Ålderseffekter på Antikroppsnivåer mot Mässling, Påssjuka och Röda Hund hos Svenska Barnafödande Kvinnor

Age Cohort Effects on Measles, Mumps and Rubella Seroimmunity in Swedish Childbearing Women

Åsa Sahl 1985-08-11
Cord blood levels of measles, mumps and rubella (MMR) antibodies are analyzed in Swedish women of differing ages and giving birth at two different points in time. Questions concern differing immunity levels between groups of different vaccination histories (one, two or zero doses MMR vaccine), taken together or divided by age; and proportion of individuals per age group who carry sufficient protective immunity against each disease.

More vaccine was associated with lower measles and rubella immunity levels for most groups. Mumps immunity displayed an inconclusive pattern. All age groups in the sample exhibited acceptable proportions of protected individuals, but with questionable ability to generalize to the population.

Keywords: measles, mumps, rubella, IgG antibody, vaccination

*Statistics C, spring term 2011.
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Introduction

Measles, mumps and rubella in Sweden
In 1982, the combined measles, mumps and rubella (MMR) vaccine was implemented in the Swedish routine vaccination program [1]. Since then, the vaccine is offered to all Swedish children, with the first dose given at 18 months of age and the second one at either 12 years (children born prior to 2002), or 6-8 years of age (children born 2002 or later; these will not be represented in this study). A vast majority accept vaccination (96.2% in 2004, [1]), and all three diseases are uncommon in Sweden today [2]. However, there is still a possibility for future epidemics to strike if population immunity is not monitored properly. This study examines the immunity situation for a particularly sensitive group, namely childbearing women.

The Swedish National Board of Health and Welfare (Socialstyrelsen) [1,3] has the following to tell about the MMR diseases in Sweden.

Measles (morbilli) is caused by a virus that is highly contagious, and can have severe consequences, including blindness, brain damage, or death. Before vaccination was implemented, practically all children were infected at some point and developed a good natural immunity. As standards of living and hygienical practices improved, infection in older children and adults became more common, with increased risk of serious complications, such as pneumonia or encephalitis. Moreover, measles that is contracted during pregnancy can lead to spontaneous fetal death. Prior to 1971, tens of thousands of children were infected each year, with several hundred needing hospital care, and some being permanently brain damaged. Vaccination against measles was initiated during the 1970s, with mixed results. After the combined MMR vaccine was implemented in two doses in 1982, prevalence of the disease has dropped dramatically, and it is now considered to be eliminated in Sweden.

Mumps (parotitis) is a contagious but generally mild viral disease that affects the central nervous system, and causes swelling and soreness to the salivary glands, often in combination with fever. It can also affect other glands, including the testes, leading to painful testicular inflammation with a small risk for sterility. Another possible complication is meningitis, which bears some risk of permanent deafness on one side or both. Mumps was common in Sweden prior to vaccination, and the number of reported cases was quickly reduced to low levels after introduction of the MMR vaccine. In Finland, where the vaccine was implemented around the same time as in Sweden, incidence of younger individuals with impaired hearing has dropped considerably.

Rubella is a relatively harmless viral disease in most cases, but it can have serious consequences if it is contracted during pregnancy. If a pregnant woman is infected, rubella can cause miscarriage or fetal death, or the child may be born with congenital rubella syndrome, including damage to its brain, heart, eyes, or hearing. Children that were exposed to rubella infection during an early fetal stage run an increased risk of deafness, behavioral disorders including autism, metabolic disorders, and a greatly increased risk for diabetes. The only way to prevent these outcomes is to keep the virus from circulating by means of an effective vaccination program. There has been no incidence of congenital rubella syndrome in Sweden since 1985, and only a handful cases of rubella, all of which were contracted abroad.

