Journal of
TRAVEL MEDICINE

ORIGINAL ARTICLE

Using Locally Derived Seroprevalence Data on Measles, Mumps, Rubella, and Varicella by Birth Cohort to Determine Risks for Vaccine-Preventable Diseases During International Travel

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DOI: 10.1111/jtm.12235

Background. Measles, mumps, rubella, and varicella (MMRV) were common childhood diseases in the United States prior to the introduction of their respective vaccines. Measles was declared eliminated in the United States in 2000. However, 628 cases were reported in 2014, the majority of which have been linked to international travel. The study team set out to investigate the seroprevalence of MMRV in our local population to determine whether such a process can lead to meaningful recommendations for assessing travelers at risk.

Methods. We conducted a cross-sectional seroprevalence study using a quota sampling method. A total of 460 leftover serum samples were collected from individuals born prior to 1996, who live in the Lehigh Valley region of southeast Pennsylvania. The samples were allocated to five birth-year cohorts, and the seroprevalence of each cohort to MMRV was compared. Additionally, overall seroprevalence of each disease was compared with data from prior national studies. Gender differences within each birth cohort were also assessed.

Results. The overall seroprevalence values of measles, mumps, rubella, and varicella were 85.8, 82.8, 96.6, and 97.4%, respectively. There were significant associations between seroprevalence and birth cohort for measles ($p = 0.01$) as well as mumps ($p = 0.037$). The overall seroprevalence for our study sample was significantly different from the national seroprevalence results of measles, mumps, and rubella.

Conclusions. Our study showed dramatically lower immunity rates for measles and mumps than those shown by prior national seroprevalence studies. The rates in many of the later birth cohorts born after 1966 were significantly lower than the rates reported as necessary to sustain herd immunity. Given that patients' immunization records are not always available or complete, collecting local seroprevalence data may be necessary to more accurately recommend antibody testing and vaccination during pre-travel assessments.

Measles, mumps, rubella, and varicella (MMRV) are often thought of as mild childhood illnesses, but mortality due to measles can be as high as 10%[1] and varicella caused 100 to 150 deaths/year in the United States prior to the introduction of the vaccine in 1995.[2] In addition, morbidities associated with these diseases include infertility, encephalitis, and shingles. Secondary negative impacts include high economic costs that, according to Centers for Disease Control and Prevention (CDC) estimates, can range from $5,000 to $167,000 per case.[3]

These diseases were common in the United States prior to the introduction of their respective vaccines. Measles vaccine was introduced in 1963; by 2000, endemic cases of measles were declared eliminated from the United States.[3,4] Mumps and rubella vaccinations were introduced in 1967 and 1969, respectively; by 2004, rubella was also declared no longer endemic.[5] The introduction of the varicella vaccine in 1995 reduced

This work was presented at ID Week on October 8, 2014 in Philadelphia, PA, and at the 14th annual conference of the International Society of Travel Medicine, May 24 to 28, 2015, in Québec City, Canada.

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the estimated annual incidence from 15 to 16 cases per 1,000[6] to current average rates of 1.1 to 3.8 cases per 1,000 people.[7]

Over the past 50 years, dramatic declines in the incidences of these common viral infections have suggested the elimination of these childhood diseases. However, there continue to be regions in the world where they are highly prevalent. Measles, eg, remains a common disease in some parts of Europe, Asia, Africa, the Pacific islands, and in some regions of the Americas,[8] with ~20 million cases occurring globally each year.[9] These continued outbreaks stress the need for increased immunization and improved pre-travel counseling.[10]

