

Guide to participants for group exercise on
THE USE OF ELECTRONIC IMMUNIZATION REGISTRIES AND HEALTHCARE DATABASES
IN SUPPORT OF IMMUNIZATION PROGRAMS

Dear Participant,

We will be examining issues and requirements for developing an immunization registry to support vaccination programs and further explore possibilities for data linkage to other healthcare databases to assess vaccine safety and effectiveness building upon experiences obtained so far in North America, Europe and Australia.

Objectives of the exercise

1. To acquire an understanding of organization and funding needed for development and maintenance of electronic immunization registers
2. To acquire an understanding of the minimum data set for an electronic immunization register to collect data on vaccines provided, generate reminders and recall vaccination notices for each client, provide official vaccination forms upon request for the individual, and allow vaccination coverage assessments
3. To acquire an understanding of the possibilities for data linkage of different electronic health care databases

Your assignment is to read the group exercise material, to read in particular the methods-sections in assigned articles, and then participate in discussions around building a model immunization register and further explore possibilities for data linkage to different types of health outcome databases to assess vaccine-preventable disease surveillance, vaccine safety and effectiveness.

You can find the articles on the course website at www.advac.org

Enjoy the exercise!

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Background

It is essential to continue development of technical support to the immunization programs. One example of such technical development is immunization registers, providing a repository of information for vaccinated individuals and vaccine providers. In addition, public health will benefit from this tool when assessing impact of vaccination programs as recently highlighted during the large immunization campaigns following the 2009 pandemic. A need for accurate and rapid information on vaccine coverage by target group was identified and individual-level data were requested by stakeholders assessing pandemic vaccine safety and effectiveness.

Most established immunization registers are able to at least (i) collect data on vaccines provided, (ii) generate reminders and recall vaccination notices for each client, (iii) provide official vaccination forms upon request for the individual, and (iv) allow vaccination coverage assessments. They are therefore also referred to as Immunization Information Systems (IISs). Such systems are confidential, population-based and computerized systems that collect vaccination data about residents within a geographic area or with a healthcare provider. IISs are among the most important tools to strengthen and improve the performance of immunization programs by consolidating vaccination records of all immunization clients from multiple vaccination providers. Access to complete records of all previous vaccinations makes it easier for the healthcare provider to ensure that individuals receive recommended vaccines. Systems can also be used to increase and sustain high vaccination coverage through identification of pockets of unvaccinated individuals or groups and serve as a basis for tailored vaccination campaigns.

Population-based electronic IISs are preferably created at birth if possible through linkage with electronic birth records. IISs can then be linked to health-outcome databases with clinical information and data on medical care provided by general practitioners, specialists or hospitals. Upon linkage of different data sources, anonymised data can be made available through newly-developed software that even permits sharing of data across national borders [14]. Linkage of such different data sources can establish brand-specific vaccine safety and effectiveness but also allow studies of programmatic issues such as optimizing immunization schedules.

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Tasks

A. Development of an immunization register

1. You are considering building a national immunization register in your country. Which functions would you like to see the system be able to conduct?

2. Several competencies are needed for successful development and maintenance of an immunization register – which human resources/functions need to be available in your team?

3. To provide support to vaccinated individuals, immunization providers and immunization program managers/public health, a core data set of information need to be collected – which information would be essential to collect for
 - vaccinated individuals
 - vaccine providers/offices
 - vaccines provided

At this stage do not consider privacy and confidentiality related issues.

4. Looking at the dataset of information you wish to include in the new immunization register – is it feasible and in line with the data protection laws available in your country? Are policies for opt-in/opt-out needed? Which level of data protection security is needed for the vaccinated individual, the vaccine provider and public health?

5. How should the newly developed immunization register be able to obtain data from the local vaccine providers? How can data-lag be avoided?

Demonstration of a demo of the Swedish Immunization registry SVEVAC

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B. Exploring data linkage of the immunization register to other health care outcome databases

1. Identify health care databases containing data of interest to link to the newly established immunization register.
2. What size of a population database population would be optimal for communicable disease surveillance?
3. What size of a population database population would be optimal for vaccine effectiveness studies?
4. What size of a population database population would be optimal for vaccine safety studies? Background incidence rate data?
5. How can obtained data through data bases be validated?
6. Are there any ethical or data protection hurdles to linkage of different databases in your country?

Short presentation of a data mining tool Jerboa developed by Erasmus University used in the

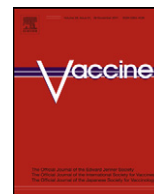
EU for data linkage

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Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain

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ABSTRACT

Two rotavirus vaccines have been available since 2006. This study evaluates the effectiveness of these vaccines using a test-negative case-control design in Navarre, Spain. We included children 3–59 months of age who sought medical care for gastroenteritis and for whom stool samples were taken between January 2008 and June 2011. About 9% had received the pentavalent vaccine (RotaTeq) and another 8% received the monovalent vaccine (Rotarix). Cases were the 756 children with confirmed rotavirus and controls were the 6036 children who tested negative for rotavirus. Thirty-five percent of cases and 9% of controls had required hospitalization ($p < 0.0001$). The adjusted effectiveness of complete vaccination was 78% (95% CI: 68–85%) in preventing rotavirus gastroenteritis and 83% (95% CI: 65–93%) in preventing hospitalization for rotavirus gastroenteritis. No differences between the two vaccines were detected ($p = 0.4523$). Both vaccines were highly effective in preventing cases and hospital admissions in children due to rotavirus gastroenteritis.

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1. Introduction

Rotavirus is the most common cause of acute gastroenteritis in children worldwide. It has been estimated that by the age of 5 years, nearly every child has been infected with rotavirus at least once [1,2]. Before the availability of a vaccine, rotavirus was responsible for over 40% of hospital admissions for gastroenteritis in children [3–6]. In Spain, it has been estimated that before the vaccine became available rotavirus annually caused 480 admissions for every 100,000 children under 5 years of age [7].

In 2006, two oral live-attenuated rotavirus vaccines were licensed for infants up to 6 months of life, a monovalent human rotavirus vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and a pentavalent bovine-human reassortant vaccine (RV5, RotaTeq, Merck Vaccines, Whitehouse Station, NJ, USA). Clinical trials of the two licensed vaccines show high efficacy against the serotypes included in the respective vaccines [8,9].

Rotavirus vaccination was first recommended to US children in February 2006 [10]. Subsequently, in April 2009, the World

Health Organization Strategic Advisory Group of Experts recommended rotavirus vaccine for all children [11]. Worldwide, a number of countries have adopted this recommendation and have added rotavirus vaccines to their pediatric immunization programs, including a limited number of European countries (Finland, Austria, Luxembourg and Belgium) [12–14]. In some of these countries, systematic vaccination has resulted in marked reductions in the incidence of rotavirus gastroenteritis and in hospitalizations for this cause [10,13–16]. In evaluations of these vaccines in the population under real-life conditions, most studies have found them to be highly effective [17–22], although no evidence of a protective effect was found in an outbreak of a heterotypic strain in Australia [23].

In Spain, RV1 and RV5 have been available since 2006. They are not included in the official schedule of childhood vaccines funded by the health administration, but many pediatricians recommend them and parents can have their children vaccinated if they pay the cost of the vaccine. The two vaccines have been used equally, with the choice between them influenced by the recommendation of the physician or pharmacist, the cost of each regimen, the parents' decision and their availability at the time of use. The Spanish Medicines Agency has provisionally suspended the marketing of RV1 since March 2010, and also of RV5 between July and August 2010, due to contamination detected in each of these

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vaccines [24,25]. As of October 2011 use of RV1 continued to be suspended.

The objective of the present study was to evaluate the effectiveness of rotavirus vaccination in children 3–59 months of age in preventing cases of virologically confirmed gastroenteritis and in preventing hospital admissions due to this cause.

2. Methods

2.1. Study population and data collection

We carried out a case–control study based on electronic clinical reports in the region of Navarre, Spain (630,000 inhabitants, including 34,000 children <5 years). The Navarre Ethical Committee for Medical Research approved the study protocol.

The Navarre Health Service provides health care, free at point of service, to 97% of the population; it comprises one tertiary hospital in the main city, two small local hospitals – all of them with pediatric wards and emergency rooms – and 54 primary health care centers. The clinical reports have been computerized since 2000, and include those from primary care, hospital admissions and laboratory test results. All vaccine doses administered are registered at the vaccination points. In all the hospitals, stool analyses were systematically performed for children hospitalized with acute gastroenteritis, while in primary care, the pediatricians requested stool analysis in children with gastroenteritis at their own discretion. The tests were conducted in three laboratories.

The study population comprised children born since 2006 residing in Navarre and covered by the Navarre Health Service. Within this cohort we conducted a nested case–control study that included all children aged 3–59 months who sought medical care for acute gastroenteritis and for whom at least one stool sample had been taken for microbiological study between 1 January 2008 and 30 June 2011. All samples were systematically cultured for bacteria and studied to detect rotavirus antigen. One fresh aliquot was used to perform the Rida Quick rotavirus/adenovirus Combi test (R-Biopharm AG, Darmstadt, Germany), a lateral-flow immunochromatographic assay, which uses labeled monoclonal antibodies against surface antigens of rota- and adenoviruses.

Cases were considered to be children in whom the presence of rotavirus antigen was detected in any of the stool samples, and controls were those who were negative for rotavirus in all samples. The date of consultation and whether it resulted in hospitalization were collected for both cases and controls. Information on each dose of vaccine received, the date and the brand name was taken from the regional vaccination registry. Each vaccine dose was taken into account when 14 or more days had elapsed since its administration. Complete vaccination was considered to be receipt of two separate doses at least 4 weeks apart for RV1, and receipt of three doses at least 4 weeks apart for RV5.

Each child's sex, date of birth, diagnosis of any major chronic conditions, place of residence and health care setting were obtained from the clinical reports.

2.2. Data analysis

To assess field effectiveness, we evaluated the effect of having received one or more doses of vaccine. The effectiveness of complete vaccination in comparison with no vaccination was also evaluated, after excluding from the analysis children with incomplete vaccination or vaccination not meeting the manufacturer's recommendations. The effectiveness of each brand of vaccine was estimated in comparison with unvaccinated children. Vaccine effectiveness in preventing cases requiring hospitalization was evaluated by comparing the vaccination status of children

hospitalized for acute gastroenteritis in whom rotavirus antigen was detected, with those hospitalized for gastroenteritis who were negative for rotavirus.

The vaccination status of cases and controls was compared by calculating odds ratios (OR) with their 95% confidence intervals (CI). Analyses were adjusted for sex, age group (3–5, 6–11, 12–23, 24–35, 36–47 and 48–59 months), birth trimester, area (tertiary or local hospital) and major chronic conditions. In comparisons for which the number of cases did not permit adjustment for all the variables, some variables were removed from the model and categories were combined in others; no relevant changes were found in the estimated effect.

The statistical significance of the associations was evaluated by the two-sided Fisher's exact test, Chi-square test or Student's *t*-test. Conventional and exact logistic regression techniques were used in the multivariate analyses. We evaluated differences in vaccine effectiveness by testing for interaction between the covariables and the vaccine effect, and this was taken into account when $p < 0.05$. Vaccine effectiveness was estimated as a percentage: $(1 - \text{OR}) \times 100$. Statistical analyses were performed with SPSS version 17 and Stata version 10.1.

3. Results

3.1. Characteristics of the study population

A total of 6792 children met the inclusion criteria, 756 (11%) of whom were confirmed for rotavirus (cases) and 6036 were negative (controls). Cases and controls did not differ with regard to distribution by sex, rural/urban residence, migrant status or pre-existing major chronic conditions. About 41% of cases were under 12 months of age versus 25% of controls ($p < 0.0001$). Cases showed marked seasonality, preferentially for the first semester of the year, whereas seasonal variation was less pronounced for controls ($p < 0.0001$). Thirty-five percent of cases and 9% of controls had required hospitalization ($p < 0.0001$). About 6% of cases vs 18% of controls had received at least one dose of rotavirus vaccine ($p < 0.0001$), and 5% vs 14%, respectively, had complete vaccination. The proportion of children who had received at least one dose of vaccine was 8% for RV1 and 9% for RV5 (Table 1). Among children older than 6 months, 90% (458/510) of those vaccinated with RV1 had received both doses, and 76% (396/521) of those vaccinated with RV5 had received the third dose ($p < 0.0001$).

3.2. Vaccine effectiveness in preventing rotavirus gastroenteritis

Field effectiveness was evaluated considering all children who had received at least one dose of vaccine. In the logistic regression analysis adjusted for birth trimester, age, sex, rural/urban residence, area, major risk conditions and health care setting, having received at least one dose of rotavirus vaccine was 78% effective (95% CI: 70–84%) in preventing rotavirus gastroenteritis in children 3–59 months of age. The effectiveness of RV1 was 76% (95% CI: 63–85%), and that of RV5 was 80% (95% CI: 69–87%), with no significant difference between the two vaccines ($p = 0.6292$) (Table 2).

In children who had received a complete course of vaccinations, the effectiveness in preventing rotavirus gastroenteritis was 78% (95% CI: 68–85%) with respect to those not vaccinated. The two-dose RV1 regimen yielded an effectiveness of 75% (95% CI: 60–85%) and the regimen with three doses of RV5 was 81% effective (95% CI: 68–89%), with no statistically significant differences between the two ($p = 0.4330$). Vaccine protection was lower in children over 24 months of age (61%; 95% CI: 0–84%) than in younger children (80%; 95% CI: 70–86%; $p = 0.0495$). In the period January 2008–December 2009 the estimator of effectiveness was 64% (95%

Table 1
Characteristics of cases and controls.

	Cases		Controls		P value
	n	%	n	%	
Sex					0.1296
Male	405	53.6	3410	56.5	
Female	351	46.4	2626	43.5	
Age group, in months					<0.0001
3–5	59	7.8	429	7.1	
6–11	254	33.6	1071	17.7	
12–23	323	42.7	2764	45.8	
24–35	99	13.1	1180	19.6	
36–47	17	2.3	427	7.1	
48–59	4	0.5	165	2.7	
Year – semester					<0.0001
2008 – 1	83	11.0	615	10.2	
2008 – 2	87	11.5	980	16.2	
2009 – 1	162	21.4	799	13.2	
2009 – 2	6	0.8	1029	17.1	
2010 – 1	189	25.0	836	13.9	
2010 – 2	16	2.1	974	15.8	
2011 – 1	213	28.2	841	13.6	
Birth year					<0.0001
2006	78	10.3	1164	19.3	
2007	173	22.9	1671	27.7	
2008	230	30.4	1625	26.9	
2009	160	21.2	1191	19.7	
2010	113	14.9	374	6.2	
2011	2	0.3	11	0.2	
Immigrant					0.1543
No	753	99.6	5976	99.0	
Yes	3	0.4	60	1.0	
Residence					0.3661
Urban	535	70.8	4367	72.4	
Rural	221	29.2	1669	27.7	
Area					<0.0001
Tertiary hospital	647	85.6	5732	95.0	
Local hospitals	109	14.4	304	5.0	
Major chronic condition					1.0000
No	743	98.3	5932	98.3	
Yes	13	1.7	104	1.7	
Rotavirus vaccination					<0.0001
No	711	94.0	4942	81.9	
Any dose but not fully vaccinated	11	1.5	245	4.0	
Fully vaccinated	34	4.5	849	14.1	
Vaccine type					<0.0001
Monovalent vaccine (RV1, Rotarix)	21	2.8	536	8.9	
Pentavalent vaccine (RV5, RotaTeq)	24	3.2	558	9.2	
Health care setting					<0.0001
Hospitalization	262	34.7	518	8.6	
Outpatients	494	65.3	5518	91.4	
Total	756	100	6036	100	

CI: 36–80%), whereas it rose to 83% (95% CI: 73–90%), in the period January 2010–June 2011 ($p=0.0903$) (Table 2).

Thirty-four cases of confirmed rotavirus gastroenteritis were detected in children who had received a complete course of vaccinations, none of whom had a known cause of immunosuppression. Within 14 days of receiving a dose of rotavirus vaccine, 23 controls but no cases sought medical attention, which rules out the possibility that cases due to vaccine strain could have affected the results.

3.3. Vaccine effectiveness in preventing hospitalization for rotavirus gastroenteritis

Having received a complete course of vaccinations yielded an effectiveness of 83% (95% CI: 65–93%) in preventing hospitalizations with rotavirus gastroenteritis and of 75% (95% CI: 62–83%) in preventing outpatient cases, with no statistically significant difference between the two estimators ($p=0.2217$).

The effectiveness of the complete course of vaccinations in preventing hospitalization from rotavirus gastroenteritis did not differ

between children older and younger than 24 months ($p=0.9601$); however, it increased from 39% (95% CI: –54% to 79%) in the 2008–2009 period to 96% (95% CI: 85–99%) in the period January 2010–June 2011 ($p=0.0009$) (Table 3). In 2008–2009 there were 7 hospital admissions for confirmed rotavirus gastroenteritis in children who were completely vaccinated. These cases were distributed across all areas, both children who had received RV1 (4 cases) and those who received RV5 (3 cases) were affected, and nosocomial infection was ruled out.

4. Discussion

Both of the available rotavirus vaccines showed high effectiveness in preventing confirmed cases of rotavirus gastroenteritis in children aged 3–59 months as well as in preventing hospital admissions with this diagnosis. Our estimates of effectiveness are slightly lower than those observed in clinical trials [8,9] and are within the range of those described in observational studies [17–22]. Unlike other studies, we evaluated both the available vaccines, covering a wide age range and including several seasons in the analysis.

Table 2
Crude and adjusted estimates of effectiveness of rotavirus vaccination in children aged 3–59 months, according to vaccine type, age group and diagnosis period.

Age and rotavirus vaccination status	Cases/controls	Crude OR (95% CI)	Adjusted OR (95% CI) ^a	Vaccine effectiveness (95% CI)
Unvaccinated	711/4942	1	1	
Vaccinated (any doses)	45/1094	0.29 (0.21–0.39)	0.22 (0.16–0.30)	78% (70–84%)
Fully vaccinated	34/849	0.28 (0.20–0.40)	0.22 (0.15–0.32)	78% (68–85%)
Type of vaccine				
RV1 (any doses)	21/536	0.27 (0.18–0.42)	0.24 (0.15–0.37) ^b	76% (63–85%)
RV5 (any doses)	24/558	0.30 (0.20–0.45)	0.20 (0.13–0.31) ^b	80% (69–87%)
RV1 (2 doses)	19/459	0.29 (0.18–0.46)	0.25 (0.15–0.40) ^c	75% (60–85%)
RV5 (3 doses)	15/390	0.27 (0.16–0.45)	0.19 (0.11–0.32) ^c	81% (68–89%)
Age group				
3–11 months				
Unvaccinated	297/1117	1	1	
Fully vaccinated	12/248	0.18 (0.10–0.33)	0.22 (0.12–0.42)	78% (58–88%)
12–23 months				
Unvaccinated	302/2197	1	1	
Fully vaccinated	16/481	0.24 (0.15–0.40)	0.18 (0.11–0.31)	82% (69–89%)
≥24 months				
Unvaccinated	112/1628	1	1	
Fully vaccinated	6/120	0.73 (0.31–1.69)	0.39 (0.16–1.00)	61% (0–84%)
Diagnosis period				
Period 2008–2009				
Unvaccinated	322/2998	1	1	
Fully vaccinated	14/317	0.41 (0.24–0.71)	0.36 (0.20–0.64) ^d	64% (36–80%)
Period Jan 2010–Jun 2011				
Unvaccinated	389/1944	1	1	
Fully vaccinated	20/532	0.19 (0.12–0.30)	0.17 (0.10–0.27) ^d	83% (73–90%)

^a Odds ratio and 95% confidence interval obtained by logistic regression models adjusted for sex, age, birth trimester, major chronic conditions, area and healthcare setting.

^b Comparison of the effectiveness of any doses of the monovalent vaccine (RV1) and the pentavalent vaccine (RV5): $p = 6292$.

^c Comparison of the effectiveness of fully vaccination with the RV1 and with the RV5: $p = 0.4330$.

^d Comparison of the effectiveness of complete vaccination in the period 2008–2009 vs the period January 2010–June 2011: $p = 0.0903$.

Table 3
Rotavirus vaccine effectiveness in preventing hospital admission due to rotavirus gastroenteritis in children aged 3–59 months.

	Cases/controls	Crude OR (95% CI)	Adjusted OR (95% CI) ^a	Vaccine effectiveness (95% CI)
Total				
Unvaccinated	249/390	1	1	
Fully vaccinated	9/80	0.18 (0.09–0.36)	0.17 (0.07–0.35)	83% (65–93%)
Aged <24 months				
Unvaccinated	207/302	1	1	
Fully vaccinated	8/69	0.17 (0.08–0.36)	0.18 (0.07–0.40) ^b	82% (60–93%) ^b
Aged ≥24 months				
Unvaccinated	42/88	1	1	
Fully vaccinated	1/11	0.19 (0.02–1.52)	0.11 (0.002–0.83) ^b	89% (17–99.8%) ^b
Period 2008–2009				
Unvaccinated	91/237	1	1	
Fully vaccinated	7/29	0.63 (0.27–1.49)	0.61 (0.21–1.54) ^c	39% (–54 to 79%) ^c
Period January 2010–June 2011				
Unvaccinated	158/153	1	1	
Fully vaccinated	2/51	0.04 (0.01–0.16)	0.04 (0.004–0.15) ^c	96% (85–99%) ^c

^a Odds ratio and 95% confidence interval obtained by exact logistic regression adjusted for age group, birth year and major chronic conditions.

^b Comparison of vaccine effectiveness in preventing cases with age <24 months vs ≥24 months: $p = 0.9601$.

^c Comparison of vaccine effectiveness in the period 2008–2009 vs the period January 2010–June 2011: $p = 0.0009$.

Complete vaccination conferred high protection against hospitalization with rotavirus in children up to 59 months of age. However, in the analysis including outpatient cases a lower protective effect, on the limits of statistical significance, was found in children aged 24 to 59 months. Although this finding cannot be considered conclusive, it could be that the proportion of susceptibles declines with age due to natural exposure to the virus, which reduces the beneficial margin of the vaccine [26–28]. The results show variability in the effectiveness of the rotavirus vaccines over time in this small region. Circulation of a rotavirus strain that is not well matched with the vaccine strains could explain the transitory decline in vaccine effectiveness in a small geographic area [23], but would tend to become diluted in multicenter studies and those

conducted in large regions or countries. Exploring this aspect would have required characterization of the types of rotavirus [23,29], which was not done in our study.

Most studies that have evaluated the effectiveness of rotavirus vaccines have focused on only one brand of vaccine [17,18,21–23]. In the present study we evaluated both types of vaccine in the same place and time, with similar levels of coverage, and found no significant differences in their effectiveness when comparing the complete course of vaccinations and when the evaluation was made in terms of field effectiveness.

Consistent with other studies [9], we found a higher point estimate of vaccine effectiveness in preventing hospitalizations than in preventing outpatient cases, although this difference did not

reach statistical significance in our study. This seems to suggest that those who are vaccinated, if they become ill, may present less severe clinical forms of the disease.

4.1. Study limitations

The interpretation of these results is subject to some limitations. Although the study size made it possible to obtain quite precise estimates of effectiveness, the statistical power does not permit totally conclusive results in some analyses. The sensitivity of the antigen detection technique used to confirm rotavirus infection is very high, but we cannot rule out some false negative results, which would lead to a slight underestimation of vaccine effectiveness.

The rotavirus vaccine is administered orally and could have been applied outside the health system. Even if this had occurred, however, the vaccination would have been registered in all but exceptional cases, since protocols call for frequent pediatric examinations in the first months of life, and particular emphasis is given to the importance of registering all activities related with childhood vaccination. Moreover, the number of doses registered is highly consistent with the number of doses sold in the region during the same period.

Finally, we were unable to serotype the rotavirus detected in our study, therefore it was not possible to study the association between vaccine failures and a possible mismatch of vaccine strains and circulating strains of rotavirus [23]. In any event, our results provide an evaluation of the effect of the vaccine against all rotavirus disease.

Vaccinated and unvaccinated children may not be comparable with regard to risk factors and the likelihood of consulting a physician or of being hospitalized. Nevertheless, the advantage of the test-negative case-control design is that both cases and controls have followed the same paths in the health care system, which rules out differences in parental attitude when seeking medical care and of physician differences in making decisions about stool samples or hospitalization. This is supported by the fact that cases and controls had similar characteristics for many of the variables analyzed, except for those that could be related with the epidemiology of the causal agents.

5. Conclusions

The monovalent and pentavalent rotavirus vaccines have high levels of effectiveness in preventing both rotavirus gastroenteritis and hospitalizations for this cause. In small geographic areas the effectiveness may vary over time, which could explain some disparity in the results of different studies. We did not detect any important differences in effectiveness between the two brands of vaccine available.

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Immunisation registers – important for vaccinated individuals, vaccinators and public health

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Vaccines save lives, protect against disability and improve health. Diseases such as smallpox, tuberculosis, poliomyelitis, diphtheria, tetanus, pertussis, invasive diseases related to *Haemophilus influenzae* type b and *Neisseria meningitidis* group C infection, that only half a century ago were all communicable disease threats to Europeans, are now rare entities or, as in the case of smallpox, eradicated [1]. Consequently, some of them are almost forgotten by the younger general public. However, despite the availability of safe and effective vaccines against measles and rubella and the considerable decline in the number of cases in the last decades, Europe is still struggling to eliminate them. In 2011 alone, over 30,000 cases of measles and more than 3,000 cases of rubella were reported in the European Union (EU) [2]. To help improve coverage with recommended vaccines in the childhood and other age or risk group-specific immunisation programmes and assess their impact, immunisation registers have been or are being developed in a number of countries. In a special issue of *Eurosurveillance*, published in two parts in this and the following week, country-specific experiences with established immunisation registers are shared in a series of articles [3-11].

During the upcoming European Immunization Week, the measles and rubella elimination 2015 goal for Europe will be advocated by EU Member States, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) through activities such as (i) communication packages [12], (ii) a video produced in collaboration between the ECDC and the European news channel Euronews that presents the severe complications that can occur following measles infections and (iii) a number of national conferences. While this creates awareness, it is also essential to continue the development of technical support to the immunisation programmes. One example of such technical development are immunisation registers, providing a repository of information for vaccinated individuals and vaccine providers. In addition, public health will benefit from this tool when assessing impact of vaccination programmes as recently

highlighted during the large immunisation campaigns following the 2009 pandemic. A need for accurate and rapid information on vaccine coverage by target group was identified and individual-level data were requested by stakeholders assessing pandemic vaccine safety and effectiveness.

Most established immunisation registers are able to at least (i) collect data on vaccines provided, (ii) generate reminders and recall vaccination notices for each client, (iii) provide official vaccination forms upon request for the individual, and (iv) allow vaccination coverage assessments. They are therefore also referred to as Immunisation Information Systems (IISs). Such systems are confidential, population-based and computerised systems that collect vaccination data about residents within a geographic area or with a healthcare provider. IISs are among the most important tools to strengthen and improve the performance of immunisation programmes by consolidating vaccination records of all immunisation clients from multiple vaccination providers. Access to complete records of all previous vaccinations makes it easier for the healthcare provider to ensure that individuals receive recommended vaccines. Systems can also be used to increase and sustain high vaccination coverage through identification of pockets of unvaccinated individuals or groups and serve as a basis for tailored vaccination campaigns.

Population-based electronic IISs are preferably created at birth if possible through linkage with electronic birth records. IISs can then be linked to health-outcome databases with clinical information and data on medical care provided by general practitioners or hospitals. Upon linkage of different data sources, anonymised data can be made available through newly-developed software that even permits sharing of data across national borders [13]. Linkage of such different data sources can establish brand-specific vaccine safety and effectiveness but also allow studies of programmatic issues such as optimising immunisation schedules.

The eight pandemic vaccines available in the EU for protection against the 2009 pandemic (Cantgrip, Celltura, Celvapan, Fluval P, Focetria, Pandemrix, Panenza, PanvaxH1N1) were closely followed and initial safety reports were provided regularly on the centrally authorised vaccines by the European Medicines Agency [14]. In August 2010, a safety signal was reported from Finland and Sweden and an association between the use of one of the adjuvanted vaccines Pandemrix and an increase in rates of narcolepsy was later confirmed in these two countries [15-18]. For the investigations of this safety signal, individual exposure data on who was vaccinated, with which vaccine (including batch number) and when the vaccination occurred were needed. In Sweden, investigations were facilitated by immunisation registers with information on vaccine exposure available for parts of the country (covering a population of more than 5 million persons). In Finland, data were available locally with each vaccinator, but had to be compiled at the national level in order to acquire an overview.

A key factor in the development of IISs is to ensure the integrity of the individual and collected information on health and access and use of data varies between countries. Many EU Member States have found difficulties in establishing electronic IISs due to strict data protection laws. However, regional or national IISs do exist in the EU and are compliant with national data protection laws in Denmark, Estonia, Finland, France, Iceland, Ireland, Italy, Norway, Scotland, the Netherlands, Portugal, Romania, Spain and Sweden. The European Commission now proposes a comprehensive reform of the data protection rules due to the fact that rapid technological and business developments have brought new challenges for the protection of personal data [19]. New technology allows both private companies and public authorities to make use of personal data on an unprecedented scale in order to pursue their activities. A reform of the EU's 1995 data protection rules has been viewed needed, not only because the scale of data collection and sharing has increased dramatically, but also because the 27 EU Member States have implemented the 1995 rules differently, resulting in divergences in enforcement. Through this new proposal, there is hope that a single law will reduce the current fragmentation. It is currently unknown whether and how this single law will facilitate establishing ISSs in EU countries with strict data protection laws. It should be emphasised here that it is important to maintain public trust in such systems and to strike a balance between keeping a level of data protection high, while at the same time delivering the protection and promotion of health that the public rightly expects [20,21].

The Council of the EU have during the last three years adopted a Council recommendation on seasonal influenza vaccination (2009) and a Council conclusions on childhood immunisations: successes and challenges of European childhood immunisation and the way forward

(2011) [22,23]. Both documents highlight the importance of and encourage Member States to gather specific and comparable data at national level regarding the uptake rates of vaccines.

Following the general success of immunisation programmes during the last two centuries eliminating or significantly reducing a number of communicable diseases, new efforts have resulted in a number of novel vaccines for diseases against which immunisation was not available before, new combination vaccines (e.g. hexavalent vaccines for vaccination of infants during the first year of life) to reduce the number of injections and visits to vaccination clinics or new formulations of vaccines earlier available (e.g. intranasal influenza vaccine). Examples of vaccines made available on the EU market during the last decade are presented in the table.

TABLE

Newly-authorised vaccines in the European Union through the central procedure or through mutual recognition, aimed for the paediatric immunisation programmes, 2000–2011

Newly-authorised vaccine	Year of authorisation	Name of product
Combination vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Hib, hepatitis B	2000	Infanrix hexa
Combination vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Hib, hepatitis B	2000	Hexavac ^a
Vaccine against invasive infections caused by <i>Neisseria meningitidis</i> group C	2001	NeisVac-C
Combination vaccine against measles, mumps, rubella and varicella	2007	Priorix-Tetra
Vaccine against rotavirus-induced gastroenteritis	2006	Rotarix
	2006	RotaTeq
Vaccine against human papillomavirus-induced cervical cancer	2006	Cervarix
	2006	Gardasil
Vaccine against invasive infections caused by <i>Streptococcus pneumoniae</i>	2001	Prevenar 7
	2009	Synflorix
	2011	Prevenar 13
Vaccine against invasive infections caused by <i>Neisseria meningitidis</i> group A, C, W-135, Y	2010	Menveo
Intranasal trivalent influenza vaccine	2011	Fluenz

Hib: *Haemophilus influenzae* type b.

^a Suspended since 2005 as a precautionary measure due to concerns about the long-term protection against hepatitis B.

As of today, vaccines against 16 infectious diseases are available but no EU Member State has implemented all available paediatric vaccines in their recommended programmes. Changes in immunisation programmes need to be performed carefully and as much as possible rely on evidence-based decisions obtained through monitoring the impact of the implemented programmes. The use of linked ISSs to outcome databases to assess first safety and then effectiveness is the best tool in the initiation phase of a new vaccine but also in assessing long term performance.

A European Conference on Immunisation Information Systems was held in Stockholm in 2010 with support from the European Commission [24]. Conference conclusions included (i) a recommendation to develop a long term EU plan to support Member States to implement immunisation and information systems able to communicate across the EU and (ii) a request to vaccine industry to implement a standardised system for bar coding vaccines to facilitate recording of each vaccination encounter.

ECDC supports these recommendations and would like to add that setting a goal to include over 75% of all European children and if possible also other age groups in national immunisation information systems by 2020 would be valuable for monitoring of future EU vaccination programmes.

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Measuring childhood vaccine coverage in England: the role of Child Health Information Systems

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Child Health Information Systems (CHISs) are computerised clinical record systems which support a range of health promotion and prevention activities for children, including immunisation and screening. There are a number of different providers of CHISs in England. These systems are managed by child health departments in each local area and not all are interoperable. The establishment of systems which record and maintain accurate information on the entire population is critical to assess vaccination coverage at both national and local levels. These systems should have the flexibility to adapt to a continuously evolving immunisation programme, a mechanism to rapidly feedback to local public health teams for outbreak prevention and control, and the ability to mount a timely response to vaccine safety scares. The ability to schedule (call and recall) immunisation appointments has contributed to improvements in vaccination coverage both in England and elsewhere. While this has been achieved in England through multiple CHISs the development of a single national register would reduce the complexities of maintaining accurate and complete immunisation records for the entire population.

Introduction

The ability to reliably measure vaccine coverage plays an essential role in evaluating the success of a vaccination programme, identifying susceptible populations for further interventions and informing future vaccine policy decisions. This is dependent on having an accurate estimate for the eligible population (denominator) and a robust method of ascertaining the number of those eligible individuals who have received a particular vaccine dose (numerator).

Data on vaccines administered in England are currently recorded on two computerised systems – general practitioner (GP) registers and population-based child health information systems (CHISs). Similar systems operate across the United Kingdom (UK) (in Scotland, Wales and Northern Ireland) which enables the production of UK-wide estimates of vaccine coverage. In England, while CHISs are generally used to estimate

vaccine coverage for the routine childhood immunisation programme, GP registers are often used to evaluate selective vaccination programmes for adults (e.g. seasonal influenza and pneumococcal polysaccharide vaccines). This paper will specifically focus on how data held on CHISs are used in England to assess the routine childhood immunisation programme in a timely and accurate manner.

The publication of the National Health Service (NHS) Health and Social Care Bill in 2011 marks a radical change to the organisational structure of the NHS in England [1]. The abolition of Primary Care Trusts (PCTs), currently responsible for maintaining CHISs, and changes to the responsibilities for the procurement of health services for local populations based on an assessment of their health needs are likely to have significant implications for the delivery and evaluation of national public health programmes including childhood immunisations. We also consider the challenges of collecting population-based vaccine coverage data through current systems in England, and of maintaining accurate collections in the newly structured NHS.

This paper focuses on how data held on CHISs have been used in England since the late 1980s to assess vaccine coverage in the routine childhood immunisation programme in a timely and accurate manner, and considers the challenges of maintaining accurate collections in light of the planned reorganisation of the English National Health Service. It also highlights the lessons learnt from an English perspective which will be of relevance to those European countries planning to implement population-based immunisation registers.

