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Editorial

Registries: An essential tool for maximising the health benefits of immunisation in the 21st century

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The variety of available vaccines and the intricacy of immunisation schedules has increased progressively over recent decades. Consequently immunisation programmes have become more complex with the addition of different vaccines such as those against *Haemophilus influenzae* type b infections, meningococcal and pneumococcal disease, human papilloma virus, rotavirus, varicella and herpes zoster to vaccination programmes, and their extension to cover the whole life course. At the same time, the survival of people with chronic and immunocompromising conditions with higher susceptibility to infectious diseases and needing specialist advice on vaccine indications and contra-indications has also increased. It is therefore not surprising that the need has also grown for better data on when, where and who received which vaccine.

High income countries have reached the point where such data are an essential part of any immunisation programme. While clinicians need good information on the protection of their patients to ensure high standard of care, the individual citizen expects to be able to access their own records as well and public health authorities need to be able to identify and respond quickly to concerns in order to maintain the confidence of an increasingly vaccine hesitant public.

Immunisation registries have great potential to be the most robust and systematic approach to providing data on the safety and effectiveness of immunisation programmes as well as information whether they reach their target communities and birth cohorts. They hold the information needed for rapid response as well as for the longer term, and can safeguard the immunisation records of individuals over their lifetime.

Many countries across the globe are working towards developing immunisation registries [1] and can usefully share many lessons along the road [2]. In that context, the collection of articles in this issue of *Eurosurveillance*, which follows on an earlier special issue on the topic in 2012 [3], illustrate the evolution and potential of immunisation registries to impact on health. Examples are provided on how an Immunisation Information System (IIS) enables better management of programmes as well as research and evaluation, all of which leads to quality improvement and innovation. Although every registry may have to be different in order to adapt to local particularities in immunisation programme recommendations, legal context, data availability and healthcare delivery systems, those working in the field can still learn much from each other [4]. For example, while countries such as those in northern Europe have data systems integrated through a unique personal identification number, countries lacking this capacity may be able to create similar functionality through data linkage. Furthermore, many requirements, processes and principles are shared. For example ‘No duplicate entry or collection’ is an excellent principle that underpins the system design in Finland as shown by Baum et al. [5].

Altogether, the results of a survey conducted by the European Centre for Disease Prevention and Control (ECDC) presented by Derrough et al. show a positive trend in the implementation of vaccination registries within European countries [4]. Of 27 responding countries of the European Union/European Economic Area, 21 answered that they have an immunisation registry in operation or being currently piloted, either at national or subnational level. Furthermore, of the six remaining countries, four mentioned that they have concrete plans to implement one in the near future. By comparison, in a survey conducted by the Vaccine European New Integrated Collaboration Effort (VENICE) I project in 2007, only 15 of the 27 responding countries had either a national or regional computerised immunisation registry [6].
Two features can be considered as essential for ensuring reliable coverage estimates; the possibility to capture vaccines administered in the past, mentioned by 14 of 16 countries, and those administered outside the public system, which is not the case in many surveyed countries. The impact will of course depend on the contribution of the private sector to vaccination coverage, information not available in the survey.

Other characteristics of registries for example, the functionality for vaccine providers to identify unvaccinated patients and the system to send vaccination reminders, access to the system by vaccine providers and the general public are very heterogeneous. The extent to which a registry can increase vaccine coverage (not only monitor it) and engage both health professionals and the public in taking a proactive role with respect to vaccination depend greatly on these characteristics.

Few countries mentioned the use of their registry for vaccine effectiveness studies. However, 13 of 14 countries mention the possibility of database linkage which would enable this use to increase in future.

The next step, as suggested by the authors, is to bring together key stakeholders involved in countries' e-health and vaccination programme management to work together on common standards and share experience, expertise and tools. ECDC has definitively, among other institutions, the legitimacy to take an important part in catalysing such an important endeavour.

Differences between registries often reflect local enablers and constraints including privacy legislation and may not be a real barrier if the clinical details included at each level in the system are well aligned with that required for adequate analysis and the needs of organisations targeted for action. For example, in larger federal countries personal health information may not be needed for aggregate coverage estimates at national level. Systems need to be designed appropriately to be able to drive action at different levels. A system which is defined by geography only [7] misses the important alignment between a registry and service providers, who may not be geographically defined.

IIS require significant technical expertise as well as resources and dedication to quality improvement. The technical expertise required is often under estimated [8], and is multi-disciplinary, not only in respect to the information technology. One of the hardest elements to track down is often details of past recommendations, leading some of us to keep hold of old immunisation guides long after they are out of date, as they are sometimes the only available historical record (Figure). In addition to familiarity with changes that have occurred during the history of the programme and the current recommendations, detailed knowledge is needed of how rules embedded in the registry may affect how immunisation status and coverage is measured. This is essential to understand the implications for identifying unvaccinated individuals and communities. The article from Norway by Hagerup-Jenssen et al. illustrates the technical knowledge and level of responsiveness required to be able to identify and delineate issues in order to improve systems and processes [9].

Good management and attention to detail are essential for the success of all immunisation programmes, when so many elements and actors are involved all the way from the vaccine industry through to the patient. When immunisation programmes are linked to elimination targets, requirements are even more stringent. Growing pressure to deliver on targets to eliminate measles in Europe require measles vaccination coverage to approach levels of nearly 100% in fact, not in fiction [6]. This may require systems with high precision to detect immunisation gaps, given that a critical community size to sustain measles transmission is only a few hundred thousand people [10].

The World Health Organization (WHO) and national reporting requirements focus on individual antigen-specific coverage data e.g. for diphtheria, pertussis, tetanus, measles etc. However, even in a country such as Denmark, where coverage is generally high, it is good to be reminded that a substantial proportion of children may have missed at least one dose of any of their recommended vaccines. Written reminders generated by vaccine registries may not be the whole answer, but seem to be effective in promoting higher coverage [11], particularly in older children in whom missed opportunities may have played a role. Further evaluation of how best to design such communications initiatives in order to increase their impact may be helpful [12]. The Danish study by Suppli et al. also shows how timing is important. Unvaccinated children need to be
identified close to the due date so that children are not left unprotected too long, but with enough distance to maximise the effectiveness of reminders. The timeliness of data collection needs to be proportionate and aligned with the effectiveness for action.

Coverage data are a key component of immunisation programme research and evaluation designed to innovate and maximise the benefits of vaccines [13,14]. Such implementation research and evaluation is applied and usually requires a multi-disciplinary approach [15]. If immunisation data are collected within the same information system as morbidity data, or easily linked, this brings additional strengths. The potential is beautifully illustrated by a study from Germany by Rieck et al., demonstrating how the registry can enable vaccine effectiveness assessment, in this case for the varicella vaccine [16].