Presently, most cases of measles occurring in the United States result from the transmission of the disease from international travelers to unvaccinated individuals.[8] Recently, the annual number of US measles cases has been growing steadily with 134 cases reported in 2008 and 222 in 2011.[11] In 2014, there were already 288 confirmed cases reported by May 23. Forty of these were direct importations and 97% associated with importations; in addition, of the people who contracted the disease, most were either not vaccinated (69%) or had an unknown vaccination status (20%).[11] By the end of 2014, a total 628 confirmed measles cases were reported—more than three times the number of cases in 2013.[12] Most were attributed by the World Health Organization to be either directly imported or import-related[13]; a majority of these were associated with an ongoing severe outbreak in the Philippines[14] where more than 57,000 suspected cases and 110 resulting deaths were reported.[15] In 2015, as of April 2, 159 measles cases were reported in the United States. The majority of these were due to a single outbreak of 111 cases that has been traced to exposures occurring in the Disneyland theme park in California.[16]

The continued prevalence of these diseases outside the United States, and increasing outbreaks within, compels investigation into populations at increased risk of acquiring these diseases as well as into measures to mitigate that risk. Previous studies have provided valuable information regarding immunity[17–20]; however, many of them have looked at only a single viral disease and, being based on national survey data, have limited applicability to our unique local population. Because previous imported measles outbreaks typically involved localized geographic regions, presumably because of the regions' lower immunity rates, determining local seroprevalence is critical. However, we have found few prior studies on local seroprevalence of these common infections.

We set out to estimate the seroprevalence of MMRV by age (birth cohort), within a local population from the Lehigh Valley region of southeast Pennsylvania, hypothesizing that we would observe significant differences by birth cohort in the seroprevalence in our population of these vaccine-preventable diseases.

Methods

This cross-sectional study, approved by our organization's institutional review board, was designed to determine the seroprevalence of MMRV in the Lehigh Valley population. A quota sampling method was used to ensure that an equal number of males and females were included in each birth cohort. Our local laboratory routinely stores serum samples for 3 days at 2°C to 8°C, according to manufacturer recommendations, in the event that tests may need to be re-run or added. From these leftover outpatient serum samples, taken between November 2013 and February 2014, we tested for viral antibodies within a 24- to 72-hour period post-collection to provide data for this study. The samples were collected sequentially, confirmed to be unique, and de-identified so that the only remaining demographic variables were sex, birth year, and zip code. Neither the laboratory personnel who tested the samples nor the researchers received any patient identifiers.

A total of 460 samples were collected and grouped into five birth cohorts, selected on the basis of previous immunity studies[17–20]: birth year before 1957 ($n = 52$), 1957 to 1966 ($n = 109$), 1967 to 1976 ($n = 117$), 1977 to 1988 ($n = 121$), and 1989 to 1995 ($n = 61$). Each sample was tested for immunoglobulin G (IgG) antibodies to MMRV using commercially available enzyme-immuno assays. The reported sensitivities of these tests ranged from 98.8% to 99.4%; the relative specificities ranged from 91% to 97%. Immunity was defined with values of IgG ≥10 IU/mL for rubella and >1.09 IU/mL for measles, mumps, and varicella. The values between 5 and 9 IU/mL for rubella were considered equivocal and excluded from the analysis ($n = 21$). Similarly, the values between 0.91 and 1.09 IU/mL for measles, mumps, and varicella were considered equivocal and excluded from the analysis ($n = 29$, 18, and 7, respectively).

We conducted an a priori sample-size analysis based on published literature, which has suggested differential baseline immunity by age cohorts. The projected sample size for this study was determined to be 400 ($n = 50$ for the before 1957 and 1989 to 1995 birth cohorts and $n = 100$ for the other three). However, to account for those samples deemed equivocal, 460 actual samples were included, enabling detection of a between-cohort difference of ~10% with 80% power and an α of 0.05, assuming a difference truly exists. The smaller sample projection for the before 1957 and 1989 to 1995 birth cohorts was based on the assumption of a higher prevalence of immunity in these groups and, hence, the greater potential difference between them and the other cohorts.