In summary, prevalence of the relevant diseases has dropped considerably, with only 6 reported cases of measles, 24 of mumps, and 3 of rubella in 2010 [4,5,6]. However, international travellers still run a risk of being infected, so it is vital that vaccination and immunity be kept at a high level of coverage. Also, as the vaccine is effective for only 95-98% of individuals [1], it is important to not only vaccinate sensitive groups – e.g. girls in the case of rubella, or boys in the case of mumps – but to prevent the disease from circulating altogether, in order to minimize exposure for those at-risk individuals for which the vaccine has limited or no effect. To prevent future epidemics, it is therefore vital to monitor protective immunity, ensure that it is kept at a sufficient level, and to take preemptive action by adjusting vaccination routines where necessary. Of particular interest is the immunity of potential mothers. As illness during pregnancy can have serious consequences for the unborn, it is crucial to maintain adequate levels of protective immunity for women of reproductive age.

Currently, two doses of the vaccine is offered to all Swedish children, but the main purpose of the second dose is to provide a second chance for those who failed to respond to the vaccine the first time, rather than to increase immunity to protective levels. Instead, to decrease the likelihood of women being infected during pregnancy, it is being considered to offer such a booster dose to adult women with questionable immunity, or to all young adults [7]. However, changing vaccination routines would be extremely costly and time consuming, so it is essential that sufficient empirical basis is provided on the necessity of such an intervention before any decision can be made.

For the above mentioned reasons, this study examines the immunity situation with regard to the MMR diseases for women of childbearing age, represented by women giving birth at the times of sampling, to attempt to serve as part of the basis for a decision on whether a booster dose of the MMR vaccine should be introduced into the Swedish routine vaccination program. For this purpose, three questions regarding immunity, age and cohort are asked.

Questions and hypotheses
The first question at issue concerns the effects of the MMR vaccine on the immunity of the childbearing population. As the vaccine was introduced into the childhood vaccination program in 1982 and was administered to boys and girls of 18 months of age, as well as those of 12 years of age, most women born in 1980 or later will have been vaccinated with both doses, whereas women born between 1970 and 1979 will have been vaccinated only once (at 12 years of age), and women born prior to 1970 are
likely not to be vaccinated at all. Thus, the first question asks whether these three cohorts differ with regard to protective immunity against the MMR diseases. Immunity is defined as seroprevalence of disease-specific antibodies, and is studied both in terms of level of immunity against each disease, and as the proportion of people who can be considered to possess sufficient protective immunity against each disease. It is expected that unvaccinated groups be associated with greater seroprevalence of antibodies, as these individuals are likely to have contracted each disease at some point in life, resulting in higher levels of protection from this natural exposure. Correspondingly, having received double doses of the MMR vaccine is expected to be associated with lower levels of immunity, as this group is unlikely to have contracted any of the diseases. The third group, having received only one dose of the vaccine, may have been more likely than the fully vaccinated group to contract the diseases due to inadequate immunity, but still less so than the unvaccinated group. In that case, immunity for this cohort would be expected to fall somewhere in between the other groups. A different scenario is possible if the single-dose group has carried lower levels of immunity than the fully vaccinated, yet the level was sufficient to prevent most from contracting the diseases. If this is true, immunity for the middle group may be even lower than for the fully vaccinated individuals.

If a difference in levels of immunity or in proportion of protected individuals can be established, the second question concerns the cause for this discrepancy. Any discerned difference is expected to be due to changes in vaccination routines, but as serum antibody level decreases naturally with time, it is possible to find a difference between age cohorts simply because the antibodies have had more time to decay in the older group. For this reason, data gathered at two points in time, 1997 and 2007, are used, allowing for comparisons between cohorts that were of the same age at the time of sampling. Pairs of age groups are constructed, containing individuals of the same age (at the time of sampling), but born 10 years apart. Thus, some of the group pairs will have received different treatments with regard to vaccination, while others will have equal within-pair vaccination histories. If any observed difference in immunity is a result of the vaccine, the pairs of age groups where vaccination history differs are expected to also differ in immunity, whereas the pairs of equally vaccinated age groups should exhibit similar levels of immunity.

