054
	30–39 years	40 (100%)	0 (0%)	1 (reference group)	
	40–49 years	39 (98%)	1 (3%)		
	>50 years	37 (95%)	2 (5%)		
Varicella		Positive	Negative		
	Total	**156 (99%)**	**1 (1%)**		
	<30 years	37 (93%)	1 (3%)		
	30–39 years	40 (100%)	0 (0%)		
	40–49 years	40 (100%)	0 (0%)		
	>50 years	39 (100%)	0 (0%)		

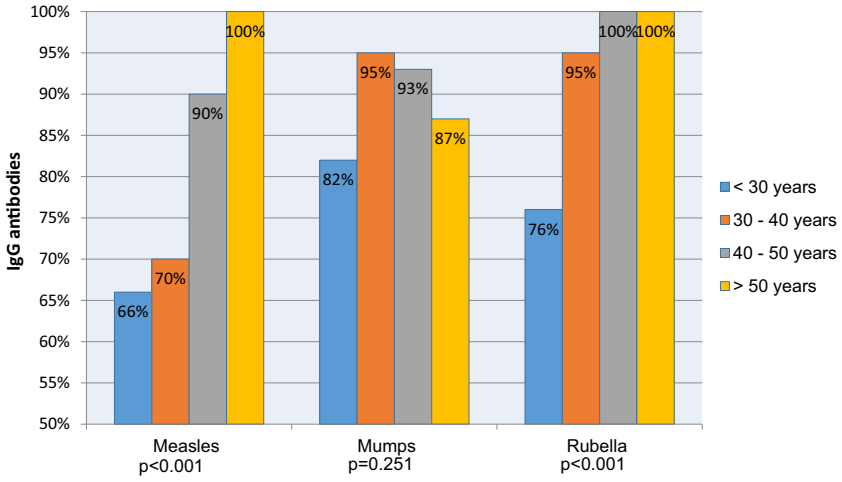

Chart 1. Measles-mumps-rubella IgG-antibody seroprevalence by age group.

(Chart 2). Anamnestically 116 nurses reported being vaccinated against HAV, but HAV-antibodies were detected in only 106 (91.4%) of them. Two nurses reported having been infected with HAV, but antibodies indicating an infection were detected only in one of them.

All 157 nurses had measurable antibodies to all three polioviruses and all of them had antibody titers >1:32 against poliovirus 2. However, seven nurses (4.5%) had low antibody titers (<1:32) against PV1 (one nurse) or PV3 (six nurses), and thus a booster vaccination was recommended for them. Only two nurses did not know whether they had been vaccinated against polio. However, both of them had antibody titers >1:32 against at least two of the polio viruses. (Table 2)

IgA antibody levels against pertussis are used for diagnosis of recent infection. None of the nurses had detectable pertussis IgA-antibodies (PT-IgA < 10 IU/ml in all of the nurses), indicating that none of them had recently been infected. Two of them (1.3%) had anti-pertussis-IgG > 100 IU/ml indicating a previous infection, approximately within a year. Neither of them had received a booster dose of pertussis-vaccine for several years. All the rest of the nurses (98.7%) had IgG levels <50 IU/ml, indicating that there was no contact with pertussis or the vaccine within a year.

Serological testing revealed that altogether 64/157 (41%) of the HCWs had suboptimal levels of antibodies towards at least one of the following antigens tested: MMR-viruses, diphtheria, HBV or polio (Table 2). These individuals were encouraged to contact their occupational healthcare to receive employer funded catch-up vaccinations. Suboptimal antibody levels were mostly seen against the MMR-diseases (Chart 3). Four nurses did not have detectable antibody levels to any of the MMR viruses and eight nurses lacked measles and rubella antibodies. Out of the 64 HCWs with suboptimal antibody levels only 20 (31%) had deficient antibodies against more than one of the antigens tested: six nurses against two antigens and three nurses against three antigens. Five nurses had deficient antibodies against 4 or 5 of the six antigens.

4. Discussion

In our study we assessed the immunity in 157 pediatric nurses working in Helsinki Children's hospital. By and large, the immunity status of the cohort was quite good. The HCWs working in the University Hospital are required to have valid immunization against the MMR-diseases, HBV, diphtheria, tetanus and polio. However, 41% of the nurses had suboptimal levels of antibodies against one or more of the aforementioned vaccine-preventable diseases. Earlier studies in Western countries have similarly reported deficiencies in healthcare workers' immunity status. This