After excluding the equivocal results, the total analysis sample consisted of 431 samples for measles, 442 for mumps, 439 for rubella, and 453 for varicella. Age was summarized for each birth cohort and reported as a mean with standard deviation and range. Also reported were the proportion of male and female samples within each birth cohort and the proportion

of samples demonstrating immunity to each disease, overall as well as within each birth cohort.

The chi-square test for independence was used to determine any statistically significant differences in the proportion of cases demonstrating immunity between birth cohorts for each disease. Multiple pairwise comparisons were conducted to identify specifically which cohorts were significantly different; consequently, the Bonferroni correction was applied to adjust the p value required for statistical significance. Fisher's exact test was used instead of the chi-square test for independence when expected cell counts were less than five. An additional analysis assessed whether there was a significant difference in the proportion of samples demonstrating immunity by gender within each birth cohort for each disease.

Comparing our study results with previously published seroprevalence data provided insight into the immunity of the Lehigh Valley population as compared with national peers. The chi-square goodness-of-fit test was used to compare the overall seroprevalence of measles, mumps, and rubella with national seroprevalence; however, as the seroprevalence of varicella was already high, it was excluded. We estimated the national seroprevalence of mumps and measles with the help of two studies that evaluated the 1999 to 2004 data from the National Health and Nutrition Examination Survey (NHANES).[18,19] A third study that evaluated the 1988 to 1994 data from NHANES III was used to estimate the national seroprevalence of rubella.[20] Because the latter study included only individuals born before 1984, we excluded our 1989 to 1995 birth cohort when comparing our local seroprevalence data of rubella with the national data.

SPSS version 22 (IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for the analysis. A p value of 0.05 was considered statistically significant unless otherwise specified (as for the multiple pairwise comparisons).

Results

During the study period, 460 samples (52% female, 48% male) were collected and grouped into five birth cohorts. The mean age and age ranges for each birth cohort are summarized in Table 1. There were approximately an equal number of males and females in each birth cohort (Table 2).

The total prevalence of humoral immunity to measles in our population was 85.8% (excluding equivocal results), significantly different from the reported US national seroprevalence of 95.9% ($p < 0.001$). The highest proportion of immunity was observed in persons born during the pre-vaccine era, before 1957 (98.1%). Overall, immunity decreased as cohorts got younger (see Figures 1 and 2). There was a statistically significant association between birth cohort and immunity to measles ($p = 0.01$). Specifically, statistically significant differences, even after the Bonferri correction adjustments (Table 3), were observed between the before 1957 and the 1967 to 1976 birth cohorts ($p = 0.005$) and between the before 1957 and the 1989 to 1995 cohorts ($p = 0.001$). More males than females showed humoral immunity in the 1989 to 1995 cohort: 92.6% of males versus 63.3% of females ($p = 0.009$).

Table 1 Mean age and range of ages by birth cohort

Birth cohort*	Mean ± SD	Range
Before 1957	72.6 ± 9.7	58–96
1957–1966	52.0 ± 2.8	47–57
1967–1976	41.8 ± 2.7	37–47
1977–1988	31.2 ± 3.5	25–37
1989–1995	21.5 ± 2.0	18–25

*Includes individuals with equivocal results.

Table 2 Gender of study population by birth cohort

Birth cohort*	Male N (%)	Female N (%)	Total N (%)
Before 1957	27 (51.9)	25 (48.1)	52 (100)
1957–1966	51 (46.8)	58 (53.2)	109 (100)
1967–1976	59 (50.4)	58 (49.6)	117 (100)
1977–1988	58 (47.9)	63 (52.1)	121 (100)
1989–1995	28 (45.9)	33 (54.1)	61 (100)
All cohorts	223 (48.4)	237 (52.0)	460

*Includes individuals with equivocal results.

Excluding the equivocal results, the prevalence of mumps immunity was 82.8%, significantly different from the reported national seroprevalence of 90% ($p < 0.001$). The percentage of immune people in each birth cohort decreased with age across the first three cohorts and then increased for the last two (Figure 2). There was a statistically significant association between birth cohort and immune status ($p = 0.037$); however, we did not have enough evidence after applying the Bonferroni correction to determine which cohorts were different (Table 3). We also failed to find a statistically significant association between gender and immunity to mumps.

