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# Vaccine coverage estimation using a computerized vaccination registry with potential underreporting and a seroprevalence study

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ABSTRACT

*Objective:* To develop a method to estimate vaccination coverage using both a computerized vaccine registry with an unknown underreporting rate and a seroprevalence study. A real example of a meningococcal C conjugate vaccine (MCCV) coverage estimation is studied to illustrate the proposed methodology.
*Methods:* We reviewed the Vaccine Information System of Valencia (Sistema de Información Vacunal, SIV) for the MCCV status of 1430 subjects aged 3–29 years as part of a seroprevalence study. When MCCV was not registered in SIV, subjects were classified into three groups (MCCV non-registered, no vaccination records and missing information) depending on the registry of other vaccines. A Bayesian model was developed to ascertain the percentage of MCCV-vaccinated subjects based on the meningococcal C seroprotection levels from the seroprevalence study.
*Results:* The seroprotection levels in subjects with no MCCV registered in SIV (358) were similar to those in subjects with MCCV registered (1072). This indicated a large proportion of vaccinated subjects with no MCCV registered. The estimated vaccine coverage was over 80% in all age groups, except >22 years, where it was 67.6% (95% CI: [54.0–80.4]), which corresponded to those aged over 13 years at the time of the catch-up campaign. An underreporting rate of 23.5–73.4%, depending on the age group, was estimated in those vaccinated in the 2002 catch-up campaign.
*Conclusion:* The Bayesian model allowed for a more realistic estimation of MCCV uptake. In this example, we quantified the underreporting of a vaccine registry, especially occurring during a catch-up campaign that occurred at the establishment of the registry.



## 1. Introduction

Accurate classification of subjects' immunization status is essential for clinical care, administration and evaluation of immunization programs as well as vaccine program research. Immunization program administrators and researchers need to institute measures to identify and reduce the misclassification of immunization status so that registries can play an effective role in the control of vaccine-preventable diseases [1]. The assessment of accurate vaccine coverage is important to understand the impact of a vaccination program and to develop new strategies.

The recent introduction of vaccines in adolescent and young adults, especially if given in mass catch-up campaigns, may result in a lower registration rate for the vaccines administered. This may be the case with meningococcal C conjugate vaccine (MCCV). This vaccine has proved to be extremely effective, not only for its direct effect but also for its indirect effect due to herd immunity. Countries with high vaccination coverage and extensive catch-up programs have shown that the vaccine prevents disease even in the unvaccinated [2,3]. In Spain, the program decreased the burden of disease, but its incidence in subjects older enough to be excluded from the catch-up program has remained stable for a long period of time. One hypothesis explaining this is that the catch-up program was not as exhaustive as in the UK or the Netherlands [2,4]. In the Valencian Region of Spain, in 2000, MCCV was scheduled at 2, 4, and 6 months of age, with an active catch-up recommended up to 6 years of age [5], and in 2002, a passive catch-up was expanded up to 19

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years of age (subjects were not called actively for vaccination; only those who came in for a visit, regardless of the reason, were vaccinated). In 2006, due to the short-term effectiveness of the infant vaccination program [6,7], a booster dose in the second year of life was implemented [8]. A significant decrease in the incidence of meningococcal C (Men C) disease in the unvaccinated group has been reported since 2009 [9].

Vaccination coverage in the Valencian Region is estimated from a computerized vaccination registry (Sistema de Información Vacunal, SIV) [10] that includes the identification of the subject by a unique identification number, the date of vaccination, the vaccine trade name and batch number, among others. This system, established in 2000, increased its accuracy over time with regard to the influenza vaccine [11]. It is possible that the MCCV doses given in the catch-up programs that were coincidental with the implementation of SIV were not accurately recorded, and therefore, SIV-based coverage rate estimates would underestimate the actual MCCV coverage rate for the whole population.

The official figures showed that MCCV coverage during the catch-up programs was 95% in children 1–6 years old at the time of vaccination (2000–2001) [8], and for those vaccinated in the 2002 catch-up, the figures were higher than 26% [12]. These figures may not represent the present vaccination coverage due to underreporting, population mobility, and further passive catch-up after the vaccination campaign ended.