Child Health Information Systems (CHISs)

CHISs are computerised clinical record systems which support a range of health promotion and prevention activities for children including screening and immunisation. There are a number of different providers of CHISs in England. These systems are managed by child health departments in each local area, previously in each district health authority and since the NHS

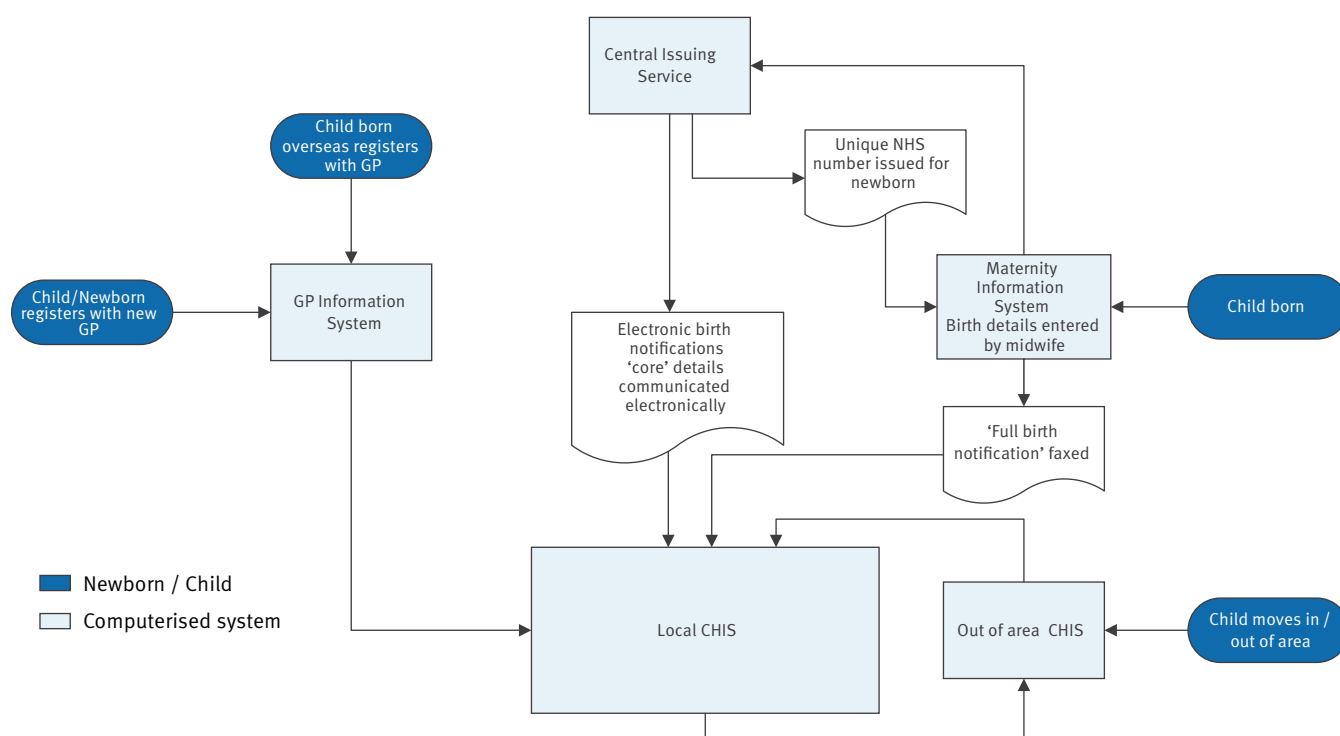
reorganisation of April 2002, in Primary Care Trusts (PCTs).

They hold data on all children in the responsible population for that PCT. The PCT responsible population is defined as all children registered with a GP whose practice forms part of the PCT, regardless of where the child is resident, plus any children not registered with a GP who are resident within the PCT's statutory geographical boundary. Note that children resident within the PCT geographical area, but registered with a GP belonging to another PCT, are the responsibility of that other PCT. Thus CHISs can provide a complete and accurate denominator for estimating vaccine coverage. Children are entered onto the local CHIS at birth or when they move into the local area. Much of the data required to start the child health record is already collected as part of the mother's maternal record stored in the local maternity information system. All new births are registered electronically by the attending midwife using the Central Issuing Service (CIS). This 'birth notification' automatically generates a unique NHS number within a few hours of delivery. An electronic copy of the birth notification containing core demographic information on the newborn and mother as well as GP registration details are sent from the CIS to the relevant Child Health department for entry onto the local CHIS. In addition, a paper record of the complete birth notification is faxed by the midwife to the local CHIS (Figure 1).

Records are transferred to the relevant CHIS for children moving into the area from other parts of the UK. When a child moves, he/she will register with a local GP who will request that all the child's health records (including their immunisation history) are transferred. Furthermore this practice will inform the local Child Health department managing the local CHIS of the newly-registered patient. A request is made to the former Child Health department to transfer their CHIS records. This transfer of information is either electronic or paper-based depending on the inter-operability of the different systems. For those children born outside the UK, a new record is created which includes all available data on vaccines that have been administered previously. Regular updating to take account of newborns and children moving in and out of the area is therefore essential. It is the responsibility of the PCT to ensure the accuracy of the data held on their local CHIS (Figure 1).

One of the primary functions of CHISs is to manage the local immunisation programme, scheduling appointments, recording data on vaccines administered and sending out reminders for those who fail to attend. Invitations for immunisation are either sent to parents / guardians from their registered GP or directly from the local CHIS. Information held on CHISs can be extracted to provide age-specific vaccine coverage estimates at local, regional and national levels. In addition, data held on CHISs are important for

FIGURE 1
Data flow to child health information system, England



CHIS: child health information system; GP: general practitioner; NHS: National Health Service.

predicting and responding to community outbreaks of vaccine-preventable diseases (VPD) where local catch-up programmes can be targeted at cohorts with poor coverage.

The majority of routine childhood immunisations are delivered to pre-school children by GPs in primary care although some selective programmes e.g. neonatal hepatitis B and Bacille Calmette Guerin (BCG) vaccines may be delivered in a combination of primary and secondary care settings. The contribution of vaccines delivered in the private sector currently is negligible. Vaccines administered in any of these settings are recorded electronically in the child's GP record and on the local CHIS. In addition, a paper copy of the children's vaccination record is held by the parent in the personal child health record (PCHR). Frequent exchange of information between CHISs, primary care and other providers is required to ensure assessment of vaccine coverage is based on accurate numerator and denominator estimates.

Generating vaccine coverage data from CHISs: COVER Programme

Historically, long-term trends in childhood vaccine coverage in England were estimated by individual health authorities and published annually by the Department of Health (DH) [2]. Initially, the denominator was the number of live births in each district health authority, but in 1988, following the increasing use of computerised child health systems (CHISs), the denominator became all resident children in the district (Körner returns) [3]. Numerator data on the number of these eligible children receiving each of the recommended vaccines was also obtained from CHISs - providing, for the first time, a genuine measurement of total population coverage. Since 1995, annual vaccine coverage has been monitored by the Health Protection Agency (HPA) (previously Public Health Laboratory Service) on behalf of the DH.

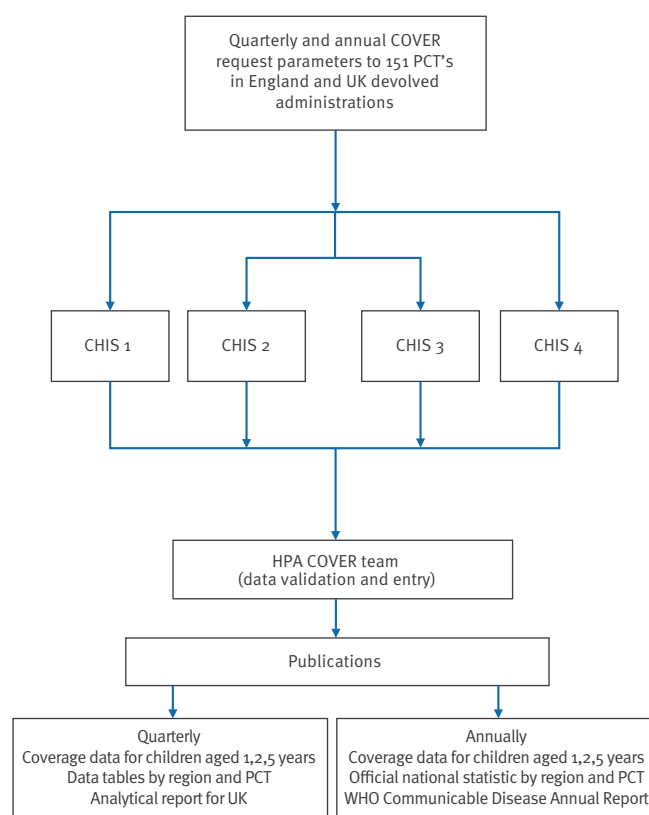
In addition to the annual collection, a quarterly collection was developed in the late-1980s to provide more rapid feedback and enable changes in vaccine coverage to be detected quickly [4]. This data collection system, known as the COVER programme (Cover of Vaccination Evaluated Rapidly) exploited the role of district immunisation co-ordinators as contacts and used standardised programmes to extract aggregate data from CHISs [4]. For a number of years, there has been a mandatory requirement for all local areas within the NHS to provide quarterly and annual returns to the HPA [5].

While the extraction processes may vary between the different CHISs, all system suppliers are provided with a specification detailing the 'request parameter's [6]. A quarterly request is made to each PCT Child Health department to provide computerised reports for these COVER parameters [7]. Information is requested for all children in the PCT responsible population who reach their first, second and fifth birthdays during a particular evaluation quarter. These data are aggregate

returns and will include the number of eligible children in each cohort and the numbers and proportion vaccinated for all routine vaccinations offered according to the current national immunisation schedule (Figure 2).

The UK immunisation programme is constantly evolving. The addition of new vaccines and changes to the schedule requires CHISs to have the flexibility to incorporate these changes in a timely manner. At the time of planning the introduction of a new vaccine or change to the routine immunisation schedule, the DH works with all the CHIS suppliers to ensure that the systems can schedule and record data on new vaccines / schedule changes ahead of their implementation. These are communicated to the system suppliers through Dataset Change Notices (DSCNs). This in turn allows for the timely collection of vaccine coverage data on the first and subsequent cohorts eligible for the new schedule. Coverage data on the first eligible cohort following the introduction of the seven-valent pneumococcal conjugate vaccine to the primary infant schedule in September 2006 was published in December 2007 [7,8].

FIGURE 2
Vaccine coverage data flows from Child Health Information Systems to the Health Protection Agency COVER programme, United Kingdom



CHIS: Child Health Information System;
COVER: Cover of Vaccination Evaluated Rapidly;
HPA: Health Protection Agency;
PCT: Primary Care Trust;
UK: United Kingdom;
WHO: World Health Organization.

Data quality requirements for vaccine coverage collections

The following section summarises the minimum data quality requirements for the collection of vaccine coverage data and the risks / implications if these requirements are not met.

Accuracy and validation

To ensure accuracy, precise definitions for the denominator (eligible population) and the numerator (number of individuals in the eligible population who have received a given vaccine(s) within a given time) are required. For the routine childhood immunisation programme, these parameters are published on the HPA website prior to each quarterly collection [6]. A number of checks are made as part of the data quality assurance process for each submission. These include verifying the evaluation period and comparing the denominator from the current evaluation quarter with the previous submissions to identify discrepancies. For example, unless there have been boundary changes, the denominator figures are unlikely to have changed significantly between evaluation periods. Significant variation in coverage estimates ($\pm 5\%$) from previous evaluation periods are also compared and investigated. Given that policy decisions and public health interventions at national and local level are informed by coverage data, inaccuracies in these data may result in inappropriate actions and the misuse of resources such as offering vaccines as part of a catch-up programme or a local outbreak response to individuals who are already fully protected.

Once the data has been collected, they are validated ('sense checking') prior to publication, within agreed timelines. This is essential to identify anomalies resulting from changes to the (i) national immunisation schedule (ii) Child Health Information Systems (CHISs) and (iii) vaccine preparations in use. There have sometimes been unexpected or temporary changes to vaccines offered due to vaccine shortages [9]. Awareness of these issues is imperative to understand the data and for the correct interpretation of current and future coverage estimates. In addition, variations in vaccine coverage for particular cohorts may result from national and local catch-up campaigns. This 'sense-checking' process requires historical knowledge and expertise of the UK immunisation schedule, an understanding of the complexities of CHISs and close working relationships with NHS staff providing these data.

Completeness

In contrast to sentinel systems, assessment of childhood vaccine coverage in England is a genuine measurement of total population coverage. In order to achieve this, data from each PCT are required and should be based on every eligible child. This is important to identify pockets of susceptible individuals who would benefit from targeted interventions.

Timeliness (collection and publication)

In England, vaccine coverage data are fed back promptly (within three months from the last evaluation quarter) to local public health teams, as provisional estimates, through the publication of UK COVER reports. These reports provide detailed commentary on the most recent coverage estimates at regional, national and UK level. Additionally, individual PCT level data for all vaccines assessed at one, two and five years of age are published on the HPA website, which allow national policy makers as well as local public health teams to consider appropriate interventions in a timely manner.

Flexibility

It may be necessary to undertake new /modified data collections in response to unexpected events. To assess the immediate impact of the adverse publicity surrounding the measles-mumps-rubella (MMR) vaccine in the UK, the COVER programme was able to set up a sentinel reporting system for monitoring MMR coverage from an earlier age and at more frequent intervals than routine collections [10]. This has provided a more timely indication of trends in MMR coverage, complementing the routine collections to inform vaccine policy decisions e.g. national MMR catch-up programme in 2008.

Operational issues with CHISs

IT issues

The number of system providers for CHISs and their functionality has expanded since their national roll-out in the 1980s, necessitating replacement and / or upgrading of existing systems. Some CHISs have suffered from data quality issues as a result of these upgrades and the replacement of existing IT services [11,12]. Furthermore, the migration of data from legacy systems has made this a particular issue for older cohorts of children. In the past, the combination of different CHISs operating across London coupled with high population mobility made it difficult to maintain accurate data on each local system and has contributed to the lower coverage reported in the capital [13]. However, during the last five years, London PCTs have moved to the same system provider and have focused efforts on increasing coverage both through improving vaccine delivery and data quality [14]. While efforts have been made to ensure the exchange of information between systems is timely and complete, there is a need to ensure all current and future systems are fully interoperable.

Denominator issues

There is historic evidence to suggest that some CHISs were poorly maintained so that children who had moved away remained on the system. These 'ghosts' inflated the denominator and therefore led to an under-estimate of vaccine coverage. A review of eight unpublished audits of data held on CHISs in 1997 suggested that COVER data underestimated true uptake by between 1% and 9% in children assessed before

their third birthdays [15]. Discrepancies increase when measuring coverage at five years given the increasing likelihood of moving PCTs with time, and fewer scheduled interventions which provide opportunities to identify children who have moved away/into the PCT. The greatest underestimates occurred in areas with lowest reported coverage and the highest population mobility.

Historically, NHS re-organisation has temporarily impacted on the quality of vaccine coverage data extracted from CHIS. For example, the last re-organisation in 2002, which coincided with a change in the definition of the denominator (from resident to responsible population), was thought to contribute to a reduction in the quality of COVER returns. This resulted in an underestimate of the denominator when compared with equivalent mid-year Office of National Statistics (ONS) population estimates [16]. The lower denominator was partly explained by delays in including unregistered children who are less likely to access primary care services and have less opportunity to be vaccinated, leading to an overestimation of true coverage. Reassuringly, however, by 2003, data quality improved as CHISs had begun to incorporate the reorganisational and population definition changes correctly [16].

Numerator issues

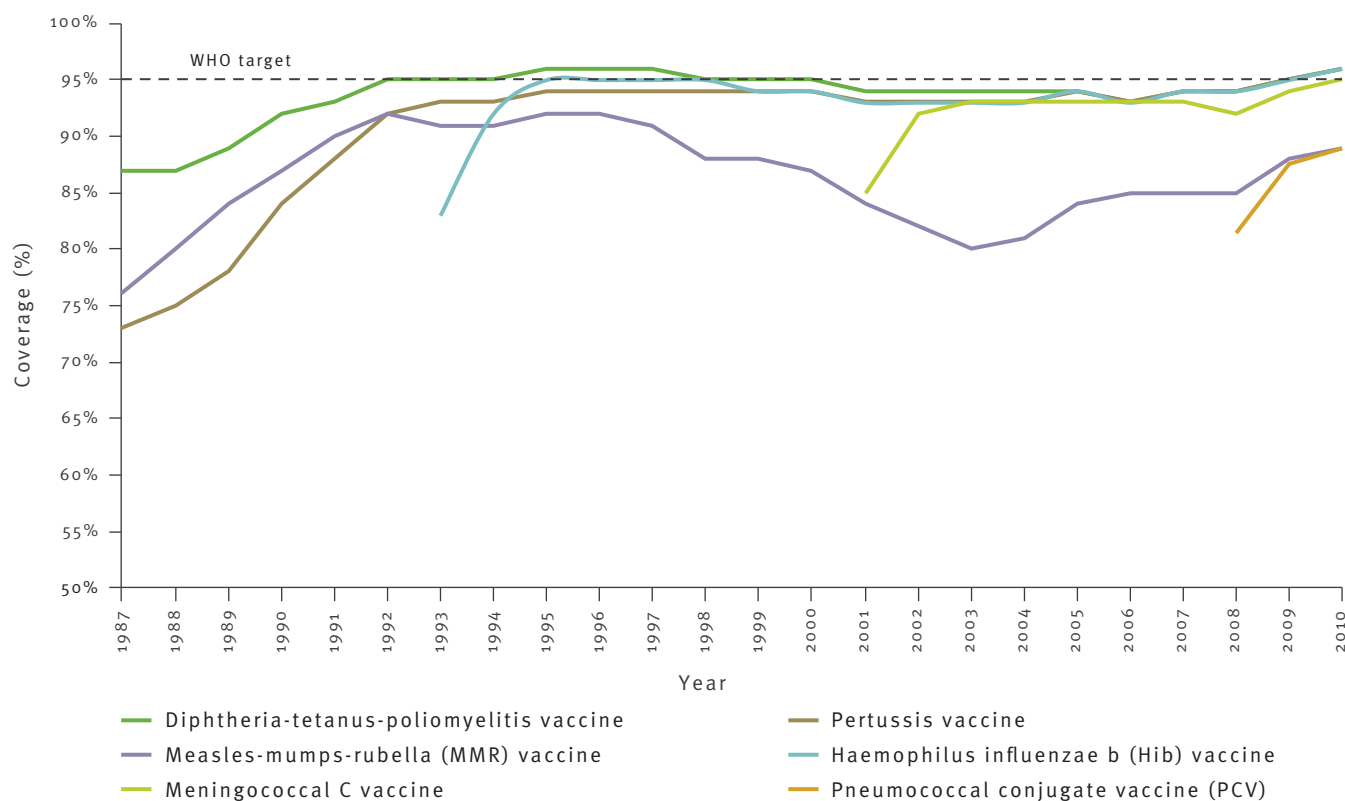
As the majority of routine childhood immunisations are delivered in GP, the accuracy of numerator data held on CHISs will be largely dependent on the accuracy and timeliness of the information supplied by GPs.

Although data held on CHISs are generally maintained until the age of 16 years, the accuracy of the numerator decreases with age given the reduced opportunities for older children and adolescents to routinely attend health services and for their records to be checked and updated. However, the introduction of the routine human papillomavirus (HPV) vaccination programme, targeting girls aged 12-13 years through a largely school-based programme, has provided a valuable opportunity to improve the accuracy of immunisation records for older children [17].

Future considerations for monitoring vaccine coverage

The radical reorganisation of NHS structures in England with the reallocation of local public health teams from the NHS to local government will necessitate maintaining the timely transfer of public health data, including vaccine coverage, across increasingly complex organisational boundaries.

FIGURE 3
Annual vaccination coverage at 24 months, England, 1987–2010



WHO: World Health Organization.

MMR replaced single measles vaccine in 1988. Hib vaccine was introduced in 1992, meningococcal C vaccine in 1999 and PCV in 2006.

The abolition of PCTs and creation of Clinical Commissioning Groups (CCGs) with different geographical boundaries is likely to temporarily impact on the accuracy of denominator estimates and permanently impair the ability to compare trends in coverage data at a sub-national level. In addition, the potential increase in the number of non-NHS service providers will contribute to the challenges in maintaining accurate, up to date population based immunisation registers.

The challenge is to sustain the accurate and timely collection of vaccine coverage data to inform national policy decisions and local public health action. A programme of work led by the Department of Health, to address these issues, is currently underway with key stakeholders. This includes a proposal to agree a set of national minimum standards for CHISs that will deliver interoperable CHISs which can schedule appointments and communicate effectively with all provider systems.

Implications for developing population-based immunisation registers in Europe

The UK has the longest running population-based child health registers in Europe that have contributed to a well organised and planned national immunisation programme. The system has survived many previous health service reorganisations in England, contributed to the achievement and maintenance of high vaccine coverage from the early 1990s and helped to minimise the impact of adverse publicity in the early 2000s (Figure 3).

Our experience has shown that there are a number of key requirements critical for success that may be relevant for European countries planning to introduce national immunisation registers. The establishment of a system which records and maintains accurate information on the entire population is critical to assess vaccination coverage at both national and local levels. These systems should have the flexibility to adapt to a continuously evolving immunisation programme, a mechanism to rapidly feedback coverage data to local public health teams for outbreak prevention and control, and the ability to mount a timely response to vaccine safety scares. The ability to schedule (call and recall) immunisation appointments has contributed to improvements in vaccination coverage both in England and elsewhere [12,18]. While this has been achieved in England through multiple CHISs which are not all interoperable, the development of a single national register would reduce the complexities of maintaining accurate and complete immunisation records for the entire population.

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The Norwegian immunisation register – SYSVAK

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The Norwegian immunisation register, SYSVAK, is a national electronic immunisation register. It became nationwide in 1995. The major aim was to register all vaccinations in the Childhood Immunisation Programme to ensure that all children are offered adequate vaccination according to schedule in the programme, and to secure high vaccination coverage. Notification to SYSVAK is mandatory, based on personal identification numbers. This allows follow up of individual vaccination schedules and linkage of SYSVAK data to other national health registers for information on outcome diagnoses, such as the surveillance system for communicable diseases. Information from SYSVAK is used to determine vaccine coverage in a timely manner. Coverage can be broken down to regional / local levels and used for active surveillance of vaccination coverage and decisions about interventions. During the 2009 influenza A(H1N1) pdm09 pandemic, an adaptation of SYSVAK enabled daily surveillance of vaccination coverage on national and regional levels. Currently, data from SYSVAK are used, among others, in studies on adverse events related to pandemic vaccination. Future challenges include maximising usage of collected data in surveillance and research, and continued improvement of data quality. Immunisation registers are rich sources for high quality surveillance of vaccination coverage, effectiveness, vaccine failure and adverse events, and gold mines for research.

Background

Norway has 15 national health registers, including the Norwegian immunisation register, SYSVAK. The national health registers have been established by national health authorities to safeguard nationwide commitments and are legally anchored in §8 of the Norwegian Law of Health Registers [1]. The registers are nationwide with mandatory notification requirements, and contain exposure and / or outcome data on selected health measures. All registration is based on unique personal identification numbers issued to Norwegian citizens at birth or immigration, which allow linking of different health registers at individual level. The general aim of the Norwegian national health registers is to support health surveillance, research, quality control and improvement of the health system performance.

The Norwegian immunisation register, SYSVAK, is a national electronic immunisation register. Prior to SYSVAK becoming nationwide in 1995, some counties had already recorded information in its precursor, SYSBARN. SYSBARN was established as a pilot project in 1976 in five of 19 Norwegian counties (Hordaland, Akershus, Hedmark, Oslo and Østfold) [2]. The aims and provisions of SYSVAK are anchored in regulations to the Norwegian health registers act, the SYSVAK regulations [3]. The scope of this paper is to describe the organisation and objectives of SYSVAK and briefly describe the Norwegian immunisation programmes. Data collection, data security measures and confidentiality issues are described, as are routines for access to SYSVAK data for surveillance or research purposes. The use of SYSVAK data for estimating vaccine coverage, surveillance and research are briefly exemplified and future challenges outlined.

Organisation of SYSVAK

SYSVAK is run and administered by the Department of Vaccines at the Norwegian Institute of Public Health (NIPH) in Oslo. The Department of information technology (IT) and e-medicine is responsible for maintenance and technical adaptations in the register. Healthcare providers in the local municipalities are responsible for administrating the vaccines and for notifying the vaccination to SYSVAK.

SYSVAK objectives

The original aim of SYSVAK was to register all vaccinations in the Childhood Immunisation Programme for the following purposes:

- to maintain an overview of the individual vaccination status of all vaccinees, ensuring that all children are offered adequate vaccination according to the schedule in the Childhood Immunisation Programme and to ensure a high vaccination coverage;
- to monitor vaccination coverage for vaccine preventable diseases in the Norwegian population at national, county and municipality levels; and to form a reliable basis for research into the effectiveness and safety of the vaccines in the programme.

Since 2009, SYSVAK has expanded and currently the register includes besides information on all vaccinations in the Childhood Immunisation Programme, all

human papillomavirus (HPV) vaccinations (including vaccinations given outside the Childhood Immunisation Programme to older girls, boys and adults), and vaccination against all other vaccine preventable diseases (influenza A(H1N1)pdm09, seasonal influenza, travel vaccines, etc.). Health professionals are obliged to notify all vaccinations in children and adults to SYSVAK. However, a set of different rules applies regarding the need for consent from the vaccinee or their parent / guardian (Table).

The Norwegian Childhood Immunisation Programme

The Childhood Immunisation Programme is organised within the public health service. The programme is set at national level and applies to the whole country. The local municipality health services are responsible for delivering the vaccines included in the immunisation programme. The immunisations are provided by public health nurses. General practitioners (GPs) usually play no role in delivering vaccines within the Childhood Immunisation Programme. Infants and toddlers are vaccinated at public health clinics, while school children are vaccinated within the local school health services. Practically all infants and pre-school children in Norway are followed up at the public health clinic, and the majority of Norwegian children are enrolled in public schools, with only 1.7% attending private schools [4].

Public health clinics and school health services are statutory services that provide health promotion and prevention services for pregnant women, parents, children from birth and adolescents up to 20 years of age. Nurses, doctors and midwives are usually the core staff at a health clinic. The service is a comprehensive offering that includes health checks, vaccinations, health education and counselling free of charge. Given the preventive nature of the service, children with acute or chronic medical conditions are referred to their GP for treatment and follow-up. Special at-risk children, for instance preterm newborns, children of hepatitis B surface antigen (HBsAg)-seropositive (infectious) mothers or those with complicated medical conditions, may receive their first vaccines in the hospital. However,

after that, most vaccinations in these children take place at the public health clinic.

All vaccinations within the Childhood Immunisation Programme are free of charge. The uptake of the vaccines in the Childhood Immunisation Programme is monitored by NIPH through the Norwegian immunisation register, and is generally high, between 92-95% [5]. All vaccinations are offered on a voluntary basis. The vaccines for the programme are distributed free of charge from NIPH to the local vaccine providers, independent of notification to SYSVAK.

The influenza immunisation programme

In Norway, influenza vaccine is recommended to defined risk groups including elderly aged 65 years or older, through the influenza immunisation programme. The influenza vaccine, as well as other recommended vaccines, is provided both by GPs and through public and private health services [6]. Some vaccinations are also provided by hospitals. Influenza vaccines are not publicly reimbursed.

Data collection

In general, notifications of vaccinations within the Childhood Immunisation Programme are electronically transferred from the patient record systems to SYSVAK. The vaccinations are entered only once in the electronic patient records (EPR) system, and transferred automatically to SYSVAK. The files are transferred in a standardised xml-format and the integration module with the EPR systems makes data entry fast and easy for the users.

SYSVAK supports reporting of the following variables:

- personal identification number and name of vaccinee;
- specific code and name of each vaccine;
- batch number of the vaccine;
- date of vaccination for each dose;
- date of notification to SYSVAK for each dose; and
- name and location of vaccinating unit (health clinic, GP, etc).

TABLE

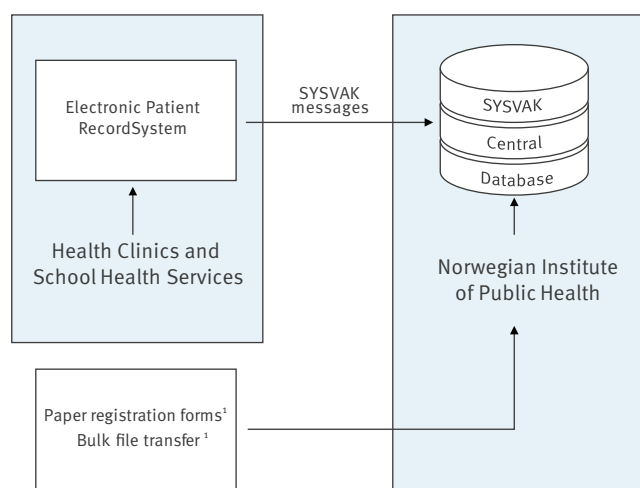
Notification to the Norwegian immunisation register SYSVAK and need for respective consent from vaccinee

Vaccination Programme	Consent	Notification
Childhood Immunisation Programme, including human papillomavirus	Not needed	Mandatory
Pandemic influenza	Not needed	Mandatory
Human papillomavirus vaccination of girls outside the Norwegian Childhood Immunisation Programme, boys, adults	Required	Vaccinee, parent/guardian can object to notification
All other vaccinations	Required	Oral consent from vaccinee, parent / guardian sufficient

All EPR systems are based on the national personal identification number as the unique identifier of the vaccinee. This is also the identifier in SYSVAK. The national personal identification number is verified against the Norwegian population register when the message is transferred to SYSVAK.

Data from public health clinics and school health services are almost entirely (>99%) electronically transferred to SYSVAK (Figure 1). At present, some other public and private health services have also adapted their EPR systems to the integration module. Those who have not installed the integration module supply data to SYSVAK via paper forms or via bulk file transfer. Electronic notification is not yet implemented in most hospitals, and hospital vaccinations of neonates are notified to SYSVAK in collaboration with the child's local health clinic that submits the notification electronically to SYSVAK, or via paper forms. There may be some potential for underreporting but to an extent that is negligible.

FIGURE 1
Data entry into the Norwegian immunisation register SYSVAK



¹ From health clinics, school health services and general practitioners lacking the integration module necessary for electronic transfer of data to SYSVAK.

Access to data and security

The EPR integration module described above allows healthcare personnel access to search SYSVAK for all vaccines pertaining to one specific vaccinee. This enables active follow-up of the individual immunisation, facilitates timely and correct immunisation, accurate vaccination history, compliance to the programme and completeness of vaccination schedules.

All health information in Norway is regarded as sensitive information, and access to SYSVAK is strictly

regulated. Access to SYSVAK is granted on an individual basis via the national health network and all activities are logged. All GPs, hospitals, public health clinics, and other public or private health services are connected via the national health network. This network provides a secure channel for communicating health information in Norway. All health information is encrypted prior to transfer via the network.

Access to data from SYSVAK for research purposes may be granted after application to the NIPH at data-tilgang@fhi.no. To ensure adequate data protection and safeguard privacy, permissions from other regulatory bodies like the Regional Committee for Medical Research Ethics or the Norwegian data inspectorate may also be required.

Vaccination coverage

Vaccination coverage for all vaccines in the Childhood Immunisation Programme is published regularly on the NIPH website [5] and reported annually to the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF). The information from SYSVAK can be broken down to regional or municipality levels, allowing active surveillance of vaccination coverage locally and making national or local interventions possible in order to optimise coverage.

Vaccination coverage is defined as the proportion of children within a birth cohort (all children residing in the municipality/county/country as of 31 December) who have been fully vaccinated i.e. who have received all vaccine doses recommended according to the schedule.

As a part of the SYSVAK quality assurance programme, annual reports are sent to the municipality health services. The reports include information on children who are incompletely vaccinated according to age, or have discrepancies in the vaccination schedule. This routine facilitates close follow-up of all children and favours the completeness of the immunisation schedule for each individual, as well as the data quality in SYSVAK.

Vaccination coverage data are based on notification of individual immunisations, and should reflect the true vaccination coverage. When comparing vaccination coverage from Norway with data from other countries using other methods for calculating the coverage, Norway seems to have slightly lower vaccination coverage than for instance Finland and Sweden [7]. This may be due to incomplete notification or delay in the registration, or may reflect that the true vaccination coverage in Norway is lower than in neighbouring countries. However, the rigid criteria in the immunisation register of being vaccinated according to the schedule (i.e. all recommended doses at timely intervals for each specific vaccine) may also be stricter than the criteria used by others in surveys or other methods of estimating and / or reporting vaccination coverage. This may

again be reflected in slightly lower vaccination coverage estimates in Norway as compared to some other countries.

Examples of vaccination coverage in two year-olds

In 2011, 94% of two year-olds had received three doses of diphtheria-tetanus-acellular pertussis (DTaP) vaccine according to schedule, 95% had received the *Haemophilus influenzae b* (Hib) vaccine and 94% were immunised against poliomyelitis. In total, 93% of the two year-olds had received the first dose of measles-mumps-rubella (MMR) vaccine. The seven-valent pneumococcal conjugate vaccine (PCV-7) was introduced in Norway in July 2006 and the vaccine was offered to all children born after 1 January 2006. In 2011, 92% of all two year-olds had received the vaccine according to the schedule (Figure 2).

Improving data quality has been a main focus in SYSVAK during the recent years. Quality assurance of data and close contact with reporting units, public health clinics and school health services have proven crucial for obtaining good quality and completeness of data in the register. A slight increase in overall coverage has been observed during the last ten years and may either reflect this activity, or represent an actual increase in the true vaccination coverage.

The reduction in the uptake of MMR vaccine in two year-olds, especially in 2002 and 2003 (Figure 2), however, reflects a true decrease in coverage. This drop coincided with the debate following the false claims about the link between MMR vaccine and autism put forward by Wakefield et al. in a later retracted paper in the *Lancet* in 1998 [8]. In Norway, this debate was brought to the public attention in a television programme in the autumn of 2001, and many parents chose not to have their children vaccinated with the MMR vaccine hereafter.

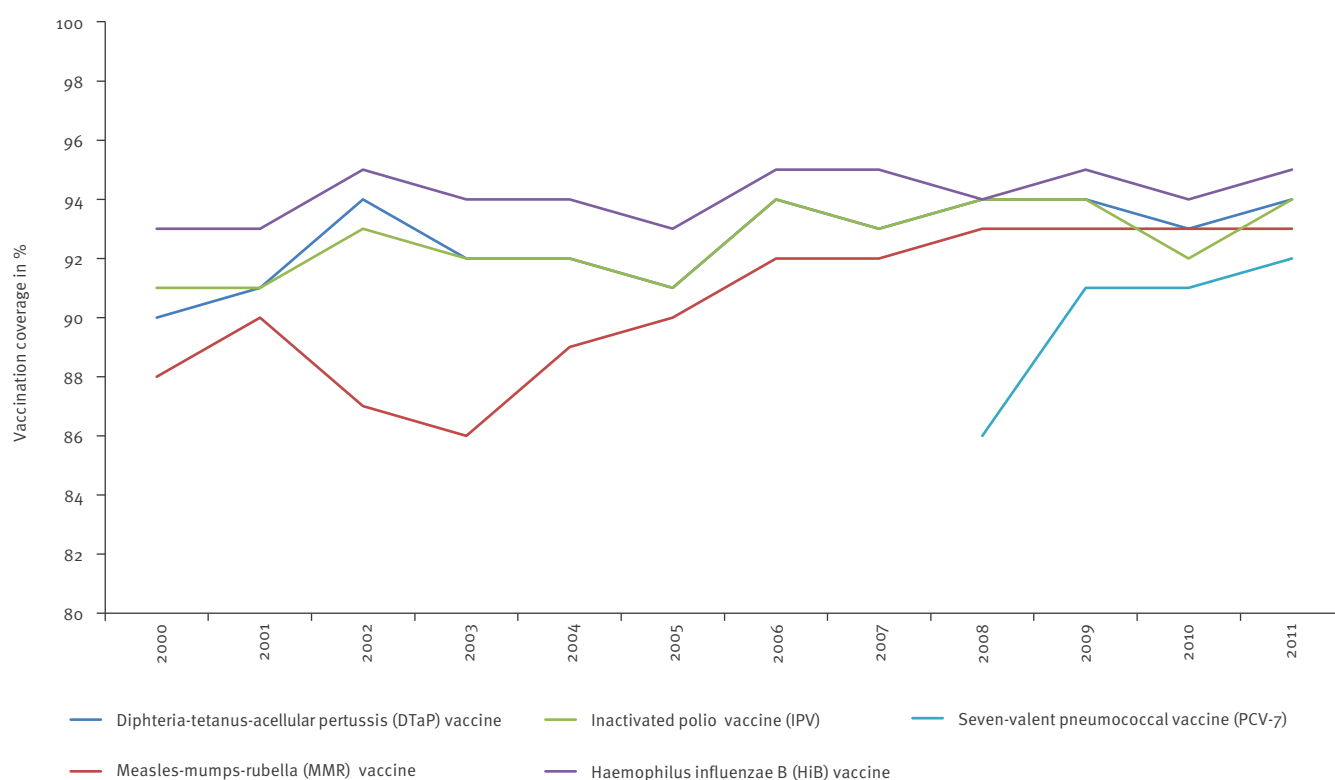
Epidemiological surveillance and research

The national immunisation register is a valuable tool in epidemiological surveillance, research and quality control. Reliable vaccination data are instantly available and can be accessed for individual ascertainment in outbreak situations, or in cases of suspected vaccine failure or adverse events following immunisation (AEFI). Additional information on outcomes and exposures on individual as well as population levels can be obtained through linkage to other national health registers for vaccine safety and effectiveness studies, as well as studies of attitudes towards vaccination and a number of other research areas.

The use of data from SYSVAK for research purposes has so far been limited, and few scientific papers published [9,10]. However, since the influenza A(H1N1)

FIGURE 2

Vaccination coverage in two year-olds who received all recommended vaccines, Norway, 2000-2011



Source: Norwegian immunisation register SYSVAK, Norhealth, 2012.

pdm09 pandemic, there has been a significant increase in applications for access to data from SYSVAK, as described in more detail below. During the years 2006 through 2009 there were five projects using SYSVAK data, whereas in 2010 and 2011 altogether 16 applications for data access from SYSVAK were received.

