

Seroprevalence and immunization history of selected vaccine preventable diseases in medical students

Gurli Baer, Jan Bonhoeffer, Urs B. Schaad, Ulrich Heininger*

Division of Pediatric Infectious Diseases, University Children's Hospital Basel, P.O. Box 8, CH-4005 Basel, Switzerland

Received 1 December 2003; accepted 19 March 2004

Available online 10 November 2004

Abstract

To evaluate protection against vaccine-preventable diseases in medical students, we obtained data on immunization status and history of diphtheria, tetanus, pertussis, poliomyelitis, measles, mumps, rubella, varicella and hepatitis B from students with elective periods in our institution. Further, serum antibodies against measles, mumps, rubella and varicella-zoster virus (VZV) and hepatitis B surface (HBs) antigen were determined on a voluntary basis. For students with incomplete immunization status or lack of protective antibodies, vaccination was offered for free. Success of catch-up immunizations was serologically confirmed 4 weeks later. From May 1999 to April 2003, 170 students were enrolled; their mean age was 26 years with a median of 25 years (range 22–48 years). Immunization records were complete in 148 (87%), incomplete in 11 (6.5%) and missing in 11 (6.5%) students. Only 26% of the cohort had a complete and up-to-date immunization status. Seroprevalence of IgG antibodies against measles, mumps, rubella, VZV and HBs (≥ 10 IU/l) in 149 students were 85, 85, 92, 97 and 90%, respectively. Indications for ≥ 1 catch-up immunization were found in 125 (74%) students and were accepted by 97 of them (78%). Sixty two (99%) of 63 immunized students available for follow-up demonstrated an adequate serological response. In conclusion, the great majority of medical students had immunization gaps. Systematic immunization programmes for medical students should be implemented.

© 2004 Elsevier Ltd. All rights reserved.

Keywords: Medical students; Immunization; Vaccines

1. Introduction

In hospital environments, transmittable infectious diseases put patients and health care workers at increased risk [1]. Therefore, most medical institutions do have immunization programmes for their staff in place. Medical students, who usually spend short periods of time in a particular institution, are also an important target group in this respective. Yet, this is frequently overlooked and only a few medical schools appear to have consistent and adequate immunization programmes for their students [2–6].

We have previously reported significant immunization gaps in medical students attending our hospital and provided suggestions for improvement [7]. In the meantime, more ex-

perience has been gathered and also serological analyses have been performed. Here we report the findings of this programme, which has now been running successfully for four consecutive years.

2. Methods

2.1. Study population

Fourth year medical students with a rotation in the University Children's Hospital in Basel, Switzerland, were eligible for participation after informed consent. The following data were obtained during a standardized interview: age; gender; nationality; personal history of varicella, measles, mumps, rubella, and pertussis. Any written documentation of previous immunizations was requested and recorded.

* Corresponding author. Tel.: +41 61 685 6528; fax: +41 61 685 6012.
E-mail address: ulrich.heininger@unibas.ch (U. Heininger).

2.2. Serological assays

An initial venous blood specimen (3 ml) was obtained on a voluntary basis for specific serum antibody analyses. IgG antibodies against VZV were determined by ELISA (enzyme-linked immunosorbent assay, Enzygnost®, DADE Behring Ltd.) as were anti-measles and anti-mumps IgG antibodies (Human®, Wiesbaden, Germany). Anti-rubella IgG antibodies were determined by an enzyme immunoassay (PLATELIA® Rubella IgG, BIO-RAD, France). Anti-measles, anti-mumps and anti-rubella IgM antibodies were analyzed by solid-phase ELISA (Human®, Wiesbaden, Germany, and PLATELIA® Rubella IgM, BIO-RAD, France, respectively).

IgG antibodies against hepatitis B surface (HBs) antigen were measured by ELISA (MONOLISA® ANTI-HBS 3.0, BIO-RAD, France).

In students with no documentation of hepatitis B vaccination but positive anti-HBs antibodies, the respective serum specimens were tested for hepatitis B core (HBc) antibodies to distinguish between undocumented immunization and infection. Serotesting for anti-HBc IgG was performed with an ELISA (MONOLISA® ANTI-HBC 3.0, BIO-RAD, France).

All tests were performed and interpreted according to the manufacturers' instructions. Values in the indeterminate range were repeated and considered to be negative if still indeterminate.

