Vaccine-Preventable Diseases Requiring Hospitalization

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abstract

BACKGROUND: Plain children often have lower immunization rates than non-Plain children. Penn State Health Children's Hospital is a tertiary medical center with large nearby Plain (Amish and Mennonite) communities. We sought to describe the characteristics of children hospitalized with vaccine-preventable diseases (VPDs). We hypothesized that Amish children would have a higher risk of VPDs than non-Amish children.

METHODS: *International Classification of Diseases, Ninth Revision* codes were used to identify patients <18 years diagnosed with a VPD from January 1, 2005, to December 31, 2015, at Penn State Children's Hospital. Demographic information, immunization status, and outcomes were obtained from medical records. By using the number of children in our primary service area, we calculated the risk of VPD requiring hospitalization for Amish and non-Amish children. We assessed the relationship between Plain affiliation and vaccination status by using the Pearson correlation coefficient.

RESULTS: There were 215 children with 221 VPDs. Most occurred in non-Plain children: 179 of 221 (81%). Except for pneumococcal infections, VPD occurred mostly in unvaccinated or immunocompromised children, regardless of Plain affiliation. There were 15 *Haemophilus influenzae* type b and 5 tetanus infections that occurred in children with an unvaccinated or unknown vaccination status. The risk of a VPD requiring hospitalization was greater for Amish than for non-Plain children (risk ratio: 2.67 [95% confidence interval: 1.87–3.82]). There was a strong correlation between Plain affiliation and lack of vaccination ($r = -0.63$, $P < .01$).

CONCLUSIONS: Amish children had an increased risk of a VPD requiring hospitalization than non-Plain children. With the exception of those with pneumococcal disease, most vaccinated children hospitalized with a VPD were immunocompromised.

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WHAT'S KNOWN ON THIS SUBJECT: Children who are not vaccinated remain at risk for vaccine-preventable diseases. Plain children are less likely to be vaccinated than their non-Plain peers.

WHAT THIS STUDY ADDS: *Haemophilus influenzae* type b infections and tetanus still occur among unvaccinated Plain children. Varicella disease occurs among immunocompromised children independent of vaccination status. Amish children have an increased risk of vaccine-preventable diseases compared with non-Amish children.

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Widespread vaccination against common infectious diseases has decreased morbidity and mortality of children in the United States.[1] Despite these successes, some children remain unvaccinated because of religious or cultural reasons, including a concern that vaccine production involves fetal tissue,[2,3] concerns about vaccine safety,[3–5] or a belief that the risk for vaccine-preventable diseases (VPDs) is low or that infection with a VPD is preferable to vaccination.[4]

Although previous studies have suggested that Plain communities are not universally opposed to vaccination, these groups often have lower immunization rates than the general population.[3,6,7] Plain peoples are also at increased risk for some immunocompromising conditions because of genetic predisopositions.[8–11] Penn State Health Children's Hospital is a tertiary care pediatric hospital that serves as a referral center for large Amish and Mennonite communities located in central Pennsylvania. We sought to describe the characteristics of patients hospitalized at our institution over the last 10 years with VPDs and to compare Plain children with VPDs to non-Plain children with VPDs.

METHODS

Study Population

By accessing the electronic medical record of Penn State Health Children's Hospital, we used *International Classification of Diseases, Ninth Revision* codes to identify all patients <18 years old discharged from the hospital with a VPD from January 2005 to December 2015 (Supplemental Table 3). Hospital stays with a code for diphtheria, pertussis, hepatitis B, tetanus, measles, rubella, mumps, or varicella; meningitis or bacteremia because of *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis*, or *Streptococcus pneumoniae*; or pneumonia because of *S pneumoniae* were included. Cases of *H influenzae* pneumonia were excluded because serotype analyses were not performed. Varicella cases with only a localized rash were excluded as presumed reactivation disease.

