Timing of Measles Immunization and Effective Population Vaccine Coverage

OBJECTIVE: To describe measles vaccination patterns in a cohort of Swiss children aged up to 3 years insured with a single health insurer.

METHODS: A dynamic cohort study evaluating measles immunizations patterns in children born between 2006 and 2008 was conducted. Time-to-event analysis was used to describe timing of measles immunization. Effective vaccine coverage was calculated by using an area under the curve approach.

RESULTS: In the study cohort, 62.6% of 13-month-old children were up-to-date for the first measles immunization (recommended at 12 months of age). Approximately 59% of 25-month-old children were up-to-date for the second measles immunization (recommended at 15–24 months of age). Most doses were delivered during months in a child’s life when well-child visits are recommended (eg, 12 months of age). For second measles vaccine dose, accelerations in vaccine delivery occurred at time points for well-child visits during the months 19 and 25 of age but with lower final uptake than for the first measles vaccine dose. Until their second birthday, children in our cohort spent on average 177 days and 89 days susceptible to measles due to policy recommendations and additional delays, respectively. In a group of children aged 6 months to 2 years reflecting the age distribution in our cohort, effective vaccine coverage was only 48.6%.

CONCLUSIONS: Timing and timeliness of measles immunizations influence effective population vaccine coverage and should be routinely reported in addition to coverage whenever possible. Proposed timing and relation of recommended vaccinations to well-child visits could help to address low coverage in infants and toddlers.

WHAT’S KNOWN ON THIS SUBJECT: Many children are vaccinated against measles with a delay. This may influence effective measles vaccine coverage even in countries with high overall immunization levels. Official vaccine coverage statistics do not usually report on the impact of timeliness of measles vaccination.

WHAT THIS STUDY ADDS: Delayed measles vaccination results in 48.6% effective coverage in children aged 6 months to 2 years when 84.5% of 25-month-olds are up-to-date for 1 measles vaccination. Analyzing patterns of measles vaccination could help to address low coverage in infants and toddlers.

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Vaccination is a key and highly successful element of well-child care worldwide. Over the last few decades, effective vaccines and immunization programs have dramatically reduced the impact of several vaccine-preventable diseases on population and individual health. Adequate population coverage to achieve high individual protection as well as for induction and maintenance of herd immunity is an important issue in the fight against many vaccine-preventable diseases.

Despite being vaccine preventable, measles is still a relevant disease that continues to be a major focus for immunization programs. Available measles vaccines are highly efficacious and are an adequate instrument to eliminate endemic measles transmission if coverage is maintained at >95%, the level necessary to achieve herd immunity. After intense vaccination efforts, interruption of endemic transmission of measles has been achieved in Finland and Iceland, as well as American countries, showing that measles vaccines can be effective in a population setting. Immunization programs with carefully chosen evidence-based recommended times for vaccination are key to ensure that elimination of measles can be achieved. In addition, such programs must be well accepted by the target populations. In Switzerland, measles vaccination coverage much below the desirable 95% coverage has been recorded repeatedly. Moreover, significant delays to measles immunization have been described for 1 region of Switzerland. A similar picture presents itself in many European countries, with reported vaccination coverage ≤84% in 2009 for, among others, Austria, Belgium, and the United Kingdom. Appropriate and valid information on vaccine coverage is crucial to maintaining, supplementing, and expanding measles immunization programs.

The aims of the current study were to assess measles immunization levels and patterns in a Swiss cohort of children born between 2006 and 2008 and insured with a single health insurer. Specific objectives were to evaluate the value of incorporating timeliness and timing of first and second dose of measles vaccine administration in describing vaccine coverage for the study population.

**METHODS**

**Setting**

Health care in Switzerland is provided within a system of compulsory health insurance administrated through a number of federally recognized insurance funds (see Supplemental Information). Health insurance is divided into basic mandatory insurance and voluntary top-up plans covering a limited range of additional services. At least 90% of costs of vaccinations and well-child visits are covered by basic insurance with a maximum annual copayment of 350 Swiss francs. Vaccinations in Switzerland are overwhelmingly administered by physicians in an office-based setting. Invoices for outpatient care are standardized, and vaccines can be identified by codes or text from submitted bills.