It is therefore important to assess the completeness of computerized vaccination registries, especially when different vaccination strategies have been implemented. The objective of this paper is to develop a method to assess the underreporting in this setting, making it possible in our case to estimate the MCCV coverage in the Valencian Region of Spain.

## 2. Methods

As part of a seroepidemiological study conducted between October 2010 and April 2012 [13], we reviewed the individual vaccination status of SIV in 1430 subjects 3–29 years old (candidates to receive the MCCV). They gave a blood sample after the subject and/or parents signed the informed consent. Only individuals older than 3 years were included in the study as we had reliable serological data from previous studies for those <3 years of age [14,15].

In Valencia, over 95% of the population is included in the Regional Health System (Conselleria de Sanitat – CS), the rest are cared by. Health Maintenance Organization. Subjects for the seroepidemiological study were recruited from 12 CS primary care health centers (PCHC) and from 3 CS-hospitals. Children were recruited in the PCHC, when attending for check ups that are followed by most of the children at different ages (3–4 years, 5–6 years, 10–12 years and 14 years). In these cases blood samples were obtained exclusively for the study. Occasionally we obtained samples from outpatient children being bled in hospitals.

Adults were sampled either together with routine blood tests from PCHC or from hospital laboratories.

In each blood sample, the serum bactericidal activity (SBA) against meningococcus C was tested using a rabbit complement as previously described [16]. We considered a subject seroprotected if their SBA was $\geq$1:8. The percentage of seroprotected subjects varied depending on age, age at vaccination and time since vaccination [13]. The population was divided into 13 age groups with different vaccine schedules and different ages at vaccination.

Information gathered from the SIV was classified into four groups:

- MCCV registered (R): subjects who had at least one MCCV registered. We considered these subjects to have been vaccinated.
- MCCV non-registered (NR): subjects that had information about other vaccines in the SIV at the time of MCCV program, but had no MCCV dose registered.
- No vaccination records (NVR): subjects who had no information on any vaccine in the SIV, including MCCV.
- Missing information (M): subjects that had vaccine(s) registered only after the MCCV campaign. We expected that most of these subjects came to live to the Valencian Region after being eligible for the catch-up program.

The last three groups were considered to be potentially different because the reason for not being recorded in the SIV could have been different for all of them. They could have been unvaccinated or could have been vaccinated but not registered because who administered the vaccine had no access to the SIV at the time of vaccination, among other reasons. Because these factors could have different weight on the composition of the last three groups of SIV vaccination status above, we considered them separately.

The published vaccination coverage of the 2002 MCCV catch-up program in subjects >6 years old was reported as "higher than 26%" (the effect of underreporting is acknowledged but not quantified) [12]. This catch-up was a passive vaccination program, and subjects were not called actively for vaccination. To assess the 2011 vaccination coverage, we divided the number of subjects by birth cohort that were registered as vaccinated by the population by the birth cohort that was in the corporate administrative record of the Health Department [17] in June 2011.

### 2.1. Statistical analysis

Meningococcal C seroprotection levels should be different for vaccinated and unvaccinated populations [4,18]. On the other hand we know the age-specific seroprotection levels for every SIV group in our sample. Bearing in mind these two considerations we developed a model to determine the percentage of vaccinated population for each of these groups. This model allowed us to estimate the percentage of vaccinated people in the whole Valencian population.

The model assumed each SIV group to be a mixture of vaccinated and unvaccinated populations distributed in unknown proportions. That is, if $\{R_i, NR_i, NVR_i, M_i\}$ represents the observed percentage of seroprotected population in the $i$th age group for the predefined SIV groups (MCCV registered, MCCV non-registered, no vaccination records, and missing information), then the model assumes that for each age group:

$$R_i = p_R V_i + (1 - p_R)U_i,$$

$$NR_i = p_{NR} V_i + (1 - p_{NR})U_i,$$

$$NVR_i = p_{NVR} V_i + (1 - p_{NVR})U_i,$$

$$M_i = p_M V_i + (1 - p_M)U_i$$

where $V_i$ is the proportion of seroprotected people for the vaccinated population in the $i$th age group and $U_i$ represents the same quantity for the unvaccinated population. On the other hand, $p_R$, $p_{NR}$, $p_{NVR}$, and $p_M$ denote the proportion of vaccinated population for each SIV group. $p_R$ was fixed to 1 because all of the registered people in the SIV database had actually been vaccinated. As a result, the model estimated these proportions ($p_{NR}$, $p_{NVR}$, $p_M$) and the age-specific seroprotection levels for both the vaccinated and unvaccinated populations ($\{V_i, U_i: i = 1, \ldots, 13\}$). Inference for the model above was made from a Bayesian point of view. Further statistical details for the corresponding Bayesian model are available as supplementary digital content.