The electronic medical records of all identified patients were reviewed, and demographic information, religious affiliation, past medical history, and immunization status were recorded. We considered patients who self-identified as belonging to either an Amish or Mennonite faith collectively as "Plain." All other patients were considered to be non-Plain. Immunocompromise was defined by the following criteria: current treatment of a malignancy; previous organ transplant, including hematopoietic stem cell transplant; having a diagnosis of a primary immunodeficiency; HIV infection; or current treatment with medications known to reduce immune function (eg, chronic corticosteroids or biologics). Patients were considered to be unvaccinated for the admission VPD if they had received no vaccines, if vaccinations were incomplete such that they were not vaccinated against the admission VPD, or if they were receiving vaccinations according to the recommended schedule[12] but were not yet old enough to have been vaccinated for the admission VPD.

Statistical Analysis

We compared demographic characteristics of Plain and non-Plain patients by using a χ^2 test or Fisher's exact test for categorical variables and a Wilcoxon rank test for continuous variables. We compared the proportion of VPD cases that occurred in unvaccinated children with that for vaccinated children by using a χ^2 test. Similarly, we compared the proportion of VPD cases occurring in immunocompromised patients with those that occurred in immunocompetent patients. We compared the proportion of immunocompetent, vaccinated patients with VPD with those who were either unvaccinated or immunocompromised by using a χ^2 test. By using the 25 618 Amish and 352 732 non-Amish residents <18 years old in our primary service area, we calculated the incidence of VPD per 10 000 children. We calculated the relative risk (RR) of hospitalization for a VPD for Amish versus non-Amish children. We assessed the relationship between Plain affiliation and vaccination status by using a Pearson correlation coefficient.

For each VPD and overall, we determined the annual frequency. Because not all pneumococcal and meningococcal infections can be prevented by vaccination, and because serotyping was not performed, we were unable to reliably determine if these infections were actually vaccine preventable. Additionally, for children hospitalized with varicella, we could not effectively distinguish between primary and reactivation disease. For this reason, we repeated our analyses with pneumococcal, meningococcal, and varicella infections excluded as a post hoc analysis. We calculated the RR of experiencing a VPD hospitalization for Amish and non-Amish children with these 3 conditions excluded as a sensitivity analysis. Data were collected and managed by using REDCap,[13] and the statistical analysis was performed by using Stata 14 (StataCorp, College Station, TX). This study was approved by the Human Subjects Protection Office of Penn State University's College of Medicine with a waiver of consent.

RESULTS

Overall, we identified 215 children with 221 VPDs requiring

hospitalization (Table 1). There were no cases of rubella, measles, hepatitis B, or diphtheria during the 10-year study period. Most VPDs occurred in non-Plain children (174 of 215, 81%) who were immunocompetent (186 of 215, 86%) (Fig 1). Most patients were vaccinated against the admission VPD (135 of 221, 61%). For those unvaccinated for the admission VPD, 20 (9%) had received the vaccination recommended for their age but were too young to have received the relevant vaccine, 9 (4%) were receiving vaccinations but were not up to date for their age (Table 2), 32 (14%) were completely unvaccinated, and 25 (11%) had no vaccine information documented in the medical record. More Plain children were unvaccinated for the admission VPD than were non-Plain children (34 of 37 [92%] vs 27 of 159 [17%], $P < .001$), and there was a strong correlation between Plain affiliation and lack of vaccination ($r = -0.63$, $P < .01$). Pneumococcal infection (159 of 221, 72%) was the most common VPD.