Measuring the effectiveness of a vaccine programme using SYSVAK data and data linkage

The fact that all registrations into SYSVAK are based on national personal identification numbers allows extensive linkage of information from different sources, both exposure data and outcome data. As an example, PCV-7 was licensed in Norway in 2001, and introduced into the Childhood Immunisation Programme in 2006. The vaccination coverage was monitored using data from SYSVAK, and quickly reached high levels. The effectiveness of the PCV-7 vaccination programme was assessed using (i) data on invasive pneumococcal disease (IPD) incidence obtained from the Norwegian Surveillance System for Communicable Diseases, (ii) pneumococcal serotype distribution obtained from the National Reference Laboratory for Pneumococci, NIPH, Oslo and (iii) vaccination coverage and individual vaccination status from SYSVAK. The incidence rate of IPD among children under two years of age declined rapidly after introduction of the vaccine. The decline was due to a significant fall in incidence rates of vaccine serotype IPD, while no decline in non-vaccine serotype IPD was seen. No cases of vaccine failures were detected [9, 10].

SYSVAK and the 2009 influenza A(H1N1)pdm09 pandemic

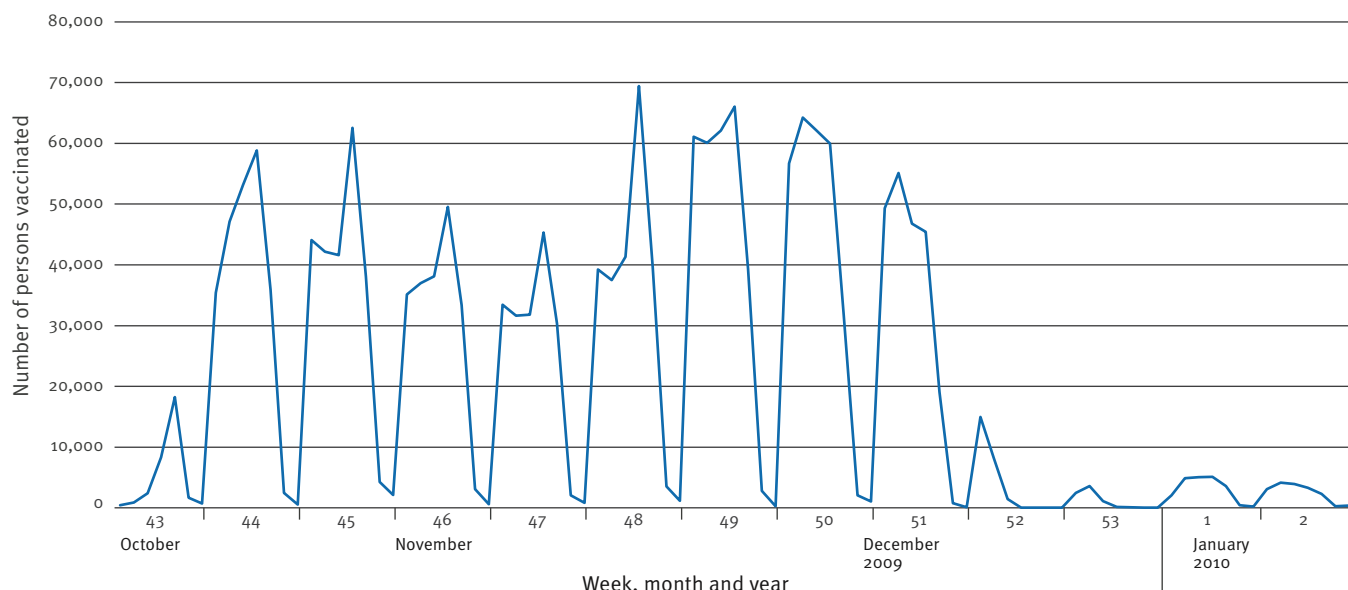
Notification and access to SYSVAK is usually not permitted via the internet. However, during the influenza A(H1N1)pdm09 pandemic, the NIPH recognised the need to register all vaccinations against pandemic influenza for surveillance purposes and a specific permit was issued to allow easy access to SYSVAK. A specific internet-based application was developed, enabling local healthcare providers to register all vaccinations through a readily accessible web-based interface. Through this system, the notification of pandemic vaccinations was transferred directly to SYSVAK at the time of the vaccination, enabling a day-to-day surveillance of vaccination coverage on national as well as regional levels (Figure 3).

According to data from SYSVAK, 1,963,895 individuals received at least one dose of vaccine against 2009 pandemic influenza. The notification to SYSVAK was, however, not entirely complete. Based mainly on the reports on remaining stockpiles in the municipalities, it is estimated that about 90% of vaccinees were registered in SYSVAK during the pandemic. A provisional estimate by the Norwegian health authorities indicates that 2.2 million people (45% of the population) were vaccinated [unpublished data].

Since the 2009 influenza A(H1N1)pdm09 pandemic, a number of studies have been set up to explore the effects of vaccination or influenza on selected health outcomes, among them pregnancy outcomes and neurological disease. Extensive linkage of register data

FIGURE 3

Daily administration of vaccine against pandemic influenza A(H1N1)pdm09, Norway, October 2009-January 2010



including SYSVAK has been performed for this purpose, and results are still pending.

SYSVAK data are currently also being linked to cohort data from the Norwegian Influenza Cohort, NorFlu. NorFlu is a cohort of 3,500 women recruited while pregnant during the 2009 pandemic [11]. The purpose is to study a number of pregnancy outcomes including fetal death, gestational length and birth weight following exposure to pandemic influenza, pandemic vaccination and antiviral medication in pregnancy. Data from SYSVAK is also being linked to the Norwegian Mother and Child Cohort Study, MoBa [12].

Reliable data on vaccination status is crucial in the assessment of AEFIs. Currently, data from SYSVAK are used in studies on adverse events related to pandemic vaccination such as a large national linkage study as well as the European Vaccine Adverse Events Monitoring and Communication (VAESCO) study on narcolepsy following immunisation against pandemic influenza A(H1N1)pdm09. A vaccine effectiveness study following immunisation against influenza A(H1N1)pdm09 using SYSVAK data was recently published [13].

Future plans and challenges

In order to make relevant information available to the public, the Norwegian Ministry of Health and Care Services launched a new web-based initiative in June 2011, allowing the public to access information on their personal health from the national health registers, via www.helsenorge.no and the NIPH website. SYSVAK is one of the first national health registers to enter this service which sets off a new application for the established national health registers. As part of this effort, the service called 'My Vaccines' was recently launched by NIPH.

'My Vaccines' holds records of an individual's vaccinations in Norway, provided that they have been notified to SYSVAK. Access requires a personal log-in procedure after which individuals can download vaccination certificates in Norwegian and English with information on their vaccinations recorded in SYSVAK. Parents can also download vaccination certificates for their children. So far, our experience with the new service is limited.

SYSVAK holds valuable data on vaccinations in Norway. With the aim to maximise the use of collected data in surveillance and research, efforts are needed to use it more actively in monitoring vaccination coverage on individual and group levels. Added value in surveillance of replacement of viral or bacterial strains or in estimating vaccine effectiveness is obtained by linkage of immunisation data to data retrieved from the Surveillance System for Communicable Diseases, which is also run and administered by the NIPH.

Linkage may also be performed to other national health registers, for instance the Cancer Register of Norway, or the Norwegian Patient Register, which holds

outcome diagnoses on all in- and out-patient contacts to Norwegian hospitals and specialist healthcare centres. Through such linkages extensive surveillance for a number of vaccine-preventable diseases may be upheld. For instance, we aim to establish a system for systematic surveillance of suspected adverse events following immunisation through linkage between SYSVAK (which holds exposure data on vaccinations) and the Norwegian Patient Register.

A national surveillance programme was set up in Norway following implementation of the HPV vaccine in the Childhood Immunisation Programme [14]. This surveillance programme includes continuous monitoring of vaccination coverage at all levels and effectiveness of vaccination against HPV infection, pre-cancerous cervical lesions and cancer in the female population. Information on vaccination status is retrieved from SYSVAK and will subsequently be linked to outcome data on HPV infection collected in ongoing population-based prevalence studies, and, at a later stage, to the Cancer Register of Norway for information on pre-cancers and cancers.

We undertake continuous efforts to improve data quality in SYSVAK. Specifically, we aim to complete registration coverage by notification requirements for all vaccinations in children and adults. A further goal is that all notifications should be delivered electronically by EPR integration modules from all public and private health services in Norway for the full set of variables. This would eliminate notification by paper forms and bulk file transfer. To help eliminate paper forms, a web-based interface to SYSVAK for registration via internet is also under development.

To our knowledge, Norway, along with Denmark which will implement a national immunisation register during 2012–13, is one of very few European countries, with mandatory, nationwide immunisation registers based on personal identification numbers [15]. We believe such registers are crucial to provide reliable information on vaccination coverage and adherence to recommended vaccination schedules. Furthermore, immunisation registers are rich sources for high quality surveillance of vaccine effectiveness, vaccine failure and adverse events, and gold mines for future research. We encourage the establishment of immunisation registers in other countries, and continue the efforts to maximise the quality and use of SYSVAK.

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Computerised vaccination register for the Murcia region, Spain, 1991 to 2011

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We describe the Murcia regional vaccination register in Spain, which was set up in 1991, detailing its main features, advantages and limitations. We also report on some recent special actions carried out that led to an improvement in vaccination coverage against measles, rubella and mumps (MMR): by using the vaccination register, we were able to identify and vaccinate persons aged under 20 years in a measles outbreak in 2010 in the town of Jumilla who were not adequately vaccinated for their age with MMR vaccine. From spring 2012, use of our register will enable us to identify susceptible individuals in our region under 40 years of age who have received fewer than two doses of MMR vaccine and call them for the appropriate vaccination. We also set out our experience in the use of barcodes to identify individuals and collect vaccine data: our data show that the barcodes help to improve data quality and completeness. Finally, we identify certain challenges in search of greater standardisation for systems and encoding that is necessary to enable an easy exchange of data between different registers.

Introduction

Vaccine information systems or registers are a major tool that allows public health personnel to measure, maintain and increase vaccine coverage levels and also to gather information automatically about an individual's vaccine needs. Among other things, such registers allow relatives or the person concerned to be given reminders about the doses still to be received in order to complete a primary or booster series – helping healthcare personnel to vaccinate a person at the most appropriate time – or for them to be asked to provide missing vaccine-related data. The registers can also provide official certificates of a person's vaccination status and detect unvaccinated groups and areas or local population groups with low coverage in which outbreaks of vaccine-preventable diseases are likely to occur [1,2]. They can also help to improve data quality and monitor the implementation of new vaccination recommendations [3]. In addition, they also enable the registration of side effects and the monitoring of vaccine effectiveness. All these advantages have been demonstrated in countries with extensive experience

of computerised vaccination registers such as Australia [4] and the United Kingdom [5].

In this article, we describe the centralised, computerised vaccination register of the region of Murcia in Spain, showing how it has been used, as well as its limitations and the resources needed. Murcia region – one of the 17 in the country – has a population of 1,471,406 inhabitants, of whom almost 18% are under the age of 14 years [6]. Over the last 10 years, the mean number of births per year was about 17,000, having risen from 13,000 in 1999 to about 18,300 in 2010 [6]. The region has received devolved powers from central government covering public health and healthcare provision, although in some matters, such as the vaccination calendar, it coordinates its activities with those of the other regions and with the national health ministry.

There are similar centralised regional registers in the Spanish regions of Galicia, Valencia, La Rioja and Andalusia, as well as in some cities such as Barcelona and Salamanca: these registers are not connected to each other. Elsewhere in Spain, vaccines administered are recorded on an individual's case report in primary healthcare: there is no centralisation of data at the country level. Work is currently under way to develop a single format for recording a person's case history at the national level that would also incorporate the person's vaccine data.

Most of the regions use official population figures for calculating coverage, except for La Rioja and Murcia which have their own population databases.

Public and private health providers, mostly in primary healthcare, carry out the vaccinations. In the primary healthcare centres, data are entered by the health professional who administers the vaccine. In the management centres of the vaccination register, clerical staff enter the data.

The vaccines included in the vaccination calendar are paid for by the regional government: those not included in the calendar are paid for by parents or guardians.

Description of the vaccination register of Murcia region

The computerised vaccinations register was set up in the Murcia region in 1991. It was founded on an earlier register for infants that recorded only the primary vaccination series (i.e. vaccines received in the first two years of life). The computerised register has evolved over time, so that it currently records all vaccines administered in the region, whether in the private or the public sector, during childhood or adulthood, and also includes vaccines that are not part of the official vaccination calendar. All primary healthcare centres in the region participate in the register.

Inclusion of individuals in the register

Murcia's vaccination register is part of the regional public health information system. The register uses a single population database (PER_SAN), which is fed with real-time updates from the regional population database of the healthcare system. These are classified as new entries, deletions, deaths, change of address, change of paediatrician or family physician, etc.

Various processes are used to include individuals in the register's population database, PER_SAN (Figure 1).

- When a child is born in hospital, the public health information system assigns them a personal regional identification code (a barcode), which is given to the parents on labels. This is part of the documentation parents receive after childbirth, which also includes notification cards that they take with them to accredited vaccination centres, be they public or private. The barcode is recorded in the PER_SAN database through the results of screening for neonatal hearing loss.
- The same barcode is also used in a programme to detect congenital errors of metabolism. Blood and urine samples are taken on the third day of life and sent to a laboratory together with a card containing the newborn's personal details. Attached to this card is one of the barcoded labels given to the parents at the hospital. This barcode is recorded in the PER_SAN database when the laboratory results have been obtained.
- When parents or guardians apply for a health insurance card for their child, the child's details are manually included in the PER_SAN database. This applies too if the child was not born in hospital.
- If a person (child or adult) comes to live in the region, when they visit a primary healthcare centre, a form containing their details (identification card) is sent to the vaccination register. These details are added to the PER_SAN database manually.

Data duplication is prevented by a double check, one automatic and the other manual.

i. Automatic check: an identification code assigned by PER_SAN to each person included in the database and the regional personal identification code (the code

issued by the public health information system) enable the duplication of individuals to be avoided, through searches that are automatically carried out when the codes are entered. In addition, whenever a person is entered into PER_SAN manually, internal search processes are run automatically to identify whether that person is already present on the database and thus prevent a duplicate entry.

ii. Manual check: two technicians work on the PER_SAN database to identify duplicates and correct any database errors.

Inclusion of vaccination data in the register

Our register can import vaccine-related information from primary healthcare case reports, but the primary healthcare information system is not currently ready to import data from our register. However, our register is available through the Internet, so any authorised healthcare professional can consult a patient's immunisation status regardless of where the person was vaccinated.

At primary healthcare centres that participate in the register, a person's vaccination details are entered into a computerised case report, using the same codes as in our register. Thus whenever we incorporate data from these computerised case reports, the system detects whether the vaccination has already been recorded for that person and, if so, does not include it in the register.

Data input

The register records the date the vaccine was administered, the vaccination post at which it was administered, the product administered, dose order number (whether this was the first or second dose, for example) and the manufacturer and batch of the vaccine. The indications for the vaccine are also recorded, either using the official vaccination calendar or any special indication due to the individual's medical circumstances, such as being in a risk group for a particular disease, having a chronic illness, etc. Whenever a vaccine-related adverse effect occurs, this can also be recorded. In addition, the reasons for not administering a vaccine, such as contraindication or refusal to receive it, are also included.

At all the primary healthcare centres in the region, around 25,000 vaccine doses administered are recorded every month, except in the influenza vaccination season, when as many as 140,000 monthly doses can be recorded. Our register imports these data, but approximately 10% of the doses recorded on the primary healthcare computerised case reports each month cannot be imported into our system due to encoding errors that arise due to the manual input of all the data (vaccine code, manufacturer and batch). In order to ensure that this information is not lost, we still use the same dose notification system we started with in 1991: the notification cards given to parents after childbirth. These cards include adhesive labels with the barcode

identifying each child. The product administered, the dose order number, batch number, date of administration and name of the vaccination centre are recorded on the card. These cards are then sent by post to one of the register's four management centres, where a check is made to see whether that dose is already recorded in the register.

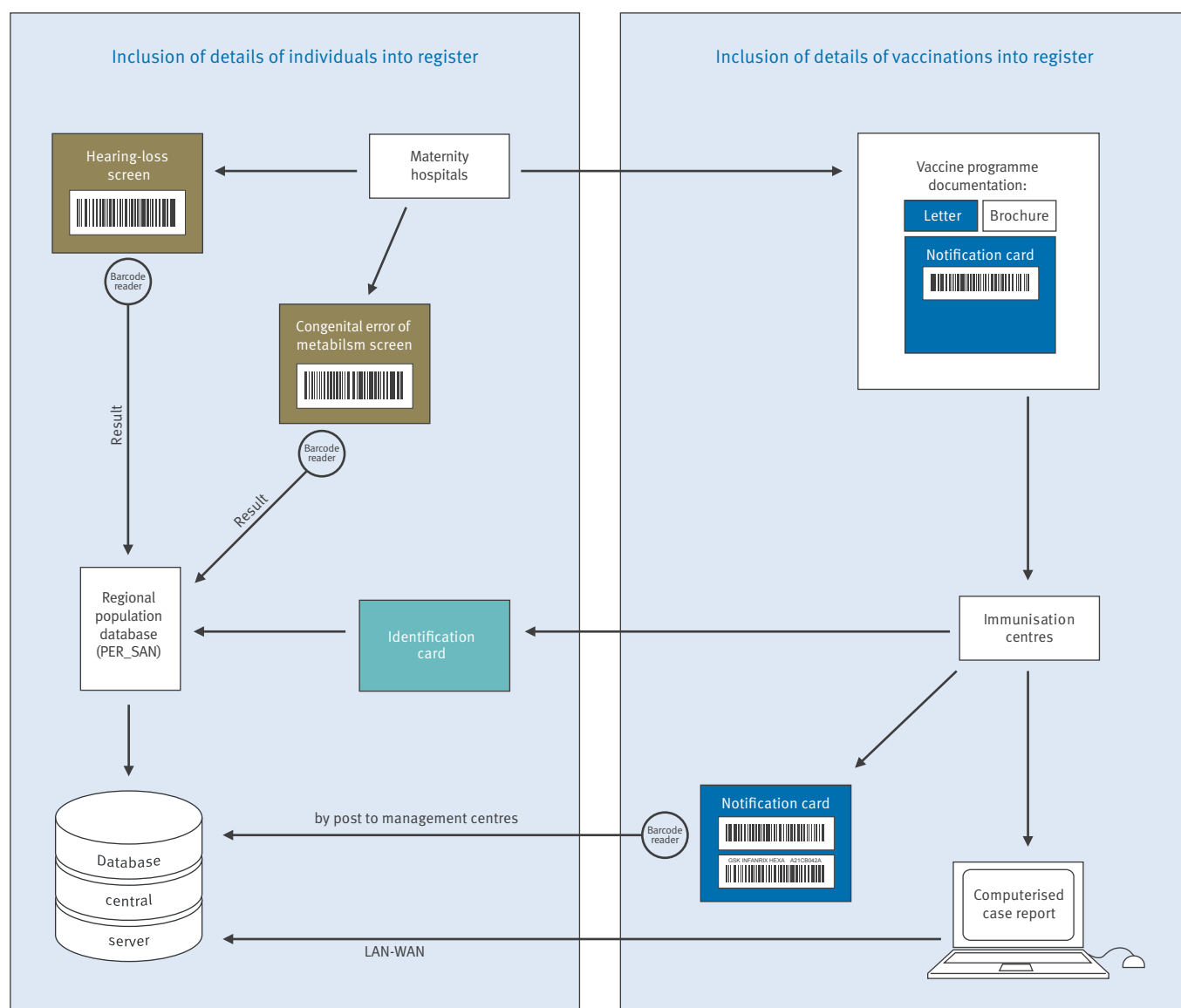
One aspect of importing dosage information is the use of a barcode scanner that reads the details of the vaccine (commercial name, manufacturer, production site and batch number). The scanner software breaks down the information from the barcode (Figure 2). Currently, four of the six manufacturers supplying the region with vaccines (GlaxoSmithKline, Baxter, Pfizer and Sanofi Pasteur MSD) include two barcode labels with each dose of vaccine: one of these is placed on

the notification card and the other on the child's own vaccine administration record.

In the Spanish regions, the use of these labels is voluntary, but the Ministry of Health has established a standard label format for manufacturers who decide to use barcodes. In order to promote the supply of such barcoded labels by manufacturers, a technical criterion for their design is included in the competitive tender procedure used for the acquisition of vaccines. Reading such labels with a barcode scanner means that only the administration date, the dose order number and the vaccination centre need to be recorded manually.

Primary healthcare centres are not equipped to scan the barcode labels. In order to assess the advantage afforded by recording doses using a barcode scanner, we analysed the details of doses recorded in the primary healthcare system for vaccines supplied with

FIGURE 1
Data flow in the computerised vaccination register for Murcia region, Spain



LAN: local area network; WAN: wide area network.

FIGURE 2

Composition of a vaccine barcode, Murcia region, Spain



barcode labels. During 2010, the region’s primary healthcare teams recorded the administration of a total of 200,352 doses of six different vaccines that have these labels. Of the total number of doses, 17,511 (8.74%) did not have their batch number correctly recorded, 1,162 (0.58%) had no batch number recorded and 16,349 (8.16%) had an incorrect batch number. Regarding the name of the manufacturer, 38,247 (19.09%) of the doses did not have this information correctly recorded: 11,059 (5.52%) had no manufacturer recorded and 27,188 (13.57%) showed the wrong manufacturer. In contrast, 100% of the doses obtained through the barcode scanner had all their details correctly recorded.

Access to an individual’s vaccination data

As mentioned earlier, one important advantage of a vaccination register is that by incorporating in a centralised system all the doses administered, any authorised healthcare professional can access an individual’s vaccination history from their work station (data security is regulated by national legislation).

There are several levels of data access, depending on the healthcare professional’s role. The access level ranges from full, for example, for coordinators of the vaccination register, to minimal, for those who can access only minimal personal and vaccination details (Table). The coordinator authorises the access and the person requesting access is given an appropriate password that safeguards the confidentiality of the data.

The case report information system used for public healthcare services in the region does not allow professionals at one health centre to consult the vaccine information recorded in the case reports at another. In order to facilitate access to this information for healthcare professionals, a web-based system has been created for the regional vaccination register so that, if granted the appropriate access, it is possible to view

vaccination details and the outcome of the neonatal hearing-loss screen.

Features of the regional register

The large amount of data collected allows us to define a number of special features of the register.

Routine interventions

- Reminders sent out for vaccine doses at the age of six years (diphtheria-tetanus-acellular pertussis vaccine, mumps-measles-rubella (MMR) vaccine), at age 11 years (varicella vaccine, only for susceptible children) and at 14 years (diphtheria and tetanus for boys and girls, human papillomavirus for girls).
- Reminders sent out for influenza vaccination for adults aged 60 years.
- Regular reminders sent out to those insufficiently immunised.

Special interventions

The register allows us to carry out special actions from time to time to help increase coverage levels and identify poorly immunised population groups – a very useful option when facing an outbreak of diseases that can be prevented through vaccination. For example, during 2010, there was an outbreak of measles in the town of Jumilla, with a total of 90 confirmed cases. By using the vaccination register, we were able to identify those persons under 20 years of age who were not adequately vaccinated for their age with MMR vaccine. A total of 3,195 letters were sent out to individuals between 6 months and 20 years of age (or their parents or guardians) and 1,667 doses were administered during the month after the letters were sent out (the mean monthly number of vaccine doses in that town is 68). Simultaneously, we were able to update the

TABLE

Levels of data access, regional vaccination register, Murcia region, Spain

Healthcare professional's role in the vaccination register	Level of access
Consulting vaccination records	Can view data on vaccines administered to an individual. Has access to minimal personal information.
Operational	Can consult and input information on vaccine doses. Has full access to personal information.
Management	Can consult, input and evaluate information on vaccine doses. Has full access to personal information.
Coordination	Has access to all the register's functions, including the management of software, and the allocation and authorisation of access levels.

information about the doses administered that we did not have on record in our vaccination register.

From spring 2012, use of our register will enable us to identify susceptible individuals in our region under 40 years of age who have received fewer than two doses of MMR vaccine and call them for the appropriate vaccination.

Having people's mobile telephone numbers (part of the information recorded in the vaccination register) allowed short message service (SMS) text messages to be sent to teenage girls who had not completed the vaccination regime against human papilloma virus, thus increasing coverage by 5.1% in the cohort of girls born in 1994 [7].

Regarding data management, our system allows vaccination coverage to be calculated at different levels of data disaggregation, making it easier for healthcare professionals to carry out actions at the level of the individual.

Resources needed for the maintenance of the register

The features of the register allow actions to be taken that would be impossible or very complicated without them. Some of these actions would probably require additional human resources and so such actions would be hard for a region such as ours to undertake. Even so, maintenance of the register requires a considerable involvement in terms of human resources. A total of 19 people – at various professional levels (medical doctors, nurses and clerical staff) – at the four management centres work on maintaining the register. In addition, two people are devoted exclusively to maintaining the PER_SAN database, which is shared by almost all public health programmes in Murcia.

To ensure that everything works correctly, we have the support of highly qualified informatics staff who, in addition to having developed the software application, enable us to incorporate improvements as and when required without having to resort to external resources.

Limitations of computerised vaccination registers

Although there are a large number of advantages associated with computerised vaccination registers, there are also some drawbacks. Vaccination coverage levels determined from such a register are always underestimated and the number of doses administered (used as the numerator) is always lower than the actual number of doses administered as there are always notification failures [8]. On the other hand, despite the maintenance efforts and the quality assurance checks, the denominator may be overestimated as insufficient information may be received about deaths or changes of address: the latter may have an impact given the extent of migration flow in and out of the region associated with seasonal agricultural activities in the Murcia region.

Challenges of vaccination registers

The first challenge is the systematic use in all countries of vaccination registers with certain minimum functional standards in order to make them compatible [9]. Standardisation in the methods for calculating coverage would make it easier to obtain and compare the levels between countries or even between areas within a single country [10 15].

Another equally important challenge is the standardisation of vaccine- and batch-encoding methods. The batch-encoding system we use – based on what was supplied by a manufacturer we were developing the project with – would help to ensure that the information provided about a batch is homogeneous in all countries using the system. It would be desirable for this or another encoding method to be agreed upon by consensus among the European regulatory agencies, as this would enable the automated inclusion of a larger number of data elements into the vaccination registers, which would be a great improvement in the quality of the information system [16,17].

Conclusions

Vaccination registers are a valuable tool for the management of vaccination programmes. Our regional register has enabled us, among other things, to improve vaccination coverage against measles, rubella and mumps, and against the human papillomavirus in adolescent girls. We believe that at global level we are still at an early stage in terms of developing and using such registers and we therefore still have the chance to take decisions that will enable improvements to be made that will facilitate widespread use of registers in those areas or countries where they are not yet present. Additionally, it is desirable that there should be a high degree of compatibility between the registers used. These are challenges facing those involved in running vaccination programmes, regulatory agencies and health authorities.

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Australian immunisation registers: established foundations and opportunities for improvement

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The National Immunisation Program Schedule in Australia is formulated and funded nationally under the population-wide Medicare system. The policy is implemented by the eight state and territory jurisdictions. The national immunisation registers consist of the Australian Childhood Immunisation Register (ACIR), and, more recently, the National Human Papillomavirus (HPV) Vaccination Program Register. Moreover, a variety of jurisdiction-based registers and primary care practice software systems exist, which interact with the national registers. General practitioners can obtain reports listing patients under seven years attending their practice and recorded as 'not fully immunised', and immunisation coverage rates for their practice linked to government incentives through Medicare. A 2011 report documents national coverage of 91.8% fully immunised at 12 months, and 92.6% at 24 months. The HPV register provides information on vaccination coverage with the potential to link with a register of cervical cancer screening results. Limitations of current national register include inability to easily access immunisation histories beyond seven years of age, and issues of underreporting and timeliness, which impact significantly the immunisation coverage estimates. The linkage of these registers with healthcare outcome data will further enhance public health outcomes by enabling rapid, population-level vaccine safety and effectiveness investigations in a nation with a track record as an 'early adopter' of new childhood vaccines.

Introduction

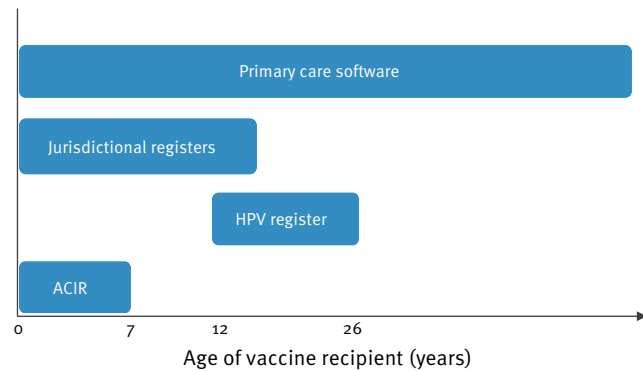
Defined as population-based, confidential systems containing vaccination histories [1], immunisation registers have been pivotal in ascertaining and improving individual and population-level compliance with

vaccination schedules [2]. Used to identify at-risk populations for vaccine-preventable diseases (VPD), registers document and increase vaccination coverage via 'planned' immunisations with recalls and reminders or opportunistic immunisations [1,3]. In certain countries, immunisation registers have also been used to assist in the establishment of health policies, as well as to provide a link for parent and provider incentives to improve immunisation rates [4]. More recently, direct linkage of immunisation registers with health outcome data has provided opportunities to examine vaccine safety and effectiveness [5, 6].

Currently, the Australian immunisation policy is formulated and funded nationally under the population-wide Medicare system, but implemented by the eight state and territory jurisdictions. The National Immunisation Program (NIP) Schedule covers all Australian population as an approved antigen-based schedule, with potentially multiple manufacturers with nationally approved vaccines purchased centrally. These include diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, *Haemophilus influenzae* type b (Hib), pneumococcal conjugate (from July 2011, the 13-valent conjugate vaccine replaced the seven-valent conjugate vaccine), rotavirus, measles, mumps, rubella, varicella, group C meningococcal conjugate and human papillomavirus (HPV) vaccines.

As a result, there is a combination of national- and jurisdiction-based registers, with overlapping and sometimes synergistic functions (Figure 1).

The national immunisation registers consist of the Australian Childhood Immunisation Register (ACIR), and more recently the National Human Papillomavirus

FIGURE 1**The Australian immunisation registers**

ACIR: Australian Childhood Immunisation Register; HPV: human papillomavirus.

Vaccination Program Register (HPV Register) [7,8]. There are a variety of jurisdiction-based registers, largely aimed at delivering local government-based immunisations, as well as primary care practice software systems that interact with the national registers. As an early adopter of such registries, the experience of this federation of eight states and territories may help illustrate issues facing similar initiatives within Europe. This review will describe the range of immunisation registers in Australia and discuss the benefits, limitations of and challenges for these current systems.

The Australian Childhood Immunisation Register

The ACIR was introduced in 1996 as part of the Immunise Australia Program, a joint Commonwealth and state/territory government programme, as part of a series of measures to help reduce incidence of VPD in Australia. The ACIR is administered and operated by Medicare Australia, the universal health insurance scheme in Australia [8]. It records details of vaccinations given to children under seven years of age who live in Australia, including vaccine batch details. Since 2001, immunisations administered overseas may be retrospectively recorded if an immunisation provider endorses their validity based on written documentation or confirmation from the previous provider. The ACIR is accessible until a child is 14 years of age and was predominantly established to capture routine NIP vaccines. It is described as the world's first attempt in developing a near-complete population-based immunisation register [1]. It is estimated that 99% of children in Australia are registered with Medicare (under a unique number for each child) by 12 months of age and those not registered with Medicare by then can be added on via supplementary numbers to the ACIR [1]. Participation of children in the ACIR is opt-out [1]. Based on a survey in 2004, approximately 3% of children have incomplete immunisation due to medical contraindications or parents' with conscientious objections to immunisation [9]. These children are still registered with the ACIR after parents have discussed the

risks and benefits with a recognised immunisation provider [1,9,10].

Data collection and coverage measurement

The ACIR receives daily information from direct online notifications, provider software applications (jurisdictional agencies and General Practice management software applications) or paper forms mailed from immunisation providers (Figure 2).

Marked proportional increase of online notifications has been observed, from an initial 6% in 1998 to 65% in 2007 [1]. Individuals registered with Medicare Australia will have a unique number that can be used across databases in Australia, although with limitations set by federal privacy legislation. Medicare Australia provides immunisation history statements at milestone ages and for requests at an individual level, information about a child's immunisation status to help determine eligibility for the Australian Government's family assistance payments, and quarterly coverage reports at the immunisation provider, local, national and state level [3]. General practitioners (GPs) are also able to obtain reports listing patients under seven years of age who attend their general practice and who are recorded as 'not fully immunised', and immunisation coverage rates for their practice which is linked to government incentive payments through Medicare.

Immunisation coverage is measured cross-sectionally at the individual or general practice level, and by cohort method at the population level. With the latter, a cohort of children is defined by their date of births in three-month groups. The immunisation status of this cohort is then assessed at the three key milestones of 12 months (for vaccines due at six months), at 24 months of age (for vaccines due at 12 months), and at five years of age (for vaccines due at four years) [8]. Children registered with Medicare who have completed the primary schedule represent the numerator and the total number of children registered in Medicare in the same age cohort represents the denominator [1,11].

To be fully immunised at the milestone ages, the following vaccines need to have been received [1,12]:

- 12 months: three doses of diphtheria (D), tetanus (T), and acellular pertussis (Pa)-containing vaccine, three doses of inactivated polio vaccine (IPV), two or three doses of *Haemophilus influenzae* type b (Hib) vaccine (depending on vaccine type), and two or three doses of hepatitis B vaccine (depending on vaccine type).
- 24 months: three doses of DTPa-containing vaccine, three doses of IPV, three or four doses of Hib vaccine, three or four doses of hepatitis B vaccine (depending on vaccine type) and one dose of measles-mumps-rubella (MMR)-containing vaccine.
- 48 months: four doses of DTPa-containing vaccine, four doses of IPV, and two doses of an MMR-containing vaccine.

As per the ACIR overdue rules, an individual is considered overdue one month post the due date for all immunisation time points detailed above [13].

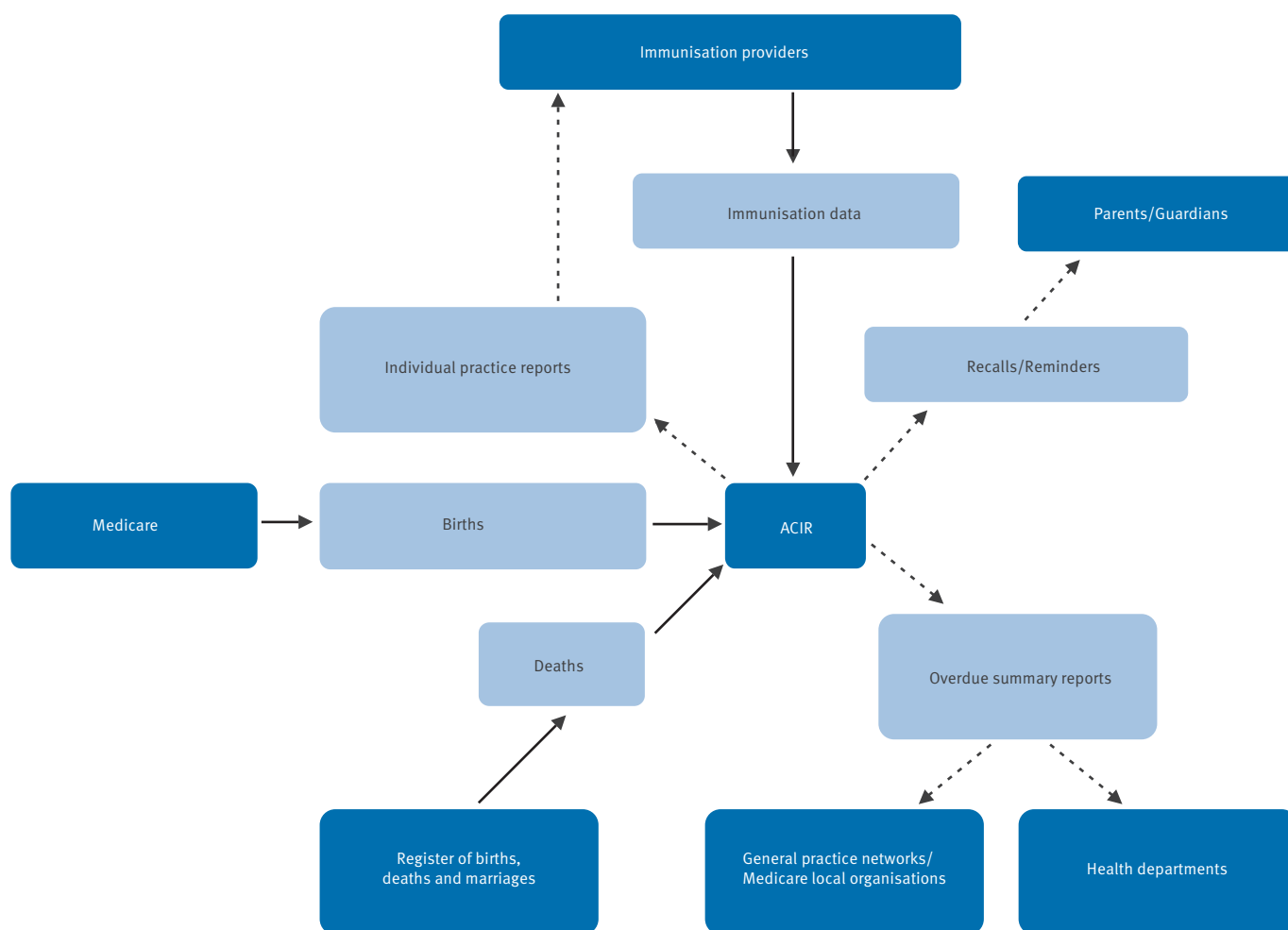
Prior to the introduction of the ACIR, coverage was estimated in 1997 for all age cohorts to be 75% or less [1,10]. The 2011 coverage reports document 91.8% fully immunised at 12 months, and 92.6% at 24 months (Figure 3) [14].