From a patient engagement perspective, it is heartening to see patient and parent access developing, as well as opportunities for proactive participation, which will be further enhanced by access to data through devices such as mobile telephones [17] and by tailored text messages [18]. In the future, vaccine barcoding will add further functionality and improved data capture to immunisation registries [19]. Functionality can be further enhanced through data linkage, for example to assess equity of access for marginalised groups such as refugees, aboriginal and migrant populations.

Immunisation registries are a long-term commitment, mirroring the fundamental nature of vaccination programmes that protect the population for the whole life course and long-term. Registries should reflect that vision; they should be designed to be sustainable and be seen as an integral part of the immunisation programme that enables maximising their health benefits in multiple ways. The resources required may not be substantial if viewed as part of the total budget for immunisation programmes and an essential intervention, within a broader e-health strategy, that will protect all the members of our communities for the long lives we hope they will lead.

Conflict of interest
None declared

References
We describe characteristics of an ongoing measles outbreak in Wallonia, Belgium, and difficulties in control measures implementation. As at 12 March 2017, 177 measles cases were notified, of which 50% were 15 years and older, 49% female. Atypical clinical presentation and severe complications, mainly among adults, in combination with late notification, low or unknown vaccination coverage of contacts, infected healthcare workers and increased workload due to contact tracing, are the main concerns for outbreak management.

Following the detection of a cluster of three measles cases in December 2016, since mid-January 2017, an increasing number of measles cases have been notified in Wallonia, Belgium. Between 20 December 2016 and 16 April 2017, 288 measles cases were reported to the Wallonian regional health authorities [1], compared with 19, 34, 10 and 14 cases in total for 2016, 2015, 2014 and 2013, respectively. We describe the main challenges in the outbreak management such as atypical clinical presentations and difficulties encountered during contact tracing and control measures implementation. As the investigation is still ongoing, we present preliminary findings until 12 March 2017.

Data collection methods and case definitions were described previously [2]. Briefly, cases were classified as possible, probable or confirmed depending on clinical criteria, epidemiological link and laboratory criteria following the case definition of the European Union (EU) Commission Decision of 2012 [3] and an outbreak was defined as two or more laboratory-confirmed cases which are related in time (with dates of rash onset occurring between 7 and 18 days apart) and have epidemiological and/or virological links [4].
Characteristics of cases and vaccination status
Cases were between 5 months and 52 years old, the median age was 14 years. Seventeen cases (10%) were infants under 1 year of age, 31 cases (17%) were 1–4 years, 24 cases (14%) 5–9 years, 16 cases (9%) 10–14 years and 89 cases (50%) were 15 years and older (Figure 3). Eighteen cases (10%) were healthcare workers (HCWs). The majority of cases were not vaccinated (61 cases, 35%) or did not know their vaccination status (95 cases, 54%). Six cases (3%) were reported to be vaccinated with two doses and 15 (8%) with one dose. The M:F ratio was 1.1.

Clinical presentation and severity
Seventy-six cases (43%) were known to have been hospitalised. Information on reasons for hospitalisation was available for 42 patients, unknown for 32 and registered without complications for two cases. Of the cases with complications, 10 were aged 0–4 years, seven were 5–14 years and 25 were 15 years and older. The main complications in children 0–4 years were: dehydration (n=6), febrile convulsions (n=1), pneumonia (n=3); in 5–14 years old: dehydration (n=4), hepatic cytolysis (n=1), gastro-intestinal problems (n=1) and otitis media (n=1); in adolescents and adults 15 years and older: dehydration (n=6), hepatic disorder and hepatitis (n=8), pneumonia (n=4). One case of acute encephalitis occurred in a young adult 20–30 years old. Other complications in adults were pancreatitis (1 case) and uveitis (1 case). Four pregnant women were confirmed with measles and hospitalised. One pregnant woman developed hepatitis and another had pulmonary complications and preterm delivery. Dehydration in both children and adults was often caused by stomatitis making it difficult to drink. No deaths were reported.

Cases did not always present with the classic triad of symptoms following the EU case definition [3]. Especially among vaccinated persons, fever or rash was sometimes absent, or symptoms appeared in an unusual order (e.g. fever and rash appearing on the same day with no other symptoms). Two vaccinated cases (confirmed by vaccination card) presented only with rhinitis but without rash. Presence of measles virus was however confirmed by PCR. These cases were identified through contact tracing. Some cases were initially not suspected to be measles since symptoms at first presentation were complications such as hepatitis, pancreatitis, pneumonia or stomatitis.

Laboratory confirmation
As at 12 March, 96 cases were laboratory-confirmed (54%), the majority by the National reference centre (NRC) for measles, mumps and rubella at the Scientific Institute of Public Health (WIV-ISP), 52 were probable cases with epidemiological link to a confirmed measles case, and 29 were possible cases based on clinical picture only.
Genotyping was performed by the NRC. As at publication date, all genotyped cases (n = 44) were classified as B3. All these cases were sequenced and identical to each other and to the strain identified in the December 2016 index case and to the strains circulating in Romania, Italy and Austria at the end of 2016, according to the World Health Organization (WHO) MeaNS database [6].

Control measures

The regional health authorities in Wallonia have responded to the outbreak according to their guidelines [7] and based on experience of previous years [2]: contact tracing and source investigation was done for each case, cases were isolated where appropriate (e.g. waiting rooms, exclusion from school) and vaccination was proposed to all susceptible contacts through their general practitioners (GPs), paediatricians, HCWs at hospital or occupational medicine. Susceptibility was verified based on vaccination status and date of birth (those born before 1970 were considered as protected according to the guidelines [7]). Two doses of measles vaccine were recommended to susceptible contacts or a second dose was recommended to those who had been vaccinated only once. Information letters to raise awareness were sent to GPs, hospitals, asylum centres and public services for social wellbeing in Wallonia and Brussels capital region, stressing the importance of early case finding, vaccination and notification. Information letters were sent to all parents of the students attending schools and/or classes where measles cases had been reported and to school directors in the province of Hainaut, the most affected region.

By the end of February 2017, the regional health authorities used large scale communication methods (press release, public website, emails, newsflash, sms, intranet for professionals, GP’s and Hospital Infection Control Teams meetings) informing the general population [8,9] and targeting health professionals [10-12] to raise awareness on the high contagiousness of measles, nosocomial infections and vaccination. A risk assessment with all health authorities was conducted at national level on 22 February, informing all regions in Belgium and raising awareness on the difficulties encountered.

WIV-ISP developed a web-based tool for restricted use by surveillance teams in all regions in Belgium, to provide a daily overview on time-place-person in real-time.

Discussion

In Belgium, measles vaccination is systematically offered since 1985 (one dose) and since 1995 (two doses) [13]. In Wallonia, vaccination coverage for the first dose of MMR measured at age of 18 to 24 months increased from 82.4% in 1999 to 95.6% in 2015 [13], and coverage for the second dose at the age of 11–12 years was 75.0% in 2016 [14]. Since the last large measles epidemic in Belgium in 2011, small outbreaks have occurred, with an average of 68 cases between 2012 and 2016. Measles continues to be considered endemic in Belgium and elimination targets are not yet reached.