TABLE 1 Demographics

	Non-Plain, $N = 179$ (%)	Plain, $N = 42$ (%)	P
Age, y			.36
<1	42 (24)	14 (33)	—
1–5	81 (45)	16 (38)	—
6–12	28 (16)	10 (24)	—
>12	27 (15)	2 (5)	—
Race			<.01
White	115 (64)	42 (100)	—
African American	22 (12)	0 (0)	—
Other	9 (5)	0 (0)	—
Not reported	33 (18)	0 (0)	—
Ethnicity			<.01
Hispanic	30 (17)	0 (0)	—
Non-Hispanic	112 (63)	29 (69)	—
Not reported	36 (20)	13 (31)	—
Male sex	111 (62)	21 (50)	.11
Vaccination status			<.01
Unvaccinated for admission VPD	27 (15)	34 (81)	—
Vaccinated for admission VPD	132 (74)	3 (7)	—
Unknown	20 (11)	5 (12)	—
Immunocompromising condition			.65
Malignancy	12 (7)	5 (12)	—
Primary immunodeficiency	5 (3)	1 (2)	—
HIV infection	2 (1)	0 (0)	—
Immunosuppressing medication use	6 (3)	0 (0)	—
None	154 (86)	36 (86)	—
Infection type			<.01
Hib	0 (0)	15 (36)	—
Meningococcus	11 (6)	1 (2)	—
Pertussis	7 (4)	1 (2)	—
Pneumococcus	148 (83)	11 (26)	—
Tetanus	1 (1)	4 (10)	—
Varicella	12 (7)	10 (24)	—
Died	2 (1)	2 (5)	.16

—, not applicable.

Hib and tetanus were the only VPDs to occur more frequently in Plain children than in non-Plain children. There were 15 Hib infections; all of these occurred in Plain children who were unvaccinated or had an unknown immunization status. Similarly, there were 5 patients with tetanus; all were unvaccinated and 4 of 5 (80%) were Plain children. We identified 22 varicella infections; most (12 of 22, 54%) occurred in non-Plain children. These patients presented with findings concerning for primary varicella: diffuse rash with or without fever, pneumonitis, or encephalitis. Eight (36%) patients had test results that were positive for immunoglobulin G before or at the time of hospitalization, which may have been because of previous vaccination or a remote primary infection. For meningococcal, pneumococcal, and pertussis infections, ~90% of cases occurred in non-Plain children. Most (6 of 8, 75%) of children admitted to the hospital with pertussis were immunocompetent but were unvaccinated because they were too young to receive the pertussis vaccine.

When pneumococcal infections were excluded, most (51 of 55, 93%) VPDs occurred in children who were either immunocompromised or unvaccinated. Sixty-eight percent of varicella cases occurred in immunocompromised children; most of these children had been vaccinated before becoming immunocompromised.

Compared with non-Plain children, Amish children had an increased risk of VPD requiring hospitalization (RR: 2.68; 95% confidence interval [CI]: 1.87–3.82). Outcomes after hospitalization for a VPD were similar for Plain and non-Plain children. Two children in each group died: 1% and 5%, respectively ($P = .16$). Both non-Plain children died after pneumococcal bacteremia; 1 Plain child died after Hib bacteremia infection and the other died after varicella infection. The child who died because of varicella was an unimmunized Amish boy with cartilage-hair hypoplasia admitted with pneumonitis who then developed refractory respiratory failure; the other 3 children were immunocompetent.

There were cases of VPD reported every year of the study period (Fig 2). The annual number of pneumococcal cases increased after the introduction of the 13-valent

TABLE 2 Reasons for Vaccination Delay

VPD	Age	Reason for Delay	Plain
Pertussis	4 mo	Ill during 2- and 4-mo well-child visits	No
Pneumococcal meningitis	3 mo	Unknown	No
Pneumococcal bacteremia and pneumonia	21 mo	Insurance problem	No
Varicella	5 y	Immunocompromised	No
Varicella	17 y	Immunocompromised	No
Varicella	9 y	Religious reasons for varicella and MMR	Yes
Varicella	5 y	Immunocompromised	Yes
Varicella	2 y	Unknown	Yes
Varicella	11 y	Immunocompromised	Yes

MMR, measles-mumps-rubella.

pneumococcal conjugate vaccine (PCV13) in 2010 rather than decreasing as would have been expected. This increased our concern that many of the pneumococcal infections seen in our hospital were because of nonvaccine strains. With these pneumococcal, meningococcal, and varicella cases excluded, 96% of the remaining VPDs occurred in children who were unvaccinated, had an unknown vaccination status, or were immunocompromised. When only including infections known to truly be vaccine preventable, the RR of experiencing hospitalization because of a VPD increased for Amish children compared with non-Plain children (RR: 31.60; 95% CI: 13.83–72.16).