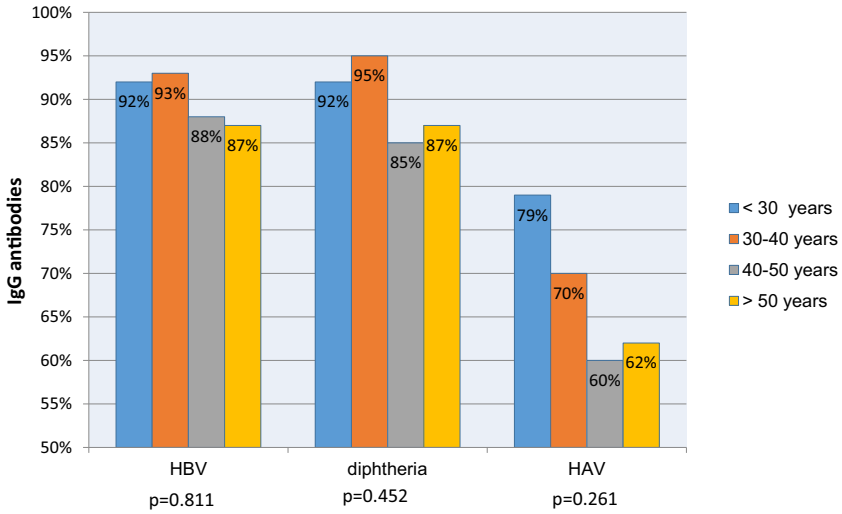

Chart 2. Hepatitis B (HBV) surface antibody (S-HBsAb), diphtheria toxin antibody (S-CodiAb) and Hepatitis A (S-HAVAbG) antibody seroprevalence by age group.

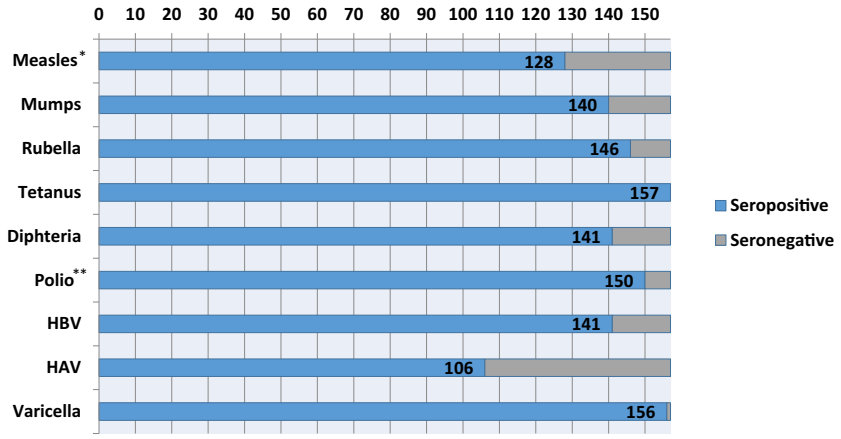

Chart 3. Seropositive individuals for tested vaccine-preventable diseases (n = 157).

study shows that there is room for improvement in the Finnish environment as well.

Measles is one of the most contagious viral infections and is associated with a number of complications. MMR-vaccine was included in Finland's national vaccination program in 1982, and measles has successfully been eliminated from the country. However, increasing travel and the recent refugee influx may raise the risk for new outbreaks in Europe [4,7]. Healthcare workers pose occupational hazards and are more likely to be in contact with infected individuals [23].

It is well known that vaccinated individuals have lower levels of measles IgG antibodies than individuals with immunity induced by natural infection [24]. Measles antibodies seem to decline in early adulthood if the second MMR-dose is given in early childhood [25]. Rubella antibodies have also been shown to decrease to seronegativity or the lowest detectable titer in over half of MMR recipients in twelve years [26].

In our study, 25% of the volunteers had inadequate immunity to one or more of the MMR-diseases. Individuals lacking measles and rubella antibodies were only seen in the youngest age cohorts, most likely due to waning immunity years after vaccination in individuals lacking contact with the wild virus [24,27,28]. Other studies have also shown the tendency of non-immune individuals to be seen in younger age groups [8,29]. This is concerning, since especially fertile individuals should be protected against rubella to avoid the risk of congenital rubella syndrome. Similar findings concerning low rubella antibodies in young age groups have previously been reported by Borras et al. [9] and Davidkin et al. [30].

Mumps immunity has also been shown to wane with time after vaccination [31,32]. However, our study found absence of mumps antibodies in all four age groups. In order to better prepare for future outbreaks, booster doses of MMR may be needed in vaccination programs, especially for the younger age groups whose immunity is induced by vaccination [31].

In addition to waning immunity, low or nonexistent levels of antibodies against the MMR-diseases may also be due to vaccination failure or incomplete vaccination with the recommended two doses of vaccine. It has also been shown that commercial EIA-tests fail to detect up to 10% of vaccine-induced measles IgG antibodies [33]. This might be the case with our cohort as well, and thus, a larger percentage of the nurses may be clinically protected than were shown to be antibody positive.

Our cohort was well protected against varicella, which is in accordance with previous reports in the Finnish population [34].