For vaccines that require more than one dose, for instance with DTPa vaccine, the child is assumed to have had earlier doses of the vaccine as long as the last dose has been given [3]. This assumption has been validated by a national population-based telephone survey demonstrating this method still underestimates coverage by up to 5% due to under-reporting [15]. All children should ideally be registered with Medicare by the age of six to eight weeks when the first doses of DTPa, IPV, Hib, rotavirus and PCV7 vaccines are due.

Children not registered with Medicare by this age are provided a supplementary number with ACIR, which may not be linked to their unique Medicare identifier number when finally registered thus reflecting incorrect vaccination histories. The lag time between date of birth and Medicare registration remains significant with lag time beyond two months doubled among those children with missing doses versus those registered promptly after birth [1,3].

The ACIR also plays a role in evaluating immunisation coverage among the indigenous population, representing 2.5% of the Australian population [16]. The status is recorded as 'indigenous', 'non-indigenous' or 'unknown' as self-reported to Medicare or by the provider to ACIR. Status reporting has improved remarkably with 99% recorded in 2007 as opposed to 42% in 2002 for infants aged 12-14 months [17]. Coverage estimates for 12 months and five years are lower for children registered as indigenous by their parent/s and

FIGURE 2
Flow of information to the Australian Childhood Immunisation Register (ACIR)



ACIR: Australian Childhood Immunisation Register.

Adapted from: Hull BP, McIntyre PB, Heath TC, Sayer GP. Measuring immunisation coverage in Australia. A review of the Australian Childhood Immunisation Register. *Aust Fam Physician*. 1999;28(1):55-60 [3].

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have remained stagnant for the last six years, although estimates at 24 months are similar, suggesting timeliness is a major factor [17]. Hepatitis A and 23-valent pneumococcal polysaccharide vaccines recommended and funded only for indigenous children are also documented in ACIR and also show suboptimal coverage estimates [1,10, 18].

Factors for improvement in recorded coverage

Immunisation coverage rates have improved with time and better understanding of the function of the ACIR. This could reflect the improvement in provider notification, less delay with increased use of electronic notifications, and the ongoing introduction of combination vaccines contributing to an increase in vaccination coverage [1].

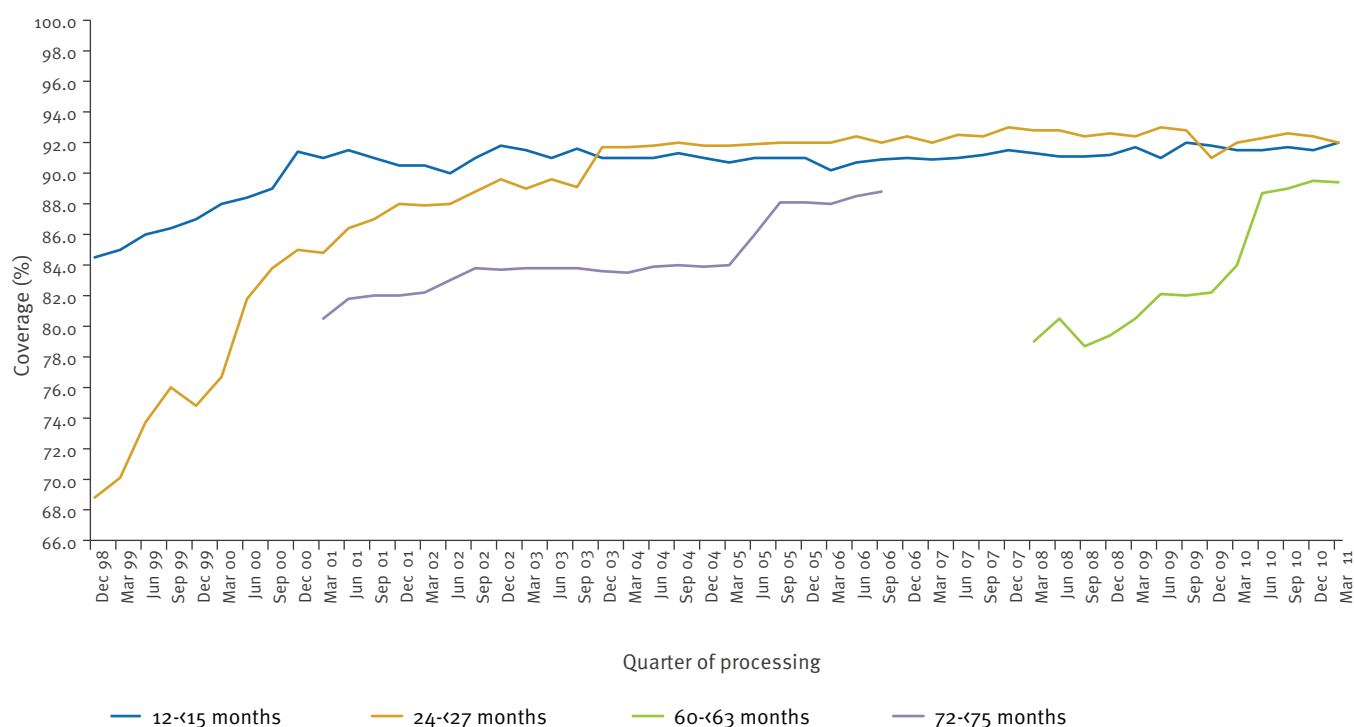
The introduction of immunisation incentives for parents and providers in 1997 and 1998 respectively have also contributed significantly to improved coverage. Parental incentives were introduced to provide a prompt for parents and providers to complete immunisation, or to confirm their conscientious objection or medical contraindication to vaccination. The income-linked parental incentives include the Maternity Immunisation Allowance (MIA) and Child Care Benefit (CCB) [1]. Paid at two separate time points, the MIA, a non-taxable amount of AUD 258 (approximately EUR 203) can be claimed on or before the child's fifth

birthday if the child is shown to have completed immunisation (or has a registered conscientious objection or medical contraindication to vaccination) [19]. However, from July 2012, MIA will be replaced by the existing Family Tax Benefit Part A supplement where children must be fully immunised for parents to receive AUD 726 (approximately EUR 571) for each child at each immunisation checkpoint at ages one, two and five years [20]. The CCB incentive partially reimburses parents who use approved or registered childcare and the amount depends on the family's yearly income, but can potentially be a much larger financial benefit than the MIA [21]. It was suggested parental incentives played an independent role in the increase of completed immunisation coverage at 24 months [1].

For the immunisation providers in primary healthcare settings, the General Practice Immunisation Incentive (GPII) Scheme was introduced in 1998 to encourage immunisation notifications and to achieve at least 90% of practices to fully immunise 90% of children aged below seven years attending their practices [22]. In 2008, the federal budget ceased the GPII Service Incentive Payment (SIP). The SIP was a payment (AUD 18.50) made for notification by the provider of completion of vaccination at a certain milestone age. To date, discontinuation of SIP has not affected immunisation coverage, however longer term analysis may be warranted [23]. The other two components of the GPII scheme remain, namely the Information Payments (up

FIGURE 3

Australian Childhood Immunisation Register (ACIR) standard coverage by age cohort, December 1998–May 2011



The coverage at five years of age is for vaccines due at the age of four–five years; this was changed in December 2007 from the age of six years. Source: Australian Childhood Immunisation Register (ACIR). Standard Coverage for Australia [14].

to AUD 6 (approximately EUR 5), paid to all immunisation providers after notification of administration of all the milestone age NIP vaccines) and the GPII outcome payments (for practices with ≥90% of fully immunised children) [10,22].

The National Human Papillomavirus Vaccination Register

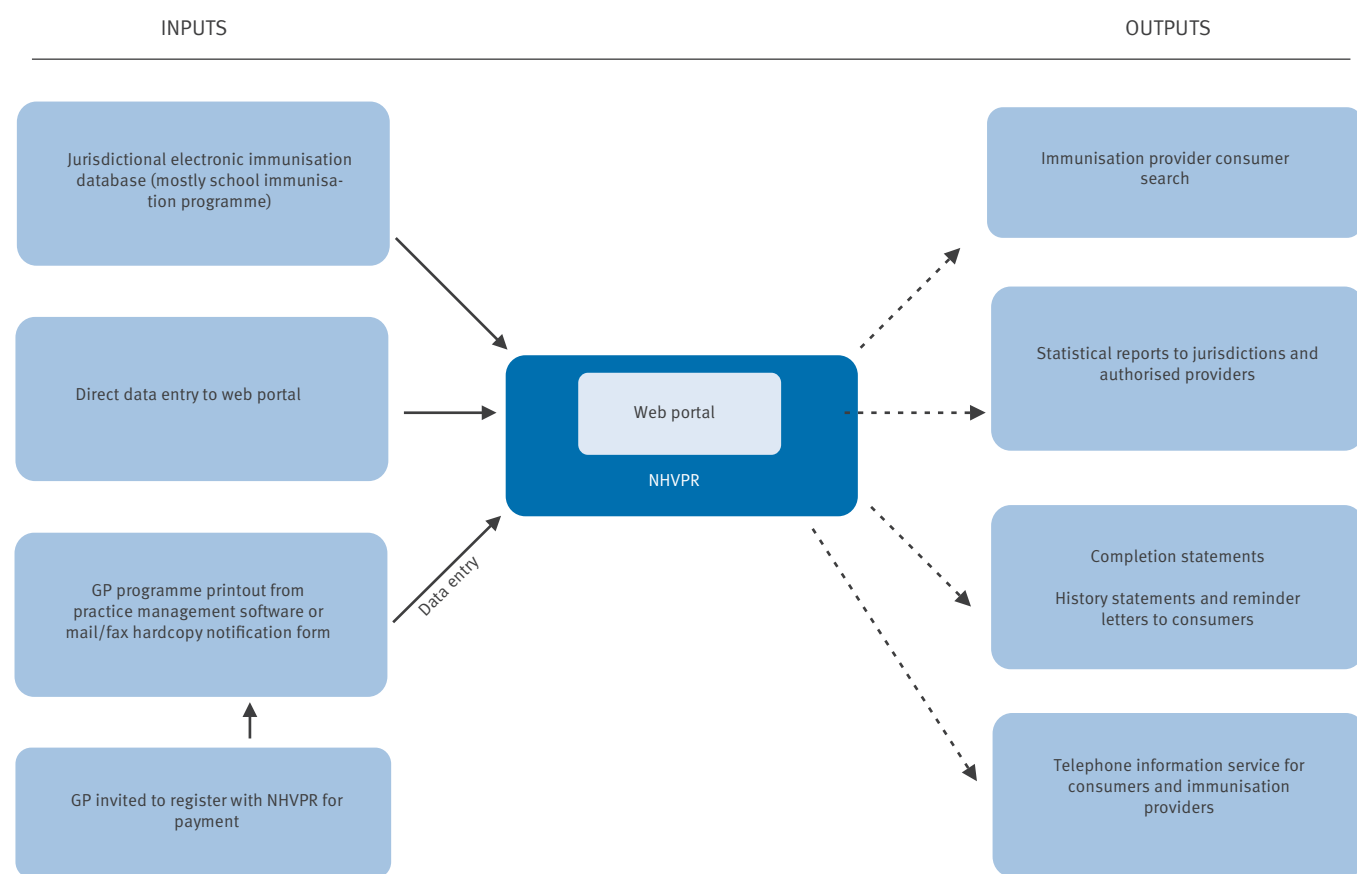
The HPV register was legislatively enabled in 2007 and became operational in 2008 [24,25]. The Australian Government funded the quadrivalent vaccine 4vHPV, (Gardasil, Merck, New Jersey, USA) as part of the programme in 2007. The bivalent 2vHPV vaccine (Cervarix, GSK, Uxbridge, UK) was licensed in late 2008, but the national programme in Australia is using the 4vHPV vaccine. This programme is targeted at pre-adolescent and adolescent females, with a funded ongoing school-based vaccination for 12- and 13-year-old girls. A two-year catch-up programme was also initially funded by the Australian Government for 13–18-year-old girls in schools and 18–26-year-old women through general practice and community-based programmes [25].

The Victorian Cytology Service currently operates the HPV register, which is also responsible for the Victorian

Cervical Cytology Register [26]. Prior to the establishment of the register in 2008, data from schools were held at local or State Health Department levels while GP-held data were recorded and held as instructed by the Australian General Practice Network [25]. HPV vaccine data can be submitted via different jurisdictional electronic immunisation databases (mostly via school immunisation programme), direct data entry to the HPV register web portal and GP notification via mail or fax from practice management software (Figure 4) [25]. To encourage registration, GPs were invited to register with the HPV register and on notification of a valid HPV vaccine dose, GPs were remunerated AUD 6 (approximately EUR 5) per vaccination encounter. This incentive attracted over 96% of GPs invited to register by March 2010, and was discontinued in June 2010, following the completion of the HPV vaccination catch-up programme [25].

The register provides information on vaccination coverage with the potential to link with a disease register of cervical cancer screening results. Coverage in Australia is currently calculated by age of all eligible females in the programme i.e. 12–26-year-olds in 2007 and 12–13-year-olds each year [25]. The numerator for

FIGURE 4
National Human Papillomavirus Vaccination Program Register (NHVPR) operations: data inputs and outputs, Australia



GP: General practitioner; NHVPR: National Human Papillomavirus Vaccination Program Register.
Source: Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. CSIRO PUBLISHING. Sexual Health. 2011;8(2):171-8. Available from: <http://www.publish.csiro.au/paper/SH10001.htm> [25].

coverage is the number of females in the target population who have received three 4vHPV doses. Coverage with one or two doses of the vaccine has also been calculated [25]. Recent data from the HPV register indicate promising 4vHPV coverage of the target group of 12–15-year-olds with 72–73% having completed three doses. International standardised coverage methods have yet to be agreed for 4vHPV, limiting comparisons of the effectiveness of HPV vaccines [24,25].

The HPV register also plays an important role in providing consolidated information on school and primary care vaccine doses, which would be useful to follow up on overdue vaccinations. In the future, this information will also provide the opportunity to notify young women if a booster dose is required [25]. A limitation of this HPV register was that it was not established before the National HPV immunisation programme commenced in 2007 and does not capture co-administered vaccines. It has also been proposed that Australia will soon begin immunising 12–13-year old boys under the NIP [27].

There have been calls internationally for HPV vaccination registers to be combined with a cervical cancer screening register, to incorporate vaccination status, cytology, histology and HPV DNA test results [25, 26]. A recent ecological study analysing the early effects of the HPV vaccination programme on cervical abnormalities in Victoria showed a decrease of 0.38% (95% confidence interval: 0.61–0.16; $p=0.003$) in high-grade cervical abnormalities in the three years after vaccine introduction, compared with four years before [26]. Linking of cervical cytology to vaccination status would allow testing of a causal link between HPV vaccines reducing cervical abnormality rates [26].

Jurisdictional vaccination registers

All jurisdictions with the exception of Tasmania and the Australian Capital Territory have separate registers: to record adolescent vaccines administered in the school-based programmes (New South Wales, Western Australia); school and local government-administered child and adolescent vaccines (South Australia, Victoria); or all childhood and NIP vaccinations administered (Queensland, Northern Territory). All are managed at the jurisdictional level, with the exception of the Immunisation Provider System (ImPS) in Victoria and South Australia, where electronic records are held at local government level, and all upload directly to ACIR or the HPV Register. Local reports of vaccine coverage are generated from ImPS and forwarded to the state Departments of Health for completion of vaccination records [28].

Primary care software

In 2007, it was estimated that Australian GPs were providing 71% of recorded vaccinations on the ACIR, with substantial jurisdictional variation [3]. Prior to the introduction of ACIR, many GPs had implemented various non-compatible decentralised immunisation record systems [29]. The introduction of the ACIR was

seen as addressing this issue and to improve population vaccination recording.

There are a number of commercial providers of GP practice software systems, with the ability to interact directly with ACIR and indirectly with the HPV Register. Varying in their immunisation recording capabilities, they represent the major data records for NIP vaccines for adults (e.g. pneumococcal and influenza vaccinations for the indigenous, elderly and ‘medical at risk’) and non-NIP vaccines (e.g. travel vaccinations), jurisdiction-funded vaccines e.g. adult pertussis (dTpa) and adult MMR vaccines, funded non-NIP vaccines requiring co-payments e.g. ‘medical at risk’ adult pneumococcal and privately prescribed vaccines). Records are held at practice level, but it is possible for anonymised data directly linking immunisations with subsequent attendances for healthcare at the practice to be extracted across multiple practices. The recently announced National Prescribing Service ‘MedicineWatch’ programme linking medicine use with potential adverse outcomes in primary care is a potential example of these systems. A limitation is that the GP software is provided by commercial companies, not the Australian Government, hence changes in the NIP are often not reflected in the software until the company decides to run an upgrade.

Other registers: Q fever vaccination register

The Q fever vaccination register is an industry-based register run by the Meat and Livestock Australia (MLA) corporation for recording vaccination and immunity status for the federally-funded Q fever vaccine in humans. It is accessible via the internet to medical practitioners and meat processors [30].

Limitations of the current immunisation registers

The absence of immunisation histories beyond seven years of age is a critical limitation of the ACIR. Whilst records are now available up to 14 years of age, late childhood and adolescent vaccines are not captured in ACIR. There has been a call for a ‘whole-of-life’ immunisation register that will record child, adolescent and adult immunisations including tetanus, influenza and pneumococcal immunisations [31,32]. Currently self-reporting of these vaccinations have been described as problematic with limited validity and poor coverage estimates of 71-79% of influenza vaccine and 51-53% of PPV23 [31]. It is anticipated that with a ‘whole-of-life’ immunisation register, health outcomes can be improved further by identifying missed vaccinations and prevent over-vaccination [32]. The HPV register for instance would seem an appropriate extension of the ACIR. Other registers such as the Australian Donor Organ register and the bowel cancer screening register have been suggested to be included in this ‘whole-of-life’ register [32]. In 2006, the Australian Government Department of Health and Ageing funded a scoping study for the redevelopment of ACIR, the results of which are still pending [32]. A National Immunisation

Strategy commissioned in 2010 and yet to be released, is anticipated to consider this issue and will hopefully provide stimulus for action on a ‘whole of life’ register.

A well-documented cause of lower immunisation coverage particularly with ACIR is inadequate reporting of immunisation encounters by immunisation providers [1,33]. ACIR has been reported to underestimate immunisation coverage by up to 5% in most states [15]. Moreover, electronic exchange of information is unilateral between primary care software systems and ACIR resulting in the tedious task of manually updating vaccines already on ACIR through individual requests or manual practice reports. A study evaluating home immunisation in a socially disadvantaged area also highlighted under-reporting with discrepancies of 11-14% between ACIR vaccination status versus actual vaccination status when checked prior to the commencement of the study [34].

Other limitations in Australia include the unreliable reporting of ‘additional’ NIP vaccines recommended for special at-risk patient groups in ACIR and the potential impact upon GP reporting to the HPV Register after the removal of the financial incentive for notification of vaccination. In addition, ACIR coverage calculations and GPII outcome exclude established vaccines introduced after 1996 (thus excluding rotavirus, pneumococcal conjugate, group C meningococcal, and varicella vaccines). However, this issue will be addressed with the latter three vaccines being included in the list of immunisations to be assessed as fully immunised from July 2013 [20]. There is also the possibility of linking ACIR to electronic health records as a way to progress vaccine effectiveness evaluations as well as rapidly investigate vaccine safety signals at jurisdiction, national or international level [35]. However, federal and jurisdictional privacy regulations and the extreme difficulty of linking immunisation databases with healthcare outcomes for those patients, limits the Australian ability to investigate potential vaccine safety signals [36]. ACIR data have been used to determine the expected number of intussusceptions following rotavirus vaccination in a post-marketing safety study identifying a potential association of new rotavirus vaccines with intussusceptions in Australia [5]. It has also been linked with hospital data to illustrate a link between MMR vaccine and idiopathic thrombocytopenic purpura [6].

Conclusion

Currently, Australia boasts a near-complete population-based childhood immunisation register with the ACIR. However, the obvious void of immunisation histories beyond seven years of age means that calls for a ‘whole-of-life’ register are ongoing. In addition, it only covers NIP routine vaccines introduced before 1996, and the HPV register sits separate to ACIR. These registers could provide a framework to expand immunisation registers linked to electronic health records. Limitations of current registers are still widespread, particularly with issues of under-reporting and

timeliness, which impact significantly to immunisation coverage estimates. Nevertheless, these available immunisation registers form a fundamental platform for further improvement in immunisation coverage. The linkage of these registers with healthcare outcome data will further enhance public health outcomes by enabling rapid, population-level vaccine safety and effectiveness investigations in a nation with a track record as an ‘early adopter’ of new childhood vaccines.

Conflicts of interest

NWC and JPB have acted as chief investigators for epidemiological studies sponsored by vaccine manufacturers (CSL) and serological testing (Merck). All payments, including for sitting on advisory boards (NWC), data safety monitoring boards (JPB), lecturing (NWC) and travel expenses for attendance at scientific meetings, are paid directly to an administrative fund held by Murdoch Childrens Research Institute.

GR has accepted funding from vaccine manufacturers (GSK) to attend two scientific meetings and to sit on an advisory board, and has lectured at GP education events that have been sponsored by vaccine manufacturers (CSL, GSK, Wyeth, Sanofi).

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Vaccine registers – experiences from Europe and elsewhere

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In this special issue, published in two parts, *Eurosurveillance* has presented a series of articles from countries in Europe, Australia and Canada, describing their various experiences with the introduction of vaccine registers [2-11]. Vaccine registers are population-based systems that contain core individual-level information on the population, together with information on immunisation status – usually for the childhood vaccination programmes. These systems are linked to a variety of programme management, surveillance and research tasks [1].

The lessons outlined in this special issue of *Eurosurveillance* illustrate the many potential opportunities of such systems and some of the challenges and the alternatives that may be available (Table).

There are a series of core attributes for any successful national vaccine register. Firstly, accurate and up-to-date ascertainment of individual-level demographic data of the population of interest is needed, as these constitute the denominator for calculation of coverage data. A small number of countries illustrate how this has been achieved through access to their national administrative population or universal healthcare registers based on personal identifiers/health numbers (2-4,7). Some of the systems presented are able to electronically transfer this population data in real-time and can automatically take into account new births, families moving address, children dying etc. Such innovations can help to minimise some of the traditional denominator problems of ghosting and unregistered populations. Secondly, information on vaccine status (numerator data) on this population needs to be both accurate and complete. Examples are provided of vaccine programmes using barcodes on vaccine vials, which can be used to record information on vaccine dose, batch number and name, thus reducing data entry time and errors [6,11]. Thirdly, register systems need to be flexible as national vaccine programmes are continuously evolving, with the introduction of new vaccines and changes in current childhood immunisation programmes. The registers are able to adapt to

such changes. Finally, as personal identifiable data are required, which is highly sensitive, the importance of developing robust data security and confidentiality mechanisms to protect these systems are highlighted by L Trogstad et al. [2].

The articles illustrate how vaccine registers can be used both as a management tool and for surveillance purposes. As a management tool, countries show how they have used registers to deliver their immunisation programmes. Examples are provided how they can be used to purchase vaccines and monitor supply [3,8]; how they can function as patient call-recall systems – producing invitation and reminder letters [3,5-8]; how they can provide certificates of vaccination for patients [2] and also how they can be linked to incentive schemes for health practitioners [7].

Vaccine registers can also be used as important surveillance tools to monitor national immunisation programmes. Data from such systems can be used to monitor vaccine uptake from national through to local level. This can identify unvaccinated sub-populations (whether by age, geography or particular risk group) and to ensure vaccine uptake is optimal in these pockets. The availability of unique personal identifiers provides the opportunity to link vaccine registers to disease registers and thus identify specific health outcomes. This provides the ability to evaluate the vaccine effectiveness and to investigate vaccine safety signals of existing and new vaccine programmes. Finally, there are examples of these systems being used to answer specific research questions, seeking informed consent from individuals on the national register to take part in vaccine trials or questionnaire surveys [3].

The challenges of developing such national systems are outlined. Firstly, the development of such systems is a significant undertaking, not least from the IT perspective, requiring substantial investment and careful planning. Secondly a number of countries have decentralised health structures, which create difficulties in establishing such a national register. Some

TABLE

Characteristics of immunisation registers in six European countries, Australia and Canada

Country	Register name	Start date	Level of information available	Description of register	Use
Denmark [4]	Danish vaccination register	2000 ^a	National	Covers programme vaccinations in children (planned for all vaccinations in children and adults) Based on unique civil registration number and national population register	<ul style="list-style-type: none"> • Call-recall (planned) • Vaccine coverage • Vaccine effectiveness • Vaccine safety • Patient access to vaccine record (planned) • Patient research
England [5]	Child Health Information Systems (CHISs) ^b	Mid -1980s	Local	Covers population up to 18 years ^c of age based on birth health registration Computerised clinical record systems for child health prevention programmes	<ul style="list-style-type: none"> • Call-recall system • Vaccine coverage • Vaccine safety • Vaccine effectiveness • Outbreak investigation and response • Child health screening
Italy [8]	Computerised immunisation register	Not available	Local	Regional-level computerised systems (15/21 regions)	<ul style="list-style-type: none"> • Call-recall system • Vaccine supply • Vaccine coverage • Management of the high-risk group target
the Netherlands [3]	Præventis	2005	National and subnational	Covers all children and adolescents Linked to population register Continuously updated (birth, death, change of address)	<ul style="list-style-type: none"> • Call-recall system • Vaccine supply • Vaccine coverage and vaccine status at individual child level • Additional research (on vaccine safety, vaccine effectiveness, acceptance of the national immunisation programme, etc.) • Other mother-child prevention programmes
Norway [2]	SYSVAK	1995	National	Covers all children Covers adult vaccinations since 2011 Based on unique personal identification number Vaccination is entered once in the Electronic Patient Record system and transferred automatically to SYSVAK	<ul style="list-style-type: none"> • Vaccine coverage • Vaccine safety • Vaccine effectiveness • Research • Link to other data systems • Healthcare personnel access to vaccine records • Vaccinee access to vaccine record
Spain – Murcia [6]	Computerised vaccinations register	1991	Regional	All children and adults Uses population register and is updated (deaths, change of address) real-time Developed vaccine barcode use	<ul style="list-style-type: none"> • Call-recall system • Vaccine coverage • Linked to other public health programmes
Spain – Navarre [10]	Computerised medical record	2000–2004	Regional	Covers all the residents and all vaccines for children and adults Represents a subsection of the computerised medical record	<ul style="list-style-type: none"> • Call-recall system • Vaccine coverage • Vaccine effectiveness
Australia ^d [7]	Australian Childhood Immunisation Register	1996	National	Covers information on all children up to seven years of age based on the health insurance scheme Data updated daily	<ul style="list-style-type: none"> • Call-recall system • Vaccine coverage (including risk groups) • Vaccine safety • Payments to parents and vaccination providers
	National Human Papillomavirus Vaccination Register	2008	National	Covers details on HPV vaccinations given to eligible females	<ul style="list-style-type: none"> • Call-recall system • Vaccine coverage • Potential to link with a disease register of cervical cancer screening
Canada [11]	Various depending on province/territory	Various depending on province/territory	Various (regional/ local to provincial/territorial) depending on specific system	Provincial level computerised systems (covers 6/13 provinces) Creating and adopting national standards Promoting interoperability between registries Developing vaccine barcode use	<ul style="list-style-type: none"> • Vaccine coverage (as part of an integrated public health surveillance system in some provinces/territories)

^a Covers data on childhood vaccinations from 1996; system under reorganisation, changes planned to be implemented in 2012-14.

^b Multiple CHISs exist in England, provided by different suppliers.

^c Sometimes up to 16 years only.

^d In addition to the two national immunisation registers, a variety of jurisdiction-based registers and primary care practice software systems exist in Australia, which interact with the national registers; there is also a Q fever vaccination register (industry-based register).

countries have overcome this problem, at least to a certain extent, by regions/provinces creating register networks. Such networks require common national standards and issues can remain around ensuring an accurate denominator. Thirdly, some countries have strict information governance regulations which do not allow personal identifiable data to be kept at national level [9]. Finally, the role of the private sector in vaccine delivery in some settings (as opposed to the central purchase of vaccine by the public sector) can provide a challenge to properly estimating the numerator.

The special issue highlights some of the future directions of travel. Countries which already have national vaccine registers are now extending these to whole life and teenage and adult vaccine programmes. The potential for synergy (and efficiencies) with other public health programmes such as maternal screening/neonatal screening is being explored. There is an increasing automation of operational processes from patient reminders through to scanning barcoded vaccine products. These need to be more standardised and at least for the latter, buy-in from the vaccine manufacturers is required. The full surveillance and research potential of such systems (under appropriate governance) is only just being realised, particularly through linkage to other electronic health records and through direct contact with patients. For some countries, there are important operational, financial and governance challenges to their establishment, for example decentralised health systems or concerns about data confidentiality. Alternative solutions need to be found, and some countries have tried to collect vaccine uptake data in other ways – such as by the use of telephone surveys [9]. Despite these challenges, national vaccine registers can play a key role in the delivery of national immunisation programmes in many countries and make important contributions to achieving national and international control and elimination targets.

Acknowledgments

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The Danish vaccination register

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Immunisation information systems (IIS) are valuable tools for monitoring vaccination coverage and for estimating vaccine effectiveness and safety. Since 2009, an advanced IIS has been developed in Denmark and will be implemented during 2012–14. This IIS is based on a database existing since 2000. The reporting of all administered vaccinations including vaccinations outside the national programme will become mandatory. Citizens will get access to data about their own vaccinations and healthcare personnel will get access to information on the vaccinations of their patients. A national concept of identification, a national solution combining a personal code and a card with codes, ensures easy and secure access to the register. From the outset, the IIS will include data on childhood vaccinations administered from 1996 and onwards. All Danish citizens have a unique identifier, a so called civil registration number, which allows the linking of information on vaccinations coming from different electronic data sources. The main challenge will be to integrate the IIS with the different electronic patient record systems currently existing at general practitioner, vaccination clinic and hospital level thereby avoiding double-entry. A need has been identified for an updated international classification of vaccine products on the market. Such a classification would also be useful for the future exchange of data on immunisations from IIS between countries.

Background

Since the year 2000 Denmark has had a national childhood vaccination database with information on all vaccinations administered to children below the age of 18 years in the framework of the national childhood vaccination programme. The information in the register allows for the data on vaccinations to be attributed to a person, hence the data is person-based.

The Danish childhood vaccination database (CVD) consists of data derived from a state-managed administrative register on services offered by general practitioners, who are electronically reimbursed from the national health insurance system. Hence the data in the CVD is the same as in the national health insurance system. Data sets are validated and imported regularly but there is a delay of up to two months from the date of vaccination to entry in the database.

The CVD includes information on date of vaccination, the unique identifier of the recipient, the so-called civil registration system (CRS) number, a vaccination code, and name and address of the vaccinator. The CVD has been a valuable data source for research studies and has contributed immensely to the knowledge on effectiveness [1–4] and safety [5–10] of childhood vaccinations. Furthermore, it has been used for providing precise estimates of vaccination coverage of childhood vaccinations by birth cohort and region in Denmark. [11–13]. The register does not include information on product name or batch number of the vaccine. The Department of Infectious Disease Epidemiology at Statens Serum Institut is the only authority which has had direct access to the CVD. They can provide healthcare personnel with information on vaccinations registered for a patient by telephone, email or fax if they receive a written consent form from the patient.

In 2007, Danish National Board of Health published a health technology assessment report about human papillomavirus (HPV) vaccination [14]. This report recommended that HPV vaccination should be included in the childhood vaccination programme for girls as a three-dose programme at the age of 12 years. Furthermore, it was recommended to establish a national HPV vaccination register with data on all administered HPV vaccinations including those given outside the HPV programme to recipients at their own cost, for instance to males or females above the age of 15. Such a register was considered a prerequisite for estimating the impact of the HPV vaccination programme on the incidence of HPV-related diseases in the future.

At the same time, there was an increased demand from the healthcare sector to get direct access to the data on vaccinations available in the CVD in order to validate the vaccination status of their patients.

Furthermore the delay of the data entry in the CVD and the lack of information on product name and batch number limited its use for studying potential side effects of vaccinations.

Taking the above considerations into account, there was a need for a new more advanced vaccination register than the CVD.

Organisation of the Danish vaccination register project

In 2008, the Danish government decided that a national vaccination register including data on all administered vaccinations as well as vaccinations administered outside the national childhood vaccination programme should be established.

Approximately 3 million EUR were allocated to Statens Serum Institut to develop and implement a new Danish vaccination register (DDV), within a three year period. The development of this register started in 2009.

The project was managed by a steering committee with participants from the Danish Ministry of Health, the National Board of Health, the National Board of Health Information Technology, the Danish Medicines Agency, the Danish Regions, the General Practitioners Organisation and the Statens Serum Institut.

The project group included a project manager, an epidemiologist, a secretary and an information technology

(IT) developer. The development of the system was outsourced to a private company, whereas the internal IT developer was responsible for developing the database for the surveillance of vaccination coverage and vaccine failures.

A simplified version of the system was used to register pandemic influenza vaccines in 2009/10. The final version of the DDV was finished in the summer of 2011 after a two month pilot phase. Because of an organisational restructure of health IT in the national administration in 2011, the responsibility of implementing the DDV in the healthcare sector and the responsibility for maintenance and support of the system were placed in the newly established National Board of Health IT. This reorganisation has delayed the implementation process of the system, but the DDV will be rolled out to general practitioners, vaccination clinics, hospitals and citizens during 2012-14.