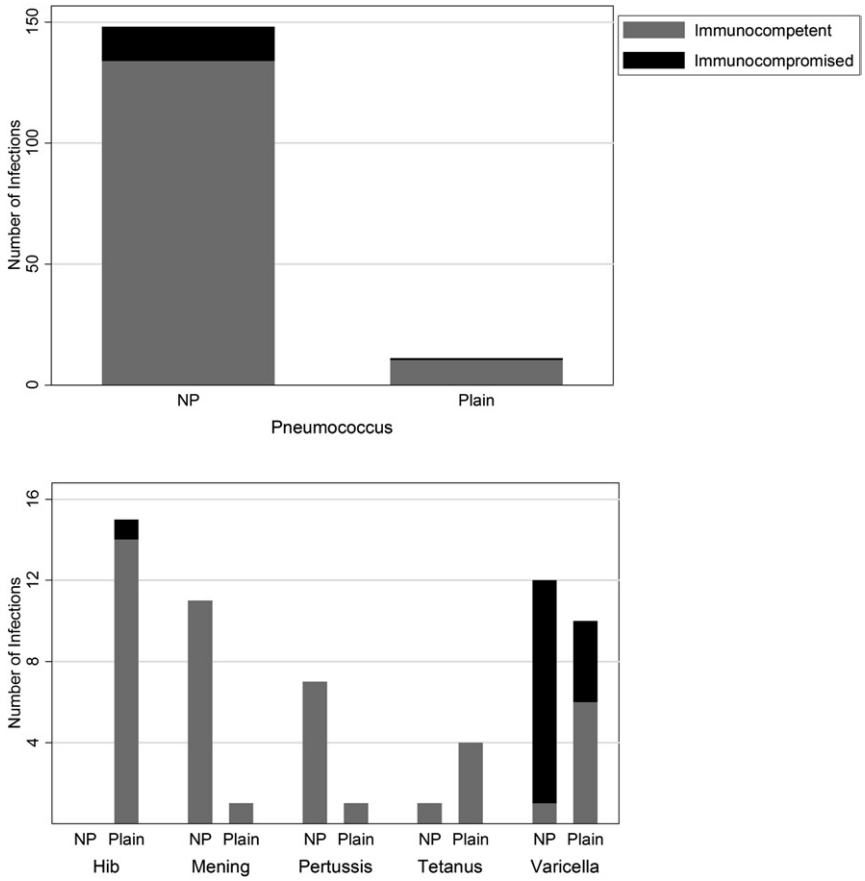

FIGURE 1
Total number of VPDs requiring hospitalization, 2005 to 2015. Mening, meningococcus; NP, non-Plain.

DISCUSSION

We found that Amish children were more than twice as likely to experience a VPD requiring hospitalization as non-Amish children. Most of the association between Plain-affiliation and VPD was driven by vaccination status. The authors of previous studies have demonstrated that Plain communities have lower vaccination rates than the general population.[3,7] Only 8% of the Plain children in our study were vaccinated. With the exception of those with pneumococcal disease, most vaccinated children hospitalized with a VPD were immunocompromised.

All Hib cases in our study occurred in Plain children who were unvaccinated or had an unknown vaccination status. Although cases have been reported in vaccinated, immunocompetent children, this is extremely rare and none occurred at our center during the 10 years evaluated.[14,15] Previous research suggests that central-Pennsylvania Plain communities may act as a reservoir for a Hib outbreak if vaccination rates in the general population decline to less than critical levels.[7] We found that Hib infections occurred sporadically throughout the study period with no major outbreaks, suggesting that current population seroprotection may be sufficient to prevent an Hib epidemic.