2.3. Procedures

2.3.1. Interpretation of immunization status and consequent procedures

Immunity against diphtheria (D), tetanus (T) and poliomyelitis (P) was considered adequate if a primary immunization series (≥ 3) had been documented and the last dose had been administered ≤ 10 years ago. If less than 3 doses of either vaccine had been documented, missing dose(s) of immunization were recommended. A booster dose was suggested if ≥ 3 immunizations had been documented and the last dose had been administered ≥ 10 years ago. With respect to pertussis, immunization status was recorded but no booster doses were recommended in accordance with current recommendations in Switzerland.

2.3.2. Interpretation of serological results and consequent procedures

Immunity to measles, mumps, rubella and varicella was assumed based on the presence of specific IgG serum antibodies. If specific IgG antibodies against one or more of those viruses were lacking, a dose of MMR and/or varicella vaccine was offered irrespective of immunization and/or disease histories. To verify success of immunization, a further blood test was performed 4 weeks later and both IgG and IgM antibodies (as a surrogate for a primary immune response) were measured.

Immunity to hepatitis B was assumed in the presence of anti-HBs IgG antibodies of ≥ 10 IU/l serum, either documented previously or as part of this study. In all other cases a primary immunization series (in previously unimmunized individuals) or a booster dose was recommended and a further blood test were performed 4 weeks later. All recommended immunizations were offered free of charge.

2.4. Statistical analysis

Statistical analysis was performed using Epi-Info 2002 (version 1.1.2. Centers for Disease Control and Prevention, Atlanta, USA). Independent proportions were compared by Fisher's exact test or Mantel-Haenszel chi square analysis as appropriate. p values ≤ 0.05 were considered significant.

3. Results

3.1. Study population

From May 1999 to April 2003, 170 students were enrolled. Their mean age was 26 years (median: 25.3 years; range: 22–48) and 61% were females. One hundred thirty eight (81%) had grown up in Switzerland, 26 (15%) in Germany, 5 (3%) in Italy and 1 (1%) in Sweden.

3.2. Immunization status and seroprevalence

One hundred forty-eight (87%) of 170 students provided complete documentation of all immunizations since childhood. Eleven (6.5%) students had no immunization records at all and the remaining 11 (6.5%) students only had records of specific recent immunizations, e.g. hepatitis B. In 149 students (88%) a voluntary serum sample was obtained.

A primary immunization series against diphtheria, tetanus and poliomyelitis was documented in 85–86% of students, whereas only 72, 79 and 59% of immunizations, respectively, were up-to-date. There were no significant differences by gender (data not shown).

In Table 1, vaccination rates and seroprevalence of specific IgG serum antibodies against measles, mumps and rubella are shown. As can be seen, 70, 64 and 61% of students had previously received one or two doses of measles, mumps and rubella vaccine, respectively. The rates for second doses ranged between 10 and 24%. Immunization rate for rubella was higher in female students (72%) compared to males (49%; $p = 0.01$). With respect to measles and mumps, no significant differences by gender were found.

Seroprevalence rates for IgG antibodies against measles, mumps and rubella were 85, 85 and 92%, respectively. Of students with a negative immunization status for measles, 96% had positive IgG antibodies compared to 81% ($p = 0.07$) in those with one or two previous immunizations. In contrast, unimmunized students had lower rates of mumps (74%) and rubella (75%) IgG antibodies compared to those with

Table 1
Seroprevalence and vaccination history for measles, mumps and rubella in 149 medical students

Vaccination history	IgG antibody positive	
	No. (%)	No. (% of category)
Measles		
Unknown	19 (13)	17 (89)
0 doses	26 (17)	25 (96)
1 dose	68 (46)	55 (81)
2 doses	36 (24)	29 (81)
Total	149 (100)	126 (85)
Mumps		
Unknown	19 (13)	16 (84)
0 doses	35 (23)	26 (74)
1 dose	73 (49)	66 (90)
2 doses	22 (15)	19 (86)
Total	149 (100)	127 (85)
Rubella		
Unknown	18 (12)	17 (94)
0 doses	40 (27)	30 (75)
1 dose	76 (51)	75 (99)
2 doses	15 (10)	15 (100)
Total	149 (100)	137 (92)

one or two doses (89 and 99%, respectively; both $p = 0.03$, $p < 0.0001$).

None of the 170 students had received any immunization against varicella zoster virus (VZV) and 144 (97%) of 149 individuals were seropositive.

Hepatitis B immunization status and results of HBs antibody analyses are demonstrated in Table 2. One hundred forty-five (85%) of 170 students had written proof of a complete primary immunization series. A further 9 (5%) students had received one or two doses, 4 (3%) students were unvaccinated and the remaining 12 (7%) had no documentation of previous immunizations.