To assess the results from this model, we calculated the posterior predictive distribution of the seroprotection levels for each age and SIV group. These predictive distributions made it possible

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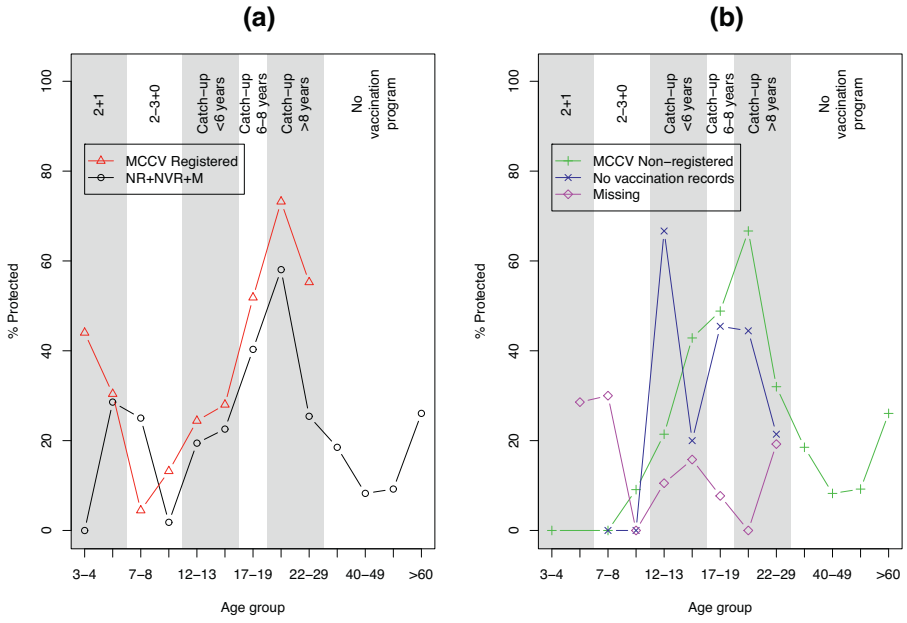


**Fig. 1.** (a) Percentage seroprotection (SBA ≥ 1:8) by age group (years) in subjects with meningococcal C conjugate vaccine (MCCV) registered (MCCV Registered) and without a MCCV record (NR + NVR + M) in the Vaccine Information System of the Region of Valencia (Sistema de Información Vacunal, SIV). MCCV Registered: at least one meningococcal C conjugate vaccine dose registered in SIV, considered as vaccinated. NR (MCCV non-registered): any other vaccines registered in SIV at the time of the MCCV campaign; no MCCV vaccine registered. NVR (no vaccination records): no information of any vaccine registered in SIV. M (missing): first vaccine registered in SIV after the MCCV campaign. (b) Percentage seroprotection (SBA ≥ 1:8) by age group (years) in subjects without a meningococcal C conjugate vaccine (MCCV) record by specific predefined SIV group (NR, NVR, M). NR (MCCV non-registered): any other vaccines registered in SIV at the time of the MCCV campaign; no MCCV vaccine registered. NVR (no vaccination records): no information of any vaccine registered in SIV. M (missing): first vaccine registered in SIV after the MCCV campaign.

to evaluate the fit of the model and to reveal any possible lack of fit.

The model above allowed us to estimate the percentage of vaccinated population for each SIV group. From these and the known age-specific distribution of populations within SIV groups, we derived the age-specific coverage of the vaccine for the whole population. As the sampling design of the study was stratified by age, we took into account that sampling scheme to estimate the global coverage of the vaccine for the general population. That coverage was also calculated within the previously mentioned Bayesian model.

The study was approved by the Ethics Committee of Dirección General Salud Pública/CSISP.