Thirdly, to prepare for the work of identifying an appropriate age at which a possible third dose of the MMR vaccine should be administered, groups of different ages and vaccination histories are examined with regard to proportion of individuals that can be considered protected against each disease. This way, it may be possible to determine a “critical age” when immunity falters, defined as proportion of protected individuals dropping below 90%. If such an age can be identified in this sample, it might provide a reference point for discussion on the timing of a potential introduction of a booster dose of MMR into the routine vaccination program. These analyses concern only measles and rubella, as no generally accepted limit has yet been established where mumps-specific antibodies are considered to provide sufficient protective immunity.

Method

Sampling procedures

The sample consists of 607 blood samples from the umbilical cord of newly born infants, sampled at two points in time, 226 samples in 1997 and 381 samples in 2007. For the first dataset, from 1997, the 226 cord blood samples were collected at geographical convenience, with the motivation that vaccination coverage being homogeneously high for children means regional differences should not affect the results. Three maternity clinics were thus selected based on sampling accessibility judged by nurses with experience of similar sampling situations. Parents were asked upon arrival at the clinic whether they consented to have cord blood drawn.

In the second dataset, 2007, the 381 cord blood samples were collected consecutively from women giving birth at 10 randomized maternity clinics.

Measurement and quantitation

Sera were collected from the blood samples and analyzed for prevalence of IgG antibodies specific to several diseases, of which measles, mumps and rubella are considered here. 15 blood samples (3 in 1997, 12 in 2007) failed to produce an observation due to low amounts of serum, leaving n=592 valid observations. Observations with measurements below minimum level of detection (MLD) were assigned half of MLD as an estimate of level of immunity. For measles, antibody concentration is measured in mL U/ml, and MLD is 150 mL U/ml, meaning no immunity level can be determined in sera with anti-measles concentrations <150 mL U/ml. Thus, observations <150 mL U/ml were coded as having an anti-measles IgG level of 75 mL U/ml. Moreover, observations <200 mL U/ml were considered to indicate insufficient protective immunity, and these observations were therefore coded as unprotected, but still included in quantitative analyses. Anti-mumps IgG level is measured in titer, with a MLD titer of 231, meaning individuals with a titer of anti-mumps concentration <231 were coded as having a titer of 115. For mumps, there is no generally acknowledged limit for sufficient protective immunity, and therefore no comparisons of proportion of protected individuals were made with regard to mumps. Rubella is measured in IU/ml, with MLD = 4 IU/ml (observations below MLD coded as 2 IU/ml), and protective immunity is considered to be sufficient at 10 IU/ml or higher.

Glossary

- IgG: Immunoglobulin G (gamma globulin). Immunoglobulins are proteins that are essential to the body’s immune system. The G class contains many of the most common antibodies circulating in the blood.
- IU: International Unit. An internationally accepted amount of a substance, defined by the International Conference for Unification of Formulae.
- Titer: The degree of dilution of a substance such as an antibody, reflecting the strength of the solution.
Statistical analyses
As described above, data were gathered in 2007 using a cluster random sampling routine. However, as vaccination coverage is high [11] and vaccination routines are the same in all parts of the country, it is unlikely that immunity will be dependent on cluster in this case. To confirm this, the 2007 data was tested for equality of population across the different clinics, and no significant deviation was detected for either disease (Kruskal-Wallis test, p=.377 for measles, .135 for mumps, .807 for rubella). This supports the assumption of geographical independence that was made with regard to the 1997 data. Accordingly, both data sets were considered simple random samples for subsequent analyses.

Immunity distribution for each disease was tested for normality within both data sets, and were found significantly non-normal in all cases (Shapiro Wilk W test, p<.01 for all). Consequently, non-parametric tests were used for all comparisons; the Kruskal-Wallis equality of populations test for the above mentioned multiple comparison, and Wilcoxon rank sum (Mann-Whitney) tests for individual comparisons. Wilson (score) confidence intervals were used for binary variables (proportion protected) as proportions were expected to be large. Statistical significance was defined as a p-value ≤.05. Analyses were performed using Stata 11.0 ((C) StataCorp LP, Texas, USA).