The present measles epidemic in Belgium started slowly with a few cases in December 2016, increasing from mid-January and rapidly progressing from mid-February 2017 onwards. At the start of the epidemic in December–January, regular control measures were taken. However, the socioeconomic context of the affected population impacted on contact tracing and active case finding, despite efforts by the health authorities. They were confronted with an unvaccinated population of central and eastern-European origin, not belonging to Sinti or Roma population, residing in Belgium and living in permanent houses, characterised by frequent travel abroad and movements mainly within Wallonia, having frequent family gatherings, language barriers and rarely attending healthcare facilities. So far, no further comparison can be made with respect to the rest of the population, as information on the origin of the patient was not systematically collected. Some cases presented at hospitals at an early stage, without rash or with severe atypical symptoms, and were not identified early as measles cases; this resulted in nosocomial transmission, including among HCWs.

Implementing control measures in newly identified risk groups needs time to understand the complexity of the community. For example, the availability of a mobile vaccination team and facilitated vaccine access might have been helpful to control the cluster in the province of Hainaut and Liège.
Further on, in all provinces, containment was hampered by multiple factors such as atypical clinical presentation with serious complications and, sub-clinical presentations, mainly among partially vaccinated patients. They facilitated the rapid spread of infections due to delay in diagnosis and notification. Moreover, most clinicians had not seen measles in their clinical practice. Delayed isolation of measles cases in hospital settings led to secondary cases including unvaccinated HCWs, resulting in a very high workload of contact tracing and case finding, since they come in contact with many patients and their relatives, especially at emergency wards. As previously described, HCWs affected by measles represented a major challenge in containing the epidemic [15-18]. Timely messages about the risk of unvaccinated HCWs and nosocomial transmission were sent to the hospital hygiene teams, but a legal framework allowing vaccination of HCWs involving occupational health medicine, would be of value.

Even if we cannot exclude an under-reporting of non-complicated cases, the proportion of persons (43%) hospitalised and with complications, is high. The general attitude mentioned by regional health authorities in their communication was to maintain as much as possible patients at home, and not to hospitalise, as precautionary measure to avoid further transmission.

In addition to the increased workload, health authorities were confronted with new case management questions, e.g. in pregnant women [19] and very young infants. The age from which measles vaccination (as a post-exposure prophylaxis) should be administered in order to be effective (e.g. children below 9 months or 6 months [20]), and the time until which this vaccination can be offered, raised questions and issues around the recommendations for the administration of immunoglobulins such as when, how (dose and timing) and to whom, when a person should be considered at risk and which exposure is required to justify immunoglobulin administration. Advice was requested to the Belgian Superior Health Council regarding these case management questions and these aspects are currently under discussion.

Vaccination status of adults is often unknown, and the electronic registry in Wallonia, existing since 2014 [21], is still underused. Especially in the case of HCWs and staff in daycare centres, this is of major concern, since no legal framework exists to guarantee staff’s vaccination against measles. In this outbreak, more than half of the cases were aged 15 years and older. Catch-up vaccination campaigns targeting this group have not yet started and might be hampered by the exclusion of the adult population in the current cost-free vaccination scheme in Wallonia. Exceptional measles in adults vaccinated with two doses against measles, but with positive PCR, have occurred, suggesting the need for serological evaluation of the protective immunity for people working in certain circumstances (e.g. paediatric ward, maternity).

Due to vaccination against measles being part of the childhood immunisation schedule, measles has become rare and a large part of the general population, as well as some physicians, seem to have forgotten measles. Therefore, we are confronted with the question on how to effectively raise awareness of the disease and its potential severity and deadly outcome. At the same time, focus must also remain on vaccination and increasing vaccination coverage to reach the target set by the elimination goals [22,23]. According to The Regional Verification Commission for Measles and Rubella Elimination at the WHO Regional Office for Europe, measles elimination was not reached in 14 of the 53 Member States (26%) of the WHO European Region at the end of 2015 [22]. In January–February 2017, 10 EU/EEA countries reported more than double, the number of cases compared to the same period in 2016 [24]. If the elimination goal is to be reached, the vaccination coverage rates with two doses of measles vaccine will have to be increased in a number of countries, including in Belgium. Also, immunisation gaps need to be closed in those who have missed opportunities for vaccination and attention to specific populations with low vaccination coverage is necessary.

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Authors’ contributions
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Reference List

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Immunisation Information Systems (IIS) are computerised confidential population-based systems containing individual-level information on vaccines received in a given area. They benefit individuals directly by ensuring vaccination according to the schedule and they provide information to vaccine providers and public health authorities responsible for the delivery and monitoring of an immunisation programme. In 2016, the European Centre for Disease Prevention and Control (ECDC) conducted a survey on the level of implementation and functionalities of IIS in 30 European Union/European Economic Area (EU/EEA) countries. It explored the governance and financial support for the systems, IIS software, system characteristics in terms of population, identification of immunisation recipients, vaccinations received, and integration with other health record systems, the use of the systems for surveillance and programme management as well as the challenges involved with implementation. The survey was answered by 27 of the 30 EU/EEA systems having either a system in production at national or subnational levels (n=16), or being piloted (n=5) or with plans for setting up a system in the future (n=6). The results demonstrate the added-value of IIS in a number of areas of vaccination programme monitoring such as monitoring vaccine coverage at local geographical levels, linking individual immunisation history with health outcome data for safety investigations, monitoring vaccine effectiveness and failures and as an educational tool for both vaccine providers and vaccine recipients. IIS represent a significant way forward for life-long vaccination programme monitoring.

Introduction

Immunisation Information Systems (IIS) are defined as confidential, population-based, computerised databases that record all immunisation doses administered by participating providers to persons residing within a given geopolitical area [1]. At the point of clinical care, they support practitioner decision-making in ensuring appropriate individual vaccination and adherence to applicable policies. At population level, IIS provide aggregate data on vaccinations for use in surveillance and programme operations, and in guiding public health action with the goals of improving vaccination rates and reducing vaccine-preventable disease. Following the introduction of a vaccine, its uptake and benefit-risk profile requires continuous assessment in order to monitor the performance of vaccination programmes [2,3] and to respond to national and international public health monitoring requirements (e.g. reporting on vaccination coverage, responding to post-licensure requirements, investigation of safety signals). One of the key performance indicators of a well-functioning immunisation programme is vaccination coverage – the proportion of the population eligible for vaccination that has been immunised. It is an indirect measurement of population immunity and determines the level of herd protection against vaccine preventable diseases. Historically, coverage assessment in European Union (EU) Member States has been performed through regular surveys (e.g. telephone-based, at school-entry), review of claims and social security databases or analysis of data from paper-based registries [4-10]. IIS can be a key tool for monitoring vaccination coverage. They can also facilitate evaluation of the safety and effectiveness of vaccines through linking individual vaccination data with other records on health outcomes [11-14]. The functionalities of such systems, including electronic patient records in the framework of e-Health initiatives, are developing
rapidly and they should be able to provide useful information to public health authorities, vaccine providers and vaccine recipients.