## 3. Results

Fig. 1a and Table 1 show the seroprotection level by age group in the four predefined groups: MCCV registered (R), MCCV non-registered (NR), no vaccination records (NVR) and missing (M). The age-specific seroprotection level for the registered group shows some fluctuations linked to the different vaccination strategies. Moreover, the rest of groups show similar, although slightly lower, seroprotection rates than the registered group.

Fig. 1b (and Table 1) shows the age-specific seroprotection levels for the three groups without registered MCCV vaccination. These three curves resemble, to a certain extent, the curve of the registered group. The model-based estimate of the proportion of vaccinated people in every group was 81.4% (95% CI: [60.0, 98.5]) for the MCCV non-registered group ($p_{NR}$), 51.9% (95% CI: [21.6, 84.9]) for the group with no vaccination records ($p_{NVR}$) and 21.4% (95% CI [1.9–49.5]) for those with missing information ($p_M$). This is in accordance with what is shown in Fig. 1b.

The age-specific percentages of MCCV registered in SIV in 2011 and the corresponding estimated vaccine coverage rates from the Bayesian model are shown in Table 2. The model-based coverage rates do not correspond to a specific SIV group, but they are a weighted mean of the group-specific coverage rates with the weights given by the proportion of people in the population corresponding to any of the groups. Differences between the SIV coverage data (official figures) and the model-based estimates are shown for the older age groups. For the 22–29 age group, both estimates vary from 18.0% (SIV) to 67.6% (model-based estimate).

As a secondary result from Table 2, the overall vaccination coverage for the population older than 2 years was estimated to be 24.8% (95% CI: [22.9, 26.7]). This estimate assumes a vaccination coverage rate of 0% for the population older than 29 because this group was not targeted in the MCCV vaccination program. For those people from 3 to ≤29 years old who were targeted to be vaccinated, the global vaccination coverage was estimated to be 82.4% (95% CI: [76.0, 88.6]).

Fig. 2 shows the validation of the results of the model using the predictive distribution of the age-specific seroprotection level for each SIV group. Most of the observed values are in the corresponding 95% prediction interval. Only one of the observed values (7–8 year old age group in the missing information group) falls outside of the corresponding 95% prediction interval. This is in clear agreement with the nominal probability level of these intervals.

## 4. Discussion

Population-based electronic immunization registries have been proposed as a valid, cost-effective and accessible option for assessing immunization status [1]. Such registries are crucial to provide reliable information on vaccination coverage and adherence to recommended vaccination schedules. Furthermore, immunization registries are rich sources for high quality surveillance of vaccine effectiveness, vaccine failure and adverse events and are gold mines for future research [19]. Before they can be considered to be a valid and reliable source of data, validation studies are needed to determine the accuracy of registry data and identify

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**Table 1**
Sample distribution by age group and according to the meningococcal C conjugate vaccine (MCCV) status in the Vaccine Information System of the Region of Valencia (Sistema de Información Vacunal, SIV).

| Age group (years) | Number (*N*) | MCCV registered in SIV | | No MCCV record in SIV ("U") | | | | |
|---|---|---|---|---|---|---|---|---|
| | | *N* (%) | Seroprotection *N* (%) (CI 95%) | *N* (%) | Seroprotection *N* (%) (CI 95%) | Distribution of "U" cases in SIV; *N* (% from total) | | |
| | | | | | | NR | NVR | M |
| 3–4 | 188 | 187 (99.5%) | 81 (43.3%) (36.1–50.7) | 1 (0.5%) | 0 (0%) (0–95) | 1 (0.5%) | 0 | 0 |
| 5–6 | 107 | 100 (93.5%) | 30 (30.0%) (21.2–40.0) | 7 (6.5%) | 2 (28.6%) (3.7–71.0) | 0 | 0 | 7 (6.5%) |
| 7–8 | 126 | 114 (90.5%) | 6 (5.3%) (2.0–11.1) | 12 (9.5%) | 3 (25.0%) (5.5–57.2) | 1 (0.8%) | 1 (0.8%) | 10 (7.9%) |
| 9–11 | 214 | 159 (74.3%) | 21 (13.2%) (8.4–19.5) | 55 (25.7%) | 1 (1.8%) (0.105–9.7) | 11 (5.1%) | 8 (3.7%) | 36 (16.8%) |
| 12–13 | 164 | 128 (78.0%) | 31 (24.2%) (17.1–32.6) | 36 (22.0%) | 7 (19.4%) (8.2–36.0) | 14 (8.5%) | 3 (1.8%) | 19 (11.6%) |
| 14–16 | 156 | 125 (80.1%) | 35 (28.0%) (20.3–36.7) | 31 (19.9%) | 7 (22.6%) (9.6–41.1) | 7 (4.5%) | 5 (3.2%) | 19 (12.2%) |
| 17–19 | 229 | 162 (70.7%) | 84 (51.9%) (43.9–59.8) | 67 (29.3%) | 27 (40.3%) (28.5–53.0) | 43 (18.8%) | 11 (4.8%) | 13 (5.7%) |
| 20–21 | 87 | 56 (64.4%) | 41 (73.2%) (59.7–84.2) | 31 (35.6%) | 18 (58.1%) (39.1–75.5) | 21 (24.1%) | 9 (10.3%) | 1 (1.1%) |
| 22–29 | 159 | 41 (25.8%) | 22 (53.7%) (37.4–69.3) | 118 (74.2%) | 30 (25.4%) (17.9–34.3) | 50 (31.4%) | 42 (26.4%) | 26 (16.4%) |