Anti-HBs-IgG antibody analyses revealed values ≥ 10 IU/l in 155 (91%) of the students, including 11 of 12 students with unknown hepatitis B immunization histories. One of the 11 seropositive students with unknown hepatitis B immunization history was anti-HBc-IgG positive (but HBs-antigen negative). This indicates that 10 of the 12 students with unknown hepatitis B immunization histories obviously had undocumented previous immunizations.

Table 2
Comparison of number of hepatitis B vaccine doses and serum anti-HBs antibody values in 170 medical students

Number of hepatitis B vaccine doses	Anti-HBs antibody values			
	All No. (%)	0–<10 IU/l	≥ 10 IU/l	≥ 100 IU/l
0	4 (2)	4	0	0
1	3 (2)	2	1	1
2	6 (4)	1	5	3
≥ 3	145** (85)	7 (5)	138 (81)	113 (78)
Unknown*	12 (7)	1 (8)	11 (92)	10 (83)
Total	170	15 (9)	155 (91)	127 (75)

* Missing immunization records.

** $n = 124$ with serology performed in this study and 21 students with previously documented anti-HBs antibodies ≥ 100 IU/l.

Anti-HBs values < 10 IU/l were found in 15 (9%) individuals: four with no previous doses, two with one dose, one with two doses, seven with ≥ 3 doses and 1 with no documentation of any immunization. However, in five of them anti-HBs antibodies had previously been measured elsewhere with values ≥ 10 IU/l.

Only 26% of the students had been immunized according to current recommendations including two doses of MMR. Thirty four percent of the students had complete and up-to-date immunizations against diphtheria, tetanus, poliomyelitis, hepatitis B and at least one documented dose of MMR; furthermore, 117 (69%) had been vaccinated in childhood with at least 3 doses against pertussis.

3.3. Recommended immunizations

Of the 170 students, 125 (74%) fulfilled the criteria for one or more catch-up immunizations. Four (3%) students declined them, 97 (78%) received them from us, 11 (9%) missed the appointments made for vaccinations and 13 (10%) preferred appointments with their family physicians and were lost for further follow-up.

The following results refer to those 97 students who were immunized by us. All 22 students who were initially seronegative for measles seroconverted (appearance of specific IgG serum antibodies) after immunization and 7 (32%) also responded with specific IgM (6 students with a previous history of a single dose of measles and one with a history of two previous doses).

Of 18 students with negative IgG values against mumps, 17 responded to one dose whereas one student required 2 further doses before seroconversion occurred. Five (28%) of the 18 vaccinees developed IgM antibodies: two who had not been immunized before and three who had previously been vaccinated once against mumps.

Eight of 10 seronegative students, who received a dose of rubella vaccine, responded with both IgM and IgG antibodies; one student developed IgG antibodies only and one remained negative. All eight vaccinees with an IgM response had a negative history of previous immunization against rubella. The student with IgG response but no IgM antibodies had previously received a single dose of rubella immunization.

Of the six students without measurable IgG antibodies against VZV, five were immunized. A post immunization blood specimen was available in four of them and all demonstrated seroconversion.

All seven students with anti-HBs antibody values <10 IU/l and no previous documentation of values ≥ 10 IU/l had previously received <3 doses of hepatitis B vaccine. Missing doses were offered, accepted, administered and documented. Success of immunization was confirmed by serology in five of those students and delegated to the family physician in the remaining two.

Necessary immunizations against diphtheria, tetanus and/or poliomyelitis were offered, performed and documented.

3.4. Personal history of previous infections with measles, mumps and rubella and seroprevalence in unimmunized students

Of the 25 students without previous immunization against measles but positive IgG antibodies, a “definite” history of measles was reported in 14 (56%), “probable” in four (16%), “possible” in three (12%) and “unknown” in four (16%) individuals. The only student with a negative history was also seronegative.

History of previous infection with mumps virus in 26 seropositive but previously unimmunized students was “definite” in 18 (69%), “probable” in two (8%), “possible” in one (4%) and “unknown” in five (19%) of them. Of the nine seronegative students, five had a negative history, one had a “definite” history, two had a “possible” history and in one it was “unknown”.

With respect to rubella, history of the 30 seropositive unimmunized students was “definite” in 14 (47%), “probable” in three, “possible” in two, “negative” in six and “unknown” in five individuals. Of the 10 seronegative students, seven had a negative history and history was “probable”, “definite” and “unknown” in one case each.