In the Swiss national vaccination schedule, the first measles vaccine dose (MCV1) is recommended at 12 months of age, with earlier immunization at 6 or 9 months of age advised for children considered at high risk of exposure to measles. For example, early measles vaccination from 9 months of age may be considered for children attending day care. The second dose (MCV2) is generally recommended at 15 to 24 months of age. Infants who were immunized with MCV1 aged <12 months should be given MCV2 at 12 months of age. Seven well-child visits are recommended between 2 and 24 months of age (Fig 1).

**Study Design**

A dynamic cohort study was conducted retrospectively looking at claims data from Helsana Health Insurance Company (hereafter referred to as Helsana) in Switzerland. All children born between January 1, 2006, and June 30, 2008,
insured from no later than 4 weeks of age with Helsana were included. Children with unknown places of residence or not resident in Switzerland at the time of birth were excluded.

The date of vaccination for each child in the cohort was assumed to coincide with the dispensing date specified on the submitted invoice. Each individual in the cohort was continuously observed from registration until the end of the observation period on June 30, 2010. Censoring of observation occurred at the following events: death of the child, change of health insurance, or erroneous billing for vaccines (eg, identical invoices with treatment dates <10 days apart).

During the observation period, vaccinations against measles alone (Measles Vaccine [live], Pro Vaccine AG, Baar, Switzerland) or in combination with mumps and rubella (Priorix, GlaxoSmithKline AG, Münchenbuchsee, Switzerland; M-M-RVaxPro, Sanofi Pasteur MSD AG, Baar, Switzerland) delivered in an ambulatory setting were recorded as significant events.

Data Analysis

Statistical analyses were conducted by using R version 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria). Health insurance data have previously been shown to provide valid estimates of vaccine coverage. Data from the claims database were used to calculate vaccination coverage by using a time-to-event analysis. The age at vaccination in days was calculated from date of birth to the visit date on submitted invoices. Inverse Kaplan-Meier curves were plotted to display cumulative measles vaccine coverage. Proportion of children vaccinated with MCV1 and MCV2 was considered at 13 and 25 months of age to reflect immunization levels at the recommended ages for measles vaccination in Switzerland. Up-to-date vaccination was defined as occurring within 30 days of the recommended age. Ninety-five percent confidence intervals (95% CIs) were calculated by using the Greenwood formula. All data presented are adjusted for market share of the health insurance on the level of canton and gender.

To assess the validity of calculated measles vaccination levels in our cohort, we compared our data against official nationwide estimates for 24- to 35-month-old children published by the Federal Office of Public Health (FOPH) for 2005–2007. Official vaccine coverage estimates are based on data from postal surveys with review of vaccination cards for 24- to 35-month-olds. The response rate to these surveys is ~85%. Nonrespondents are known to be more likely German-speaking, non-Swiss, and urban, but the exact effect of these findings cannot be quantified. The average measles vaccine coverage in the same age range was calculated from our data by using an area under the curve approach. 95% CIs were calculated for these proportions with bootstrapping (80% sample with replacement). The same area under the curve approach was used to estimate effective vaccine coverage for children up to the age of 2 to 3 years, taking into account any delays in immunization. All information in the database was fully anonymized in accordance with Swiss data protection laws.

RESULTS

Description of Study Cohort and Administered Vaccine Doses

A total of 42,950 infants (52% males) born between January 1, 2006, and June 30, 2008, were included in the cohort. The cohort represents just <20% of children born in Switzerland during the same period (19.6% for males, 19.1% for females). The average observation period for successive annual birth cohorts was 978 days, 868 days, and 601 days for infants born in 2006, 2007, and 2008, respectively.

During the observation period, 45,605 measles-containing vaccine doses were administered to children in our cohort. For MCV1 and MCV2, a combination vaccine of measles, mumps, and rubella was used in 99.3% and 99.5% of cases, respectively. The remaining immunizations consisted of a stand-alone measles vaccine.