Meningococcal C seroprotection levels in subjects with (MCCV registered) and without ("U") a MCCV record in SIV.
MCCV Registered: at least one meningococcal C conjugate vaccine dose registered in SIV, considered as vaccinated.
No MCCV record in SIV ("U"): no meningococcal C conjugate vaccine doses registered; "U": unknown MCCV status = NR + NVR + M.
NR (MCCV non-registered): any other vaccines registered in SIV at the time of the MCCV campaign; no MCCV vaccine registered.
NVR (no vaccination records): no information of any vaccine registered in SIV.
M (missing): first vaccine registered in SIV after the MCCV campaign.

**Table 2**
Percentage of the population registered as vaccinated with the meningococcal C conjugate vaccine in the Vaccine Information System of the Region of Valencia (Sistema de información Vacunal, SIV) in 2011, and the estimated vaccine coverage derived from the Bayesian model [95% CI]; *6 years old could be vaccinated 2–3 + 0; **16 years old could be vaccinated in 2002.

| Year of the vaccination program | Vaccination schedule | Age group (years) | Coverage from SIV in 2011 | Estimated population vaccine coverage [95% credible interval] |
|---|---|---|---|---|
| From 2006 | 2 + 1 | 3–4 | 97.2% | 99.1% [97.8, 99.8] |
| | 2 + 1 | 5–6* | 97.4% | 93.9% [88.9, 97.3] |
| From 2000 | 2–3 + 0 | 7–8 | 89.7% | 92.1% [86.8, 96.0] |
| | 2–3 + 0 | 9–11 | 78.7% | 83.6% [77.3, 89.6] |
| | Catch up <6 years of age | 12–13 | 86.8% | 87.7% [82.0, 92.8] |
| | Catch up <6 years of age | 14–16** | 83.7% | 87.4% [81.6, 92.4] |
| | Catch up 6–8 years of age | 17–19 | 68.3% | 89.3% [83.5, 94.2] |
| From 2002 | Catch up >8 years of age | 20–21 | 53.3% | 88.5% [80.5, 95.3] |
| | Catch up >8 years of age | 22–29 | 18.0% | 67.6% [54.0, 80.4] |

areas for improvement [11]. This work makes a new contribution in that direction.

The information registered in SIV is verified by audit data, and users can obtain the indicators of an audit [10]. In a previous study we compared the influenza vaccination status recorded in SIV with that obtained from a patient recall for two separate influenza periods (2004–2005 influenza season and the post-pandemic first semester of 2010). The sensitivity and specificity of the influenza vaccination data in the SIV improved over time. The capture–recapture measured completeness of SIV for the seasonal vaccine was 66% in 2004–2005 and 82% and 92% for the seasonal and pandemic vaccine, respectively, in 2010 [11].

There are different ways to address misclassifications in vaccination registries, such as by comparing the information in a computerized registry with that on a vaccination card [20], by the response from subjects or parents to postal surveys, or by combining both methods [1]. In our case we did not request paper records as, since the introduction of the computerized system, vaccination cards may not be exhaustively filled in, especially in older age groups; therefore, we used this system as an alternative to those approaches.