History of previous VZV infection in 144 seropositive students was “definite” in 102 (71%), “probable” in 17 (12%), “possible” in two, “negative” in 11 (8%) and “unknown” in 12 (8%) individuals. Of the five seronegative students two had a negative history and history was “probable”, “definite” and “unknown” in one case each.

4. Discussion

It has been shown in the past that medical schools frequently do not control the immunization status of their students and in consequence outbreaks with vaccine-preventable infectious diseases involving students do occur [2–4,6,8–10]. We performed a study to explore the immunization status of students with a rotation in our hospital and also examined seroprevalence rates for selected vaccine preventable infectious diseases. Further, intervention was offered if necessary.

Not surprisingly, we discovered significant immunization gaps and suboptimal seroprevalence rates indicating inadequate immunity against various vaccine-preventable diseases among the 170 students. Eighty seven percent of them had immunization records dating back to birth. Although the great majority of students had a complete primary immunization series against diphtheria, tetanus and poliomyelitis, up to 41% of them were lacking one or more booster doses. Similarly, a survey from Geneva had revealed immunization gaps for tetanus, diphtheria and poliomyelitis in 29–54% of medical students [3].

Regarding pertussis, 31% of the students were unimmunized; this probably mirrors safety concerns with pertussis whole cell vaccines from the past [11]. Also, immunization rates for measles, mumps and rubella were low, ranging from 61 to 70%. This is disappointing in light of the fact that measles vaccine has been recommended for children in Switzerland since 1976 and MMR combination vaccine was introduced in 1981. Furthermore, catch-up immunization has been generally recommended since 1985 [12]. Of immunized students, 10–20% had no IgG serum antibodies against measles and mumps whereas almost all of them were positive for rubella. The lack of measles and mumps antibodies either reflects primary vaccine failure or more probably loss of detectable antibodies over time. In accordance with this hypothesis, rubella vaccine had frequently been administered in adolescence and therefore antibodies were still measurable in almost all vaccinees.

In comparison, unimmunized students demonstrated specific IgG antibodies against measles, mumps and rubella at rates of 96, 74 and 75%, respectively. The lower seroprevalence of mumps and rubella antibodies compared to those against measles probably reflect the different endemic situations in the past with a higher likelihood for unimmunized individuals to contract measles than mumps or rubella during childhood and adolescence. In accordance with our findings, significant MMR immunization gaps and serological evidence for susceptibility has previously been demonstrated in medical students from other parts of Switzerland [2,3] and several other countries [9,13–15].

The results regarding hepatitis B in this study are of concern. Two percent of the students were unimmunized, 6% were partially immunized and in 7% hepatitis B immunization status was unknown. Overall, 9% of all students had never documented anti-HBs ≥ 10 IU/l.

In consequence of these results, catch-up immunizations were deemed necessary for 74% of the students and the great majority (88%) accepted them. No serious adverse reactions occurred. As expected, one dose of vaccine was generally sufficient to induce measurable IgG serum antibodies against measles, mumps and rubella. Most students who were initially seronegative responded with IgG antibodies only, which is in accordance with a secondary immune response. However, about a third of the vaccinees, most of them previously

unimmunized, responded with IgM and IgG serum antibodies, which is compatible with a primary immune response [16,17].

Although the combination of historical and serological screening has been advocated because of reduced costs compared to a universal vaccination strategy [18], historical information on measles, mumps and rubella infection was not a reliable predictor of immunity in unimmunized students in our study. Other surveys among medical students came to similar conclusions [15,19]. Given the considerable risk of acquisition and transmission of these viruses to patients, serological screening or, alternatively, universal administration of MMR to those without at least two documented previous doses, appears to be justified.

With respect to varicella, it has also been shown that a positive history does not assure the presence of protective serum antibody values and universal testing of new house officers has been recommended [20].

Based on the findings of this study, we established the following immunization policy for our medical students [7]:

- (1) Missing primary or booster immunizations against diphtheria, tetanus and poliomyelitis are recommended and administered if accepted.
- (2) Missing doses of primary immunization against hepatitis B are recommended and administered if accepted, followed by anti-HBs antibody analysis 4 weeks after the final dose. If a complete primary immunization series against hepatitis B has been documented but no proof of an anti-HBs antibody value of ≥ 10 IU/l is available, serum antibody analysis is offered. If the result is < 10 IU/l, a booster dose is offered and serum analysis is repeated 4 weeks later.
- (3) Immediate catch-up immunization is recommended to students with less than 2 documented doses of MMR.
- (4) Serological testing for VZV-IgG is recommended and followed by immunization in seronegatives.