The seroprevalence of IgG antibody to rubella virus in our study population was 96.6% (excluding the equivocal results). Overall, after excluding the 1989 to 1995 cohort, it was 96.1%, significantly different from the reported US national seroprevalence of 89.4% ($p < 0.001$). The percentage of population immune to rubella followed a trend similar to that of those immune to mumps, although the change was more gradual. Immunity decreased across the first three cohorts and increased in the last two (Figure 2). We failed to find statistically significant associations between birth cohort or gender and immunity to rubella.

The overall prevalence of varicella antibody among our study population was 97.4% (excluding the equivocal results). The seroprevalence within each cohort was relatively high compared to the other diseases. We failed

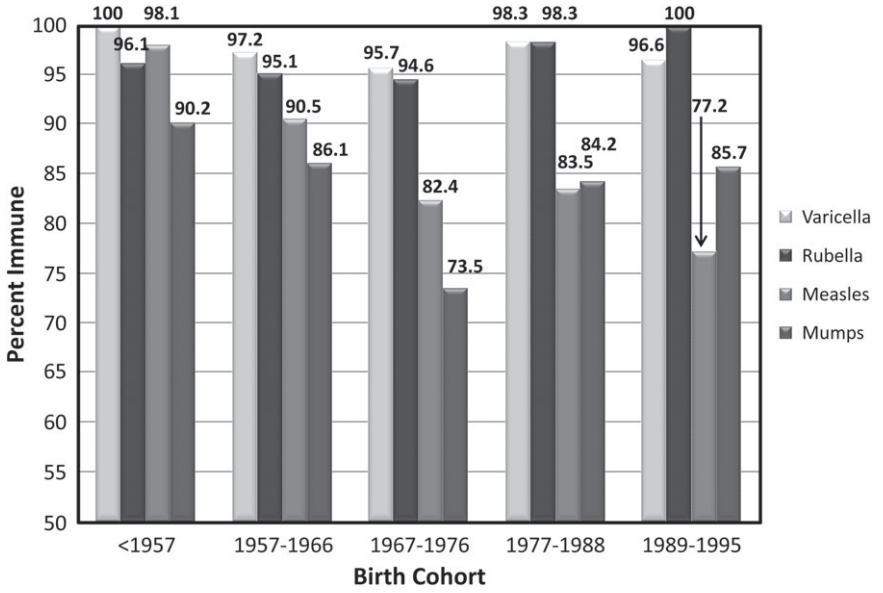

Figure 1 Bar chart of percentage of birth cohort immune to each disease (excluding equivocal).