For an IIS to fully support vaccination programmes, there are various features that are considered important. These can include: (i) complete and accurate denominator populations from different sources; (ii) secure vaccine recipient and record identification through uniform unique identifiers (UID); (iii) complete, timely and correct vaccination records with real-time electronic access to the IIS; (iv) recording of vaccinations given to the recipient and vaccine details (batch and vial ID etc.) facilitated by pre-entered information, selection menus and reading of barcodes; (v) production of automated outputs; (vi) the facility to offer services that are useful to all parties including vaccine recipients, parents and vaccine providers. This includes for example: recall functions, trusted medical information, and the possibility for parents and vaccine recipients to request certified records of immunisation history.

The European Council conclusions on childhood immunisation in 2011 and on vaccinations as an effective tool in public health in 2014 both recommend the adoption of such systems and the World Health Organization European Vaccine Action Plan 2015–2020 recognises IIS as ‘an integral part of well-functioning health systems’ [15-17].

This article presents the findings of a survey conducted by the European Centre for Disease Prevention and Control (ECDC) across EU/European Economic Area (EEA) countries that assessed the level of implementation of IIS and their functionalities, as well as the challenges encountered during the design and implementation. The aim of the survey was to share knowledge about IIS in the EU/EEA in order to build consensus on the characteristics of an optimal system and to describe differences in core functionalities and standards across countries.

**Methods**

Following a review of the literature and in consultation with subject-matter experts, two cross-sectional surveys were developed to assess the status of IIS
The United States Centers for Disease Prevention and Control (US CDC) definition of an IIS was used as a reference in this survey [1] (Box).

**Results**

**Participation in the different surveys**

Information was received from 27 countries of the 30 contacted, with 16 countries answering the full comprehensive survey, nine countries answering the brief survey and two countries (Luxembourg and Slovakia) answering only to the basic set of five questions.

The list of responding institutions and which survey they completed is shown in Table 1. The respondents were staff from public institutions at national or subnational level with responsibility for national vaccination programme or IIS managers.

**Governance and financial support**

Among the 27 countries who responded to either the comprehensive or brief survey or the basic set of five questions, 17 provided information on governance and financial support. In the survey, governance was defined as ‘the body at national or regional level that is in charge of the day-to-day management of the IIS and of the data contained in the system’.

For eight of the 13 countries with national systems, governance of the IIS is the sole responsibility of the National Institute of Public Health (NIPH). For two countries governance is held by the Ministry of Health (MoH), for Latvia it is held by the National Health Service (NHS), in Romania it is held by both the NIPH and MoH, and in Slovakia it is held by the National Health Information System (NHIS).

Among the four countries with subnational systems, i.e. Belgium (described through Flanders), Spain (described through Andalucía) and the United Kingdom (UK) (described through England), governance is held by subnational or regional health authorities. In Portugal (described through mainland) it is held by both the NIPH and MoH (Table 2).

Financial support for the IIS comes from the national government for thirteen countries. In Latvia and Slovakia the IIS is funded by the national government and EU funds. The regional government finances the IIS in Belgium (Flanders) and Spain (Andalucía).

**Implementation status of Immunisation Information Systems**

The status of implementation of IIS in the 27 countries is as follows (Figure).

**Countries with Immunisation Information Systems in place**

Eight countries have a currently operating national system that meets the US CDC definition of an IIS, i.e. Denmark, Finland, Iceland, Ireland, Malta, the
Two countries (Germany and Sweden) have national systems in place that do not fully meet the US CDC definition of an IIS. In particular, their systems have no ability to consolidate immunisation histories for use at point of clinical care and only provide aggregated data on vaccinations at population level.

Five countries have more than one subnational IIS, including Austria (number not specified), Belgium (Flanders, with the system also covering parts of Brussels, and in the Walloon region where the system also covers parts of Brussels), Portugal (mainland and Madeira), Spain (Andalucía, Illes Balears, Cataluña, Comunidad Valenciana, Castilla y León, Galicia, Comunidad de Madrid and Región de Murcia) and the UK (England, Northern Ireland, Scotland and Wales). For Belgium, Portugal, Spain and the UK, the survey describes the systems in operation in Flanders, mainland Portugal, Andalucía and England respectively. The systems in Belgium, Portugal and Spain fulfil the criteria of the US CDC IIS definition. The UK systems vary, some systems do meet the CDC definition of an IIS while others do not. This information was not available for Austria as they completed the short version of the survey where this question was not asked.

Countries piloting Immunisation Information Systems
Four countries, Greece, Hungary, Latvia and Slovakia are piloting a national system. Latvia had planned to pilot its system in 2017.

France is piloting more than one subnational IIS. Bulgaria is piloting one subnational IIS. Among the countries piloting an IIS, whether at sub-national or national level, how the IIS was defined was only provided by Hungary and Latvia, as these two countries participated in the comprehensive survey. Both countries had an IIS fitting the US CDC IIS definition.

Countries with no Immunisation Information Systems
Six countries, including Croatia, Cyprus, Czech Republic, Estonia, Luxembourg and Slovenia have no IIS in operation or being piloted. Cyprus, Estonia, Luxembourg and Slovenia all have concrete plans to implement an IIS in the future.

Characteristics of Immunisation Information Systems
The results discussed in the following sections are based on questions only included in the comprehensive survey, hence only the 16 countries that responded to this survey (Table 1) are included in the sections below.

Immunisation Information Systems definition
Of 16 countries, which participated in the comprehensive survey, 13 have systems fitting the US CDC definition of an IIS [1] (Box and Table 2). In Finland the definition exceeds the US CDC definition in that the system is also used at individual level to provide immunisation information for use in surveillance, vaccine efficacy and impact studies.

IIS in two countries (Germany and Sweden) do not fulfil the criteria of the US CDC definition of an IIS. The sub-national systems in the UK (England) are varied, with some fulfilling the US CDC definition and others not. In Germany the system is based on insurance claims data from all physicians providing medical services (including vaccinations) to the statutory health ensured population in Germany (around 85% of the total population). Physicians or vaccination providers (at the point of clinical care) do not have access to this database. In Sweden the objective of the national vaccination register is to improve monitoring of the national vaccination programmes and is not used by vaccination providers in determining appropriate client vaccinations at the point of clinical care. In the UK (England) availability of vaccination history at point of clinical care is variable. In primary care, it is dependent on the supplier of the General Practice Information Technology (GP IT) system and the local Child Health Information System while in secondary care it is not available.