The above mentioned methods are briefly described below. Additionally, as standard practice in undergraduate level statistics is to use the Wald confidence interval, further motivation is given for the choice of the less commonly used Wilson interval.

Wilcoxon rank sum (Mann-Whitney) test [15]
The WMW test is a non-parametric (distribution free) test of whether observations in one group tend to be larger than observations in another. The test statistic used here, U, is attained by ordering the observations from both groups in a single ranked series, from low to high. Thereafter, for each observation in group 1, the number of observations from group 2 that precedes it (i.e., that are lower), are counted. Observations from group 2 that are the same as the current group 1 observation, are counted half. U(group 1) is the sum of these counts. The procedure is repeated for group 2, and the smaller of the two Us is used as test statistic. As U is approximately normally distributed in large samples, a standardized test statistic is formed as below, and can be compared for test significance against the standard normal distribution.

\[
z = \frac{U - \mu_U}{\sigma_U} \quad \text{where} \quad \mu_U = \frac{n_1n_2}{2}, \quad \sigma_U = \sqrt{\frac{n_1n_2(n_1 + n_2 + 1)}{12}}
\]

Kruskal-Wallis equality of populations test [16]
The Kruskal-Wallis test is an extension of the Wilcoxon test, allowing for comparisons between k groups. Ranks are assigned in the same way, by ordering observations regardless of group. Ranks are then summed for each group. The test statistic, H, is approximately \( \chi^2 \) distributed, with \( k-1 \) degrees of freedom, and has the following form:

\[
H = \frac{12}{n(n+1)} \sum_{i=1}^{k} \frac{R_i^2}{n_i} - 3(n+1) \quad \text{where} \quad R_i = \text{sum of ranks in sample } i, \quad n_i = \text{number of observations in group } i
\]

Wilson (score) confidence interval
This study utilized the binomial interval developed by Wilson in 1927, as recommended by Brown, Cai, & DesGupta (2001) [17] for its beneficial properties at extreme values of \( p \). All of the current section refers to the same article unless any other is mentioned.

The interval is based on the following test statistic:

\[
\left| \hat{p} - p \right| \leq \frac{z_{\alpha/2}}{\sqrt{p(1-p)/n}}
\]

Note that null standard error is used instead of estimated standard error, as is the case for the standard Wald interval. By inverting the above equation, one can form the interval below.

\[
CI_W = \frac{X + z_{\alpha/2}^2/2}{n + z_{\alpha/2}/2} \pm \frac{z_{\alpha/2}n^{1/2}}{n + z_{\alpha/2}/2} \left( \hat{p}(1 - \hat{p}) + \frac{z_{\alpha/2}^2}{4n} \right)^{1/2}
\]

The Wilson interval is superior to the standard interval in that its coverage probability (probability that the true value of \( p \) is covered by the interval), averaged over all possible \( ps, \) is closer to the nominal value (e.g. 95% when \( \alpha=.05 \)) for any realistic sample size. This is especially the case when \( p \) is close to 0 or 1, or when \( n \) is small, but even for such seemingly appropriate parameters as \( n=40, \; p=0.5, \) as shown by Brown et al., the standard interval has an actual coverage probability of only .919. Several more illustrative examples of the problematic properties of the standard interval are available in the referenced article.

As proportion protected is required to be .90-.95 to ensure sufficient population immunity [2], it is reasonable to expect that proportions observed in the current study be of similar magnitude. At such high \( ps, \) the standard interval is not appropriate unless sample size is extremely large, and even then, the Wilson interval is likely to display a more accurate coverage probability. For these reasons, confidence intervals for all binary variables were based on Wilson’s formula.
Group allocations according to age and year of birth

Observations were grouped according to mother’s age and year of birth in a manner that ensured that, within each dataset, each age group and birth year group contained only samples from women of equal estimated vaccination status (number of doses likely received, based on year of birth). Furthermore, groups with large number of observations were split to allow for more detailed comparisons. Table 1 shows the final grouping, as well as number of valid observations and estimated vaccination status for each group. Note that number of years included varies between groups. This is due in part to forced cutoffs at points in time where vaccination status was changed, and partly because age distribution differs between the two datasets, yet for simpler comparison between them, allocations should be the same in both sets. Consequently, both time variables are here of ordinal level only, and one should take note not to draw careless conclusions about the quantitative effect of time on immunity in any results acquired from the upcoming analyses.