There were a total of 145 invalid measles vaccinations either because of immunization before the recommended minimum age (before 6 months of age for MCV1 and before 12 months of age for MCV2, respectively; n = 92) or due to an insufficient time interval between vaccinations (<4 weeks, n = 53). These constituted 0.003% (145 of 45,605) of all observed measles vaccinations and were ignored for subsequent analyses.

Proportion of Children Up-to-Date for MCV1 and MCV2

Only 62.6% (95% CI: 62.3–62.8) of 13-month-old children in our cohort had received MCV1 and were up-to-date with respect to the recommended schedule. Still, only 84.5% (95% CI: 84.3–84.7) of 25-month-old children had been given MCV1. An even larger discrepancy was noted for MCV2, with only 59.4% of children immunized at 25 months of age (95% CI: 59.1–59.6).

Measles immunization levels in the study cohort were compared with survey-based estimates produced by the FOPH for the period 2005–2007. Our results for average proportions of children immunized with MCV1 and MCV2 by age 24 to 35 months broadly corresponded to officially reported immunization levels (Table 1). A basic sensitivity analysis to explore various proportions of MCV coverage for the nonrespondents in the FOPH survey found that the current data were compatible with official estimates unless all nonrespondents are unvaccinated (Table 2).
TABLE 1 Vaccine Coverage for 24- to 36-Month-Olds Comparing Data for the Study Cohort Insured With a Single Health Insurer Between 2006 and 2010 Versus Official Nationwide Postal Survey-Derived FOPH Data for 2005 to 2007a

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Age</th>
<th>Vaccine Coverage, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MCV1</td>
</tr>
<tr>
<td>Helsana</td>
<td>13 mohb</td>
<td>62.6 (62.3–62.9)</td>
</tr>
<tr>
<td></td>
<td>25 mohb</td>
<td>84.5 (84.3–84.7)</td>
</tr>
<tr>
<td></td>
<td>24–35 moe</td>
<td>85.7 (85.3–86.2)</td>
</tr>
<tr>
<td>FOPH</td>
<td>24–35 mo</td>
<td>86.9 (NA)</td>
</tr>
</tbody>
</table>

NA, not available.

a Data from Lang et al.9
b Cumulative proportion vaccinated at indicated age.
e Calculated average proportion vaccinated in indicated age range.

TABLE 2 Calculating Range of Possible Measles Vaccine Coverage for Comparison of Official Nationwide Survey Data With the Helsana Cohort: Sensitivity Analysis Assuming Different Vaccination Status Among Nonrespondents With Official Nationwide Surveya

<table>
<thead>
<tr>
<th>Assumed Vaccination Status of Nonrespondents</th>
<th>Calculated Vaccine Coverage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vaccinated</td>
<td>MCV1</td>
</tr>
<tr>
<td>Coverage of respondents = nonrespondents</td>
<td>89.9</td>
</tr>
<tr>
<td>All unvaccinated</td>
<td>87.5</td>
</tr>
<tr>
<td></td>
<td>73.7</td>
</tr>
</tbody>
</table>

a Data from Lang et al.9
b Total FOPH survey sample size = 9787; respondents = 8286 (84%).

timeliness and timing of measles immunization activity after the recommended ages for MCV1 and MCV2 vaccination.

In addition to considering measles vaccination status by looking at proportion of children up-to-date at specified time points, the effect of timeliness and timing on vaccination coverage was explored (Fig 2).

Of the MCV1 doses in our cohort, about one-half were administered within a narrow time band between 365 (19.6% immunized) and 395 days (62.6% immunized) of age, corresponding to the recommended age for MCV1 administration. Another 21.9% of children received MCV1 thereafter up to the age of 25 months. Almost 20% of MCV1 immunizations occurred before the generally recommended age of 12 months (2.7% immunized at 9 months, 19.4% immunized at 11 months of age), probably reflecting vaccine uptake before day care attendance. The majority of MCV2 doses also were administered during the recommended interval (6.6% immunized at 15 months, 59.4% at 25 months). However, delivery occurred more spread out over time, with the rate of MCV2 vaccination accelerating at 15 months but even more so during months 19 and 25 of age at times of recommended well-child visits. MCV2 administration continued to occur after 25 months of age, reaching 71.2% (95% CI: 71.0–71.5) for 36-month-olds.