Immunisation Information Systems software
In 15 of the 16 countries, the government authority is the owner of the IIS software; whereas in the UK (England), there are five major private sector software suppliers. Fifteen of 16 countries provided information on software source code development, this information was missing for Hungary. Seven countries used a private company and six countries used programmers from the government authority. Two countries systems were developed by a mix of private and government programmers.

Fourteen of the 16 countries provided information on the type of software used. Seven countries used commercial software. Three countries, Germany, Latvia and Spain (Andalucía) had both a partially open and partially commercial source. In Finland and Malta, it was open source with no license required, whereas in Romania, it was a free to use software, but a license was necessary. In Portugal (mainland), the software was developed specifically by the MoH. Information on the type of software was missing for Belgium and Hungary.

The survey did not collect elements related to data hosting, applied standards and system architecture.

Core attributes
Information included in the IIS is fed by a population registry in 13 of 16 countries. Of these 13, seven used the civil population registry, three used the healthcare registry, Denmark and Iceland used both the civil and the healthcare registries and Finland’s system is fed by patient data system records. In Germany, Ireland and Romania personal data are entered manually when
the patient comes for their first vaccinations. Ten of 16 countries reported that an individual vaccination record was created automatically in the IIS database when a live birth is registered (or a time later). In seven countries vaccination records were also set-up automatically at the time of immigration to the country.

Ten countries record life-long vaccination data in the IIS with no restriction of age or vaccination setting (Table 3). The IIS in Ireland records only vaccinations in the recommended school-based vaccination programme. Hungary, the Netherlands, Romania, Sweden and the UK (England) do not include >18 year-olds vaccination data in their systems.

All 16 systems use a unique personal identifier for each immunised individual recorded in the IIS (Table 3). In 11 countries the unique identifier used in the IIS is the same one that is given to citizens at birth or immigration. In Portugal (mainland) the unique identifier is the one given for healthcare services, whereas for four countries the unique identifier is specific to the IIS.

Fourteen of 16 countries can record vaccinations administered in the past and 13 systems can record vaccinations administered abroad (Table 3). This is not possible in Ireland, Germany and Sweden. In four countries with subnational systems (Belgium (Flanders), Portugal (mainland), Spain (Andalucía) and the UK (England)), vaccinations administered in other regions can be recorded in the IIS. The ability of the various systems in the EU to automatically share data was not assessed as it is known to not occur in the EU.

For 15 countries, to ensure that a vaccination entry is valid, vaccine providers are able to select the vaccination to be administered from a list included in the system. For seven countries the data captured in the IIS is validated automatically by the system through pre-set rules and similar. The measures that countries use to

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**Table 1**

Institutions in EU/EEA countries that participated in ECDC surveys on IIS implementation, 2016 (n = 27 countries/institutions)

<table>
<thead>
<tr>
<th>Countries with respective institutions responding to the comprehensive survey (n=16)</th>
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<tbody>
<tr>
<td>Belgium</td>
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<td>Spain</td>
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<td>Sweden</td>
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<td>United Kingdom</td>
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<table>
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<tr>
<th>Countries with respective institution responding to the brief survey (n=9)</th>
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<tbody>
<tr>
<td>Austria</td>
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<tr>
<td>Bulgaria</td>
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<td>Croatia</td>
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<td>Cyprus</td>
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<td>Czech Republic</td>
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<td>Estonia</td>
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<td>France</td>
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<td>Greece</td>
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<td>Slovenia</td>
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</table>

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<tr>
<th>Countries with respective institution responding to the basic set of five questions after the survey deadline (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luxembourg</td>
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<td>Slovakia</td>
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</table>

IIS: Immunisation Information Systems; ECDC: European Centre for Disease Control and Prevention; EU/EEA: European Union/European Economic Area.
When a vaccine is administered, vaccination information is entered into the IIS in real-time in Denmark, Iceland, Malta, Norway, Portugal (mainland), Spain (Andalucía), Sweden and the UK (England).

Use for surveillance purposes
In order to estimate vaccination coverage nine countries of 15 use the civil population registry as the source of denominator data for the IIS. Germany, Hungary, Portugal (mainland) and Spain (Andalucía) use healthcare registries as the denominator. In Ireland the number is manually obtained from the school census and Romania uses the number of newborn children from maternity hospitals. Information on vaccine coverage denominator was missing for Latvia.

In order to compute aggregated vaccination uptake on the smallest administrative area, eight countries of 16 used nomenclature of territorial units for statistics (NUTS) 3 [22] and Hungary computed on NUTS 1. Seven countries were able to calculate coverage below NUTS 3: Sweden and Denmark could compute data at municipality level, Belgium (Flanders), Iceland and the Netherlands at postal code level, and Portugal (mainland) as well as Finland at healthcare centres’ level.
Six countries of 16 can use their systems to record adverse events following immunisation (AEFI). In Belgium (Flanders), AEFIs can be added and marked in colour, so at the time of future vaccination when the provider goes online this can clearly be seen. In two countries (Ireland and Latvia) the system is used for routine passive reporting of AEFIs to health authorities. In Portugal (mainland), the system allows recording of AEFIs, however reporting to fulfil regulatory requirements is done through another system.

Eleven countries can link their IIS with various health outcome registers. For five countries some of these registers are integrated within the IIS and for the other six countries linkage with other health outcome registers is either routinely carried out or performed for specific purposes. Thirteen of 14 countries allow public health organisations to use IIS data for research, such as in vaccine effectiveness studies and safety studies. Latvia has not yet defined this and there was no information from Spain (Andalucía) for this question. In five of these 14, other non-public health organisations can have access to the IIS data for research.

Ten countries can use their IIS to identify unvaccinated individuals in the event of an outbreak.

**Use for management purposes**

Five of 16 countries (Latvia, Malta, the Netherlands, Portugal (mainland) and the UK (England)), have automated systems that can send reminders to people who are due to get vaccinated. The systems in Latvia, Spain (Andalucía), Portugal (mainland) and the UK (England) can send automatic reminders to the vaccine provider to call a patient for the next vaccination.

In five of 15 countries (Denmark, Iceland, Latvia, Norway and Portugal (mainland)), the vaccine recipient or guardian has access to the IIS. There was no information available for Hungary for this question. These five countries, plus Belgium (Flanders), also provide vaccine recipients with the ability to independently obtain an individual immunisation history that is accepted as an official immunisation record directly through the IIS or through an exchange platform.

Regarding outputs from IIS systems, five of 16 countries have a system that allows vaccine providers to identify which vaccines to administer based on the recipient’s age, previous vaccination, allergies, travel and risk factors. In Belgium (Flanders), Portugal (mainland) and Spain (Andalucía), the IIS can be used to communicate information on new vaccines, updated policies, safety concerns and out-of-stock situations to vaccine providers. Thirteen countries can use it to identify individuals who are incompletely vaccinated according to age and ten countries can use it to record reasons for refusing vaccination.