TABLE

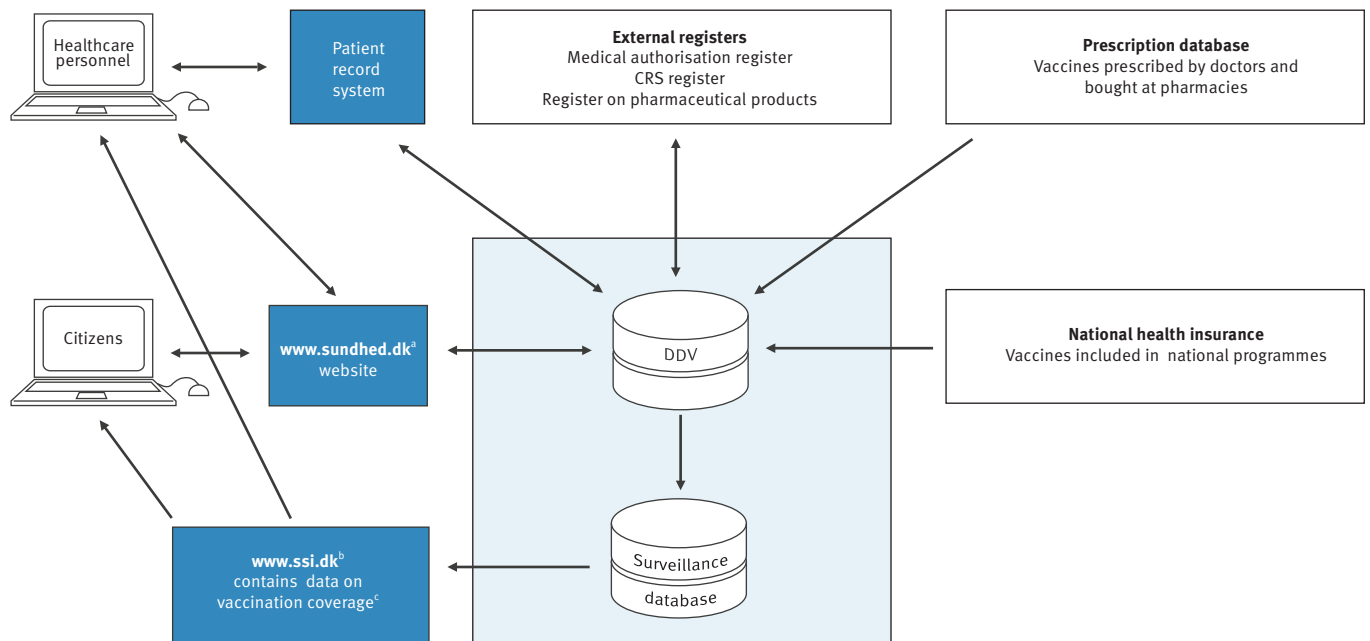
Differences between the childhood vaccination database and the Danish vaccination register

	The childhood vaccination database (CVD) ^a	The Danish vaccination register (DDV) ^b
Registered vaccinations	Only childhood vaccinations and influenza vaccinations given as part of a national programme	All vaccinations including those given outside a national programme
Variables included	<ul style="list-style-type: none"> • Date of vaccination • Type of vaccine • Personal identifier of vaccinee • Name of vaccinator • Organisation of vaccinator 	<ul style="list-style-type: none"> • Date of vaccination • Type of vaccine • Personal identifier of vaccinee • Personal identifier of vaccinator • Product name • ATC code • Dosage • Batch number • Organisation of vaccinator
Registration	Vaccinations only registered from existing administrative electronic registries	By healthcare personnel real-time on date of vaccination and also through retrospective data-capture from existing administrative registries in case of non-entry on vaccination date
Timeliness	Up to two months delay	Real-time registration
Mandatory reporting	No	Mandatory reporting of all given vaccines
Access	Only Statens Serum Institut	Healthcare personnel, citizens and Statens Serum Institut
Accessibility	Not applicable	Either through a web-based system or by integration with an existing electronic patient record system
Informed consent from patient	No	No
Data retrieval and linkage allowed for surveillance or research	Yes	Yes
Other characteristics	A simple database	An advanced IT-system with user interfaces, which support healthcare workers in decision making

ATC: anatomical therapeutic chemical.

^a In existence since 2000.

^b Will be implemented in 2012-14.

FIGURE 1**Architecture of the Danish vaccination register**

CRS: civil registration system; DDV: Danish vaccination register.

^a www.sundhed.dk is the official website of the public Danish healthcare services and enables patients and healthcare professionals to find information and communicate.

^b www.ssi.dk is the webpage of Statens Serum Institut, which is responsible for the control and prevention of infectious diseases.

^c Vaccination coverage of vaccines administered in the framework of the DDV, presented real-time in an interactive website by birth cohort, sex, region or municipality.

The aims of the Danish vaccination register

The aims of the register are to:

- provide access for healthcare personnel to information on vaccinations for their patients, through user-friendly interfaces;
- provide access for citizens to data on their own vaccinations, through user-friendly interfaces;
- improve the surveillance of childhood and influenza vaccination coverage and all other vaccinations;
- improve the quality of the data that can be used for measuring vaccine effectiveness and estimate the overall impact of national vaccination programmes on the incidence of vaccine-preventable diseases;
- improve the quality of the data for studying potential side effects of vaccinations.

Reporting all administered vaccinations to the register will be mandatory. The DDV will differ from the current system, the CVD, in several ways (see Table).

Description of the Danish vaccination register

Import of data from existing sources

Data will continuously be imported from the following electronic data sources: (i) the prescription database, and (ii) the national health insurance system. Furthermore, the DDV captures relevant information from a wide range of other administrative registers with information on the vaccinator, the vaccinee or the vaccine used (see Figure 1).

The prescription database contains real-time data on vaccinations prescribed by doctors and delivered at pharmacies. The database includes variables such as date of delivery, type of vaccine, personal identifier of recipient, name of the prescribing doctor, product name, anatomical therapeutic chemical code and dosage.

From the outset the DDV will comprise data on childhood vaccinations from 1996 and onwards, imported

from the national CVD and data from the prescription database, from 2006 and onwards.

Access to the Danish vaccination register

After identifying themselves, healthcare personnel can get access to information on vaccinations for their patients either (i) by entering an online web-based system (ii) by integration of their local electronic patient record system with DDV web services from a central platform, or (iii) by integration of a so called 'Smart Frame' in the local patient record system. The Smart Frame is an embedded browser that allows the exchange of data between the browser and the patient record system. Integration with the existing patient record systems with web services or Smart Frame is the preferred choice in order to avoid double entry of vaccinations in both the DDV and the patient record system.

Healthcare personnel identify themselves by a digital signature. Citizens can access their own data on the official website for the public Danish healthcare services that enables patients and healthcare professionals to find information and communicate. The website, www.sundhed.dk, also contains person-based information on e.g. laboratory results, medication and hospitalisations. The concept of identification is the so called NEMID which is a national solution combining a personal code and a card with codes. This concept of identification is also used by all Danish banks and Danish authorities, which means that the concept is widely known and used in the population.

Data in the Danish vaccination register

The DDV has access to several external registers. The CRS is an administrative register which includes information on all citizens in Denmark such as civil registration number, date of birth, name and address. The medical authorisation register is used to identify healthcare personnel. The register of pharmaceutical products contains names and ATC codes of all medical products, including vaccines, sold at pharmacies in Denmark. This register has proven to be insufficient for the DDV as many vaccines are not sold at pharmacies but delivered exclusively from Statens Serum Institut. As it is possible also to report vaccinations given previously in Denmark or in other countries, the database on vaccines has had to be expanded with information about a wide range of historical vaccinations and vaccine products. This database is currently administered by the Statens Serum Institut.

Healthcare personnel enter information on administered vaccinations in real time but because of a delay in the importing of data from the other registries, specific matching criteria are set up to avoid duplicates. The variables that they enter in the register include: CRS number of the recipient, date of vaccination, product name and/or vaccine type, dosage and batch number. Other variables are captured automatically through the identification procedure for healthcare personnel such

as the CRS number of the vaccinator or the assistant and the place of vaccination.

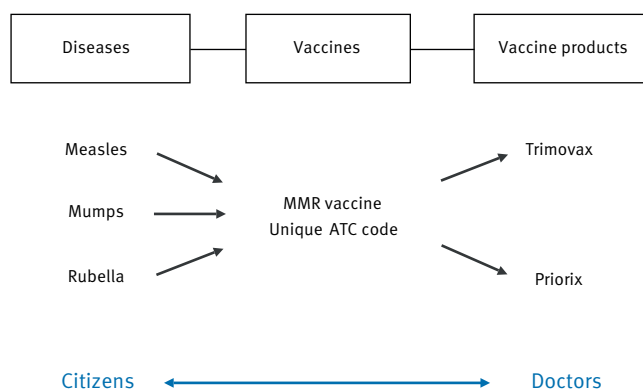
Functionalities

In the DDV, healthcare personnel can register both newly administered vaccinations, and vaccinations administered previously by another doctor in Denmark or in another country. Medical doctors can delegate their rights to register vaccinations to their assistants.

The system supports the healthcare workers in decision making. All vaccinations foreseen in the childhood vaccination programme will automatically appear in the system for all registered newborn children and the healthcare personnel only have to tick a box to register the vaccinations. If a vaccination is given too late in the programme, the system will automatically adjust the dates of the following vaccinations to secure minimal intervals between vaccinations. For a vaccination programme or a series where there is need for a booster dose, the system will automatically provide the duration of the protection by vaccine.

After identifying themselves, citizens have access to a list of vaccinations that they already received and a list with dates of vaccinations that have been planned for the future. They can register previously administered vaccinations, which after validation by a doctor will be registered on the immunisation chart. The data model ensures that the system can handle different levels of specificity of vaccinations registered by the citizen and the healthcare worker (Figure 2). A citizen may only report a disease for which they have been vaccinated whereas the healthcare worker will tend to report a vaccine product administered.

FIGURE 2
The relation between vaccination against diseases, vaccines, and vaccine products in the Danish vaccination register using the example of measles-mumps-rubella vaccine



ATC: anatomical therapeutic chemical; MMR: measles-mumps-rubella.

Healthcare personnel and citizens can print an updated immunisations chart. In the future the system can provide the data for generating recall reminders automatically.

Surveillance of vaccination coverage and vaccine failures

Vaccination coverage of childhood vaccinations and influenza vaccinations given to people >65 years will be calculated automatically in real time by sex, birth cohort, region and municipality and presented on an interactive website of the Statens Serum Institut. The denominator is calculated on the basis of information from the CRS including information on age, sex, and address of every individual living in Denmark. The absolute number of influenza vaccinations given to risk groups will be presented on the website by sex, region and municipality. Notifications on mandatory notifiable vaccine-preventable diseases will automatically be linked with the DDV to identify vaccine failures. Vaccine effectiveness and safety studies will be conducted ad hoc.

Experiences during the development of the Danish vaccination register

Advantages

Compared with other countries Denmark has had several advantages in the process of developing the new IIS. First of all Danish citizens have a unique identifier which makes it possible to match information on vaccinations coming from different electronic data sources, similar to Norway [15]. In the majority of European countries this is not possible. Secondly, Denmark has previously had only one register of childhood vaccinations and therefore did not have the challenge of integrating different existing systems to one new system. The electronic person-based data on childhood vaccinations administered from 1996 and onwards that is available from the Danish CVD means that the DDV will be of value for healthcare personnel and citizens as soon as it becomes available for use.

There has been political, economical and legislative support from the Ministry of Health for the development and implementation of the DDV in the healthcare sector. It will be mandatory to report all given vaccinations to the register, which is crucial for the completeness of the DDV. Finally the national concept of identification, the NEMID, results in an acceptable and secure access to the register for both healthcare personnel and citizens.

With permission from the Danish Data Protection Agency it is possible to carry out register linkage studies using a unique identifier given to all Danish citizens without obtaining informed consent from the participating individuals. This means that the data from the DDV can be used for surveillance and research projects at the national level on vaccine effectiveness and safety, which is not the case in many other European

countries. In Denmark, informed consent from the patient is not required for the registration of any vaccinations, as is the case in Norway for most vaccinations given outside a national programme [15].

Challenges

In Denmark, there are at least 14 different medical record systems in use by general practitioners and several different electronic patient record systems in use at hospitals. This means that IT developers from a wide range of different companies have to integrate the vaccination register into their existing system. Furthermore, a wide range of private vaccination clinics with less mature health record systems may have problems with integrating DDV into their electronic patient record system.

There has been some debate regarding the workload of mandatory reporting which has to be dealt with in agreements with the stakeholders. We have identified a need for a classification system of vaccine products on the market. The ATC classification system is not specific enough. If the data on vaccinations has to be used to study potential side effects of vaccinations, it is necessary that information on the specific product used is available in a standardized format. A standardised classification of vaccine products will also promote future exchange of data between countries.

Conclusions

The Danish CVD has been a valuable tool for surveillance of vaccination coverage and for estimating vaccine effectiveness and safety since 2000. With the new IIS, to be implemented in 2012-14, citizens and healthcare personnel will benefit by getting access to an up-to-date overview of the vaccination status of themselves or of their patients. Mandatory real-time registration of all administered vaccinations will allow us to also estimate the effectiveness and safety of vaccinations not included in the national programme. According to experience it is crucial that resources are allocated to (i) development of the system (ii) integration and implementation of the system into existing electronic patient record systems, and (iii) support of the users of the system after the system has implemented. The main challenge in Denmark is to integrate the IIS with the wide range of existing different patient record systems, which has required close collaboration between the IT companies that develop and maintain the patient record systems. It is important that the IIS will ease the daily procedures regarding immunisations for the healthcare workers and eventually support decision making to encourage the use of the DDV. We have experienced that access to a continuously updated international classification of international vaccine products would be useful, also in case of future exchange of data on immunisations from IIS between European countries.

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Præventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme

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Vaccination coverage is an important performance indicator of any national immunisation programme (NIP). To monitor the vaccination coverage in the Netherlands, an electronic national immunisation register called 'Præventis' was implemented in 2005. Præventis has a link with the population register and can produce letters of invitation for the NIP, register and validate administered vaccinations. The database is used to monitor the vaccination process, produce reminder letters, control the stock of vaccines and provides information used for paying the fees to the different executive organisations involved. Præventis provides a crucial tool for the evaluation of the NIP by producing (sub)national vaccination coverage estimates with high accuracy and allowing additional research: identifying populations at high risk for low coverage based on existing data, conducting specific studies where individuals included in the immunisation register are approached for further research, using vaccination coverage data for the interpretation of (sero)surveillance data, and linking the immunisation register with disease registers to address vaccine safety or vaccine effectiveness. The ability to combine Præventis data with data from other databases or disease registers and the ability to approach individuals with additional research questions offers opportunities to identify areas of priority for improving the Dutch NIP.

Introduction

The Dutch National Immunisation Programme (NIP) started in 1957. Today, the immunisation schedule includes vaccination against diphtheria, tetanus, polio, pertussis, infection with *Haemophilus influenzae* type b, measles, mumps, rubella, meningococcal C disease,

pneumococcal disease (10 serotypes), cervical cancer (human papillomavirus type 16/18) and hepatitis B (Table 1). In the Netherlands, vaccinations within the NIP are administered free of charge and voluntary. The overall direction of the NIP rests on the programme manager at the Centre for Infectious Disease

TABLE 1

Immunisation schedule of the National Immunisation Programme, the Netherlands, 2011

Age	Vaccination-dose
At birth (<48 hours)	HepB-o ^a
2 months	DTaP-IPV-Hib-HepB-1 ^b + PCV-1
3 months	DTaP-IPV-Hib-HepB-2 ^b + PCV-2
4 months	DTaP-IPV-Hib-HepB-3 ^b + PCV-3
11 months	DTaP-IPV-Hib-HepB-4 ^b + PCV-4
14 months	MMR-1 + MenC
4 years	DTaP-IPV-5
9 years	DT-IPV-6 + MMR-2
12–13 years	HPV-1 + HPV-2 + HPV-3 ^c

DTaP: diphtheria-tetanus-acellular pertussis vaccine; HepB: hepatitis B vaccine; Hib: *Haemophilus influenzae* type b vaccine; HPV: human papillomavirus vaccine; IPV: inactivated polio vaccine; MenC: meningococcal C-conjugate vaccine; MMR: measles-mumps-rubella vaccine; PCV: pneumococcal conjugate vaccine.

^a Only for children whose mother tested positive for hepatitis B surface antigen (HBsAg).

^b From August 2011 all newborns have received vaccination against hepatitis B; before August 2011 this vaccination was only offered to risk groups.

^c Only for girls; three doses with vaccination scheme 0-1-6 months.

Source: [1].

Control of the National Institute for Public Health and the Environment (RIVM). She is responsible for implementing the ministry's vaccination policy in the NIP and defines the operational conditions. The execution of the NIP is coordinated operationally by the department Regional Coordination of Programmes/Purchase, Storage and Distribution (RCP/IOD). Five local offices of RCP/IOD coordinate the execution of the NIP in their own region. Vaccinations are administered at local level by the network of Child Health Clinics (CHC) and by Public Health Services (PHS). The Epidemiology and Surveillance (EPI) unit is responsible for evaluation of the NIP through surveillance and epidemiological research of the impact of (future) target diseases including vaccination coverage.

With regard to evaluation of the NIP, vaccination coverage is an important performance indicator. To be able to monitor the Dutch vaccination coverage, an electronic national immunisation register called 'Præventis' was implemented in 2005 and is managed by RCP/IOD. Before the introduction of Præventis, different regional immunisation registers were in place, producing invitation letters and reminders and registering vaccinations. Præventis has these functionalities and moreover includes an algorithm to validate administered vaccinations. The database is used to monitor the vaccination process, to produce reminder letters and to control the stock of vaccines, and it provides information used for paying the fees to the different executive organisations involved in the vaccination process. Thus Præventis provides a crucial tool for the evaluation of the NIP by producing vaccination coverage reports and allowing additional research. In this paper we describe this in more detail.

The immunisation register Præventis

All children under the age of 19 years eligible for the NIP are registered in the national immunisation register Præventis (files are stored for a period of 15 years, until the age of 34 years). Through a link with the population register (gemeentelijke basisadministratie, GBA), Præventis receives continuous updates on all newborn and deceased children and on changes in the address of children (due to movement within the country or immigration/emigration). In general, these GBA updates are processed automatically with the use of the personal public service number (burgerservicenummer, BSN) as a unique identifier; only in case of a problem with processing an update, manual validation takes place by an employee of RCP/IOD. For each newborn or immigrated child a new NIP record with a unique client number is automatically created in Præventis. Therefore, Præventis includes a record for each child, irrespective of participation in the NIP. Præventis is used as the national immunisation register but is also the database to facilitate other collective preventive programmes such as maternal screening for hepatitis B, syphilis, infection with human immunodeficiency virus (HIV), blood group and irregular antibodies, as

well as neonatal screening for congenital diseases such as inborn errors of metabolism.

Vaccination process through Præventis: from invitation to registration

The letters to invite parents to get their child(ren) vaccinated according to the NIP are automatically created in Præventis and sent by RCP/IOD for all children at the age of one month, around four years, and around nine years, as well as for girls around 12 years. This invitation includes personalised vaccination cards that parents need to bring along at each vaccination (Table 1) of their child. Vaccinations are administered by the CHC for children up to the age of four years and by PHS for school-aged children. Subsequently, administered vaccinations (vaccine characteristics, dose, date of administration, executive organisation) as well as possible principal objections to vaccination are registered on the vaccination cards. The CHC and PHS return the vaccination cards by post to one of the five local offices of RCP/IOD, where the data are entered in Præventis with a barcode reader. Alternatively, the CHC and PHS can choose to enter the data directly in Præventis through an internet application 'RVP Online' (i.e. NIP online), which is increasingly used. Parents of children that do not respond to the initial invitation to get their child(ren) vaccinated within a certain time limit receive a reminder by letter by the RCP/IOD centrally or on request at regional level by one of the local executive organisations.

Validation

RCP/IOD is responsible for managing the registration process in both Præventis and RVP Online. The local organisations are only allowed to make corrections in their own regional data. Præventis includes criteria to judge the validity of each vaccination within the current NIP guidelines. This means that in some cases administered vaccinations are registered in Præventis but automatically rejected, for example because they are not administered at the right moment (the time interval between two vaccinations was too short) or with a deviant vaccine product. If needed, the parents of the concerned child receive a new invitation for additional vaccination.

Authorisation and confidentiality

Access to Præventis is only allowed to people who need to administer or register vaccinations and to the medical advisors and regional managers of the NIP. The data are saved on the level of the individual (i.e. they are not anonymous) but are only accessible at individual level for people who need to register vaccinations or assess the immunisation status of a particular child. All data requests made for the purposes of additional research through Præventis are assessed by a multidisciplinary team, specifically with regard to privacy aspects.

Residents do not have access to Præventis but they are able to request information on their vaccination history at the local organisation responsible for the

execution of the NIP in their own region. Furthermore, there is no connection between healthcare records of clinicians and Præventis but a link with the electronic youth health files that are used by the CHC and PHS to monitor the child's health on different aspects, is being developed.

Tool to evaluate the National Immunisation Programme

Besides a powerful tool to facilitate the daily delivery of the NIP with high quality, Præventis is also a very useful tool to evaluate the coverage of the NIP. The information in the register enables evaluation by various approaches. Here we describe these approaches and present our experiences with the immunisation register.

To measure (sub)national vaccination coverage

Monitoring vaccination coverage is important in order to follow the progress towards goals for controlling and/or eliminating vaccine-preventable diseases. Præventis does not include a standard threshold to indicate low vaccination coverage. An additional reporting tool, 'Præmis', was developed to be able to compose different reports on vaccination coverage. At central level, the RIVM determines annually the national vaccination coverage for specific birth cohorts. On individual level and at different moments in life we determine if, according to the NIP guidelines, sufficient vaccinations have been given before a fixed age. Table 2 gives an overview of the different ages at which the vaccination coverage is determined for each of the (combination of) vaccines.

Besides determination of the national vaccination coverage it is also important to have insight into the vaccination coverage at subnational level since a high

national vaccination coverage is no guarantee for a high vaccination coverage at subnational level and consequently no guarantee against outbreaks of vaccine-preventable diseases [3-6]. Annually, the vaccination coverage is reported by province (n=12) and by municipality (n=415 on 1 January 2012).

The data on (sub)national vaccination coverage are disseminated in the form of an annual RIVM report that is publicly available [2]. Through this annual report we inform not only the Ministry of Health and other organisations such as the European Centre for Disease Prevention and Control and the World Health Organization but also the CHC and PHS. With the subnational data in this report the latter are able to evaluate their local efforts to reach high vaccination coverage in their own region. An example of the standard geographical presentation in the annual report of the vaccination coverage by municipality is presented in the Figure. These maps are also available online through the Dutch National Atlas of Public Health [7]. This website shows the current and historical vaccination coverage in each municipality simply by clicking on one of the municipalities. If needed the five local offices of RCP/IOD are also able to break down the regional vaccination coverage at a lower level, such as the four-digit postcodes. Furthermore, they are able to produce more timely management information at any time during the year to be able to monitor the progress in regional participation more closely than through the annual report.

To identify populations at high risk for low vaccination coverage based on existing data

Understanding reasons for a low vaccine uptake is important to provide recommendations to improve vaccination coverage and to determine which aspects

TABLE 2

Individual age at which vaccination coverage is determined per (combination) vaccine, the Netherlands, 2011

Newborns 3rd day of life	Infants 1 year	Toddlers 2 years	Preschool children 5 years	School children 10 years	Adolescent girls 14 years
	DTaP-IPV-3	DTaP-IPV-4	DTaP-IPV-5	DT-IPV-6	
	Hib-3	Hib-4			
	PCV-3	PCV-4			
		MMR-1		MMR-2	
		MenC			
					HPV-3
HepB-o ^a		HepB-3/4			

■ primary immunisation

■ basic immunity

■ revaccinated

■ fully immunised

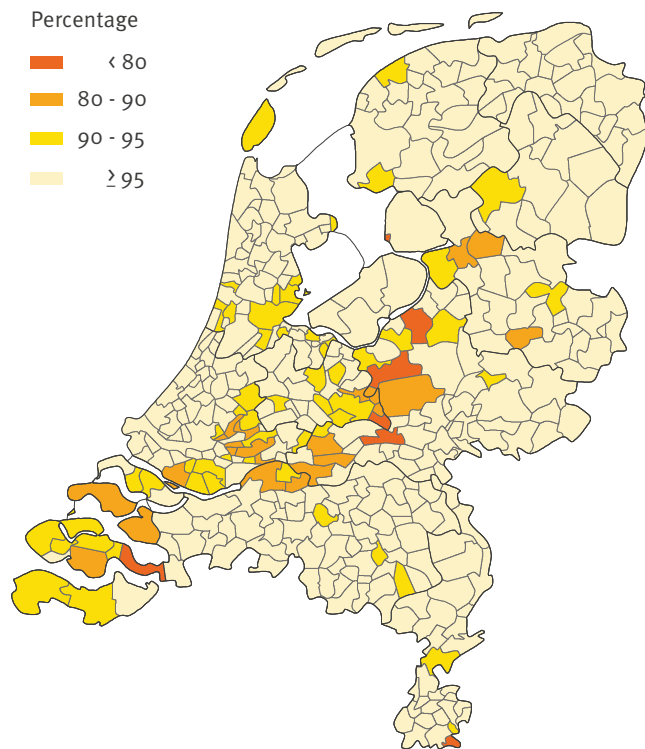
DTaP: diphtheria-tetanus-acellular pertussis vaccine; HepB: hepatitis B vaccine; Hib: *Haemophilus influenzae* type b vaccine; HPV: human papillomavirus vaccine; IPV: inactivated polio vaccine; MenC: meningococcal C-conjugate vaccine; MMR: measles-mumps-rubella vaccine; PCV: pneumococcal conjugate vaccine.

^a Only for children whose mother tested positive for hepatitis B surface antigen (HBsAg).

Source: [2].

FIGURE

Vaccination coverage for the first measles-mumps-rubella vaccination in birth cohort 2008 (determined at the age of two years), by municipality, the Netherlands, 2011



Source: [8].

future studies should focus on. Besides data on vaccination history, some background characteristics are also available on individual level through Præventis (sex, age, country of birth of the parents). Since Præventis includes all children in the Netherlands, these data can be used to determine whether there are differences in background characteristics between vaccinated and unvaccinated children so as to identify risk groups.

Præventis also makes it possible to combine immunisation data with other existing databases, even if these data are not available on an individual level. An example of this is a study on human papillomavirus (HPV) vaccination coverage: voting data for two political parties (Reformed Political Party (SGP) with predominant orthodox reformed adherents and Christen Unie (Christen Unie) with Christian adherents) by municipality from Statistics Netherlands and socioeconomic status data by postcode from the Netherlands Institute for Social Research were incorporated in the analysis of possible determinants of HPV vaccination coverage since information on religion and socioeconomic background was not available in Præventis [9]. A similar analysis was conducted for other vaccinations (data not shown).

Future research areas

In the future we would like to determine vaccination coverage per school to identify risk schools that need

priority attention during an outbreak situation. This is important for the Dutch situation since people belonging to the orthodox Protestant minority and anthroposophists, who more often object to vaccination, tend to cluster at school level [10]. At first, possible privacy issues with regard to combining data from Præventis with data from schools (who is going to which school?) need to be explored. Another future research area is to find out if premature newborns follow the NIP guidelines in the same way as the rest of the newborns by combining data from Præventis with data on pregnancy duration from neonatal screening. Based on literature the hypothesis is that premature newborns receive their first vaccination somewhat later than full-term children [11,12] and could therefore be more at risk for vaccine-preventable diseases.

To approach individuals included in the immunisation register for further research

Participants of studies aimed at evaluating the NIP can be recruited through the immunisation register: Præventis enables the inclusion of both vaccinated and unvaccinated individuals. These individuals are asked by post whether they are willing to participate in a specific study. Such studies include questionnaire studies (e.g. on hepatitis B vaccination acceptance [13]), vaccination trials (e.g. pneumococcal disease), studies with focus groups (e.g. acceptance of the NIP) and vaccine effectiveness studies (e.g. mumps outbreak [14]). Individual vaccination records are regularly used for this kind of studies. When informed consent is obtained from participants in a specific study, their vaccination history can be checked in Præventis. Thus information on immunisation status can be obtained that is more reliable than self-reported vaccination history. In the nationwide serum collection [15] used to evaluate the NIP and in a mumps outbreak study [14] this information was retrieved from Præventis for all participants.

To use vaccination coverage data for the interpretation of (sero)surveillance data

With reliable nationwide data on vaccination coverage we can interpret observations from other surveillance sources on the occurrence of particular diseases and on immunity profiles. The screening method can be used to estimate vaccine effectiveness using the proportion of cases vaccinated [14,16]. This proportion is compared to the nationwide vaccination coverage. To prevent bias in this method, it is essential that the cases' vaccination history as well as the nationwide data are reliable. This method is particularly suitable to study changes in vaccine effectiveness over time and was used in the Netherlands to interpret the re-emergence of pertussis [17]. Also to interpret sero-profiles measuring the immunity in the population by assessing specific antibodies, vaccination coverage is needed, since the immunity of the population reflects the result of the level of vaccination coverage, vaccine effectiveness and occurrence of natural infection.

To link the immunisation register with disease registers to address vaccine safety or vaccine effectiveness

Secondary use of healthcare data may advance medical knowledge especially with regard to disease aetiology and outcome. Extending linkages between databases will create a useful tool for knowledge discovery in the area of disease aetiology and outcome. In the Netherlands we plan to link Præventis to a large, well-established population-based medical record database, IPCI (Interdisciplinary Processing of Clinical Information [18]). The linkage itself will be done by a trusted third party (TTP). This TTP will store the linkage file that comprises the patient identifier of Præventis, the IPCI identifier and a matching weight which indicates the probability that record pairs may be accepted as links. The researchers will receive a study file with data from the linked databases but without patient identifiers.

At present, we are performing a study on the validity of the linkage of Præventis and IPCI. The association between measles-mumps-rubella (MMR) vaccination with febrile convulsions (true positive association) and fractures (true negative association) will be tested. Based on the results of this study future linkage studies can be performed to monitor effectiveness and safety of vaccination.

Another example is an ongoing study to estimate the association between the HPV vaccination status of daughters and the participation of their mothers in cervical cancer screening. The aim of this study is to identify risk groups for inclusion in (educational) campaigns in order to increase participation in cervical cancer prevention programmes. It uses data from Præventis combined with data from the cervical cancer screening, which was also linked by a TTP [19].

Discussion

A survey on vaccination coverage assessment among the countries in the Vaccine European New Integrated Collaboration Effort network (VENICE) in 2007 showed that 15 countries in Europe had national or local computerised immunisation registers in place and five countries had future plans to develop such a register [20]. The VENICE survey on functional standards for computerised immunisation registers in Europe revealed that in a number of countries such as Belgium, Spain, Italy, Ireland and the United Kingdom (UK), the register does not consist of one national immunisation register, such as in the Netherlands since 2005, but of different local immunisation registers [21].

An important advantage of Præventis is that it is one registration system with a central database that covers the whole country. Therefore, there are almost no linkage and definition problems between local regions any more compared to the period before 2005 when different regional immunisation registers were in place. Having one national immunisation register also

simplifies evaluation of the NIP, since the data can be extracted from the register at a central level instead of combining several data sets extracted at regional level. In the Netherlands, the vaccination coverage in the NIP is evaluated annually and published in an RIVM-report. In the UK, the vaccination coverage is evaluated quarterly by COVER (Cover of Vaccination Evaluated Rapidly), which might allow earlier detection of changing trends [22]. However, in the Netherlands the vaccination coverage has been very stable for a long time [2,23] and the five local offices of RCP/IOD are able to produce timely management information at any time during the year to be able to monitor the progress in regional participation more closely than through the standard annual report. Furthermore, in specific situations such as during the introduction of HPV vaccination, the national participation is evaluated ad hoc and more frequently than annually.

Another advantage of Præventis is that it is continuously updated by data from the population register (GBA) and can therefore produce an accurate figure of the denominator for calculating vaccination coverage. This in contrast to some other immunisation registers such as in the UK where the denominator is based on a combination of general practitioner registration and place of residence for unregistered patients, and where children can sometimes be registered more than once because they are not always removed from a system when they move to a different area [22].

Because only one immunisation register has been in place since 2005, the system is also vulnerable. Different operations such as regular backups are established to guarantee the continuous accessibility of Præventis. Regular changes in the NIP require regular adjustments of Præventis. These changes in the software carry certain risks for the continuation of the registration process. Good standard procedures, for example standard procedures for implementing changes and test reports are necessary and have been formulated and implemented for Præventis. At this moment, only vaccinations included in the NIP are registered in Præventis. Certain vaccinations are therefore not registered, for example seasonal influenza vaccination which is covered by a separate programme (vaccinations administered by the general practitioners), travel related vaccinations, and all other vaccinations that are administered outside the NIP.

Conclusion

The Dutch immunisation register Præventis does not only support the daily delivery of the NIP but allows the assessment of vaccination coverage with high accuracy at both national and subnational level. The ability to combine Præventis data with data from other databases or disease registers and the ability to approach individuals with additional research questions depending on their vaccination history offers opportunities to explore areas of priority to improve the Dutch NIP.

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Immunisation registers in Canada: progress made, current situation, and challenges for the future

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Immunisation registers have the capacity to capture data on the administration of vaccine doses at the individual level within the population and represent an important tool in assessing immunisation coverage and vaccine uptake. In 1999, the National Advisory Committee on Immunization recommended that a network of immunisation registers be established in Canada. The Canadian Immunization Registry Network (CIRN) was established to coordinate the development of standards and facilitate the sharing of knowledge and experience to develop a national network of such registers. In 2003, the National Immunization Strategy identified immunisation registers as an important component in improving national immunisation surveillance. In addition, there has been consistent public and professional interest in a national immunisation register being available and considerable progress has been made in developing technologies to facilitate the capture of immunisation-related data. More specifically, the automated identification of vaccines, through the use of barcodes on vaccines, will facilitate collection of data related to administered vaccine doses. Nevertheless, challenges remain in the implementation of immunisation registers in all Canadian provinces and territories such that Canada still does not currently have a fully functional network of immunisation registers with the capacity to be interoperable between jurisdictions and to allow for data to be captured at the national level.

Introduction

In Canada, several millions doses of vaccines are administered every year. According to the immunisation schedules recommended by the National Advisory Committee on Immunization (NACI), the national committee tasked with making scientific recommendations on the use of vaccines in Canada, a child will receive 18 vaccinations to protect against 13 diseases by the age of two years, and 26 vaccinations by the age of 19 years [1]. These figures do not include seasonal influenza immunisation whereby the seasonal influenza vaccine may be received on an annual basis. In addition, several vaccines may be administered during a single immunisation visit. During each immunisation event,

a healthcare provider must manually record details of the immunisation event in the patient's health record as well as in the patient's personal immunisation card or hand-held immunisation record.

Thus, information related to each immunisation event should become part of an individual's permanent health record. Access to this information is critical in the event of a vaccine recall, vaccine failure or of suspected adverse event following an immunisation (AEFI). Hand-held immunisation records can contain information such as antigen, brand name of vaccine, dose, date of immunisation, vaccine lot number, expiry date, route of administration, and injection site. Unfortunately, surveys conducted across Canada have shown that as many as 30% of parents have misplaced their child's immunisation record by the time their child is seven years old, 15% of immunisation records are incomplete, and 24% contain data entry errors [2]. Incomplete immunisation records result in up to 10% of the population being re-immunised needlessly, delays in the appropriate follow-up of AEFI, and vaccine supply issues. These issues result in increased costs to the health system and may potentially result in adverse health outcomes for vaccine recipients.

Reliable immunisation records at the individual level are essential to ensure that immunisations are provided according to the recommended immunisation schedules such that optimal protection against vaccine-preventable diseases (VPD) can result from immunisation [3]. At the population level, reliable and complete data from immunisation records are necessary for the assessment of vaccine uptake and coverage, vaccine effectiveness [4] and vaccine safety. Accurate and readily accessible immunisation records are also crucial in the event of a lot recall or vaccine failure because they can provide information necessary to track down potentially affected individuals.

Immunisation registers are information or software applications that have the capacity to perform the scheduling of immunisation appointments, the management and recording of immunisation events, notify

when immunisations are due. These functions of immunisation registers allow them to serve as a tool to assess immunisation coverage. These population-based databases have the potential ability, depending on the specific system used, to accurately assess, in real time, vaccine uptake at the national and regional levels, and personal immunisation status for individuals residing within a jurisdiction. Immunisation registers can also assist with the timely reporting of vaccine coverage, assessment of vaccine supply, identifying populations with low coverage, monitoring immunisation programmes designed to achieve specific target immunisation rates [5], as well as generating reminders to patients and recalls for immunisation visits. As a result, immunisation registers are considered to be one of the most effective strategies for improving coverage irrespective of provider [6]. Immunisation registers can also provide basic data to conduct vaccine effectiveness studies [7-9] as well as contribute to monitoring existing and new immunisation programmes. A number of countries have been successful in building and utilizing national population-based immunisation registries [4]. The Australian Childhood Immunization Register (ACIR) was the first complete national immunisation register and has been operational since 1996 [10].

The usefulness and power of a population-based immunisation register depend on the quality and quantity of the information it contains [8,9]. Keeping the records up-to-date and ensuring comprehensive use by all providers is important to warrant accurate projections for immunisation eligibility, vaccine supply and assessment of uptake. In some settings such as in Australia, monetary incentives have been supplied to providers for entering their patient immunisation data and for using immunisation registers to monitor their patient immunisation history and background [11].

In 1999, NACI recognised the importance of reliable, accessible, and standardised electronic immunisation records by passing a resolution recommending that a network of immunisation registers be established across Canada. A network of immunisation registers from the jurisdictions was proposed instead of a national immunisation register due to the fact that immunisation programme delivery is a provincial/territorial mandate in Canada. The goal of this resolution was to facilitate the maintenance of accurate immunisation records and the improvement of the management of vaccine supply.

The Canadian Immunization Registry Network (CIRN) was established to coordinate the development of standards and facilitate the sharing of knowledge and experience to develop a national network of immunisation registers [12]. CIRN is a Canadian immunisation committee working group made up of immunisation programme experts from all 13 Canadian provinces and territories involved in the development of immunisation registers as well as monitoring vaccine uptake in their respective jurisdictions. While CIRN members

from the provinces and territories volunteer their time to the working group, the secretariat for CIRN is currently housed in the Centre for Immunization and Respiratory Infectious Diseases at the Public Health Agency of Canada (PHAC) where employees provide support to the working group. In addition, the working group has two co-chairs; a provincial/territorial co-chair and a federal co-chair. The mandate of CIRN is to guide the provinces and territories in the development of a national network of compatible immunisation registries. CIRN works with Canadian provinces and territories to develop and agree upon national standards for immunisation registers as well as immunisation coverage assessment and provides input and expertise in the development of the national immunisation coverage surveys.