**Cohort Effect of Delayed Vaccination on Vulnerability to Measles**

For calculations of effective population coverage, we assumed waning of maternal antibodies at 6 months of age and 92.5% and 94% vaccine effectiveness for MCV1 and MCV2, respectively.4,21 Therefore, children were taken to be susceptible to measles from 6 months before the recommended age for MCV1. Taking into account the timing and timeliness of measles immunization, children in our cohort spent on average 266 days (95% CI: 265.1–266.8) unvaccinated and susceptible to measles until their second birthday. Of the susceptible days, 66.5% were spent susceptible due to the policy of recommending MCV1 for 12-month-olds and despite early uptake of MCV1 between 9 and 12 months by ~20% in our cohort. Conversely, 33.5% of susceptible days were due to delayed vaccinations.

To investigate the impact of vaccination timing and timeliness on effective coverage among young children, we calculated the proportion of susceptible children for a hypothetic group of infants and toddlers aged 6 months to 2 years. The chosen age range is representative of a substantial proportion of children in day care groups in Switzerland and elsewhere, an environment where measles transmissions could easily occur during an outbreak. The relative age distribution and measles vaccination levels in this group reflected that in our cohort. In such a group and under the same assumptions as detailed previously, on average 48.6% of children are susceptible to measles at current levels of vaccination. The recommended timing of MCV1 and the resulting 6 months that children may spend susceptible to measles even when up-to-date with respect to the immunization schedule had the largest impact on effective coverage.

Inclusion of older children in this hypothetical group shows the additional effects of timeliness. Among children aged 6 months to 3 years, effective vaccine coverage would be 61.3%, the higher coverage largely reflecting ongoing immunization activity after the recommended ages for MCV1 and MCV2 vaccination.

**DISCUSSION**

By using health insurance data for a cohort of >40 000 Swiss children born between 2006 and 2008, we were able to demonstrate that 62.6% and 59.4% of our cohort were up-to-date for MCV1 and MCV2 at 13 and 25 months of age, respectively. Average coverage at 24 to 35 months of age was found to be broadly in the range of official estimates, with 85.7% and 66.7% for MCV1 and MCV2.
By conducting a time-to-event analysis, we were able to consider the additional impact of timeliness and timing of administration of measles vaccine on effective vaccine coverage. In a group of children aged 6 months to 3 years, ~40% of children were susceptible to measles despite a vaccination level of 71.2% for MCV2 at 36 months in our cohort, clearly demonstrating the combined impact of policy considerations (time point for recommended MCV1 and MCV2) and individual delayed immunization on overall population coverage.

Our data confirm previous observations that when describing immunization levels in a given population, the choice of reported parameters influences the interpretation of vaccine coverage.\textsuperscript{18,20,22–25} Where vaccination achieves much of its population effect through herd immunity, simply considering immunization levels at a given age may overestimate protection in the population of interest.\textsuperscript{20,22,24} The effect of individual delayed childhood vaccinations on the fraction vaccinated in whole populations was shown to effect whether critical population immunity levels could be achieved.\textsuperscript{24} Time-to-event analysis results in a more comprehensive representation of population vaccination levels than proportions of individuals up-to-date at key ages alone. Timing is relevant in that spread-out vaccine delivery can result in relevant reductions in effective vaccine coverage even when overall final uptake of vaccinations is similar.\textsuperscript{25} In our cohort, most vaccinations took place during the time periods recommended in the national schedule. This in itself gave rise to a considerable number of days spent susceptible when waning immunity from maternal antibodies was assumed to occur at 6 months of age.\textsuperscript{21} Thus, around two-thirds of, on average, 266 days spent unvaccinated and susceptible to measles until 2 years of age were due to a gap between policy recommendations and waning immunity with the remainder being down to delayed immunizations in the cohort. For MCV1, timing of recommended vaccination seemed to be the key driver for when children were vaccinated. Conversely, administration of MCV2 was drawn out during the recommended time period of 15 to 24 months, reflecting poor timeliness of vaccination. Greater delays for later vaccinations in young children have been noted in other settings.\textsuperscript{26,27}