**Challenges in implementation**

Countries had encountered a number of challenges during the different phases of IIS implementation.

The most common challenges faced during the decision to set up an IIS were a lack of human resources (12/15 – no answer from Spain (Andalucía) and a lack of funding (11/15 – no answer from Spain (Andalucía)), followed by issues relating to data protection (9/14 – no answer from UK (England) and Spain (Andalucía)).

During the design phase, challenges faced by most countries included defining the functions required by the system (12/15 – no answer from UK (England)) and a lack of standards to provide a point of reference for developing the system (10/15 – no answer from UK (England)), and defining the core dataset of information to be collected (10/15 – no answer from UK (England)).

During the early use phase (those countries that were piloting IIS were asked to leave this section blank), the main issues encountered included training vaccine providers to use the system (10/14 – Latvia piloting, no answer from UK (England)), validation of data entered by different users (9/13 – Latvia piloting, no answer from Malta and UK (England)) and quality control of data completeness (9/13 – Latvia piloting, no answer from Malta and UK (England)).

For the nine countries with no IIS in place or in the initial stages of implementation and who answered the brief survey, the main challenges were a lack of standards (7/8 – no answer from Austria), main issues encountered included training vaccine providers to use the system (10/14 – Latvia piloting, no answer from UK (England)), data protection issues (7/9) and issues relating to governance and ownership of the system (6/8 – no answer from Austria).

**Discussion**

The findings of the survey provide information on the extent of IIS implementation and systems functionalities in 27 EU/EEA countries. Most EU/EEA countries either have an operational IIS or are piloting one. Of the countries who have no systems in operation, Estonia, Luxembourg and Slovenia all have concrete plans to implement an IIS as part of their larger eHealth strategies in the coming years and Cyprus plans to implement a system as part of the new National Health System [23]. This wide scale implementation of IIS is a major achievement and represents a substantial step towards improving the delivery and the monitoring of vaccination programmes in the EU/EEA as part of a broader strengthening of health service capacity.

Monitoring vaccination programmes relies not only on accurate and complete denominators and numerators for calculating vaccination coverage but also ensuring that the data captured in the system is reliable. The quality of data contained in each of the IIS in operation was not assessed through this survey. However, in regards to the source used for denominator data, an IIS that is populated automatically from birth and civil population registers, from national health insurance...
In regards to the characteristics of an IIS it is desired that the data captured in the IIS are complete, timely and of high quality. To ensure completeness, the IIS should ideally be populated with data from all vaccine delivery sites (whether public or private providers), they should cover the entire population and hold information on all vaccines recommended by health authorities regardless of funding. Many countries’ systems only capture vaccines provided in public health services and for those vaccines that are recommended and funded under the national immunisation schedule. To ensure timeliness and reduce underreporting it is essential that the time between vaccination and the information being entered into the IIS is minimised so that the information is in real-time. This is particularly relevant during emergency situations [25] or outbreaks when the prompt identification of unvaccinated people is necessary [26]. Systems in Belgium (Flanders), Denmark, Finland, Germany, Iceland, Latvia, Malta, Norway, Portugal (mainland) and Spain (Andalucía) allow for life-course vaccination information to be recorded. In 14 countries it is also possible to add vaccinations that were administered before the implementation of the IIS.

The IIS can also be used as a tool for informing public health decisions and research beyond vaccination coverage. The IIS constitutes large datasets that can be used in pharmaco-epidemiological studies to assess vaccine safety and effectiveness. Interoperability of the IIS with other health information systems has been used in studies such as the investigation of narcolepsy.

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### Table 3
Population included, recording of individuals and vaccinations in the IIS of EU/EEA countries, 2016 (n = 16 countries)

<table>
<thead>
<tr>
<th>Country</th>
<th>Does the IIS record whole-of-life vaccination data?</th>
<th>Each immunised individual is recorded with a unique UI?</th>
<th>Does the IIS use the UI given to citizens at birth or immigration?</th>
<th>Can vaccinations administered in the past be recorded?</th>
<th>Can vaccinations administered abroad be recorded?</th>
<th>Are vaccination data entered selected from a list?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium (Flanders)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Denmark</td>
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<td>Yes</td>
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<tr>
<td>Finland</td>
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<tr>
<td>Germany</td>
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<td>Hungary</td>
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<tr>
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<tr>
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<td>Latvia</td>
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<td>Netherlands</td>
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<td>Portugal (mainland)</td>
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<td>Romania</td>
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<td>Yes</td>
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<tr>
<td>Spain (Andalucía)</td>
<td>Yes</td>
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<tr>
<td>United Kingdom (England)</td>
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<td>Yes</td>
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</table>

IIS: Immunisation Information Systems; UI: unique identifier.
with pandemic influenza vaccination in Finland [27]; and similarly to investigate and provide reassurances following signals or claims of adverse effects, such as the investigation of the occurrence of adverse events affecting adolescents girls after human papillomavirus (HPV) vaccination in Sweden and Denmark [28]; the association of thimerosal-containing vaccines and autism in Denmark [29]; and the investigation of vaccines and auto-immune disorders in France [27].

Other important features of an IIS include automated reminder/recall, access and education. At present, systems in Latvia, Malta, the Netherlands, Portugal (mainland) and the UK (England) can send reminders to people who are due to get vaccinated and the systems in Latvia, Portugal (mainland), Spain (Andalucia) and the UK (England) can send automatic reminders to the vaccine provider to call a patient for the next vaccination. Providing public access to the IIS and allowing vaccine recipients to print immunisation records are valuable features. Vaccine recipients can view their records in the IIS in six countries (Denmark, Iceland, Latvia, Malta, Norway and Portugal (mainland)). Six countries allow recipients to directly access an official immunisation record through the IIS. By providing vaccine recipients with some level of ownership over their records and having online access to information on particular vaccines and the disease they protect against may be beneficial to the uptake of vaccination. Such systems also provide the opportunity for being used as educational tools for both vaccine providers and recipients. This can be done by including an easily accessible platform that provides clear information and visualisation of data, using, for example, dashboards. The systems in Denmark and Norway are linked to a web-based application that allows users to visualise in real-time the coverage at communal level with a graphical snapshot of current or historical vaccination coverage trends. This can be useful for informing interventions and raising community awareness.