Immunisation registers in Canada

The 2003 National Immunization Strategy (NIS) identified the importance of coordinating common approaches to immunisation registers. One of the five key components of the NIS was to 'improve national surveillance and the transfer of (and access to) individual immunisation records, by establishing and maintaining a comprehensive, compatible national immunization registry network' [13]. Also in 2003, during the follow-up to the Severe Acute Respiratory Syndrome (SARS) outbreak in Canada, the 'Naylor Report' recommended CAD 100 million (approximately EUR 77 million) 'in incremental federal funding on new vaccines as well as improving the information systems to ensure that Canada meets an articulated health goal (and international norms) as regards vaccination coverage' [14].

In March 2004, responding to the lessons learned from the SARS outbreak, the federal government tasked Infoway with the development, in partnership with the Canadian provinces and territories, of a country-wide public health surveillance system. Infoway is a not-for-profit organisation created and funded by the federal government to accelerate the use of electronic health records (EHRs) in Canada through collaboration with the Canadian provinces and territories, health-care providers and technology solution providers [15]. While CIRN and Infoway are two separate entities, the two groups are currently collaborating by the participation of some CIRN members in Infoway's Standards Collaborative Working Group [16] in developing agreed-upon standards to be used in EHRs. The public health surveillance system developed through the partnership with Infoway was eventually called Panorama. Initially, a CAD 100 million (approximately EUR 77 million) fund was provided to support application software development. This funding initiative required the Canadian provinces and territories to provide the resources for training, equipment and implementation of the surveillance system. In 2008, an additional allotment of CAD 100 million was provided to advance the development and the implementation of Panorama [17]. Initially, Panorama had seven modules which were to be developed using existing commercially-available software

applications, and which could be modified to respond to specific provincial and territorial needs. Two of the modules, the immunisation management and inventory management modules, were envisioned to provide the basis for a national network of immunisation registers. These modules were to be developed to include nationally agreed-upon functional and data standards. Moreover, the modules were to eventually provide each jurisdiction access to a standardised electronic immunisation register and an inventory management system to better manage immunisation events and vaccine supply, and assess immunisation coverage in their jurisdictions, as well as report standardised vaccine uptake data nationally. Panorama allows healthcare workers to view the immunisation history for individuals and particular groups in the population. In addition, lists of clients who are eligible and overdue for immunisation can be displayed by antigen, demographic or particular risk factors.

While the original scope of Panorama was to include, among other things, a Pan-Canadian approach to immunisation registers, some individual provinces and territories have developed and are currently using other immunisation register systems. These systems vary between jurisdictions in their availability to immunisation providers as well as to the extent of the data which they capture. Variability also exists between jurisdictions in validation procedures for immunisation register data as well as for the specific information contained in the register. For example, the currently available registers differ between jurisdictions in terms of the age groups for which information is captured. While data linkage between immunisation registers and clinical outcome databases is highly desirable, the capacity to link immunisation status to clinical outcome remains an issue in some contexts.

Role of the federal government in immunisation registers

Although Canadian provinces and territories are responsible for immunisation programme delivery and for implementing immunisation registers within their jurisdiction, the federal government is considered to provide leadership to the development of a national network of immunisation registers across Canada. Through NIS and CIRN, the federal government has provided leadership and coordination by supporting the development of national data and functional standards to guide immunisation register development and technologies such as the automated identification of vaccines. Automated identification of vaccines, or the use of scanners and barcodes on vaccine products, enhances considerably the quality and accuracy of the data captured in electronic registers by reducing the amount of time required by immunisation providers to create and maintain immunisation records and also reduces the possibility of errors related to data entry. The federal government has also contributed funds for the development of Panorama.

Vaccine coverage assessment in Canada

As is the case for other countries, Canada reports national vaccine coverage information to the World Health Organization. However, in order to compensate for the lack of a national network of immunisation registers to facilitate the accurate assessment of vaccine uptake, the PHAC currently uses telephone surveys to assess immunisation coverage in the Canadian population. The Childhood and Adult National Immunization Coverage Surveys are conducted approximately every two years to assess routine childhood immunisations and adult selected vaccines [18,19]. Cross-sectional vaccine coverage data are obtained for a selected set of age milestones for children and target groups for adults. Results from these surveys are used to monitor progress towards national targets, to report immunisation coverage estimates to international organisations, to improve planning for pandemic influenza, and to develop appropriately-targeted public education strategies.

These surveys are conducted using random-digit dialling or pre-existing sampling frames to contact households where eligible respondents might reside. Among the drawbacks associated with this current methodology are the facts that it is expensive and results in small sample sizes which do not permit for provincial and territorial vaccine coverage estimates, or the identification of under-served or under-immunised populations. The sample size selected for the national immunisation coverage surveys allows for immunisation coverage estimates with a 5% margin of error for each group. The use of surveys also precludes performing most studies related to immunisation programme effectiveness or evaluation. Finally, the use of telephone surveys introduces a responder bias as it is also becoming increasingly difficult to recruit representative samples, due partly to the increase in the use of cell phones, and in the number of cell-phone-only households and changing lifestyles.

While national immunisation coverage estimates are obtained through surveys, provinces and territories use different methods to assess immunisation coverage within their jurisdiction depending on the availability of registers and other methods of collecting coverage data. To facilitate the collection of vaccine coverage data from the provinces and territories, PHAC and CIRN have developed national immunisation coverage reporting standards [20]. However, while these standards provide guidance to jurisdictions in reporting vaccine coverage, the standards have yet to be adopted. This is due to the fact that PHAC does not have the mandate to collect surveillance data from the jurisdictions. Thus, the adoption of a standardised methodology to estimate coverage remains problematic. Therefore, the PHAC will continue to implement national immunisation coverage surveys to estimate vaccine uptake nationally until a national network of immunisation registers is fully functional in all jurisdictions across Canada.

Challenges to the implementation of immunisation registers across Canada

Despite overwhelming demand and clear support for a national network of immunisation registers [21,22], and approximately a decade after the NACI recommendation, only six of the 13 provinces and territories have developed centralised electronic immunisation registers that conform to national functional and data standards. Although Panorama was initially scheduled to roll out to the provinces and territories in 2009, it is substantially behind schedule and now will provide only a partial solution towards a national network of immunisation registers as some jurisdictions consider using other systems. While progress has been made, Panorama continues to face serious challenges due to cuts in scope and escalating costs leading to important delays. As a result, several provinces and territories have decided to opt out of using Panorama. The cuts in scope mean that several important agreed-upon national functional standards will not be included in Panorama. These include, but are not limited to, interoperability, or the ability to electronically share immunisation records between jurisdictions, and inclusion of automated identification technology.

Public versus non-public immunisation providers

In Canada, vaccines can be administered by immunisation providers that operate either in the public or in the non-public setting, depending on the jurisdiction where some provinces/territories deliver vaccines either through public health clinics or private physician's offices or a combination of both. The majority of immunisation registers in Canada currently capture information obtained only from public immunisation providers. These differences in immunisation delivery methods create considerable data completion issues in the larger Canadian provinces such as Ontario, Quebec, and British Columbia where physicians in private clinics administer most of the immunisations given in these jurisdictions.

Acceptance of registers and 'knowledge, attitudes and beliefs' information

The development, implementation and use of immunisation registers are well accepted amongst stakeholders and healthcare providers in Canada. However, beyond the development and implementation challenges previously discussed, and given the provincial and territorial mandate for immunisation programmes and delivery, data sharing agreements need to be developed and in place for jurisdictional level data to be shared with the federal government and included as part of national immunisation coverage estimates. Moreover, each province and territory needs to assess and deal with potential issues related to requirements regarding privacy for the use of such data before the implementation of an immunisation register or a public health surveillance system within a jurisdiction. While the use of immunisation registers to obtain coverage information represents an important tool to assess

immunisation programmes, information on knowledge, attitudes, and behaviours/beliefs related to immunisation in the general population will need to be collected separately from coverage data obtained from immunisation registers thus making it impossible to assess the relationship between different knowledge, attitudes, behaviours/beliefs and vaccine uptake and to use this information to develop outreach and education programmes.

Vaccine barcoding and automated identification technology

To reduce the errors occurring from clinic staff manually entering vaccine name, lot number and expiry date into inventory and client records, NACI issued a recommendation in 1999 that barcodes be placed on all vaccine products manufactured in Canada to facilitate the automatic entry of scanned vaccine data [23]. A pilot project implemented with front-line immunisers in Alberta and Manitoba showed a 48% to 69% reduction in the time to record data and a 33% reduction in immunisation errors using peel-off, tagged and direct barcodes instead of manual entry [24]. In light of these findings and in support of NACI's recommendations, the Automated Identification of Vaccines Project Advisory Task Group (AIVP ATG) was founded, including representation from the vaccine and clinical software industries, healthcare professional organisations, and standard setting organisations [25].

In 2008, the AIVP ATG developed a five-year strategic plan. One of the first tasks was to perform an independent cost benefit analysis for the adoption and implementation of barcoding of vaccine products in Canada. Six different implementation options - varying in technical detail and the relative costs and benefits anticipated - were selected by the AIVP ATG for consideration. The study concluded that barcodes on vaccine products would be very beneficial and that these benefits would increase over time as technology advanced and new vaccines were introduced [26].

In 2009, AIVP ATG reached a consensus on vaccine barcode standards in Canada, including the placement of a Global Trade Identification Number (GTIN) - a unique product identifier - and lot number on primary packaging, with expiry date as an optional addition [25]. Canadian vaccine manufacturers have committed to adhering to these new standards over the next several years [25], and PHAC has developed the Vaccine Information Database System (VIDS), a web-based repository of information on all vaccines approved in Canada [27]. Vaccine manufacturers provide data (including GTIN, lot number, expiry date) for all of their products to the database (GS1) and transfer the data to PHAC, who is responsible for entering this information as well as lot number and expiry date into VIDS. Thus, when the barcode on a vaccine vial is scanned, the information is downloaded into the electronic immunisation or inventory record, eliminating the need for manual entry or paper-based recording.

Vaccine manufacturers in Canada committed to voluntarily adopt the barcode standards and to include GTIN, lot number and expiry date on vaccine packages. By 2016, all vaccine products in Canada will be required to adhere to the agreed upon standards. Some vaccine labelling lines in Canada and the United States are currently able to print two-dimensional (2D) barcodes, and these vaccine products are shipped all over the world. Products manufactured in Europe will be the last to have the 2D barcodes as manufacturers have not yet agreed to the standards. A 2D barcode (such as the DataMatrix symbology from GS1, a barcode standard setting organisation) consists of printed squares or dots, spiralling outwards from the centre of the symbol. The 2D barcode includes a 14-digit Global Trade Identification Number (GTIN), expiry date and lot number [25]. Including the expiry date in the barcode is an optional labelling requirement, as the expiry date can be determined through lot number. Lot number and expiry date will continue to appear in human readable form on vaccine primary packaging as per Canadian labelling requirements.

The AIVP ATG is working with Canadian provinces and territories to encourage both public and private health-care professionals to include barcoding in their software applications as well as to encourage the purchase of scanners required to read barcodes. With the numerous different applications used in healthcare across the country, support to this community is essential in ensuring that barcodes on vaccine products are used to their fullest potential and that entering barcodes into immunisation registers results in reliable and timely immunisation and inventory records.

To support the use of barcodes in Canada, the AIVP ATG has committed to supporting early adopters of barcode technology, both in private and public health-care settings, at point of vaccine administration as well as at the vaccine inventory level. Previous studies implementing barcode scanning on medications have employed linear barcodes containing a product identifier only [28-30]. However, placing a vaccine's GTIN and variable data (lot number and expiry date) on the limited space of a small vial requires a 2D matrix barcode.

To facilitate future adoption of barcode scanning technology, barcode readability and the incorporation of scanning the primary packaging into vaccination clinic workflow need to be examined. As the adoption of a new system can encounter user resistance, especially if it is unable to integrate into user workflow [31-32], it is important to understand how potential users perceive barcode scanning of vaccines and to identify aspects of the process requiring modification before its implementation in vaccination settings.

PHAC, in partnership with the PHAC/CIHR Influenza Research Network (PCRIN) and the Ontario Niagara Region, studied the integration of automated identification of vaccine products into inventory recording

during seasonal influenza vaccination campaigns across Canada. Results demonstrated the readability of barcodes and positive user perceptions of this technology. While barcoding scanning was perceived to be beneficial in reducing errors, individual vial scanning for high volume clinics was found to be time consuming and may hinder adoption of this technology in these clinical settings [33]. These results highlight the importance of reviewing workflow processes and encouraging efficient practices specific to vaccination settings. It is possible that the benefits of barcode scanning may be more apparent in settings where multiple vaccines and lot numbers are used [33].

Two early adoption studies are currently in the planning stages and will examine the use of barcode technology in a public or private health care setting where multiple vaccines are administered. A second study (in progress) examines the benefits of barcode technology in inventory management at the provincial depot level. Results from these studies are expected to be available and published in 2012.

Conclusion

Progress has been made in the last decade to develop a national network of immunisation registers. The federal government has contributed considerably through funds and leadership to this initiative. However, considerable challenges remain to the development and adoption of immunisation registers in all provinces and territories and even with the adoption of Panorama as a public health surveillance system or other immunisation registers, the vision of a national network of immunisation registers will not be realised unless innovative cost-efficient solutions are developed and the issue of interoperability between jurisdictions is resolved. Nevertheless, while several challenges need to be overcome for a fully operational network of immunisation registers to be available, several areas related to immunisation registers have made substantial progress. These include the development of standards and the automated identification of vaccine products through the barcoding of vaccines. While there have been challenges in the development of immunisation registers in Canada, other countries and regions with different immunisation surveillance systems in place such as in Europe have dealt with similar issues related to the need for homogeneous systems to provide comparable immunisation-related data across a region [34]. Nevertheless, other federated countries such as Australia have been successful in setting up a national immunisation register and benefit from an operational national immunisation register to provide immunisation coverage data and vaccine safety data [35,36]. Finally, the upcoming years will most likely see greater developments in the availability of immunisation registers and in the accessibility of the relevant public health data.

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Estimating vaccination coverage in the absence of immunisation registers – the German experience

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Immunisation registers are regarded as an appropriate solution to measure vaccination coverage on a population level. In Germany, a decentralised healthcare system and data protection regulations constrain such an approach. Moreover, shared responsibilities in the process of immunisation and multiple providers form the framework for public health interventions on vaccination issues. On the national level, those interventions consist mainly of conceptualising immunisation strategies, establishing vaccination programmes, and issuing recommendations. This paper provides an overview on sources and methods for collecting appropriate coverage data at national level and their public health relevance in Germany. Methods of data collection and available information on immunisations are described for three approaches: school entrance health examination, population surveys and insurance refund claim data. School entrance health examinations allow regional comparisons and estimation of trends for a specific cohort of children and for all recommended childhood vaccinations. Surveys deliver population based data on completeness and timeliness of selected vaccinations in populations defined by age or socio-demographic parameters and on knowledge and attitudes towards vaccination. Insurance refund claim data inform continuously on immunisation status (e.g. of children aged two years) or on vaccination incidence promptly after new or modified recommendations. In a complex healthcare system, the German National Public Health Institute (Robert Koch Institute, RKI) successfully compiles coverage data from different sources, which complement and validate one another. With the German approach of combining different data sources in the absence of immunisation registers, it is possible to gain solid and reliable data on the acceptance of vaccination programmes and target groups for immunisation. This approach might be of value for other countries with decentralised healthcare systems.

Introduction

Germany has a population of 82 million people living in 16 federal states. Health legislation with regard to communicable diseases is national and recommendations on vaccination are released annually by the German Standing Committee on Vaccination (STIKO) [1,2]. STIKO recommendations are not legally binding but are usually closely complied with or complemented by the official recommendations of the federal states. The official recommendation is necessary for receiving compensation in case of adverse events following immunisation. STIKO recommendations are the basis for the decision by the Joint Federal Committee (self-governing body of physicians and health insurance funds), whether the costs of vaccinations are covered by the statutory health insurances. In Germany, health insurance is obligatory. The majority (85%) of people living in Germany are members of a variety of statutory health insurances, all of which provide a basic healthcare plan by statute and are funded by fixed fees paid by the members and their employers. The remaining 15% are mainly insured with private health insurance companies.

STIKO recommendations do not include specific vaccines but antigens and refer to specific target groups (defined by age, risk etc.). Beyond recommendations, all licensed vaccines can be administered, but have to be paid by the patients at their own expense.

Vaccination is voluntary in Germany. People are not only free to decide whether or not they get vaccinated but also which physician they want to consult.

Private physicians administer about 90% of all vaccinations and may choose from all available vaccines that are licensed. The remaining 10% are given in public health clinics, schools, or day care centres through special programmes of the federal states or by occupational health physicians [3]. Every vaccination has to be documented in the vaccination card of the vaccinee. Documentation includes antigen, brand name, batch number, and application date. The administering

physician enters the same information into his patient file. Vaccination cards and files are not centrally registered.

The decentralised healthcare system together with data protection regulations which emphasise everyone's right to a self-determined use of personal data [4], are strong constraints for national registers. In only one German federal state, all vaccinations of children up to the age of seven are to be reported to the local public health services by law. However, informed consent of the parents is required prior to reporting and regulations concerning how these data should be registered and processed are lacking [5].

As vaccinations affect health at individual and population level, the assessment and evaluation of trends and of regional and demographic differences in vaccination coverage are major public health tasks. At the level of the federal states, the commitment to these tasks and their prioritisation vary and range from state campaigns and intensive monitoring of immunisation to leaving all action to the capacities and responsibility of the local health offices.

At national level, the development of immunisation strategies, the establishment of vaccination programmes, and the evaluation of recommendations are the main tasks requiring reliable and representative data on vaccination coverage. The Robert Koch Institute (RKI) as the German National Public Health Institute in the portfolio of the German Ministry of Health is responsible for collection and analysis of these data. This paper provides an overview on sources and methods used by the RKI for collecting appropriate coverage data at national level in the context of the German healthcare system and with regard to their public health relevance.

Methods

The RKI uses primary and secondary data to monitor the uptake of vaccines and to evaluate vaccination programmes. While primary data refer directly to the immunisation status as measured in, documented for or remembered by the respective individual, secondary data are obtained from sources with an original purpose different from assessing immunisation status or coverage. Primary data on vaccination coverage are gathered by the assessment of vaccination cards of children prior to school entry or by population surveys [6]. Secondary sources of information on vaccinations are data originating from physicians' refund claims from health insurances [6].

School entrance health examination

The Communicable diseases Law Reform Act (Infektionsschutzgesetz, IfSG) [7] requires to collect the vaccination status at school entry and to send aggregated coverage data to the RKI. Health examinations are carried out as a precondition for school entrance and concern children whose age varies from four to six

years, depending on the federal state. The school entry cohort includes children, who should have completed their primary vaccination courses. Part of the examination is to check the completeness of recommended childhood vaccinations as documented in the vaccination card and give individual catch-up reminders where necessary. The school entrance health examinations (SEE) are carried out locally, vaccination data are aggregated at county level and sent to the federal state. Data are then transferred to the RKI once a year and include the number of investigated children, the number of children presenting the vaccination cards and the number of fully and of partly vaccinated children by defined antigens per federal state. Vaccination coverage of the respective school entry cohort is calculated based on children presenting their vaccination cards and the results, stratified by federal states, are published by the RKI in the Epidemiological Bulletin annually [8].

Population surveys

The RKI regularly conducts health examination surveys and health interview surveys, which are described in more detail below. These surveys both include cross-sectional and longitudinal components in subsequent follow-ups, and are periodically carried out. The study population is geographically and socio-economically representative for the German population [9]. According to pre-defined sampling procedures, people are invited either to present to dedicated study units (for health examination and face-to-face interview) or to be interviewed by phone only (interview survey). Both forms – health examination including health interview as well as health interview only – are alternately conducted.

Vaccination status is included into these surveys as one of multiple core indicators of the population's health status. It is assessed for selected antigens on the basis of either vaccination cards or reports by the subjects themselves. In the health examination surveys, data is complemented by serological testing for specific antibody.

The health examination and interview surveys for children and adolescents are conducted separately from that for adults. The nationwide representative 'German Health Interview and Examination Survey for Children and Adolescents' (KiGGS) was carried out between May 2003 and May 2006. KiGGS was based on a sample of 17,641 children and adolescents aged 0–17 years with main residence in Germany. The 'German Health Interview and Examination Survey for Adults' (DEGS) is the respective representative survey for adults conducted by the RKI, succeeding previous adult surveys, the last of which was in the late 1990s. The DEGS was carried out from November 2008 until November 2011 in a total of 180 cities and municipalities all over Germany and included 7,988 adults aged 18–79 years. Like in KiGGS, in DEGS vaccination cards and serological tests are used to assess the immune status.

The examination survey is periodically accompanied by the 'German Health Update' (GEDA) by waves of telephone surveys which started in July 2008 and involved already 25,000 and 23,000 people aged 18 years and over in 2008–09 and in 2009–10, respectively. Questions on vaccination status for influenza, tetanus and pertussis were included into the interviews [10].

Additional sporadic and smaller surveys for defined research questions are conducted by the RKI to gather information on knowledge, attitude and behaviour towards vaccination in the general population or in defined groups. For example, during the 2009/10 influenza season, uptake of seasonal and influenza A(H1N1) pdm09 vaccines as well as acceptance and progress of the pandemic influenza vaccination campaign was monitored by consecutive representative surveys. The RKI commissioned a professional market research agency to carry out computer assisted telephone interviews (CATI) by experienced interviewers [11].

Insurance refund claim data

Statutory Health Insurance Funds are billed by the Associations of Statutory Health Insurance Physicians (ASHIP) on the basis of quarterly reports on medical services, including vaccinations, delivered by physicians. ASHIPs are regionally organised, mostly one ASHIP per federal state. In 2004, the RKI established an ongoing project together with ASHIPs using their insurance refund claim data for epidemiological assessment of vaccine preventable diseases and vaccination coverage. The methods of the project, including a detailed description of quality assurance have been described elsewhere [12]. Pseudonymised data are quarterly transmitted from the ASHIPs to the RKI and include demographic characteristics of the vaccinees (month and year of birth, sex, county of residence), information on the vaccination (vaccine, date of vaccination), and information on medical contacts (medical specialisation of physician, county of physician's office).

According to the public health question of interest, different applications of these data are possible for monitoring vaccination coverage, i.e. follow-up of birth cohorts and vaccination incidence. Information on distinct individuals can be tracked over time for receiving vaccinations. Thus, birth cohorts can be followed-up and compared by vaccination status at a certain age (i.e. 24 months) and by ASHIP region [13].

Vaccination incidence is defined as the number of vaccinated individuals in relation to the number of insured individuals of the same age and per time. Taking into account that the number of vaccinated persons accumulates over time, the cumulative vaccination incidence by a defined age and year can be calculated.

We used the insurance refund claim data and the methods described to determine varicella vaccine coverage. Varicella vaccination is part of the recommended childhood immunisation schedule since 2004. It was

therefore not included in KiGGS and firstly recorded at SEE in 2008.

Results

In the following sections only selected results of the above described methods are shown as example of their feasibility and practical use.

School entrance health examination

With more than 90% in total, the vast majority of children had vaccination cards available at SEE 2009. While the percentage of children having their vaccination cards has increased over time, the range between the federal states' highest and lowest value has decreased, however the minimum was still below 90% in 2009.

SEE for 2009 showed, that vaccination coverage of children fully immunised against diphtheria, tetanus, polio (>95% each) and *Haemophilus influenzae* type b (Hib, 94%) was high [8]. Figure 1 shows the vaccination coverage for selected antigens. Immunisation gaps existed particularly for hepatitis B (90% coverage) and for the second dose of measles (90%). Moreover, increasing vaccine uptake was visible in recent years, especially for the second dose of vaccines containing measles antigens. Data on varicella vaccination in 2009 were available from 15 federal states and varied between 15% and 71%. For almost all vaccinations, SEE-data analysis also revealed a higher coverage in eastern federal states (Saxony, Brandenburg, Saxony-Anhalt, Thuringia, Mecklenburg-West Pomerania, n=5) than in western federal states (North Rhine-Westphalia, Bavaria, Baden-Württemberg, Hesse, Lower Saxony, Rhineland-Palatinate, Berlin, Hamburg, Schleswig-Holstein, Saarland, Bremen, n=11).

Population surveys

According to KiGGS, the average prevalence of completed immunisation series for tetanus, diphtheria and polio as well as the coverage for the first dose of measles vaccination was above 90% in children aged 2–17 years. Primary courses were often not completed at the recommended age of two years. Vaccination coverage for pertussis, Hib and hepatitis B was higher in younger children than in adolescents [14]. Multivariate analyses revealed predictors for not being vaccinated or for negative serology i.e. regarding measles, such as born abroad and critical attitudes of parents towards vaccination [14,15]. Children not presenting the vaccination cards were more likely to be seronegative.

First results of GEDA revealed immunisation gaps for tetanus of more than 25% in the adult population [16].

About 1,000 randomly selected German speaking persons aged 14 years or older, living in private households, were included in each of the consecutive bi-weekly telephone surveys on the influenza A(H1N1) pdm09 vaccine, during the influenza season 2009/10, so that by week 53 in 2009, a total of 4,003 people had

been interviewed. Vaccination coverage was shown to be low reaching only 8% at the end of December 2009 (Figure 2) [11].

Insurance refund claim data

For one dose of varicella vaccine, coverage at two years of age was 34% for birth cohort 2004 and differed regionally between 13 examined ASHIPS [13]. Children of birth cohort 2005 were the first to be vaccinated with two doses of a combined vaccine against measles, mumps, rubella and varicella (MMRV) at two years of age. The varicella coverage for birth cohort 2005 was 51%, including 5% of children who received two doses of MMRV. For birth cohort 2007, preliminary analysis of data from six ASHIPS showed a further increase of coverage with one dose of varicella vaccine at two years of age to >80% (unpublished data).

Annual vaccination incidence for one dose of varicella vaccine was highest in one year old children and increased here from 4% in 2004 to 50% in 2006 (Figure 3). Cumulative vaccination incidence for the age group comprising four to six year-olds increased from 1% to 47% between 2004 and 2009.

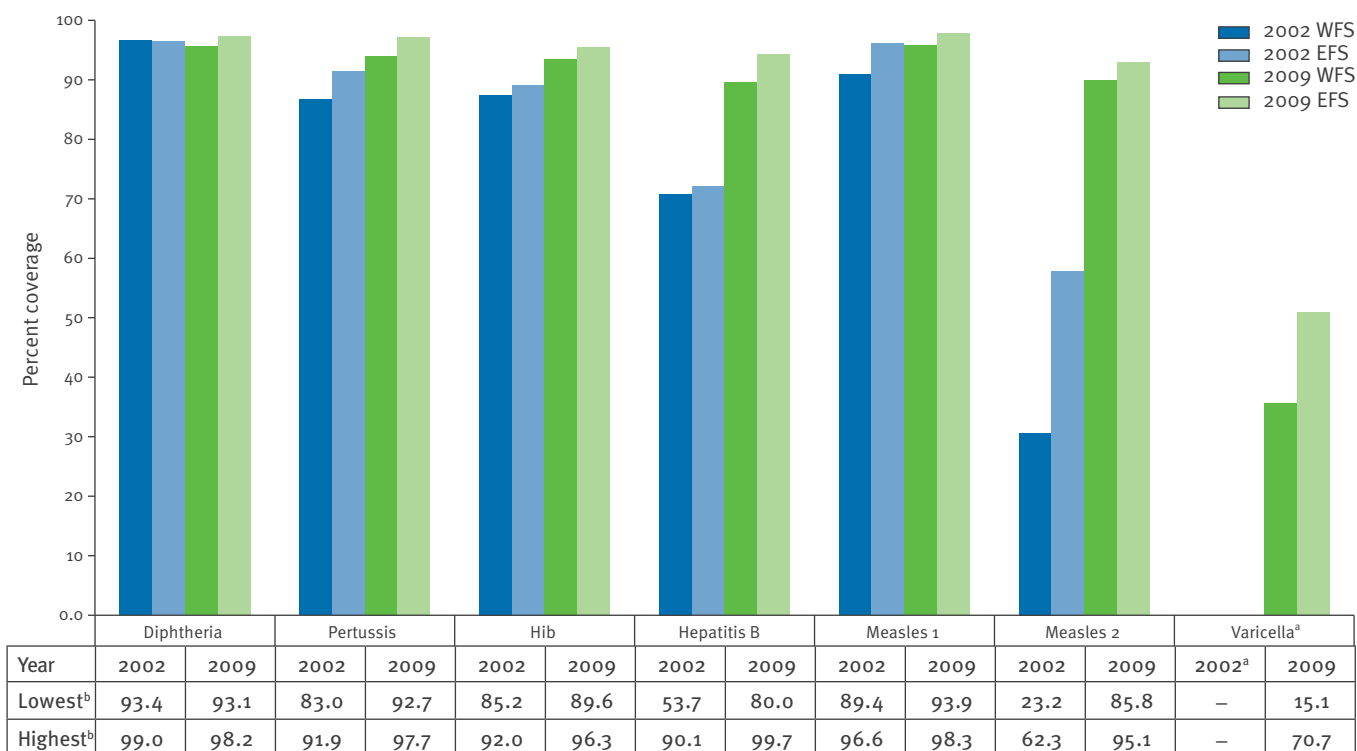
Discussion

For the estimation of vaccination coverage at national level vaccination data as retrieved at SEE are the only routine data required by law (IfSG) in Germany [7]. Based on SEE coverage across regions can be compared and trends for complete cohorts can be assessed by all recommended childhood vaccinations. Thus, representativeness, completeness and validity are high. However, shortcomings of this approach are that timeliness of vaccination cannot be assessed at national level and that vaccinations which are newly introduced into the childhood immunisation schedule are eligible for assessment at school entry only several years thereafter. For example, since its recommendation in 2004, varicella vaccination coverage was still not available from all federal states for the school-entry cohort 2009 for publication in 2011.

Data from SEE cover only a limited children's age group and vaccination status at other ages is not routinely collected in all federal states. Thus, they do not provide data for high interest target groups such as children at two years of age and adults for longitudinal analysis at national level.

FIGURE 1

Vaccination coverage by selected vaccinations, at school entry, in western (n=11) and eastern (n=5) federal states, Germany, 2002 and 2009



Hib: *Haemophilus influenzae* type b; WFS: western federal states; EFS: eastern federal states.

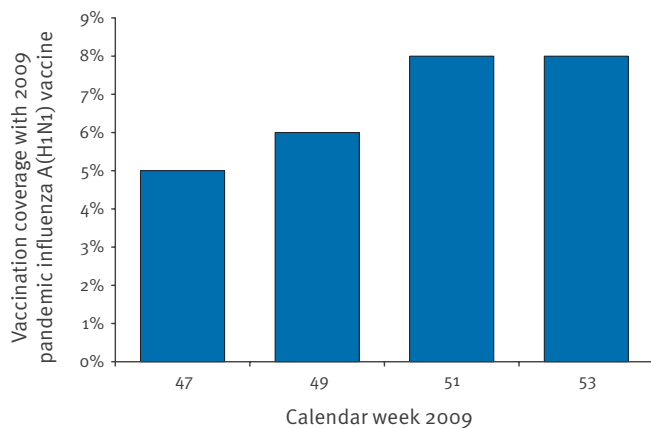
Vaccination coverage is given by vaccinated children per children presenting vaccination cards at school entry.

^a Varicella vaccination was not yet recommended in 2002. In 2009, data on varicella vaccination were available from 15 federal states.

^b Lowest and highest federal state vaccination coverage values [8].

FIGURE 2

Real-time monitoring of coverage with monovalent influenza A(H1N1)pdm09 vaccine by countrywide telephone interviews of individuals aged 14 years or older, Germany, 16 November–29 December 2009 (n=4,003)



The calculated coverage from SEE based on children presenting their vaccination cards is probably overestimated. Children not presenting the cards were less likely to have been vaccinated in an outbreak investigation [17] and had a higher prevalence of seronegativity in KiGGS [18] as compared to children with vaccination cards.

Coverage as assessed by KiGGS was comparable to that of data from SEE in the same age groups, thus the respective results are validating each other. The huge benefits of examination surveys such as DEGS or KiGGS are their socio-demographic representativeness. This allows population based information on completeness and timeliness of vaccination in different groups defined by age and social status. By comparing documented vaccinations with serological results and socio-demographic parameters, risks for not being vaccinated can be predicted and essential information for composing prevention strategies is gained.

However, regular examination surveys are expensive, laborious, and complex and do not allow to estimate for recently recommended vaccinations. These shortcomings are partly overcome by telephone interview surveys. They are fast and flexible methods for collecting data and enable decision makers, for instance, to respond quickly to inadequate immunisation rates. In addition, information on perceptions on vaccination issues can easily be gained. The balance between practicability and representativeness according to the aim of the survey may lead to limitations. A general shortcoming of interviewing people for their vaccination status might be the reliability of information as compared to the documented vaccinations in official documents [19].

Insurance refund claim data may compensate the limitations of data from SEE. Moreover, if continuously collected, they can fill the gaps remaining between discrete population surveys.

ASHIP data were the only available population based source for calculating vaccination coverage by age group and region shortly after introduction of varicella vaccines into the childhood immunisation programme in July 2004. Besides a growing acceptance of the recommendation and increasing coverage particularly in the recommended age group, the data showed that a considerable amount of vaccinations were given later than recommended and that the availability of vaccines as well as the reimbursement influenced the vaccine uptake [13]. In 2009, cumulative varicella vaccination incidence for children aged 4–6 years was in the same range as coverage calculated by SEE. Moreover, based on ASHIP data the vaccination coverage for children at two years of age will be routinely assessed and indicate whether the primary courses of immunisation are completed as recommended.

ASHIP data have been available since 2004, but vaccinations were also administered before that time, so only incident vaccinations per year since the time data collection started can be analysed. This leads to an underestimation of the true coverage, particularly in older age groups. Vaccination coverage, however, can be estimated for birth cohorts since ASHIP data collection. These data are particularly useful to monitor uptake of vaccines which are newly introduced or recommended for other age groups than before.

ASHIP data may be of limited representativeness for the total population as they are only related to statutory health insured persons, while vaccination coverage of privately health insured persons may differ. Availability, validity and reliability of coverage estimates based on data sources with an original purpose different from assessing vaccination status or coverage are highly dependent on a stable database and data structure.

ASHIP data so far have been primarily used to answer specific questions that could not be answered by other data sources. Currently, these data are being established as the official vaccination coverage of children aged 24 months in Germany. In addition, a comparison between data sources is being done to validate results whenever possible.

In summary, the described methods are of different public health relevance. Data from SEE allow to continuously analyse trends and regional differences in vaccination coverage related to childhood immunisation. With population surveys, target groups of immunisation can be defined by age or socio-demographic characteristics, and insight on the acceptance of specific vaccines can be gained. In addition, vaccination programmes and campaigns can be assessed and

attitudes and behaviour towards vaccination examined. ASHIP data give rapid information on the compliance with vaccination schedules but also about the general acceptance of immunisation programmes, in terms of vaccination coverage by region and age, and thus are helpful for identifying target age groups for (supplementary) immunisation.

The exploitation of further primary and secondary data sources for retrieving information on vaccination coverage has been tested by the RKI with limited public health relevance.

Immunising physicians were asked for the number of administered first and second doses of varicella and measles vaccines per month in a network of private doctors (sentinel). As the sentinel is not population based, coverage could not be calculated but trends in vaccine uptake were detected and related to different physician groups, regions and availability of vaccines [20]. As the documentation workload is high, attempts are ongoing to retrieve data automatically from the software systems used by physicians, but limiting factors are the variety of those systems together with data protection.