Table 1

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<td>2007 n</td>
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a Doses indicate estimated number of doses MMR vaccine received, based on vaccination routines at time of birth.

Results

Descriptive statistics

Number of women in the sample by year of birth is displayed in figures 1 (sampled 1997) and 2 (sampled 2007). Mean age was 29.2 years in 1997 and 29.3 years in 2007.

Figure 1
Year of birth distribution for women sampled in 1997.

Figure 2
Year of birth distribution for women sampled in 2007.

Median levels of IgG antibodies for the two datasets were as follows. Measles 1997: mdn=6893 (96.90% had levels >200 mIU/ml); 2007: mdn=2471 (97.64% >200 mIU/ml). Mumps 1997: mdn=2147; 2007: mdn=1737. Rubella 1997: mdn=108.7 (94.69% >10 IU/ml); 2007: mdn=70.5 (96.59% >10 IU/ml).

Medians per birth year group are displayed in figures 3 through 5. For the most part, these seem to indicate lower levels of immunity for individuals born in the later years, with regard to measles and rubella. Mumps immunity displays a less conclusive pattern.
Figure 6 displays antibody concentration levels in groups of different vaccination status for the three diseases, as well as Wilcoxon rank sum test results for the difference in level between vaccination groups 0 and 1, and between groups 1 and 2. As shown, for all three diseases, the double-vaccinated groups display a lower level of immunity than their one-dose counterparts. This is in line with the speculation that single-vaccinated individuals are more likely to have contracted each disease in the past than are double-vaccinated persons. Comparisons between unvaccinated and single-vaccinated groups, however, yield different results for each disease. Measles immunity exhibits the expected pattern; high levels of antibodies for the unvaccinated group, where most are likely to have contracted measles and thus developed more durable protection, and considerably lower immunity levels for the vaccinated groups. Mumps immunity deviates from expectations in that the unvaccinated group displays a significantly lower level of immunity than does the single-vaccinated group. Rubella levels trend towards the expected, in that sample level of anti-rubella IgG is higher for the unvaccinated than the one-dose group, but the difference is not statistically significant.

In summary, these results imply that single- or double-vaccinated women are less likely to be protected against measles at the time of child birth than are unvaccinated women; that the same is true for rubella with regard to double-vaccinated, but not necessarily single-vaccinated women; and finally, that single-vaccinated women actually carry stronger protection against mumps than both the unvaccinated and the double-vaccinated groups.
Immunity over age and time of sampling

Table 2 shows comparisons of immunity level between the two datasets, within each age group. Groups 16-18 and 43-44 are omitted from analysis as they are represented at only one of the times of sampling. Bold face indicates statistical significance.

Comparisons between single- and double-vaccinated groups (age groups 19-24 and 25-27) show that the latter exhibit significantly lower levels of anti-mumps and anti-rubella IgG. For measles, the same is true for the older age group, but the difference is non-significant for age group 19-24. Instead, age groups vaccinated once display significantly lower measles-specific IgG levels than their unvaccinated counterparts (age groups 28-29, 30-32 and 33-37), whereas the corresponding comparisons for mumps and rubella are non-significant. Finally, comparisons between groups that are both unvaccinated (age group 38-42) yield, as expected, no significant difference with regard to measles and mumps. More troubling is the observation that, for this age group, individuals sampled in 2007 have significantly lower levels of anti-rubella IgG, in spite of equal vaccination status. As these are the groups with the fewest observations, however, they are more vulnerable to chance, and it is therefore plausible that this deviation from expectations is unreliable.

### Table 2

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*Doses indicate estimated number of doses MMR vaccine received, based on vaccination routines at time of birth.