Nearly all cases of tetanus in the United States occur in incompletely vaccinated individuals.[16,17] In our cohort, tetanus was the least common VPD among those with at least 1 case and occurred only in unvaccinated children. Compared with other VPDs, tetanus had the highest median age, with the youngest child being 3 years old. This is likely because of increased exposure of older children to spores during outdoor play.

Meningococcal vaccination is first recommended at 11 to 12 years.[18]

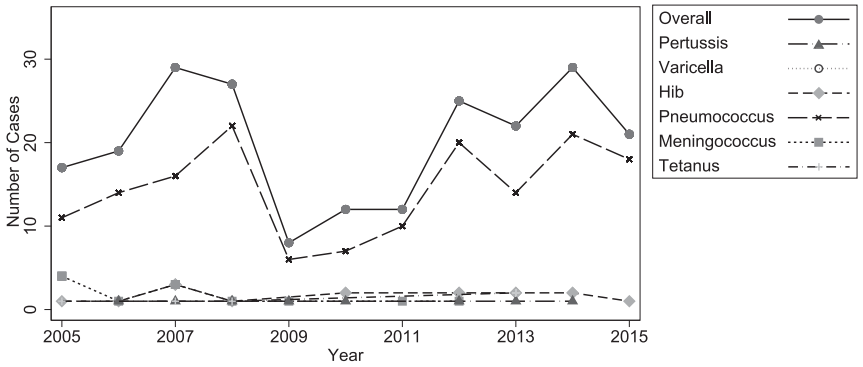

FIGURE 2
Annual number of VPDs requiring hospitalization, 2005 to 2015.

Earlier vaccination beginning at the age of 2 months is recommended for children with asplenia or complement deficiency.[19] Serogroup B vaccines were recently approved for individuals 16 to 23 years old. These vaccines are not yet widely used, and it is unlikely that any children included in this study would have received these vaccines.[18] Although vaccination has reduced cases of meningococcal disease among teenagers and adults, the current vaccination schedule leaves young children vulnerable to infection.[20] We found that 75% of patients with meningococcal disease were <11 years old and had not received any meningococcal vaccinations because of their ages. This is consistent with other studies that have revealed that the majority of meningococcal infections occur in children younger than the recommended vaccination age.[21] With this study, we confirm a continued susceptibility among many children and the need for additional studies to evaluate the safety and efficacy of meningococcal vaccines for universal use in younger children.[22]

A single dose of varicella vaccine is highly effective in preventing severe varicella disease.[23] Deaths caused by varicella have nearly been eliminated.[24] Most varicella cases in our cohort occurred in immunocompromised children. In contrast to most vaccines, varicella vaccination is contraindicated for immunocompromised patients because it contains live virus.[25] The only immunocompromised child in our cohort who died had varicella pneumonitis. Families of immunocompromised children should be counseled on the potential dangers of varicella infection and early use of acyclovir or varicella immune globulin should be considered for infected or exposed immunocompromised children.[26]

The 7-valent pneumococcal conjugate vaccine (PCV7) was 96% effective in preventing invasive disease because of the 7 serotypes contained in the vaccine.[27] In 2010, PCV13 added 6 serotypes to those contained in PCV7, further reducing the incidence of invasive pneumococcal disease by 64% overall and by 93% for PCV13 serotypes.[28] Pneumococcal infection was the most common VPD diagnosed at our hospital. In contrast to the other VPDs in our study, most children with pneumococcal disease were vaccinated (77%) and immunocompetent (91%). This suggests that at least some of these cases were caused by serotypes of *S pneumoniae* not covered in the vaccine, such that some cases were not truly vaccine preventable. Because serotype analysis is not routinely performed on pneumococcal isolates at our center, it is unknown how many cases were because of vaccine versus nonvaccine strains. During the study period, the recommended pneumococcal vaccine changed from PCV7 to PCV13.[29] However, we did not observe a change in the annual number of pneumococcal cases after this change. This further suggests that non-PCV13 serotypes may predominate in our cohort such that the additional serotype coverage did not result in additional decreases in the number of clinical infections.