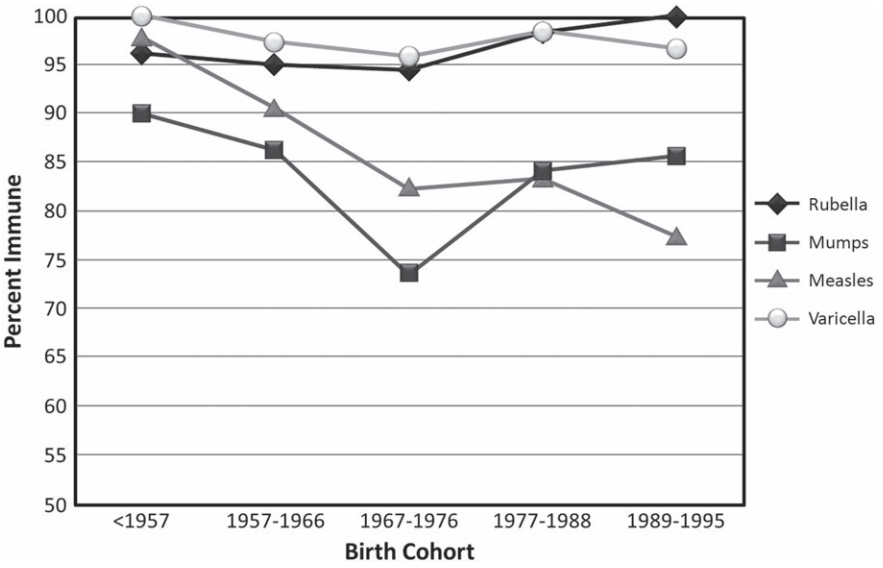

Figure 2 Line chart of percentage of birth cohort immune to each disease (excluding equivocal).

to find statistically significant associations between birth cohort or gender and immunity to varicella.

Discussion

Vaccination has lost popularity and credibility among many US residents for religious, philosophical, and personal reasons.[9] Given the global burden of illness, international travelers are at higher risk of contracting and becoming sources of disease. With the subsequent spread of disease to unvaccinated regional populations in the United States, it becomes increasingly important to either document immunity or immunize travelers for protection against these illnesses when going abroad.

Our study population showed significantly lower immunity rates to measles when compared with prior national data,[19] potentially explained by differences in demographics between our sample and that used for the comparison. Despite this finding, our data still follow a similar trend to the seroprevalence reported in NHANES in that measles immunity decreases among the first three cohorts and then increases slightly in the 1977 to 1988 cohort.[17,19]

In our data, the 1989 to 1995 cohort unexpectedly had the lowest immunity rate to measles, in direct contrast to data from McQuillan and colleagues,[19]

Table 3 Cross-tabulation results of pairwise comparisons for birth cohort by disease

Pairwise comparison	Rubella*	Mumps†	Measles†	Varicella*
<1957 to 1957–1966	1.000	0.468	**0.102**	0.552
<1957 to 1967–1976	1.000	0.015‡	0.005§	0.325
<1957 to 1977–1988	0.586	0.305	0.007‡	1.000
<1957 to 1989–1995	0.221	0.478	0.001§	0.497
1957–1966 to 1967–1976	**0.855**	0.019‡	0.086	0.723
1957–1966 to 1977–1988	0.257	0.691	0.130	0.675
1957–1966 to 1989–1995	0.161	0.945	0.021‡	1.000
1967–1976 to 1977–1988	0.162	0.047‡	0.833	0.446
1967–1976 to 1989–1995	0.097	0.072	0.420	1.000
1977–1988 to 1989–1995	1.000	0.798	0.323	0.604

*Calculated with Fisher's exact test (bolded number calculated with Pearson's chi-square test).
†Calculated with Pearson's chi-square test (bolded number calculated with Fisher's exact test).
‡Significant at the $p < 0.05$ level.
§Significant at the $p < 0.005$ level.

who demonstrated highest immunity rates in their 1987 to 1998 birth cohort. We had anticipated a similar finding in our youngest cohort because of the introduction of the measles, mumps, rubella (MMR) booster in 1989,[21,22] and plan to further assess our results. If our youngest population's low immunity rates are confirmed, re-evaluation of the current immunization practices in our region may be necessary.

Our measles data revealed seroprevalence that clearly falls below the threshold of herd immunity, the 93% to 95% vaccination rate needed to prevent disease re-introduction,[23] in all cohorts except for persons born before 1957. This birth cohort, not surprisingly, demonstrated the highest level of immunity against measles, probably because these individuals had measles exposure at some point in their lives. The low level of measles IgG seroprevalence across all cohorts may provide insight into the ongoing measles outbreaks, consistent with the 2014 outbreak reports[11,12] demonstrating that the overall immunity of the US population has diminished to below herd-immunity levels. Further national and local seroprevalence studies are needed to continue evaluating this trend.