Proportion protected

Figures 7 and 8 show Wilson confidence intervals for population proportion that can be considered to carry protective immunity against each disease, by age group and vaccination status. Groups with very few observations (ages 16-18, n=4, and ages 43-44, n=2) are excluded, as intervals for these proportions would be too wide to provide any useful information.

To keep diseases from circulating, protective immunity needs to be strong enough to prevent infection in 90-95% of the population [2]. Therefore, population immunity is considered acceptable in this study when proportion protected exceeds 90%, and satisfactory when exceeding 95%. These bounds are represented in figures 7 and 8 by areas marked as light gray (satisfactory), medium gray (acceptable) and dark gray (at risk).

In this sample, as shown, all the age groups have an at least acceptable proportion of protected individuals, with the borderline exception of age group 33-37, where the unvaccinated cohort has a protection rate against rubella that is only slightly above 90%. Precision is relatively low, however, with confidence bounds wider than 10 percentage points in several cases. To make any definitive conclusions regarding age effects on proportion protected, one might need to repeat the current analyses on a larger sample. This is addressed in the discussion section.
Discussion

This study has focused in large part on the negative effects of mass vaccination: the unreliability and shorter life span of the resulting immunity, and the risks involved if immunity falters at an age at which many women become pregnant, and give birth. The reader may, at this point, wonder why vaccines are at all being administered to children – would it not be better to let everyone acquire the stronger, natural kind of immunity? Indeed, as more people get sick, subsequently developing life-long protective immunity, population immunity is improved as well. But the process includes much physical, emotional and economical suffering to the persons affected, their families, and to society at large, unnecessarily burdening health care, increasing employee absence due to sickness, and with no vaccination program, even lives would be lost. With such conditions as the alternative, it is not surprising that many countries, Sweden included, choose to go the route of offering vaccination to everyone. With that in mind, it is vital to make sure that the vaccination program serves its purpose: to keep diseases from circulating, and to
provide life-long immunity to the population. The latter objective is at issue in the current study. Vaccination generally provides good protective immunity, but the effect is not as durable as natural immunity. Additionally, diseases that are contracted in adulthood can often be more aggressive, with higher risk of serious complications. In order to minimize personal suffering, as well as economical strain to society, population immunity towards each disease needs to be monitored closely and separately with regard to longevity, with particular attention being paid to groups that are sensitive to the relevant diseases.

In the case of the MMR vaccine, such additional attention is given to the population of young to middle-aged women, out of which many will carry and give birth to a child within the near future. As infants are born with immunity provided by the mother during pregnancy, and as that immunity is sustained through nursing, it is important for mothers to carry strong protective immunity. In that case, immunity from their vaccination, but that, should they be tested again in ten years, population immunity will have decreased to unacceptable levels due to natural antibody decay. In that case, an unknown number of women may become at risk of infection in the near future, while they are still of fertile age. Unfortunately, this study provides little to no clue either in favor of or against such an outcome.

To conclude, the cases of measles and, to some extent rubella, make it relatively clear that immunities against these diseases in the vaccinated population are considerably lower than for the unvaccinated, naturally immune group, regardless of age. This is somewhat countered by analysis of proportion protected, which is shown to be at an acceptable level in the entire sample. However, great width of confidence intervals and underrepresentation of age groups who are most likely to be at risk, make it questionable to claim the same about the target population. Instead, one must conclude that, while the doubly vaccinated population seems to be less protected against measles and rubella, it is unclear from these data whether the discrepancy is large enough to warrant intervention. To discern whether there are older women at risk of prenatal infection one might perform a study where a large number of women are sampled purposely according to age, making sure to include as many persons as possible that are vaccinated, not necessarily pregnant or recently having given birth, but that are at the medium-to-older range of fertile age. This way, one may have greater chances of identifying any at-risk age groups, where immunity has decayed below acceptable levels. A longitudinal study of antibody levels over the course of life for a smaller set of individuals would make for even more detailed analysis, and might provide some understanding of any discernible decay function of artificial immunity.
References