With the exception of those with pneumococcal infections, most VPD patients were unvaccinated for the organism causing their VPD. Although not common in our cohort, we did observe cases of VPD requiring hospitalization occurring in children whose vaccinations had been delayed (2%). A survey conducted by the Centers for Disease Control and Prevention found that 27% of parents had delayed at least 1 vaccination for their child, with measles, mumps, and rubella; varicella; and influenza delayed most often.[30] Expert consensus suggests that a delay of 15 days to 1 month for the first dose of most vaccinations represents a "potentially dangerous delay."[31]

We found that Amish children had an increased risk of VPD requiring hospitalization compared with non-Plain children. Most, but not all, of this increased risk was driven by differences in vaccination coverage ($r = -0.65$). The Centers for Disease Control and Prevention estimates that 73% of children in Pennsylvania and 72% nationally are fully vaccinated.[32] The authors of previous studies of vaccine coverage among Pennsylvania Amish have noted coverage rates of 7% to 28%.[7] Additionally, a large survey of Ohio Amish found that most families that refuse vaccinations do so secondary to concerns about vaccine safety.[6] We were not able to determine the specific reasons that vaccines were

not administered for individual patients in our cohort.

There were several important limitations to this study. Because this was a retrospective study, laboratory testing was sent at the discretion of the treating clinician and was not standardized. *International Classification of Diseases, Ninth Revision* codes, rather than test results, were used to identify patients, so some cases of VPD may have been missed. Because patient information was obtained through review of the medical record, the immunization status and Plain affiliation could not be determined for a small number of patients. Additionally, because the immunization status was obtained from the medical record, it is possible that the vaccination status of some children was misclassified because the parent was mistaken about the child's immunization status or because the information was recorded incorrectly; this misclassification is believed to be small and unlikely to affect our overall conclusions. The authors of previous studies have found the accuracy of parental recall of vaccination status to range from 66% to 98%, and parents more often overreported the vaccines that were recieved.[33–36] We would expect the parental report that no vaccines had been received to be accurate. Because we do not have reliable estimates of the number of Mennonite families living in our service area, we were not able to calculate the incidence of VPDs requiring hospitalization for Plain peoples overall but were only able to do so for Amish children.

We only included children with VPDs who were hospitalized at Penn State Health Children's Hospital. It is likely that there were additional VPDs in the region that did not require hospitalization but were successfully treated as outpatients. As such, in our study, we describe incident cases of more severe VPDs rather than providing a comprehensive evaluation of all VPDs in the region. It is possible that some cases of VPD were treated at other hospitals in the region; however, our hospital is the only children's hospital within a 75-mile radius, and most pediatric patients requiring hospitalization for these infections were likely to have been admitted to our institution. It is possible that some of the infections in the non-Plain children were because of transmission from Plain children. However, Plain children often have little contact with non-Plain children, so the impact of these potential transmission events is likely to be small. Finally, no serotyping was performed on the meningococcal or pneumococcal isolates; it is possible that many of these infections were not actually vaccine preventable.

However, when these infections were excluded from the analysis, the risk ratio comparing Amish and non-Plain children increased, suggesting that the association between Amish affiliation and hospitalization because of VPD is robust.

CONCLUSIONS

Although more VPDs occurred in non-Amish children, Amish children had an increased risk of a VPD requiring hospitalization compared with non-Amish children. Except for pneumococcus, all VPDs were more common in children who were either unvaccinated or immunocompromised. Ninety-two percent of Plain children were unvaccinated, suggesting that interventions to increase vaccination among these communities could decrease the number of VPDs admitted at our center.

ABBREVIATIONS

Hib: *Haemophilus influenzae* type b
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
RR: relative risk
VPD: vaccine-preventable disease

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