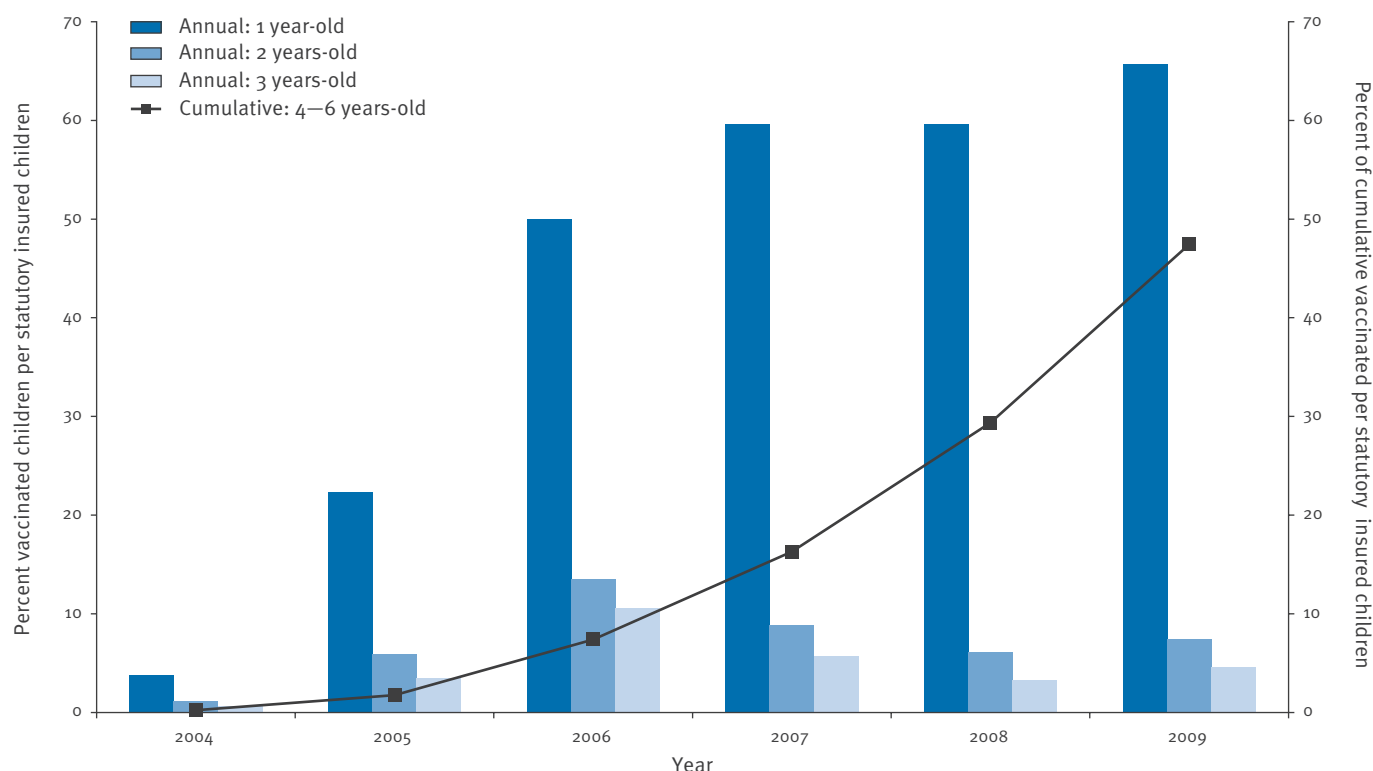
Commercial data on sale or prescription figures deliver trends in number of sold or prescribed vaccine doses over time by brand name, region and physician's speciality. Trend comparisons by region and by physicians' speciality are possible. Moreover, with different vaccines available, insight is gained on preferred vaccine brands. These data show trends in vaccine uptake in total but not the coverage, as the number of immunised persons remains unknown. The completeness of individual vaccination series cannot be assessed, particularly if multiple doses are needed.

In conclusion, complex health systems require complex approaches to gain data on vaccination coverage or on other vaccination issues.

In the absence of immunisation registers several primary and secondary data sources have been explored by the RKI for assessing nationwide vaccination status and coverage. Different approaches for the utilisation of the various sources, either routinely or on specific demand, have been successfully implemented. Each of them has its strengths and limitations and they complement one another, thus validating the information retrieved from different sources.

FIGURE 3

One-dose varicella vaccination, annual rates for children aged one, two and three years, and cumulative rates for children aged from four to six years, Germany, 2004–2009



The proportion statutory insured children who are vaccinated is according to data from nine of 17 Associations of Statutory Health Insurance Physicians (ASHIP).

The German experience with collecting vaccination coverage data at national level in a decentralised healthcare system, dominated by the private sector and in the absence of immunisation registers, might be of value for other countries with federal or otherwise decentralised healthcare systems.

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Immunisation registers in Italy: a patchwork of computerisation

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In Italy, the 21 regional health authorities are in charge of organising and implementing their own vaccination strategy, based on the national vaccine plan. Immunisation coverage varies greatly among the regions for certain vaccines. Efforts to increase childhood immunisation coverage have included initiatives to develop and implement computerised immunisation registers in as many regions as possible. We undertook a cross-sectional online survey in July 2011 to provide an updated picture of the use, heterogeneity and main functions of different computerised immunisation registers used in the Italian regions and to understand the flow of information from local health units to the regional authorities and to the Ministry of Health. Comparing current data with those obtained in 2007, a substantial improvement is evident. A total of 15 regions are fully computerised (previously nine), with 83% of local health units equipped with a computerised register (previously 70%). Eight of the 15 fully computerised regions use the same software, simplifying data sharing. Only four regions are able to obtain data in real time from local health units. Despite the progress made, the capacity to monitor vaccination coverage and to exchange data appears still limited.

Introduction

Childhood vaccination services in Italy are usually provided by vaccination centres in local health units (LHUs). To date, there are 157 LHUs in the 21 Italian regions. Since the decentralisation of the Italian national health system in 2001 [1], regional health authorities were charged with organising, coordinating and implementing their vaccination strategy, based on the national vaccine plan [2]. The plan was prepared by the Ministry of Health in collaboration with the National Institute of Health (Istituto Superiore di Sanità, ISS), scientific societies, experts and regional health authorities. In March 2012, a new national vaccine plan for 2012 to 2015 was released [3].

Currently, all the LHUs in Italy estimate vaccine coverage using the administrative method – with the number of vaccinated people as numerator and the local population, obtained from the administrative database or from the health system database, as denominator. The Ministry of Health collects annual data from all the regions on immunisation coverage and on the number of doses administered for most vaccines. The data are collected on paper and the form used is currently under revision to include all the vaccines recommended in the national vaccination schedule.

Even though immunisation coverage in Italy for vaccinations included in the 2005–2007 national vaccination plan is higher than 90%, there are still concerns about the coverage at subnational level (e.g. coverage at age 24 months for diphtheria-tetanus-acellular pertussis-inactivated polio vaccine at the national level is 96%, whereas it ranges from 88% to 98% among the regions). Pockets of lower vaccination coverage still exist in certain geographical areas and among hard-to-reach population groups, as highlighted by the current resurgence of measles in the country [4]. Furthermore, conjugate pneumococcal, meningococcal C and varicella vaccines are offered by some regions to all children and by others only to people in at-risk groups, leading to variations in coverage rates [5]. However, since the new vaccine schedule adopted in the recently approved national vaccination plan includes human papillomavirus, pneumococcal and meningococcal C vaccines for all newborns and postpones the introduction of mass immunisation against varicella to 2015, it is likely that the differences between regional vaccination coverage will decrease.

Childhood vaccines included in the national vaccination plan are bought by the LHUs and are administered free of charge in the vaccination services. The vaccination services' personnel are in charge of keeping individual records of the administered vaccine doses and

enter the data into the computerised register, if there is one.

Efforts to increase childhood immunisation efficiency have included initiatives to develop and implement computerised immunisation registers in as many regions as possible. Such registers allows public health personnel to evaluate whether an individual's immunisation history is complete and up to date. This functionality is used to identify individuals who are in need of further immunisation, to generate recall/reminder notifications for immunisations and to produce immunisation coverage reports, which can be used to evaluate immunisation programmes [6,7]. The register should be a confidential, population-based, computerised database that records all immunisation doses administered by participating providers to persons residing within a given geopolitical area [8]. In addition, such registers can facilitate the monitoring of larger areas and evaluation of the impact of the vaccine strategies and also permit a fast and reliable exchange of data.

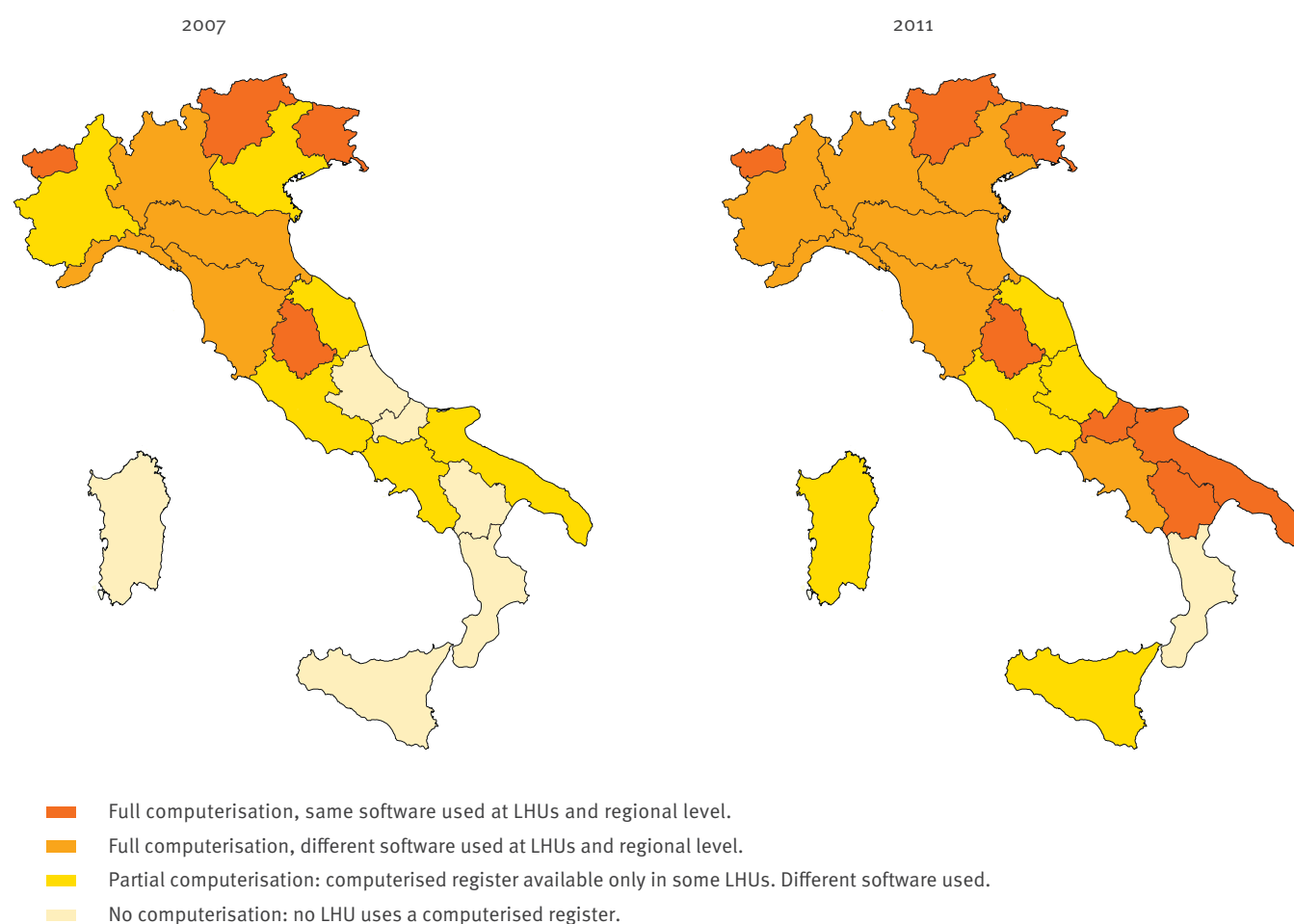
Implementation of a computerised register was first identified as a priority in Italy in 2003, in the first

national plan for the elimination of measles and congenital rubella [9] and use of such registers has been endorsed in subsequent national plans [3,10,11]. Within the framework of a larger project named 'MATTONI', funded by the Italian Ministry of Health [12], an inter-regional working group in 2007 defined a common minimum set of variables to be included in local computerised registers, to enable the development of a national system capable of aggregating data from all the Italian regions. Furthermore, a recommended information flow from local vaccination centres to the national level was described. The metadata identified included information on a single individual that could facilitate local logistic management and also allow vaccination coverage to be more precisely estimated. It also includes information that allows the vaccination register to be linked with other relevant demographic databases.

At the national level, the aim of the MATTONI project is to feed a centralised information system able to support monitoring of vaccine coverage, evaluation of vaccination strategies and assessment of vaccine effectiveness by collecting aggregated data from the LHUs. This would allow areas with pockets of

FIGURE

Existence of computerised immunisation registers in Italy, by region, 2007 and 2011



LHU: local health unit.

Source of 2007 data: [13].

susceptible individuals to be identified and would create a link between vaccine coverage and incidence data and identify vaccine failures.

A survey conducted in 2007 to assess the existence of computerised immunisation registers in Italy showed that 70% (126/180) of LHUs were using such registers and that only nine of the 21 regions were fully computerised [13]. The present study aims at providing an updated picture of the use, heterogeneity and main functions of different computerised immunisation registers adopted in the regions and to understand the flow of information from the LHUs to the regional health authorities and to the Ministry of Health.

Methods

In July 2011, we undertook a cross-sectional survey on the level of computerisation of immunisation registers in the 21 Italian regional health authorities. All regional coordinators for infectious diseases and vaccinations were contacted and asked to fill in a standardised

online questionnaire. It included 20 questions about the number of computerised LHUs, use of different or the same software in the LHUs that were computerised, the name and basic characteristics of the software used. In order to explore the flow of information between LHUs and the regions, we also asked about the method and the frequency of data collection (i.e. shared data, transmission of individual or aggregated data). Availability of vaccine coverage for vaccines not included in the national immunisation plan in 2011 (i.e. pneumococcal, meningococcal, varicella and rotavirus vaccines) and for high-risk children was also requested. The questionnaire also asked whether regions with no computerisation or those using more than one such register were planning any changes in the coming years.

Regional coordinators who reported having a single computerised regional register were asked by email or telephone about the characteristics of the software used in the register, confidentiality issues,

TABLE 1

Computerisation of immunisation registers in Italy and data management at regional level, 2011

Degree of computerisation	Number of regions	Proportion of LHUs using computerised register	Proportion of regions that automatically calculate immunisation coverage	Frequency of submission from computerised LHUs to regional health authorities	Regions that have access to computerised individual data
Full (same software) Same software used at LHUs and at regional level	8	21/21	5/8	Real time (n=3)	Direct access to LHU individual data in real time (n=3)
				Quarterly (n=1)	Access after periodic individual-data transmission by LHUs (n=1)
				Every six months (n=4)	No access to individual data (n=4)
Full (different software) Different software used at LHUs and at regional level	7	84/84	1/7	Real time (n=1)	Direct access to LHU individual data in real time (n=1)
				Every six months (n=3)	Access after periodic individual-data transmission by LHUs (n=1)
				Yearly (n=3)	No access to individual data (n=5)
Partial Computerised register available only in some LHUs. Different software used	5	25/46	0/5	Quarterly (n=2)	No access to individual data (n=5)
				Every six months (n=1)	
				Yearly (n=2)	
None No LHU uses a computerised register	1	0/6	0/1	—	—

LHU: local health unit.

perspectives for future development and any aspects to be improved.

The information obtained was compared with results from the previous survey conducted in 2007 [13].

Results

Information was collected for all 21 regions, which included a total of 157 LHUs. As shown in the Figure, to date, 15 of the regions and 130 (83%) of LHUs are fully computerised, five regions are partially computerised and one does not use a computerised register (Figure, Table 1).

Among the 15 fully computerised regions, eight use the same software in all LHUs, while the remaining seven use different software (Table 1). In the five regions not fully computerised, the proportion of LHUs that are computerised ranges from 25% to 92% of the LHUs.

LHUs must transmit data to the regional level. Individual data are accessible in only six of the 15 fully computerised regions (Table 1); in the remaining nine, individual data are stored in each LHU and only aggregate data on vaccine coverage are sent to the regional level, as in the regions with partial or no computerisation.

Eight of the 21 regions receive data every six months from the LHUs, four receive data in real time, three receive them quarterly and five yearly (Table 1). The capacity of the different systems to manage vaccination coverage data at regional level is very heterogeneous: of the 15 regions that are fully computerised, only six

are able to calculate vaccine coverage automatically. Of these six, only three can calculate the coverage using individual data available in real time from the LHUs. From the regional level, vaccination coverage data are forwarded to the Ministry of Health once a year.

The main features of the immunisation registers used in the eight fully computerised regions using the same software are presented in Table 2.

The findings of the survey highlight that for paediatric vaccinations not included in the national vaccination plan in 2011, coverage data for children at risk are available at regional level in eight regions for pneumococcal, in seven for meningococcal C, in six for varicella and in three for rotavirus vaccines.

In some of the fully computerised regions, an evolution of the software is already scheduled; in particular, three regions have planned to shift to a web-based system, which is easier and faster than the current computerised register.

All regions not yet fully or not at all computerised are planning to extend the system to the entire region or implement one in the coming years.

Discussion

In Italy, estimation of vaccine coverage and assessment of vaccination status are always based on individual records for each vaccinated child. There is a large variability in the type of registers used (paper or electronic) but basic information, such as date of vaccination, number of dose, brand and vaccine lot, is always collected. The quality of collected data is good and comparable with those provided by a national cluster sampling survey performed every five years to estimate vaccination coverage with an alternative method [14]. There is, however, considerable variability in the methods used to manage the list of children to call for vaccination, the kind of call (i.e. active versus passive) and in the ability to calculate the vaccine coverage. Extensive use of computerised immunisation registers could help to increase vaccination coverage, but because of the decentralisation of the Italian health system, a single national immunisation register seems to be difficult to realise. This situation appears to be common in Europe: a survey conducted by the Vaccine European New Integrated Collaboration Effort (VENICE) network in 2007 found that only four countries in Europe have a national computerised immunisation register [15] and many countries, as in Italy, have regional systems. A new survey conducted by VENICE in 2011 showed that five countries have a national register and six have subnational ones [16].

As Italy has a fragmented health system, it seems reasonable that all the existing computerised immunisation registers in the regions could adopt the common minimum dataset proposed by the MATTONI project [12]. These metadata include demographic information

TABLE 2

Main features of the immunisation registers at local health unit level in the fully computerised regions using the same software, Italy (n=8)

Feature	Number of regions
Capacity to list the persons to be invited for vaccination	8
Calculation of vaccination coverage for risk groups	8
Printing of invitation letters	8
Managing vaccination appointments	7
Collecting information on reason for missed vaccinations	6
Managing vaccine storage	6
Producing a list of vaccination delays	5
Management of the high-risk group target	5

on the individuals, history of all the administered vaccines (who administered them, when, what and where) and information about non-administration of scheduled vaccinations (including the reasons). All this information should allow a better management of the vaccine centre's activities and a faster calculation of vaccine coverage. Furthermore, using the same metadata, individual-based data exchange among LHUs and regional and national authorities should be facilitated.

A great heterogeneity among regions about health matters has emerged in Italy, sometimes with differences even within the same region [17]. An optimal situation is present only in four regions (with a population equal to 18% of the total Italian population), where individual data on vaccination history collected at LHUs is shared in real time with the regional level. However, comparing the findings of our survey with those obtained in 2007, it is evident that there has been some improvement. Currently, of the 15 fully computerised regions, eight use the same software in all their LHUs. These regions are relatively small (all but one have fewer than 1,500,000 inhabitants): it may be that in small regions (with therefore a small number of LHUs), it is easier to reach a consensus on a common tool.

Although the percentage of LHUs with computerised immunisation registers increased from 70% in 2007 to 83% in 2011, there are still important geographical differences and some regions have not yet covered all their territory. Only one region, in the south, does not yet have any of its LHUs equipped with a computerised register. Moreover, there is considerable difficulty in guaranteeing the transmission of individual data from local to regional level, as only six regions have access to individual vaccination histories.

All the regions with a unique immunisation register that covers all their LHUs agreed that the most important advantages of the register are the simplification of the management of the vaccination centres and the timely availability of coverage data. However, the capabilities of the systems adopted can still be improved – such as the management of the appointments, collection of information on the reasons for missed vaccinations, management of vaccine storage, calculation of vaccine coverage for specific target groups or birth cohorts, management of adverse events, recording linkages between the vaccine register and notification database of communicable diseases and transmission of data to the regional level – are all powerful tools of computerised immunisation register but are not present in all the registers in the eight fully computerised regions that have the same software (Table 2).

Increasing the current frequency of annual vaccination coverage assessment seems currently not feasible: data on the vaccination coverage for HPV is collected by the National Institute of Health every six months and it is perceived as an excessive workload in some regions (data not shown). Although there are

difficulties at regional level, there are some improvements that should be introduced at national level: aggregated coverage data for recently introduced vaccines are still not routinely collected and there is still no technical document that describes how to send electronic vaccine coverage data from the regions to the Ministry of Health.

In conclusion, this study shows progress has been made towards a more extensive use of computerised immunisation registers in Italy. The adoption of such registers all over the country should improve the management of the vaccination services and the control, at local level, of vaccine-preventable disease. Notwithstanding, the patchy situation in the Italian LHUs, in terms of systems adopted, even within the same region, does not allow an easy transmission of data from the periphery to the centre. The existence of metadata recommended by the MATTONI project is not enough because many regions still do not have access to the individual records present in the LHUs. Furthermore, the Ministry of Health does not require the aggregated data to be sent electronically.

A reasonable objective for the next three years is to have vaccine coverage data at national level for all vaccinations using exclusively electronic data management and transmission from each level (from LHUs to regional health authorities and from there to the Ministry of Health). This will provide more complete and timely data that can be used for monitoring the national vaccination strategies. A flexible and standardised data format should be decided upon for exchange of data among different systems. Furthermore, the new paper form prepared by the Ministry of Health for the collection of regional data should be substituted by a web-based version, in line with the pilot experience of the European Centre for Disease Prevention and Control (ECDC) in collecting vaccine coverage data from European Union Member States at subnational level. In this pilot experience, data entry or file transmission are accepted [18].

Finally, more effort should be made to calculate vaccine coverage for specific target populations (i.e. risk groups or health professionals), as is done for influenza vaccination in Italy and in many other European countries [19]. The new Italian national vaccination plan – with the specific objective of a countrywide diffusion of computerised immunisation registers and a new vaccination schedule for all the diseases common to all the regions – should accelerate the process of computerisation. This should make it easier to identify and actively call unvaccinated children, thus leading to a better control of vaccine-preventable diseases at local level and a better planning of resources and strategies at regional and national level.

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Use of the vaccination register to evaluate influenza vaccine coverage in seniors in the 2010/11 influenza season, Navarre, Spain

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People aged 65 and older have a high risk of suffering from complications of influenza, therefore it is recommended that they receive annual influenza vaccination. However, vaccination coverage falls far short of the target of 75%. In this study we use the vaccination register to evaluate the coverage of influenza vaccine in non-institutionalised persons aged 65 and over in Navarre, Spain, in the 2010/11 season (104,427 persons). Vaccination coverage was 58.6%, lower than the 62.7% coverage in the 2009/10 season. In the multivariate analysis, lower coverage was associated with being female, age under 80 or over 94 years, immigrant status and hospitalisation in the previous year. In contrast, persons with major chronic conditions, high level of dependence or those with more visits to the general practitioner in the previous year had higher vaccination coverage. Influenza vaccination in the previous season was a strong predictor of vaccination in the current season (odds ratio: 37.0, 95% confidence interval: 35.7–38.4). The vaccination register has been shown to be useful to monitor the coverage of influenza vaccination in seniors and may help guide strategies to improve coverage.

Introduction

Computerised vaccination records have been shown to be useful in reducing the frequency of missed opportunities for immunisation, facilitating reminder notices, preventing over-immunisation, and providing information about immunisation delivery and documentation on a population level [1,2]. Vaccination records can also be useful tools for clinicians and public health officials, for monitoring immunisation coverage and for providing feedback to clinicians, patients and case management workers [3,4].

Seasonal influenza can cause serious complications in the elderly and in subjects with chronic health conditions. Annual vaccination against influenza is the most

effective measure for reducing morbidity and mortality associated with this disease [5-7]. In Spain, the recommendations for preventing seasonal influenza include annual vaccination of all people aged 65 and over, but the coverage reached in this population is far from the 75% target proposed by the World Health Assembly for 2010 [8]. This highlights the importance of monitoring the vaccination coverage and identifying possible ways to improve it.

The present study aims to explore the utility of a population-based vaccination register to quantify seasonal influenza vaccine coverage and to describe its determinants in non-institutionalised subjects aged 65 and older.

Methods

Vaccination register

The Regional Health Service of Navarre, Spain, provides free healthcare to approximately 97% of the population of the region (642,051 inhabitants). All Navarre residents at birth are registered into the healthcare computerised system and people who change their residence to Navarre are registered at the first visit to a healthcare centre. From 2000 to 2004 the computerised medical record was implemented throughout the whole Navarre Health Service, in both hospitals and primary care. A specific section in the computerised medical record is provided to register vaccinations. Whenever health professionals administer a dose of vaccine they must register online the type of vaccine, dose number, brand, batch, date of administration, person who administers it and possible incidents. The type and brand of vaccine are registered using predefined codes to avoid errors and make it easier to consult the information recorded. Software filters are applied to ensure valid data entry. The same registration system is used for all vaccines, both those administered in childhood

or adult vaccination programmes and all other vaccines that are not included in these programmes. The information in this register is available to the physician and is part of each patient's computerised medical record. It provides an alert about the doses required to complete the vaccination schedules and performs the functions of the vaccination record, regardless of whether the patient retains a paper copy.

The information contained in the vaccination register is exported weekly to an individual-level database. In this format, the information from the vaccine register can be linked to other databases (as described below) with complementary data, such as data on demographics or data on incidence of vaccine-preventable diseases. The combined data can be used to monitor the coverage of each vaccine, to plan improvements in coverage, to detect vaccine failures and to evaluate the effectiveness of different vaccines.

Influenza vaccination campaign

In the 2010/11 season, the influenza vaccination campaign in Navarre took place from 11 October to 26 November, following a system similar to that used in previous seasons [9]. The trivalent inactivated vaccine was used, with the composition recommended by the World Health Organization [10]. In Navarre, the vaccine was indicated for all persons aged 60 and over, and for persons with chronic diseases that increase the risk of influenza complications [9]. The vaccines for this programme were purchased centrally by the regional government and were distributed to all primary healthcare centres. Before the vaccination campaign began, an information campaign focusing on the target population was carried out by means of posters in the healthcare centres and notices in the media to let people know the population groups for whom the vaccine was indicated and where they could go to be vaccinated. Physicians and nurses in primary care centres were sent a detailed protocol of the programme with the objectives, dates, indications, logistics, instructions on how to register the doses administered, and phone numbers for further information [9]. Healthcare staff in the healthcare centres took advantage of all contacts with patients to remind them of the benefits of being vaccinated against influenza.

Study population and variables

Using computerised databases of physicians, we selected all non-institutionalised persons aged 65 and older who were covered by the Navarre Health Service at the beginning of the vaccination campaign. According to the national and regional protocols all subjects in this study population had indication for influenza vaccination [9]. From the computerised database of primary healthcare, we obtained the following baseline variables: sex, age, migrant status, district of residence, major chronic conditions, high level of dependence (Barthel's index <40), number of outpatient visits during the previous 12 months and hospitalisation in the previous 12 months. Residence in municipalities

TABLE 1

Characteristics of the population aged 65 and older and respective 2010/11 seasonal influenza vaccine coverage, Navarre, Spain (n=104,427)

Characteristic	Number of people (%)	Number of vaccinated people (%)
Total	104,427 (100)	61,195 (58.6)
Sex		
Male	45,712 (43.8)	27,201 (59.5)
Female	58,715 (56.2)	33,994 (57.9)
Age group, years		
65–69	27,543 (26.4)	12,605 (45.8)
70–74	21,995 (21.1)	12,715 (57.8)
75–79	22,353 (21.4)	14,289 (63.9)
80–84	17,220 (16.5)	14,289 (63.9)
85–89	10,291 (9.9)	6,905 (67.1)
90–94	3,749 (3.6)	2,426 (64.7)
95–99	1,081 (1.0)	601 (55.6)
≥ 100	195 (0.2)	61 (31.3)
Number of major chronic conditions		
0	45,049 (43.1)	22,750 (50.5)
1	33,767 (32.3)	21,204 (62.8)
>1	25,611 (24.5)	17,241 (67.3)
Major chronic conditions		
Liver cirrhosis	2,214 (2.1)	1,320 (59.6)
Diabetes	20,827 (19.9)	13,545 (65.0)
Heart disease	21,333 (20.4)	14,261 (66.8)
Haematological cancer	1,026 (1.0)	629 (61.3)
Non-haematological cancer	16,806 (16.1)	10,539 (62.7)
Immunological disease	838 (0.8)	525 (62.6)
Pulmonary disease	15,038 (14.4)	10,101 (67.2)
Renal diseases	8,590 (8.2)	5,814 (67.7)
Dementia	4,429 (4.2)	2,926 (66.1)
Stroke	6,848 (6.6)	4,516 (65.9)
Rheumatic disease	1,800 (1.7)	1,117 (62.1)
Morbid obesity (BMI ≥40 kg/m ²)	1,962 (1.9)	1,197 (61.0)
Visits as outpatient in the previous year		
0–3	36,670 (35.1)	16,928 (46.2)
4–7	31,403 (30.1)	19,415 (61.8)
>7	36,354 (34.8)	24,852 (68.4)
Seasonal influenza vaccine		
2009/10	64,245 (61.5)	55,700 (86.7)
2008/09	62,385 (59.7)	53,604 (85.9)
2007/08	58,607 (56.1)	50,332 (85.9)
Vaccinated in all three previous seasons	49,247 (47.2)	44,699 (90.8)
Place of residence		
Rural area	50,341 (48.2)	30,010 (59.6)
Urban area	54,086 (51.8)	31,185 (57.7)
Immigrant	1,699 (1.6)	542 (31.9)
High level of dependence	858 (0.8)	621 (72.4)
Hospitalisation in the previous year	12,191 (11.7)	7,772 (63.8)

BMI: Body mass index.

with more than 10,000 inhabitants was considered urban and any other was defined as rural. The major chronic conditions were defined according to the International Classification of Primary Care, version 2 [11], and included: heart disease (K71, K74-77, K81-K84, K99), lung disease (R79, R95, R96, R99), renal disease (U99), cancer (A79, B72-B74, D74-D78, F74, H75, K72, L71, N74, N76, R84, R85, S77, S79, T71, T73, U75-U77, U79, W72-W73, X75-X77, X81, Y77-Y79), diabetes (T89, T90), liver cirrhosis (D97), dementia (P70), stroke (K90, K91), immunodeficiency or transplants (B78, B79, B90, D28, K28, U28), rheumatic disease (L88) and morbid obesity (body mass index of 40 kg/m² or greater).

From the vaccination register we obtained information on influenza vaccination in the 2010/11 season, as well as influenza vaccination in the three previous seasons. Individuals with no information on vaccination status were considered unvaccinated.

The Navarre Ethical Committee for Medical Research approved the study protocol.

Analysis

This study was conducted in Navarre after the 2010/11 influenza vaccination campaign was concluded. The distribution of the baseline covariates in the population

was evaluated. Age was categorised in 5-year groups, and number of outpatient visits in the previous year was categorised in tertiles.

Influenza vaccine coverage in the 2010/11 season was quantified as the percentage of people vaccinated in each population group. This data was compared with coverage in the previous seasons which was calculated the same way as for 2010/11. Possible determinants of influenza vaccine coverage in the 2010/11 season were investigated using univariate and multivariate logistic regression models. The analyses were conducted using SPSS 18.

Results

Characteristics of the population

A total of 104,427 non-institutionalised individuals aged 65 or older were included in the analysis. They represented 94.4% of the population in this age group in the region. The 5.6% remaining were those who were institutionalised or people without coverage by the public healthcare service of Navarre. Some 32,536 (31%) were aged 80 or older, 58,715 (56%) were women, and 59,378 (57%) presented at least one major chronic condition, most frequently, heart disease (21,333, 20%)

TABLE 2

Determinants of 2010/11 seasonal influenza vaccine coverage, Navarre, Spain (n=104,427)

Factor	Crude odds ratios (95% confidence interval)	Adjusted odds ratios (95% confidence interval) ^a	P
Female vs. male	0.94 (0.91–0.96)	0.91 (0.88–0.93)	<0.001
Age group (in years)			
65–69	Reference	Reference	
70–74	1.62 (1.57–1.68)	1.56 (1.50–1.62)	<0.001
75–79	2.10 (2.03–2.18)	1.91 (1.84–1.98)	<0.001
80–84	2.44 (2.35–2.54)	2.18 (2.09–2.27)	<0.001
85–89	2.42 (2.31–2.53)	2.17 (2.07–2.28)	<0.001
90–94	2.17 (2.02–2.33)	2.03 (1.89–2.19)	<0.001
95–99	1.48 (1.31–1.68)	1.50 (1.32–1.70)	<0.001
≥100	0.54 (0.40–0.73)	0.66 (0.48–0.90)	0.008
Major chronic conditions			
None	Reference	Reference	
1	1.65 (1.61–1.70)	1.41 (1.36–1.45)	<0.001
>1	2.02 (1.96–2.09)	1.50 (1.45–1.55)	<0.001
Visits as outpatient in the previous year			
0–3	Reference	Reference	
4–7	1.89 (1.83–1.95)	1.79 (1.74–1.85)	<0.001
>7	2.52 (2.45–2.60)	2.19 (2.12–2.27)	<0.001
Immigrant vs. Spanish citizen	0.33 (0.29–0.36)	0.40 (0.36–0.45)	<0.001
Residence in urban area vs. rural area	0.92 (0.90–0.95)	1.00 (0.98–1.03)	0.836
High level of dependence	1.86 (1.60–2.16)	1.27 (1.09–1.49)	0.003
Hospitalisation in the previous year	1.28 (1.23–1.33)	0.89 (0.85–0.93)	<0.001

^a Logistic regression model including all the variables listed in the table.

or diabetes (20,827, 20%), and 12,191 (12%) had been hospitalised in the previous year (Table 1).

Influenza vaccine coverage in the 2010/11 season

Overall influenza vaccine coverage reached 58.6% of the study population. The coverage was slightly higher in men (59.5%) and differed by age group, with the highest vaccine coverage observed for the 85 to 89 year age group (67.1%) and the lowest for subjects older than 99 years (31.3%) or aged 65 to 69 years (45.8%).

Subjects with major chronic conditions were more likely to be vaccinated, and an upward trend was seen with increasing number of diseases. People with renal (67.7%), pulmonary (67.2%) and heart diseases (66.8%) had the highest vaccination rates.

The proportion of vaccinated people increased with the number of visits as outpatient in the previous year,

from 46.2% in subjects with zero to three visits to 68.4% in those with more than seven visits.

The highest influenza vaccine coverage was observed in subjects who had been vaccinated in all three previous seasons (90.8%). Vaccination coverage was also high in subjects who had been vaccinated against influenza in the 2009/10 season (86.7%).

Similar coverage was observed among persons with urban or rural residence. Immigrants had the lowest vaccination rates (31.9%) (Table 1).

Determinants of seasonal influenza vaccine coverage

Multivariate analyses showed that having at least one major chronic condition, more than three visits as an outpatient in the previous year, and high level of dependence were associated with greater vaccination uptake. Age was significantly associated with vaccine uptake, especially in the age group 85 to 89 years (odds ratio (OR): 2.18, 95% confidence interval (CI): 2.09–2.27) and 80 to 84 years (OR: 2.17, 95% CI: 2.07–2.28) as compared with those aged 65 to 69. On the other hand, being female, being older than 99 years of age, being an immigrant or having been hospitalised in the previous year were associated with a lower seasonal vaccination uptake. Residence in an urban area was not significantly associated with differences in seasonal influenza vaccine coverage (Table 2).

When each type of major chronic condition was considered separately after adjusting for all other covariates, vaccination rates were found to be higher among people with pulmonary disease (OR: 1.25, 95% CI: 1.20–1.30), diabetes and heart disease (OR: 1.18, 95% CI: 1.14–1.22 for both diseases). Non-haematological cancer and renal disease were also associated with significantly higher influenza vaccine coverage. The other chronic conditions evaluated were not associated with vaccination uptake (Figure).

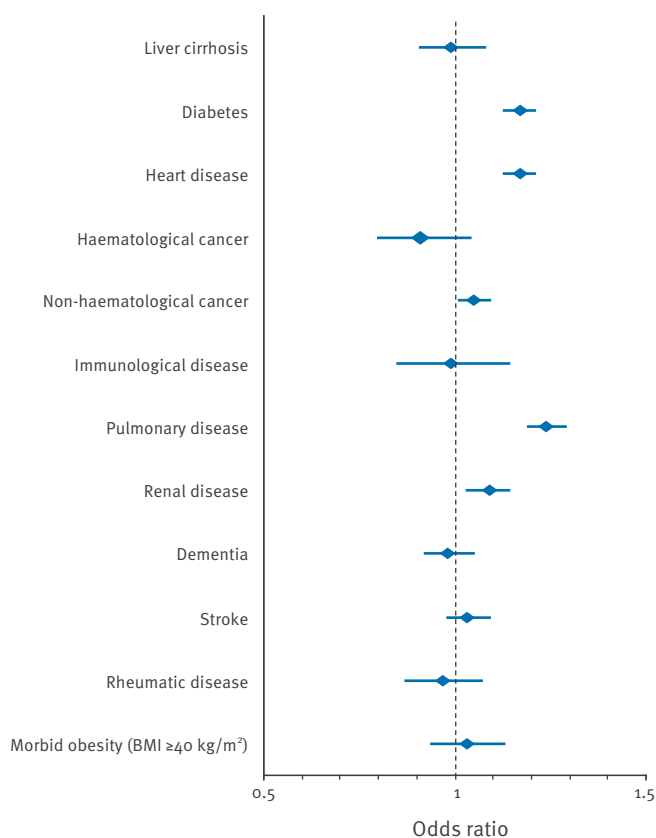
When influenza vaccination in the previous season was introduced in the adjusted model, it was found to be a strong predictor of vaccination in the current season (OR: 37.0, 95% CI: 35.7–38.4). Having been vaccinated in all three previous seasons improved the predictive value (OR: 55.8, 95% CI: 53.5–58.2) (Table 3).