The implementation of an IIS is a significant commitment at national and subnational levels in terms of financial investment to cover both human resources and technology developments as well as ensuring supportive legislation to allow for personal data to be recorded and used. Some of the challenges identified through the survey include the need for human resources and funding. Other challenges brought forward included the lack of standards. ECDC is well-placed to facilitate such exchange and collaboration in a more systematic way such as supporting EU countries in developing and agreeing to a minimal set of functionalities for an IIS, as a reference to help countries with IIS in the development phase. ECDC could also help in identifying lessons to be learned from other countries outside the EU/EEA. In the US, individuals and organisations with an interest in IIS have formed the American Immunization Register Association (AIRA), which in collaboration with the US CDC, has published platform neutral IIS best practices and standards [30]. Also the experience gathered from other countries outside of the EU with long-standing experience in IIS such as Australia and Canada will serve the EU setting. The Australian Immunisation Register was established in 1996 initially to record vaccinations given to Australian children up to seven years of age. In January 2016 the register was expanded to include vaccination history for adolescents up to the age of 20. It then further progressed later in 2016 to capture all vaccines given as part of the national immunisation programme given to people of all ages and thereby provides a whole of life immunisation history [31].

The survey had some limitations. First, the survey did not include interviews with immunisation programme managers or other key stakeholders, such as decision-makers, programme and IT staff, which would have been useful to provide a more detailed overall picture of the IIS in countries surveyed. Second, the survey did not cover the transition period from paper-based to electronic registries. Last, the survey did not cover in detail the measures that countries use to audit the quality of the data in the IIS, such as the use of a paper-based questionnaire to compare with the data captured in the IIS. Despite these limitations this survey has provided critical information about systems across the EU/EEA and can be used as a further step for in-depth assessment of system performance. The survey also provided key information about the challenges and barriers that countries faced at different stages of implementation of the IIS. Sharing this knowledge and lessons learnt can potentially assist countries to overcome these issues especially those countries that are in the early stages of developing/using an IIS or are planning to implement a system in the future.

Conclusions
Within the EU/EEA, countries vary considerably with respect to recommended vaccines, organisation of health services, mandate of public health agencies, legislation on confidentiality and other relevant factors. Despite this, the exchange of information and experience between national programmes has been useful in the development of IIS in many EU/EEA countries.

The setting up of an IIS is an important commitment for countries and requires careful planning of resources and time. ECDC can play an important role in bringing together key stakeholders, defining common areas of work and challenges, and facilitating exchange of knowledge and experience in order to support countries to implement or upgrade an IIS. The current focus on eHealth in the EU and at national level provides the perfect opportunity for IIS to become an integral part of electronic health systems.

Acknowledgements
We would like to thank Cristina Giambi and Paolo D’Ancona for providing input to the survey questionnaire. We would like to thank Vladimir Mikic and Alexei Ceban for their support in
the survey analysis. We would like to thank ECDC National and Operational Focal points for Vaccine-Preventable Diseases in the EU/EEA.

Conflict of interest

None declared.

Authors' contributions

Tarik Derrough coordinated and drafted the survey, contributed to the analysis and drafted the manuscript. Kate Olsson and Vincenza Gianfredi analysed the survey and drafting of the manuscript. Francois Simondon and Harold Hejbel provided extensive reviews of the manuscript. Niklas Danielsson contributed to survey and to the manuscript. Lucia Pastore-Celentano and Piotr Kramarz contributed to revising the manuscript, providing substantial intellectual input. All authors have read and approved the manuscript.

References


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In Germany, routine childhood varicella vaccination was implemented in 2004 with two doses recommended since 2009. We used an immunisation information system based on countrywide health insurance claims data to analyse vaccine effectiveness (VE) and factors influencing VE. We applied proportional hazard models to estimate VE under various conditions and compared the risk of acquiring varicella among unvaccinated children in regions with high vs low vaccination coverage (VC). Among 1.4 million children we identified 29,404 varicella cases over a maximum follow-up of 8 years post-vaccination. One-dose VE was 81.9% (95% confidence interval (CI): 81.4–82.5), two-dose VE 94.4% (95% CI: 94.2–94.6). With dose one given 1–27 days after measles-containing vaccine (MCV), one-dose VE was 32.2% (95% CI: 10.4–48.6), two-dose VE 92.8% (95% CI: 84.9–96.6). VE was not associated with age at vaccination (11–14 vs ≥ 15 months), time since vaccination, or vaccine type. Unvaccinated children had a twofold higher risk of acquiring varicella in low VC regions. Our system generated valuable data, showing that two-dose varicella vaccination provides good protection for at least 8 years. Unvaccinated children benefit from herd effects. When the first varicella vaccine dose is given shortly after MCV, a second dose is essential.

Introduction
Immunisation Information Systems (IIS) are defined by the Centers for Disease Control and Prevention as confidential, population-based, computerised databases that record all immunisation doses administered by participating providers to persons residing within a given geopolitical area [1]. At the point of clinical care, IIS may support vaccination providers in decision-making towards appropriate individual vaccinations. At the population level, IIS provide aggregate data on vaccinations for use in surveillance and programme operations, and in guiding public health action with the goals of improving vaccination rates and reducing vaccine-preventable disease. In 2004, Germany started to implement a nationwide IIS for the monitoring of vaccination coverage (VC) and selected vaccine-preventable diseases based on health insurance claims data. The German IIS covers the statutory health-insured population (ca 85% of the total population in Germany) and has proved to be a reliable source of VC data [2-5]. Moreover, the data were used to estimate the incidence of selected vaccine-preventable diseases such as measles, mumps and herpes zoster in Germany [6-8]. Varicella is primarily clinically diagnosed [9], thus the German IIS seems suitable for the identification of varicella cases in the population.

Germany is one of the few countries worldwide that has introduced routine childhood varicella vaccination [10]. Since 2004, single-dose varicella vaccination has been recommended for all children aged 11–14 months. Two single-compound varicella vaccines (VAR; Varivax, Sanofi Pasteur MSD; Varilrix, GlaxoSmithKline) were initially available. In 2006, a combined measles-mumps-rubella-(MMR)-varicella vaccine (MMRV; Priorix-Tetra, GlaxoSmithKline) was licensed with a two-dose schedule. A universal two-dose schedule has been recommended since 2009 targeting children with the second dose at age 15–23 months. Since 2011, the first immunisation has been given preferentially as two separate injections of VAR and MMR due to higher rates of febrile seizures following immunisation with MMRV [11]. Catch-up vaccinations are recommended until 17 years of age.

The impact of routine varicella vaccination was initially monitored in a countrywide physician-based sentinel system. Sentinel data indicated a continuous overall 84% decrease of varicella cases per sentinel site between 2005 and 2012, most dominantly among 1–4 year-olds [12]. Based on data from the IIS, VC in
Several post-marketing studies on varicella vaccine effectiveness (VE) have been published [13-22]. However, of these, only few studies assessed the effectiveness of two doses [13-16]. In addition, little is known about the duration of vaccine-induced protection and the optimal age for vaccination [17-19]. Finally, there is little evidence on the minimum time interval between the first and second varicella vaccine dose as well as between varicella and measles-virus containing vaccines (MCV) [18,20].