We described that it is possible to validate an immunization registry with seroprotection results, taking into account natural immunity values. This method can be used elsewhere to assess underreporting in vaccination registries and to estimate vaccination coverage by knowing seroprotection levels of a particular vaccine preventable disease for the unvaccinated population. The method described would be suitable if alternative approaches are not feasible; or under specific circumstances that might (at least temporarily) predispose to poor registry performance, as the case of MCCV during catch -up.

The seroprotection level for the MCCV registered group was similar to that in the other three predefined groups. This similarity of age-specific seroprotection patterns revealed a substantial presence of vaccinated people in all three non-registered groups.

When analyzing the MCCV-unregistered subjects in SIV, we divided them into three groups that we anticipated would be different. In fact, their estimated vaccine coverage from our model was different, especially in the missing information group, where it barely reached 21%. We speculated that this group included subjects coming to live to the Valencian Region after the catch-up campaign and that their place of origin did not have a scheduled

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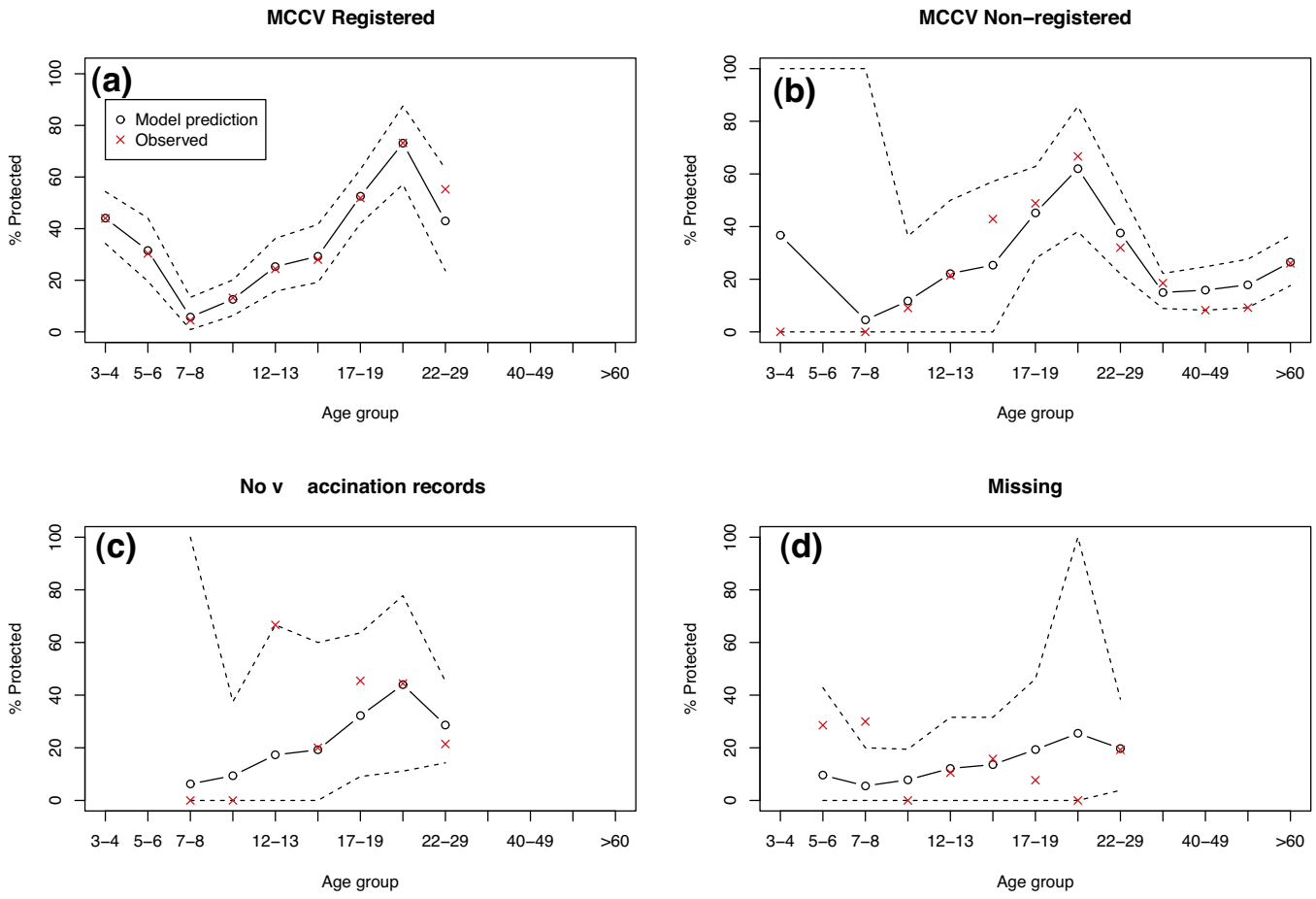