In conclusion, medical students frequently have immunization gaps. Compliance with both evaluation and corrective intervention was excellent. We would like to propose consideration of similar immunization programmes for other medical schools, preferably to be conducted before the students get in contact with patients.

Acknowledgements

We are most grateful to our laboratory technicians Jacqueline Glaus and Gaby Tusch for performing serum antibody analyses. Continuous support by Mrs. Hildegard Schär, registered nurse in our employee health care service, is acknowledged.

References

- [1] Clever LH, LeGuyader Y. Infectious risks for health care workers. *Annu Rev Public Health* 1995;16(1):141–64.
- [2] Germann D, Matter L. Raising the immunization rate in medical students against measles, mumps and rubella at the University of Berne. *Schweiz Med Wochenschr* 1999;129(13):499–507.
- [3] Loutan L, Maitre B, Zuber P. Are medical students sufficiently vaccinated? results of a serological survey and of vaccine coverage. *Soz Präventivmed* 1994;39(2):86–92.
- [4] Poland GA, Nichol KL. Medical schools and immunization policies: missed opportunities for disease prevention. *Ann Intern Med* 1990;113(8):628–31.
- [5] Radon K, Klewer J, Nowak D. Vaccination status of medical students in Munich—results of a questionnaire survey. *Gesundheitswesen* 2001;63(8–9):573–7.
- [6] Rowan MS, Carter AO, Walker VJ. Immunization policies in Canadian medical schools. *Can Med Assoc J* 1994;151(7):957–61.
- [7] Baer G, Bonhoeffer J, Schaad UB, Heininger U. Protection against vaccine-preventable diseases in medical students. *Pediatr Infect Dis J* 2003;22(4):373–4.
- [8] Lane NE, Paul RI, Bratcher DF, Stover BH. A survey of policies at children's hospitals regarding immunity of healthcare workers: are physicians protected? *Infect Control Hosp Epidemiol* 1997;18(6):400–4.
- [9] Villasis-Keever MA, Pena LA, Miranda-Novales G, et al. Prevalence of serological markers against measles, rubella, varicella, hepatitis B, hepatitis C, and human immunodeficiency virus among medical residents in Mexico. *Prev Med* 2001;32(5):424–8.
- [10] Poland GA, Nichol KL. Medical students as sources of rubella and measles outbreaks. *Arch Intern Med* 1990;150(1):44–6.
- [11] Cherry JD. Historical review of pertussis and the classical vaccine. *J Infect Dis* 1996;174(suppl 3):S259–63.
- [12] Bundesamt für Gesundheit, Schweizerische Kommission für Impffragen. Richtlinien zur Bekämpfung übertragbarer Krankheiten: impfplan für routinemässige Schutzimpfungen. In: Schorr D, editor. Infektionskrankheiten: diagnose und Bekämpfung. Bern, Bundesamt für Gesundheit, 1998, suppl VIII, p. 1–4.
- [13] Oliveira J, Dias N, Ferreira TM, et al. The determination of susceptibility to measles, rubella, mumps and chickenpox in students of health-related areas. *Acta Med Port* 1999;12(4–6):155–60.
- [14] Schoub BD, Johnson S, McAnerney JM, Borkon L. Susceptibility to poliomyelitis, measles, mumps and rubella in university students. *S Afr Med J* 1990;77(1):18–20.
- [15] Murray DL, Lynch MA. Determination of immune status to measles, rubella, and varicella-zoster viruses among medical students: assessment of historical information. *Am J Public Health* 1988;78(7):836–8.
- [16] Butler AB, Scott RM, Schydlower M, Lampe RM, Schwab JA, Muelenaer AA. The immunoglobulin response to reimmunization with rubella vaccine. *J Pediatr* 1981;99(4):531–4.
- [17] Matter L, Kogelschatz K, Germann D. Serum levels of rubella virus antibodies indicating immunity: response to vaccination of subjects with low or undetectable antibody concentrations. *J Infect Dis* 1997;175(4):749–55.
- [18] Ferson MJ, Robertson PW, Whybin LR. Cost effectiveness of prevaccination screening of health care workers for immunity to measles, rubella and mumps. *Med J Aust* 1994;160(8):478–82.
- [19] Nichol KL, Olson R. Medical students exposure and immunity to vaccine-preventable diseases. *Arch Intern Med* 1993;153(16):1913–6.
- [20] Alagappan K, Fu LK, Strater S, Atreidis V, Auerbach C. Seroprevalence of varicella antibodies among new house officers. *Ann Emerg Med* 1999;33(5):516–9.