These disturbingly low immunity levels in certain defined age cohorts stress the importance of vaccination campaigns in our region. Previous large measles outbreaks have occurred in areas with low vaccination rates: in Philadelphia from 1989 to 1991, 1,500 children acquired the disease and 9 died (most of them unvaccinated).[4] The largest and most recent outbreak in June 2014 is attributed to infected, unvaccinated travelers returning from the Philippines, spread primarily among unvaccinated Amish communities, with 374 cases reported.[14]

Like many of the cases that occurred in 2014, most of the 2015 cases can be linked to travel-related importations (96% of the 159 cases reported). In the Disneyland outbreak, which eventually spread beyond US borders, the index source was never identified. Of the total US cases reported in 2015, 45% were not vaccinated and 38% had no record of immunization available, confirming the importance of the two-dose measles vaccination schedule. Personal or religious beliefs were cited as reasons by 70.7% of those who were eligible for, and chose against, immunization. Of particular concern is that 40% of the described 2015 cases occurred in US citizens too young to be vaccinated.[16]

In our study population, the 1967 to 1976 cohort had the lowest level of immunity for all these diseases with the exception of measles, for which it had the second lowest level. This finding, consistent with prior national seroprevalence studies,[17,19,24] can be explained by low vaccination coverage among children before the 1981 implementation of school immunization requirement laws and the decline in availability during the 1967 to 1976 suspension of federal funding for measles vaccine. Additionally, during this cohort period, there was no recommendation for the second MMR booster, which was introduced in 1989.

Other interesting findings of this study include the higher immunity levels to rubella and varicella across all birth cohorts. Although the cause is unclear, we can postulate that the rubella vaccine has a longer-lasting immune response than the measles vaccine and that, because the varicella vaccination added a booster soon after introduction of the vaccine, seroprevalence levels were raised. We also noted an unexpected large gender difference in only the 1989 to 1995 birth cohort for measles, which may possibly be explained by the nonrandom sampling method used.

Our study has several limitations. Because of the retrospective nature of the study, we were not able to access the actual vaccination records for our sample population, which may have led to an underestimation of the actual degree of immunity. Also, we used a nonprobability sampling method as opposed to taking a true random sample of the population, which may have resulted in sampling bias. Although this method ensured an equal number of males and females within each cohort, the nonrandom sampling somewhat limits the generalizability of our results. Our inability to conclude

specifically which mumps cohorts were significantly different could be attributed to an insufficient sample size. Finally, we did not collect data on any potential confounders of immunity status other than birth cohort and gender. Therefore, some uncontrolled extraneous factors, such as country of birth or religious/ethical beliefs, could play a part in the results we observed.

Conclusion

The results of this study demonstrate the critical value of determining the local seroprevalence of vaccine-preventable diseases. The growing likelihood of ongoing global outbreaks reaching the United States via infected travelers makes paramount the importance of fostering routine childhood vaccinations and promoting pre-travel advice. The information gained from this study will guide our approach to assessing travelers' vaccination needs: specifically, antibody titers will be requested when recommended booster doses are not documented in the more vulnerable age groups. Such interventions, reproduced on a wider scale, may reduce travel-related importations of these diseases and their subsequent spread within under-immunized populations in the United States.

Acknowledgments

The authors acknowledge the very generous contributions by Jacqueline Grove, Network Office of Research & Innovation, Lehigh Valley Health Network, in the preparation and review of this manuscript. In addition, we acknowledge Kimberly A. Pacella, MT(ASCP)QCYM, Director of Clinical Operations, Health Network Laboratories, for her assistance in the specimen testing procedures. The authors are grateful to the Luther V. Rhodes Infectious Diseases Endowment for supporting this project.

Declaration of Interests

The authors state they have no conflicts of interest to declare.

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These kind of medical advertising boards stand at every check-in counter in Kaohsiung International Airport. Measles is one of the vaccine-preventable diseases, covered in the article by Rosario-Rosario et al. Setting: Kaohsiung, Taiwan. *Photo Credit: Eric Caumes*.