At current effective coverage levels in infants and toddlers, a double-pronged approach may be necessary to reduce susceptibility to measles in young children. On the one hand, delays in vaccination will need to be tackled. This must include addressing parental concerns and physician knowledge to ensure children are vaccinated in a timely fashion in the absence of medical contraindications.\textsuperscript{28–30} Because delays in primary vaccination in the first months of life are associated with reduced vaccination levels against measles, an inclusive
approach to immunization programs is necessary.\textsuperscript{31,32}

Conversely, changes to recommended timing may have to be considered when evaluating national immunization schedules. System factors have been suggested as potentially having an impact comparable to individual level risk factors on untimely vaccination.\textsuperscript{2,24} In our cohort, acceleration in the rate of MCV2 vaccination could be observed during months 19 and 25 of age corresponding to 2 well-child visits within the recommended time period (Fig 2). This finding suggests that recommendations for a specific time point rather than a time period may lead to better adherence, especially if the recommended time point corresponds to a scheduled well-child visit. Parental satisfaction with preventive pediatric care in early life is associated with fewer immunization delays.\textsuperscript{33} Structural features of health care systems, in particular integration with key components of primary care such as well-child visits, thus seem to encourage parents to accept timely immunization and enable providers to offer vaccinations when most appropriate.\textsuperscript{7}

In fact, the greatest impact on effective population coverage among preschool-aged children is achieved by early and timely MCV1 administration. Assuming waning immunity from maternal antibodies at 6 months and 84.5\% MCV1 vaccine effectiveness for 9 to 12 month-olds,\textsuperscript{4} immunization of all children at 9 to 12 months with MCV1 and by 13 months with MCV2 would push the effective vaccine coverage from \(\sim 60\%\) to \(\sim 80\%\) in a group of 6-month-olds to 3-year-olds with uniform age distribution. Well-child visits in Switzerland are recommended at 9 and 12 months of age. It must therefore be considered whether adapted recommendations for measles vaccination to mirror these visits (MCV1 at 9 months and MCV2 at 12 months of age) may improve effective coverage in children up to 2 years of age. This change would shorten the period children spend at risk for measles through improved timing of vaccination. However, it would ensure that 2 definitive time points coinciding with well-child visits are recommended, thereby potentially improving timeliness of vaccination.

Several limitations must be considered in this type of analysis. Out-of-pocket payments for vaccination and incomplete submissions of invoices may have led to differential misclassifications in the vaccination status of some children. Overall, the proportion of infants with a high voluntary deductible was very small (<1\%); therefore, most likely claims were made extensively where applicable. Any children receiving vaccinations during an inpatient stay were not identified as immunized in our study. Because vaccination opportunities are known to be underused in the hospital setting, the impact of this is likely to be small.\textsuperscript{34} Lastly, patients joining from other health insurance programs during the first 2 years of life were not observed and may differ in vaccination behavior from patients who remain with the same insurer throughout their early childhood.\textsuperscript{16}

**CONCLUSIONS**

Focusing on immunization against measles, we offer evidence in support of incorporating data on timeliness of vaccination in the evaluation of vaccine coverage. The good agreement between our data and official estimates indicates the validity of using health insurance data. Such an analysis, using routinely collected information, may also be less costly. Vaccine coverage, timeliness, and patterns of vaccination activity in relation to age and recommended schedules can all be identified. To move toward the eradication of endemic measles in Switzerland, several measures are necessary. First, promoting acceptance of measles immunization will help to achieve high rates of vaccine uptake. Second, timely application of measles immunization at the individual level will reduce the time any 1 child spends susceptible to measles. This must include considerations regarding the ages at which measles vaccinations are recommended. Lastly, the relationship with overall well-child care must be considered to reduce system barriers to optimal measles immunization. Such barriers may be contributing to the slow progress toward the elimination of endemic measles in Switzerland and in other similar settings.

**REFERENCES**


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