**Fig. 2.** Validation of the results of the model by means of the predictive distribution of the age-specific seroprotection level for every Vaccine Information System (Sistema de Información Vacunal, SIV) group.

MCCV. In contrast, most people living in the Valencian Region at the age of their MCCV are probably vaccinated, regardless of whether they were registered or not in the SIV.

A potential limitation of our study was the representativeness of the sample obtained for the serosurveillance study. According to Spanish law, all samples used for investigation require a signed informed consent, which increases the possibility of bias in the studies, as subjects willing to participate in a study may differ in some aspects to those that reject participation. In order to improve representativity of the sample, we recruited individuals from 12 PCHC and three hospitals whose population represented a sample of the whole population of the Valencian Region, including rural and urban areas. A large sample size and its age distribution provide useful patterns of seroprotection [13]. Regarding the effect of the age distribution in our sample, we have taken into account the stratified design of the sample in our analysis, therefore in this sense the results drawn from our study should be representative of the population.

From our study, we estimated a high vaccine coverage in the Valencian Region of over 80% for subjects 3–29 years old (those who were target of a MCCV vaccination program), with a lower coverage for those who received a catch-up dose when they were over 6 years of age. This represents an underreporting rate of 23.5–73.4% from subjects vaccinated in the 2002 passive catch-up, depending on the age group. In this campaign, subjects >14 years of age were vaccinated in visits to GPs who may have not been familiar with the SIV.

A second limitation of the analysis comes from the statistical modeling itself. Statistical models make assumptions on the data that may be sometimes inappropriate. The quality of the final results will depend on the fit of these assumptions to the mechanism generating the data. Nevertheless in some situations we do not have a valid alternative. If we had the real vaccination status (not that recorded in SIV but the real one) we could check the proportion of them who are recorded in SIV and therefore to assess its completeness. Moreover individuals do not usually remind their vaccination history or we do not usually have a secondary registry to retrieve this information. Therefore, although they should not be the preferred option, sometimes statistical models can be the only alternative to validate registries.

Due to the need to protect adolescents and young adults to prevent carriage and decrease transmission, the MCCV program has been recently modified, with a booster dose now given in early adolescence [12,21]. Evaluation of vaccination registries is therefore required to have reliable figures of vaccination coverage in all age groups to allow the impact of a new schedule to be modeled. This work provides new tools to achieve this goal, hopefully leading to better decisions regarding the implementation of new vaccination schedules.

Further statistical details for the corresponding Bayesian model are available as supplementary digital content.

## Author's contribution

LPB participated in the design and coordination of the study and drafted the manuscript. She contributed to the collection and interpretation of data and statistical analysis. JDD designed the study. He was responsible for the general supervision of the study

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and participated in the coordination of the study and helped to draft the manuscript. He contributed to the interpretation of data and statistical analysis. MAMB participated in the design of the study and performed the statistical analysis. He helped to draft the manuscript. JPB participated in the design of the study and contributed to the interpretation of statistical analysis. He helped to draft the manuscript. All of the authors read and approved the final manuscript.

## Conflict of interest

JDD is acting as national coordinator and principal investigator for clinical studies and is receiving funding from non-commercial funding bodies as well as commercial sponsors (Novartis Vaccines, GlaxoSmithKline, Baxter, Sanofi Pasteur MSD, Med Immune, and Pfizer Vaccines) conducted on behalf of CSISP-FISABIO. He serves as a board member for GSK. He received payment for lectures from SPMSD, Novartis and Baxter, which included support for travel and accommodations for meetings.

The other authors declare that they have no competing interests.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.02.048.

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