Time trends in vaccine coverage

The vaccine register made it possible to obtain estimates of influenza vaccination coverage in seniors in the most recent seasons using comparable criteria. In 2006 influenza vaccine coverage in non-institutionalised persons aged 65 or over was 59.9%, rising to 61.3% in 2007 and peaking at 62.7% in the 2008/09 and 2009/10 seasons. The coverage achieved in the 2010 campaign (58.6%) represents a decline with respect to coverage in the previous campaign ($p < 0.001$) and breaks the previous upward trend.

FIGURE

Major chronic conditions as determinants of 2010/11 seasonal influenza vaccine coverage, Navarre, Spain (n=104,427)



BMI: Body Mass Index.

Odds ratios obtained from a logistic regression analysis adjusted for sex, age, outpatient visits in the previous 12 months, immigrant status, urban/rural residence, level of dependence and hospitalisation in the previous 12 months.

Discussion

Our results show the utility of the vaccination register in monitoring the coverage of influenza vaccination in seniors in Navarre and in identifying factors that affect this coverage.

Vaccination registries have been shown to be useful in clinical assessment and in estimating coverage [12]. In Navarre, the vaccine register is used primarily so that physicians and nurses can consult the vaccine status of their patients at any time and to programme the dates to administer the doses of the vaccine schedule. This register allows more rigorous research, because it contains individual-level information that can be used to conduct population-based studies to measure the impact of vaccination programmes, to evaluate vaccine effectiveness, and to monitor vaccine safety [13-21].

Although the completeness and accuracy of the vaccine register have not been evaluated in Navarre, there are multiple data that support it. The number of doses registered is very close to the number of doses distributed from the regional vaccination programme, and the small differences can be explained on the basis of stock, expired doses, cold chain failure or other incidents. No discrepancies have been detected in healthcare or public health practice between the vaccination data in the register and the information in patients' vaccination records. The person who administers the vaccine documents it at the same time. Furthermore, one of the indicators used in quality assurance of primary care in Navarre is the vaccination coverage in people for whom the vaccine was indicated, which serves as an incentive for physicians to record all doses administered.

Vaccination registries make it possible to evaluate coverage continually in the whole population in a way that is comparable over time. Vaccination coverage has also been studied through surveys in population samples [22-24]. Although the coverage of influenza

vaccination in our study (58.6%) is within the range of what other authors have reported [22-24], it is far from the programme objective and leaves considerable margin for improvement [8]. Vaccination coverage in Navarre had increased in recent years through efforts to improve information and vaccine uptake. However, coverage fell appreciably after the influenza A(H1N1) pdm09 pandemic in 2009. Women had lower vaccination coverage than men, and people with chronic conditions were more likely to be immunised, in particular those with pulmonary disease, diabetes or heart disease. All these results are consistent with what has been described in the literature [22,25]. However, coverage in persons with major chronic conditions could still be improved. Hospitalisation in the previous year was associated with a lower probability of vaccination, which suggests that in these patients' primary care, measures like vaccinations may be forgotten, despite the fact that their potential benefit in these persons may be even greater.

Influenza vaccination in previous seasons was a strong predictor of vaccination in the current season, which shows that efforts to improve vaccine uptake may be rewarded by increased commitment to the programme in successive seasons. It is likely that people's objections to and reservations about the vaccine are largely overcome after being vaccinated for the first time.

Although influenza vaccination is considered an effective measure against influenza, the decision whether or not to accept the vaccine is influenced by many factors. Low immunisation coverage is usually attributed to a combination of patient characteristics, beliefs and attitudes about vaccines, and barriers to access [22]. In this study we only evaluated factors depending on the subject, even though some healthcare factors may also influence the vaccination coverage achieved. Some authors have pointed out that the single most important factor is the recommendation of a healthcare

TABLE 3

Previous seasonal influenza vaccinations as determinants of 2010/11 seasonal influenza vaccine uptake, Navarre, Spain (n=104,427)

Vaccination status	Crude odds ratios (95% confidence interval)	Adjusted odds ratios (95% confidence interval) ^a	p
Analysis 1			
Not vaccinated in 2009/10 season	Reference	Reference	-
Vaccinated in 2009/10 season	41.2 (39.7-42.7)	37.0 (35.7-38.4)	<0.001
Analysis 2			
Not vaccinated in 2009/10 season	Reference	Reference	-
Vaccinated in 2009/10 but not in all three previous seasons	17.4 (16.6-18.2)	16.2 (15.5-17.0)	<0.001
Vaccinated in 2009/10 and in all three previous seasons	62.0 (59.5-64.7)	55.8 (53.5-58.2)	<0.001

^a Logistic regression model adjusted for sex, age, major chronic conditions, outpatient visits in the previous 12 months, immigrant status, urban/rural residence, level of dependence and hospitalisation in the previous 12 months.

professional [24]. When vaccination in elderly people has been explored, perceptions of enjoying good health and the feeling of not being susceptible to influenza were the reasons most frequently mentioned for non-compliance. It was also associated with the opinion that the complications of influenza were not dangerous [25].

Our results demonstrate the need to improve influenza vaccination coverage in Navarre. Activities should be directed to increasing awareness of those who belong to high-risk groups, encouraging healthcare workers to proactively propose influenza vaccination, promoting the use of patient reminders, and developing effective communication and education campaigns [6,26].

Conclusion

The Navarre vaccine register has been shown to be a useful tool in determining vaccine coverage in the population, its evolution over time, and the influence of different factors. This information has made it possible to detect possible ways to improve coverage and may aid the design of more efficient measures to achieve this objective.

Acknowledgments

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Ten years polio-free: anniversary in the World Health Organization European Region

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In 2002, the World Health Organization (WHO) European Region was declared polio-free [1]. This week, 21-27 April 2012, the seventh European Immunization Week highlights the ten-year anniversary of the polio-free status [2]. In spite of a large outbreak of imported wild poliovirus in Tajikistan in 2010, the Region has retained its polio-free status, as confirmed by the European Regional Certification Commission for Poliomyelitis Eradication in August 2011 [3].

It was on 23 April 2010 that the WHO announced the confirmation of wild poliovirus serotype 1 (WPV1) in seven samples obtained from children with acute flaccid paralysis (AFP) in Tajikistan. Genetic sequencing determined that the poliovirus was most closely related to virus from Uttar Pradesh, India. In total 136 (80%) of the AFP cases were in children aged under five years (age range 0-17 years). Cases were mainly reported from districts bordering Afghanistan and Uzbekistan [4].

While remaining polio-free is an achievement to celebrate and a good example of how immunisation can control the spread of disease, the 2010 outbreak was a poignant reminder of the need to stay vigilant. Due to ongoing threats in countries bordering or nearby the European region such as China and Pakistan, polio continues to be a threat [5].

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Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures

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Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures

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KEY WORDS

measles, varicella, seizures, vaccine, fever

ABBREVIATIONS

MMRV—measles-mumps-rubella-varicella

ACIP—Advisory Committee on Immunization Practices

MMR—measles-mumps-rubella

VSD—Vaccine Safety Datalink

RCA—rapid cycle analysis

ICD-9—*International Classification of Diseases, 9th Revision*

RR—relative risk

CI—confidence interval

aOR—adjusted odds ratio

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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WHAT'S KNOWN ON THIS SUBJECT: We previously alerted the ACIP to preliminary evidence of a twofold increased risk of febrile seizures after MMRV when compared with separate MMR and varicella vaccines after monitoring with the VSD RCA surveillance system.



WHAT THIS STUDY ADDS: Using VSD data on twice as many vaccines, we examined the effect of MMRV on risk of seizure and describe here the postvaccination risk interval for increased fever and febrile seizures after vaccination.

abstract

FREE

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000–2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83 107) were compared with recipients of MMR + varicella vaccines (376 354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43–2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10 000 doses (95% confidence interval: 2.6–5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines. *Pediatrics* 2010;126:e1–e8

The combination measles-mumps-rubella-varicella (MMRV) vaccine was licensed by the US Food and Drug Administration in 2005. The MMRV vaccine was subsequently recommended by the Advisory Committee on Immunization Practices (ACIP) in 2006, at which time the committee stated a preference for its use over separate measles-mumps-rubella (MMR) and varicella vaccines.

In previous studies, associations between MMR and increased risk for febrile seizures 1 to 2 weeks after vaccination were observed.¹⁻⁴ Although precensure studies of MMRV vaccine among 12- to 23-month-old children revealed higher rates of fever and measles-like rash 1 to 2 weeks later when compared with separate MMR and varicella vaccines,⁵⁻⁷ it was unknown at the time of MMRV licensure whether the higher rate of fevers was similarly associated with increased risk for febrile seizures.

The Centers for Disease Control and Prevention–sponsored vaccine safety surveillance system known as the Vaccine Safety Datalink (VSD) comprises 8 managed care organizations encompassing data on >9 million members annually. The VSD has developed a near-real-time vaccine safety surveillance system known as rapid cycle analysis (RCA),⁸⁻¹⁰ which was designed to monitor for potential associations between specific vaccines and pre-specified adverse events by using weekly data and sequential statistical analysis.¹¹

Beginning in 2007, we used the RCA surveillance system to monitor weekly 6 specific outcomes after MMRV vaccination. On the basis of ~43 000 MMRV doses administered between February 2006 and August 2007, we detected a preliminary signal for an approximately twofold increased risk of febrile seizures occurring 7 to 10 days after MMRV vaccination compared

with separately administered MMR + varicella vaccination. We reported these findings to the ACIP in February 2008, after which the ACIP changed its recommendations from a stated preference for MMRV to no preference for either MMRV or separate MMR + varicella vaccination.¹²

We continued monitoring children vaccinated with MMRV through October 2008, which resulted in approximately twice as many MMRV doses administered within the VSD than we originally reported. Using this expanded number of vaccinated children and comparing them to recipients of separately administered same-day MMR + varicella vaccines, we report here the risk of febrile seizures after MMRV during both the 7 to 10 days and 42 days after vaccination.

METHODS

Surveillance and Signal Detection

The VSD creates aggregated, dynamic data sets that are updated weekly and contain vaccine information and outcomes as described previously.⁸ MMRV RCA surveillance monitored children 12 to 23 months old during the 42 days after vaccine receipt for 6 outcomes: seizures, thrombocytopenia, encephalitis/meningitis, ataxia, allergic reactions, and arthritis. In this report we focus exclusively on seizures.

Children aged 12 to 23 months who were members of the 7 participating VSD sites and received their first dose of MMRV (Merck & Co, Inc, West Point, PA) were eligible for study inclusion. We defined a seizure event as the first instance during the 42 days after MMRV vaccination with *International Classification of Diseases, 9th Revision* (ICD-9) codes 345* (epilepsy) or 780.3* (convulsion) in the emergency department or hospital. We censored seizures after the first occurrence within the 42 days. To minimize inclusion of follow-up visits as seizures, we ex-

cluded children who had received either ICD-9 code in any inpatient or outpatient setting during the 42 days before the seizure. “Seizure” refers to an event identified electronically, whereas “febrile seizure” refers to a chart-confirmed febrile seizure.

We monitored seizures weekly and compared the cumulative number observed to the number expected on the basis of the historical VSD seizure rates from 2000 to 2006 after MMR vaccine was administered with or without varicella. We defined a “signal” as occurring when the number of seizures 42 days after vaccination significantly exceeded the number expected according to the maximized sequential probability ratio test¹¹; the threshold was set to a level designed to keep the cumulative chance of making a type I error below 5% over several years of weekly analyses. We assessed the statistical significance of temporal seizure clustering by using SaTScan software.^{13,14} Separately for each vaccine exposure, SaTScan evaluated all potential risk-window combinations 1 to 21 days in length, adjusting for multiple testing inherent in the hundreds of time intervals considered.

We examined postvaccination outpatient fever visits by using ICD-9 code 780.6 for fever or febrile illness at all 7 participating VSD sites from January 2000 through October 2008. Similar to seizure cases, fever visits were censored after the first occurrence within the 42 days.

The participating VSD sites were Group Health Cooperative (Washington State), Kaiser Permanente Colorado, Kaiser Permanente Northwest (Oregon), Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Northern California Kaiser Permanente, and Marshfield Clinic (Wisconsin).

Chart Reviews

To assess whether postvaccination seizures were febrile seizures, we conducted the following chart reviews: (1) all seizures during days 0 to 42 after MMRV vaccination; (2) all seizures 7 to 10 days after separately administered, same-day MMR + varicella vaccination; and (3) a random sample of seizures during days 0 to 6 and 11 to 42 after MMR + varicella vaccination. The number of seizures reviewed in group 3 was equivalent to the number of chart-reviewed seizures during days 0 to 6 and 11 to 42 after MMRV vaccination.

We accepted a chart diagnosis of febrile seizure regardless of the presence of a concurrent febrile illness. When available, we captured data regarding previous seizure history, family history of seizures, and whether the seizure resulted in hospitalization. Trained medical record analysts, blinded to the study and the vaccines received, conducted the chart reviews.

Assessment of the Effect of MMRV on Seizure Risk

Seizure risk after MMRV vaccination was compared with seizure risk after 3 comparator vaccines from January 2000 through October 2008: (1) MMR + varicella; (2) MMR alone; and (3) varicella alone. The primary comparison was with MMR + varicella vaccination.

We focused the primary analyses on days 7 to 10 after vaccination because early temporal scan statistics indicated that seizures clustered most significantly during days 7 to 10 after MMR + varicella vaccination, a time period consistent with post-MMR fever and seizures.^{1–4} Because we initially defined the 42-day surveillance period, we also examined seizure risk for days 0 to 42, as well as days 0 to 30, to permit comparison with the results of a recent study on MMRV vaccination and febrile seizures.¹⁵

Using the electronic data, we used Poisson regression to compare seizure risk across the 4 different vaccine exposures during days 7 to 10, as well as 5 other risk windows (days 0–4, 5–6, 11–12, 13–30, and 31–42). Additional covariates adjusted for 5 age groups (12, 13–14, 15–16, 17–19, and 20–23 months), 7 VSD sites, respiratory virus seasons (November 1 to April 30 versus May 1 to October 31¹⁶), and 9 calendar years (2000–2008). The dependent variable was the seizure count; the offset (ie, denominator for the seizure count) was person-time. Additional concomitant vaccines were not included, because neither the number nor the receipt of concomitant vaccines was a significant seizure predictor in preliminary analyses.

We also conducted 3 supplementary analyses to (a) account for the result of the chart reviews and the remaining uncertainty regarding unreviewed charts, (b) focus on chart-confirmed febrile seizures during days 7 to 10, and (c) adjust for potential confounders that could differ in the comparison group but should remain stable in each vaccine recipient during the postvaccination period. Because we did not have concurrent controls throughout the entire study period, this self-controlled analysis (c) (“case-centered”¹⁷) was particularly important, because it inherently controlled for unmeasured confounding.

We conducted supplementary analysis (a) by repeating Poisson regressions ($n = 1000$), for which before each analysis we applied to each unreviewed seizure a “confirmation rate” randomly drawn from a normal distribution centered on 83% with a standard error of 5 percentage points (see “Results”).

For (b), we used logistic regressions focused entirely on chart-confirmed febrile seizures during days 7 to 10 after MMRV versus MMR + varicella vac-

ination. For (c), we conducted case-centered logistic regressions by using a data set with only 1 record per seizure.¹⁷ The dependent variable was whether the seizure occurred in the risk window; the key predictor was whether exposure was MMRV versus MMR + varicella.

As with the primary analyses, all supplementary analyses were adjusted for age group, site, calendar year, and respiratory virus season. We calculated the excess risk by using the estimated relative risk (RR) and the seizure rate (S) after MMR + varicella vaccination: excess risk = $(RR - 1) \times S$. We used SAS 9.1 (SAS Institute, Cary, NC) for all analyses.

RESULTS

The study population included 83 107 children vaccinated with MMRV between January 2006 and October 2008 and 376 354 vaccinated with MMR + varicella between January 2000 and October 2008. The secondary comparison groups consisted of 145 302 children who received MMR vaccine alone and 107 744 who received varicella vaccine alone from 2000 to 2008 (Table 1).

After vaccination with all measles-containing vaccines, seizure incidence peaked during days 7 to 10; the most prominent peak was recorded after MMRV vaccination (Fig 1). Temporal scan statistics revealed that seizures clustered most significantly during days 8 to 10 for MMRV vaccination (RR: 7.6; $P < .0001$), 7 to 10 days after MMR + varicella vaccination (RR: 4.0; $P < .0001$), and 7 to 11 days after MMR vaccination alone (RR: 3.7; $P < .0001$). No seizure peak was observable after varicella vaccination alone, nor was there any significant temporal clustering. During days 7 to 10, unadjusted rates for seizures were 84.6 seizures per 1000 person-years after MMRV vaccination, 42.2 seizures per 1000

TABLE 1 Age at Vaccination, Number of Seizures, and the Number of Doses Administered in Each of 3 Time Periods According to Vaccine Received: VSD Study Population, 2000–2008

	MMRV (<i>n</i> = 83 107)	MMR + Varicella (<i>n</i> = 376 354)	MMR Alone (<i>n</i> = 145 302)	Varicella Alone (<i>n</i> = 107 744)	All (<i>N</i> = 712 507)
Age at vaccination, <i>n</i> (%)					
12 mo	44 182 (53.2)	192 912 (51.3)	57 217 (39.4)	27 452 (25.5)	321 763 (45.2)
13–14 mo	19 534 (23.5)	92 117 (24.5)	27 737 (19.1)	14 381 (13.3)	153 769 (21.6)
15–16 mo	11 319 (13.6)	59 254 (15.7)	37 718 (26)	31 702 (29.4)	139 993 (19.6)
17–19 mo	5292 (6.4)	21 723 (5.8)	15 571 (10.7)	23 923 (22.2)	66 509 (9.3)
20–23 mo	2780 (3.3)	10 348 (2.7)	7059 (4.9)	10 286 (9.5)	30 473 (4.3)
Seizures 0–42 d, <i>n</i>	189	598	151	129	1067
Seizures 7–10 d, <i>n</i>	77	174	42	15	308
Doses administered between 2000 and November 2003, <i>n</i> (%)	1134 (1.4)	205 572 (54.6)	95 470 (65.7)	64 520 (59.9)	366 696 (51.5)
Doses administered between December 2003 and January 2006, <i>n</i> (%)	149 (0.2)	105 629 (28.1)	32 039 (22.0)	26 475 (24.6)	164 292 (23.1)
Doses administered between February 2006 and October 2008, <i>n</i> (%)	81 824 (98.5)	65 153 (17.3)	17 793 (12.2)	16 749 (15.5)	181 519 (25.5)

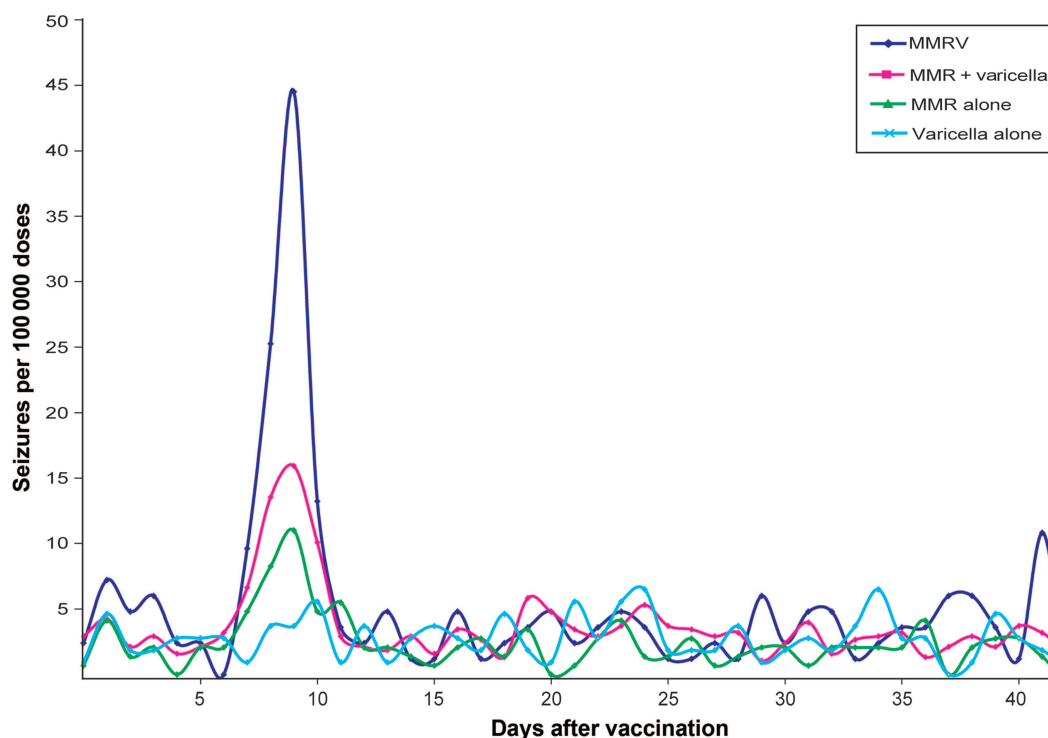


FIGURE 1 Postvaccination seizures among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

person-years after MMR + varicella vaccination, and 26.4 seizures per 1000 person-years after MMR vaccination alone. Unadjusted rates during days 7 to 10 were nearly 8 times higher for MMRV and 4 and 3.5 times higher for MMR + varicella and MMR vaccination alone, respectively. At the largest VSD site (113 MMRV lots used), increased seizure risk was not limited to particular lots.

We next explored receipt of MMRV vaccine and outpatient visits for fever. Similar to the timing of postvaccine seizures, outpatient fever visits sharply increased during days 7 to 10; the most activity occurred after MMRV vaccination (Fig 2). Temporal scan statistics revealed significant clustering during days 7 to 10 for all measles-containing vaccines (RR after MMRV: 6.1; RR after MMR + varicella: 4.4; RR

after MMR alone: 4.3; $P < .0001$ for all). There was no temporal clustering of fever visits after varicella vaccination alone.

We subsequently reviewed the charts of seizure cases during the 42 days after MMRV or MMR + varicella vaccination. Of the 491 cases identified, 40 charts were missing or had missing data. Review of the remaining charts

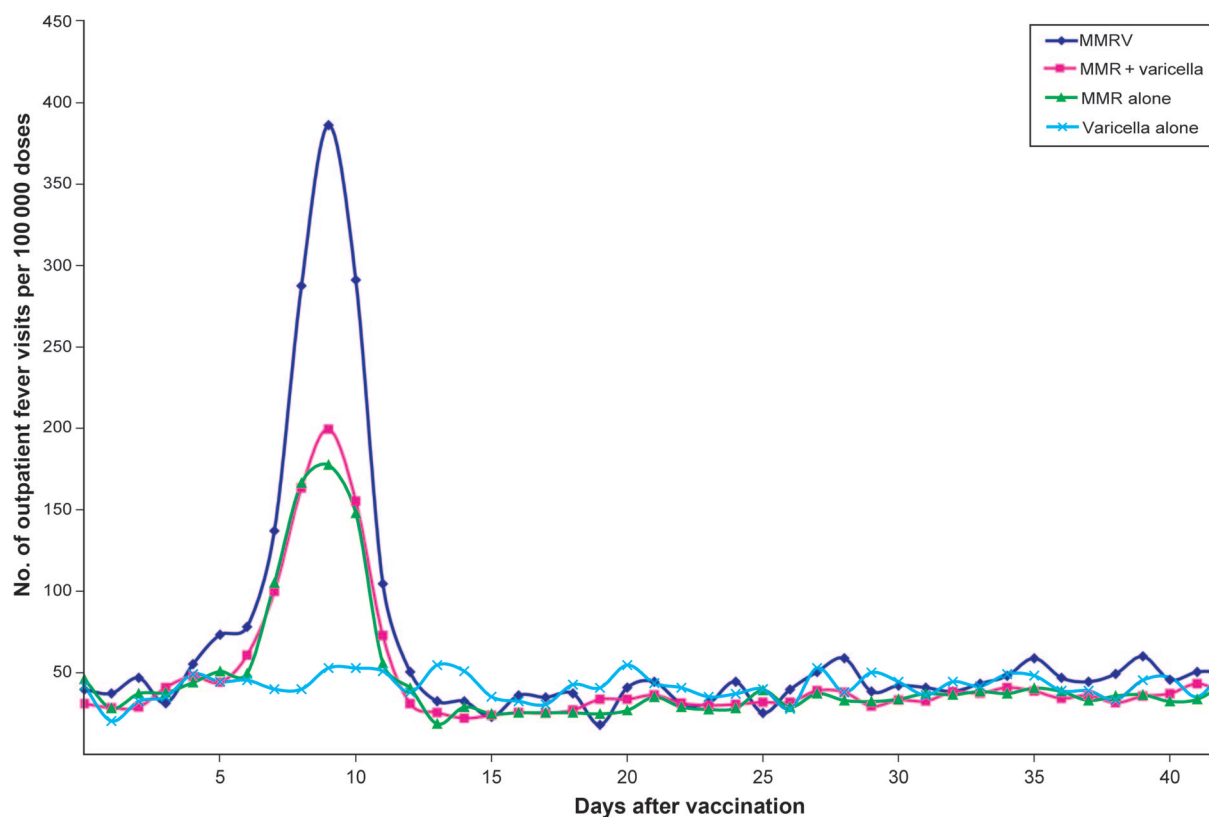


FIGURE 2

Postvaccination outpatient fever visits among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

($n = 451$) revealed that 424 (94%) of the cases were acute seizures and 392 (87%) were febrile seizures. The overall confirmation rate of febrile seizures after vaccination was consistent between the MMRV and MMR + varicella vaccines (Table 2). Regardless of vaccine, the overall febrile-seizure confirmation rate was significantly higher within days 7 to 10 (90% [95% confidence interval (CI): 87–94]) when compared with outside days 7 to 10 (83% [95% CI: 78–88]; $P = .024$); there were no differences in febrile-seizure confirmation rates between recipients of the MMRV and MMR + varicella vaccines (Table 3).

Primary analysis revealed significantly higher seizure risk after MMRV than after MMR + varicella vaccination during days 7 to 10 (RR: 1.98 [95% CI: 1.43–2.73]), as well as during 2 longer intervals (Table 4). MMRV vaccination was

not associated with significantly elevated seizure risks during any of the 5 intervals outside days 7 to 10 (data not

shown). In all risk windows, seizure risk after MMR vaccination alone was similar to that after MMR + varicella

TABLE 2 Chart Verification of Electronically Identified Postvaccination Seizures in the Emergency Department and Hospital

	All Reviewed Charts ($N = 451$), n (%) ^a	MMRV ($N = 183$), n (%)	MMR + Varicella ($N = 268$), n (%)
Acute seizure diagnosed	424 (94)	172 (94)	252 (94)
Not an acute seizure	8 (3)	3 (2)	5 (2)
No evidence of seizure event/ insufficient information	19 (4)	8 (4)	11 (4)
Febrile seizure diagnosed	392 (87)	160 (87)	232 (87)

^a Does not include 40 cases in which either the charts or the visit of interest were missing.

TABLE 3 Febrile-Seizure Rate: Percent That Were Chart-Confirmed

Risk Window After Vaccination	Vaccine		P^a	Overall Percent Confirmed (95% CI)
	MMRV, % (N Confirmed/ N Reviewed)	MMR + Varicella, % (N Confirmed/ N Reviewed)		
Days 7–10	92 (70/76)	90 (138/154)	.55	90 (87–94)
Days 0–6 and 11–42	84 (90/107)	82 (94/114)	.74	83 (78–88)

The total number of MMRV-recipient charts reviewed was 183; the total number of MMR + varicella-recipient charts reviewed was 268.

^a Comparison between percentage confirmed between MMRV and MMR + varicella vaccines for the stated postvaccination period.

TABLE 4 Risk for Febrile Seizures After MMRV Compared to Separately Administered Same-Day MMR and Varicella Vaccines (2000–2008) During Different Postvaccination Risk Periods

Days After Vaccination	Analysis Incorporates Chart-Confirmation Rate?	RR (95% CI) ^a	P	Excess Risk per 10 000 Doses (95% CI)
7–10	No	1.98 (1.43–2.73)	<.0001	4.6 (2.8–5.9)
	Yes	2.04 (1.44–2.90)	<.0001	4.3 (2.6–5.6)
0–42	No	1.42 (1.11–1.81)	.005	6.7 (1.7–12.9)
	Yes	1.46 (1.11–1.92)	.008	6.2 (2.0–9.5)
0–30	No	1.40 (1.06–1.85)	.017	5.1 (0.8–10.8)
	Yes	1.44 (1.05–1.97)	.023	4.7 (0.7–7.6)

^a All analyses were adjusted for age, VSD site, and each year and respiratory season by using Poisson regression analysis.

vaccination, whereas seizure risk after varicella vaccination alone was relatively low (<0.17 per child-year follow-up). Restricting the analyses from November 2003 through October 2008 yielded similar results for MMRV vaccine (RR for postvaccine days 7–10: 2.46 [95% CI: 1.46–4.08]; $P = .0008$; RR for postvaccine days 0–42: 1.44 [95% CI: 1.12–1.86]; $P = .0049$).

Supplementary Poisson regression analyses that accounted for chart reviews (a) yielded a comparable seizure RR for MMRV vaccine during days 7 to 10 (RR: 2.04 [95% CI: 1.44–2.90]) (Table 4). Supplementary logistic regression restricted to chart-verified febrile seizures during days 7 to 10 (b) produced a slightly higher estimate (adjusted odds ratio [aOR]: 2.17 [95% CI: 1.61–2.93]). Finally, case-centered analyses (c) for MMRV versus MMR + varicella vaccines also indicated increased risk of seizures during both days 7 to 10 (aOR: 1.92 [95% CI: 1.39–2.66]) and days 0 to 42 (aOR: 1.3 [95% CI: 1.03–1.65]) when compared with postvaccination days 43 to 180.

Estimates of the excess number of febrile seizures per 10 000 children given MMRV instead of MMR + varicella vaccines are listed in Table 4. MMRV vaccination was associated with 4.3 additional seizures per 10 000 doses (95% CI: 2.6–5.6) during the 7 to 10 days after vaccination.

The proportion of children with postvaccination febrile seizures with a history of seizures was similar between

MMRV vaccine (23 of 141 [16%]) and MMR + varicella vaccines (42 of 193 [22%]; $P = .21$; data were available for 334 of 392 cases). Of those with a febrile seizure, there was a positive seizure family history among 30% of MMRV vaccine recipients compared with 29% of those who received the MMR + varicella vaccines ($P = .90$); data regarding family history were missing from 47% of the charts (206 of 392). During days 7 to 10, 6% of the subjects with febrile seizures after MMRV vaccination were hospitalized versus 17% after MMR + varicella vaccination ($P = .023$).

DISCUSSION

We analyzed >459 000 12- to 23-month-old children vaccinated with either MMRV or separate MMR and varicella vaccines and found the MMRV vaccine to be associated with increased fever and seizures 7 to 10 days after vaccination. Our different analytic approaches (Poisson, logistic, and case-centered regressions) yielded similar results, indicating that the MMRV vaccine, when compared with MMR + varicella vaccines, was associated with a twofold increased risk of having a febrile seizure 7 to 10 days after vaccination. In particular, the case-centered analyses strengthened our results, because they addressed confounding caused by coding or diagnostic practices, data errors, patient demographics, or care-seeking behavior; such confounding would not selec-

tively affect seizures during postvaccination days 7 to 10 more than other postvaccination days. Our findings are consistent both with results of prelicensure studies during which higher fever after MMRV vaccination was noted^{5–7} and a recent postlicensure study from which MMRV vaccination was reported to be associated with increased febrile seizures during days 5 to 12.¹⁵ We estimate that there will be an additional 4.3 febrile seizures 7 to 10 days after vaccination for every 10 000 doses of MMRV vaccine given instead of MMR + varicella vaccines, or that there will be 1 additional febrile seizure 7 to 10 days after vaccination for every 2300 MMRV doses administered to 12- to 23-month-olds instead of separately administered same-day MMR + varicella doses.

To our knowledge, this report represents the first instance of confirming the association of an adverse event with a particular vaccine after a signal detected by a real-time active vaccine safety surveillance system. The large size of the VSD population, along with our validation of electronically identified seizures with chart review, demonstrates the versatility and validity of the VSD RCA surveillance system, which we believe can serve as a framework for future vaccine- and drug-safety endeavors.

In this study, chart review verified 94% of electronically identified seizures as acute seizures, with 87% of all being febrile seizures. Our findings contrast with those of other studies for which lower confirmation rates were reported when they identified seizures in emergency departments and outpatient settings.^{3,18} We attribute our high confirmation rate to limiting case identification to the emergency department or inpatient setting. A recent VSD study similarly reported a high positive predictive value for seizures identified in emer-

gency department and inpatient settings.¹⁹ The reason for fewer hospitalizations after MMRV vaccination is not clear; however, possible explanations include changes in clinical practice during the time period of the study, growing awareness by physicians of associations between measles-containing vaccines and febrile seizures (and a tendency not to hospitalize such patients), or other unmeasured differences in the clinical features of the febrile seizures.

We found no evidence of an increased risk for postvaccination seizures outside the defined 7- to 10-day risk period, yet the overall RR remained elevated for the entire postvaccination time period (both 30 days and 42 days) because of the risk during the 7- to 10-day period. Our results contrast with those of a Jacobsen et al¹⁵ study, in which the authors, despite finding a significantly increased febrile-seizure risk during days 5 to 12 days, were unable to determine if there was an overall increase in seizures during the 30 days after vaccination; we attribute the disparities to their smaller sample size and differences in seizure case definitions. Our results provide evidence that MMRV vaccine is associated with an overall increased risk in postvaccination febrile seizures regardless of whether the risk period evaluated was 7 to 10, 0 to 30, or 0 to 42 days. An important consideration is that the increased risk for febrile seizures during longer postvaccine time periods does not indicate that MMRV causes a sustained increased risk for febrile seizures; rather, the increased overall risk for febrile seizures after MMRV vaccination is caused by the excess of febrile sei-

zures that occur 7 to 10 days after immunization.

Previous studies have revealed that MMR vaccine is associated with increased fever and seizures after vaccination.^{3,4} Consistent with these reports, our study results show that both MMRV and MMR vaccines, but not varicella vaccine alone, are associated with increased outpatient fever visits and seizures 7 to 10 days after vaccination, with MMRV vaccine increasing fever and seizure twice as much as the MMR + varicella vaccines. This is an important consideration for providers evaluating the excess risk of febrile seizures associated with MMRV compared with MMR + varicella vaccines; MMRV vaccine doubles an already elevated risk for febrile seizures. The Centers for Disease Control and Prevention recently recommended that although either vaccine may be used as the first dose for 1- to 2-year-olds (and the costs of purchasing either vaccine are similar²⁰), families without a strong preference for MMRV vaccine should receive the MMR + varicella vaccines. Providers who consider using MMRV vaccine should discuss with families and caregivers the risks and benefits.²¹

Our study had several limitations. The first was that we used a largely historical comparison group. We do not believe, however, that this method affected our findings, because we obtained similar results when we restricted the analyses to more recent years and with the case-centered approach, which inherently controls for the possible confounders of most concern with historical comparisons. Another potential limitation was that our febrile-seizure case definition was a clinical diagnosis in the chart. Because

the febrile-seizure confirmation rate was the same regardless of vaccine, we do not believe that this created meaningful bias in our results. In addition, in the context of large safety studies designed to evaluate potential safety signals, we believe that it is appropriate to include probable cases so that we do not overlook a true vaccine safety signal.

CONCLUSIONS

Among 12- to 23-month-olds receiving their first dose of measles-containing vaccine, the risk of fever and seizure are elevated 7 to 10 days after vaccination. The use of MMRV vaccine instead of separate MMR + varicella vaccines approximately doubles the risk for fever and febrile seizures, resulting in 1 additional febrile seizure for every 2300 doses of MMRV vaccine administered instead of separate MMR and varicella vaccines. Providers who choose to use the combination vaccine should be aware of and clearly communicate this increased risk to the families and caregivers of their patients.

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Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures

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