All of the HCWs in all age groups were well protected against tetanus, which is in contrast to a recent Catalonian study reporting poor immunity in older HCWs [10]. A previous study in the Finnish population showed that the proportion of population protected against tetanus has increased in 2000–2001 as compared to studies done in the same population in the 1980's and the 1990's. The proportion of the protected individuals among the under 40-year-olds increased from 84% to 100% already by the 1990's and in the over 50-year-olds from 49% to 54% and further on to 64% by 2001 [35]. In our study in 2015, however, deficiencies were not seen in any age group.

Almost 90% of the individuals in our cohort had sufficient levels of antibodies against diphtheria toxin. This is a much higher proportion than in an earlier study in Catalonia, where only 46.4% of the HCWs had protective levels of diphtheria toxin antibodies [10]. The proportion of HCWs protected in our study was also higher than that previously reported in the general Finnish population [35].

None of our study subjects had been infected with HBV and 90% of them had protective levels of vaccine induced HBsAb. This is a clearly higher rate of protected individuals than reported in studies in Southern Europe. It is currently considered that booster doses are not needed for HBV immunization and subjects with low antibody levels (<10 mIU/ml) might still be protected. A recent study showed that 94% of vaccinees either had protective levels of antibodies or responded quickly to a booster dose indicating antigen recognition thirty years after primary vaccination [36]. Whether or not the individuals in our study with antibody levels below 10 mIU/ml were protected remains unclear. It is possible that some of our low-responders or no-responders may still be immune to HBV-infection as has been shown in previous studies [37].

A substantial proportion of the HCWs did not have protective antibodies against Hepatitis A, which is not surprising as HAV is not endemic in Finland and vaccination is mainly recommended for travelers.

To our knowledge there are no studies on the immunity against poliomyelitis in HCWs. In our cohort all of the nurses had measurable levels of antibodies against all three polioviruses, and were most likely protected against the disease. However, titers below 1:32 have been considered a cut-off level for booster recommendation by the Finland's National Institute for Health and Welfare. The lowest titers were almost exclusively seen against polio virus type 3, which has not been circulating in the community for years. Until global polio eradication has been established, it is important that our health care personnel are still protected against poliovirus 1 and 3.

Our study found two nurses with serological evidence of a recent pertussis infection. Neither of them was aware of a possible infection. This is alarming as asymptomatic transmission is known to be a risk factor for spread of the disease [38]. It has been shown that pertussis-antibodies wane rapidly within years after vaccination with the current pertussis-vaccines. The fact that pertussis infections among pediatric HCWs still exist warrants a booster dose in this particular group to protect the unvaccinated infants in the hospital setting. However, protection against pertussis seems to be mediated by both antibody and cell-mediated responses, and thus an individual with low and waning IgG-titers can still be protected by efficient cell-mediated immunity [39].

It is well known that protection against infectious agents is mediated by complex immunological mechanisms. However, specific antibodies induced by immunization correlate with protection against most vaccine preventable infections. At the moment, assessment of the quality and quantity of antibodies after immunization is probably the most cost-effective way to assess immunity against most vaccine-preventable diseases. Protective antibody levels have been validated for tetanus and diphtheria, and they pose a good correlate for clinical protection [20]. There is also valid evidence linking a protective level of anti-HBV and clinical protection [20,37].

We recorded a poor correlation between each individual's antibody levels and the history of vaccinations, which is consistent with previous findings [29]. It is clear that better mechanisms for recording individual immunizations should thus be developed. Measuring the antibodies against each vaccine-preventable disease of all new workers is not feasible nor cost-effective, and other more practical ways should be considered. All vaccinations should be recorded in a single database. Pertussis-booster vaccines (Tdap) should be given to all HCWs working with children, if they have not been vaccinated during the previous five years. A study done in Switzerland showed major improvement in pertussis coverage (from 17% to 88%) of 427 voluntarily responding HCWs when efforts to implement vaccination guidelines were made [40]. Our results demonstrate the need for optimizing processes for giving HCWs all the vaccines needed for their own and the patients' safety. Better education of HCWs is also needed on the subject. The diseases threatening HCWs and their patients change with time and it is thus important that there are up-to-date vaccination guidelines that can be implemented.

Participating in the study was voluntary and it may be that nurses who had not taken the recommended vaccinations were less willing to participate, which may have caused a certain bias. The study was conducted in a single university hospital and may not represent the situation in other parts of the country.

In conclusion, the immunity status of the HCWs in Helsinki Children's Hospital was good compared to findings in other European hospitals. However, we have showed some immunity gaps against vaccine-preventable diseases, even in those HCWs who reported being immunized. Furthermore, a great portion of workers were ignorant of their immunity status, suggesting that there is a dire need of vaccination records for HCWs as well as for the general population.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.02.018.

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