We used data from the German IIS with the objectives to estimate dose-specific VE against all varicella, varicella-associated complications and varicella without complications, and to investigate factors that might influence VE, such as age at vaccination, time interval between varicella and MCV doses, type of vaccine, and time since vaccination (TSV). Furthermore, we aimed to quantify the degree of herd protection that is conferred in regions with high vs low VC.

**Methods**

**Dataflow and database**

Data were generated and collected within the German IIS, also called the ‘Associations of Statutory Health Insurance Physicians (ASHIPs) vaccination monitoring project’. The system has been described in detail previously [3]. In brief, ASHIPs regularly receive insurance refund claims from all ASHIP-associated physicians for outpatient medical services provided to those covered by statutory health insurance. These claims data include all recommended vaccinations and diagnosed diseases. The latter have to be documented in order to justify medical services. Approximately 85% of the population in Germany is covered by statutory health insurance. The remainder are mainly privately insured. The administrative regions of most ASHIPs are organised by federal state. Data relevant for the project are extracted from the ASHIPs’ databases and anonymised. Data are quarterly transferred to the Robert Koch Institute (RKI, German national public health institute), and imported into a central database. Since 2006, the database contains patient information, data on vaccinations and diagnoses of selected vaccine-preventable diseases, and since 2008, dates of individuals’ physician consultations (Table 1).

**Data protection**

The Federal Commissioner for Data Protection and Freedom of Information in Germany has approved the ASHIP vaccination monitoring project.

**Sampling and data preparation**

The unique patient identifier in the anonymised data is generated differently between ASHIPs. Therefore, medical services received by a single patient can only be assigned to a unique patient identifier in the data anonymised by a single ASHIP but not by different ASHIPs. As a consequence, we would identify an individual receiving the first varicella vaccine dose in one ASHIP region and the second dose in another region (e.g. due to moving into another federal state) as two individuals in the central database, both with incomplete vaccination series. For this reason, we selected individuals according to inclusion criteria as described previously [2,3]: Any individual (i) born between January 2006 and October 2013, (ii) receiving any vaccination (i.e. not necessarily varicella) soon after birth at 0–4 months of age, (iii) with contact with a physician within the second half of 2015, (iv) residing at the time points of (ii) and (iii) in the region of the ASHIP that transferred the data, and (v) born in an ASHIP region where diagnosis information was available and specific vaccination claim codes for varicella vaccines had been introduced since birth. Within this sampling period, i.e. from birth to the second half of 2015, the actual analysis time in the follow-up period went from the quarter in which the child turned 11 months until June 2015 at maximum. We assumed included children presented at physicians exclusively within their associated ASHIP region during the follow-up period because both in the beginning and in the end of the period, physician contacts were documented within their resident ASHIP region.

Data from 12 of 17 ASHIP regions were analysed, starting from either birth cohort 2006 (ASHIPs Brandenburg, Hamburg, Mecklenburg-West Pomerania, Lower Saxony, Saarland, Saxony-Anhalt, Schleswig-Holstein, Thuringia) or later birth cohorts due to late introduction of MMRV-specific claim codes, i.e. birth cohort 2007 (ASHIP Saxony) or 2008 (ASHIPs Baden-Württemberg, North Rhine, Berlin). Data from the remaining ASHIPs were either missing for several years, did not contain the variable ‘diagnosis type’, or were incomplete regarding physician contacts.

We applied a four-step algorithm to only select confirmed and incident (diagnosis type: current state) varicella diagnoses and to limit these to the earliest and to the most severe varicella diagnosis for each selected patient as described previously [6,7]. Briefly, step 1 excluded incompatible or implausible coding combinations for varicella diagnosis reliability; step 2 excluded observations with diagnosis reliability other than confirmed (i.e. suspected, excluded, recovered); step 3 excluded observations with diagnosis type other than incident (i.e. previous state, unknown, not provided); step 4 limited the data selection to the earliest ICD-10 code per patient while, in addition, keeping the information about the most severe ICD-10 code (within up to one quarter following the initial diagnosis) using the following ranking (in descending order of severity):
varicella with encephalitis, meningitis, pneumonia, other complications, no complications, no further details, with the latter equalling ‘no complications’.

The date of diagnosis was quarter-specific. Therefore, the unit of analysis time used in our models was one quarter of a year. Individual analysis time in the models started with the quarter in which the child turned 11 months of age (i.e. the ‘entry’ in the time-series analysis), and lasted until the last quarter of the follow-up period (i.e. the ‘exit’). We reduced the vaccination date from day-specific to quarter-specific for calculations of analysis time. Children with varicella vaccinations and/or a varicella diagnosis before the entry quarter were excluded from VE analysis. Due to the granularity of the date of diagnosis, we could reliably identify breakthrough infections, defined as varicella infection being diagnosed ≥ 42 days post vaccination, only when the vaccine was received at least three quarters preceding the diagnosis. We therefore excluded the first two quarters of analysis time of each vaccination status of a patient in the time-series models. Hence, this excluded patients with half a year or less of analysis time. We also excluded children where sex was not recorded and those with presumably erroneous documented VAR plus MMRV or MMRV plus MMR vaccinations on the same day.

Data analysis
Individual histories of first and second varicella vaccination and varicella diagnosis were set up for time-series analysis in Stata 13 (StataCorp, US). We used Cox-like piecewise proportional hazard models allowing for the analysis of potentially varying hazard ratios over TSV. We stratified the observations at an individual level into the period of > 0.5–1.0 years TSV and seven annual periods from > 1.0–2.0 to > 7.0–8.0 years TSV to analyse VE by TSV. For all other analyses of VE, we did not stratify the observation periods but performed the analysis over the whole TSV beginning at > 0.5 years TSV. The individual analysis time either ended due to censoring or failure, respectively, or stopped with each change of vaccination status while restarting at zero with assigning the patient’s new vaccination status.

We verified the proportional hazard assumption – a prerequisite for modelling Cox regression for time-series data – for each covariate and globally at the stratum level using formal significance tests and graphical evaluation of unscaled and scaled Schoenfeld residuals. Additionally, we performed graphical assessment of proportional hazards using log-log survival curves.

In the Cox regression model we used vaccination status and TSV as the categorical predictor variables. We stratified by sex, year of birth, and ASHIP to ensure comparing children of similar age and region. Strata were weighted using probability weights generated from sex-, birth cohort-, and ASHIP region-specific live-births and sample size (German Federal Statistical Office; State Office for Information and Technology North Rhine-Westphalia).

We calculated VE as ‘(1-hazard ratio) x 100’, and modelled incremental VE as the additional effectiveness provided by the second dose compared with a single dose ([VE2-VE1] / [100-VE1] x 100). We calculated VE in the whole sample but also by exclusion of children with incompliant spacing of vaccinations, i.e. varicella vaccinations given 1–27 days after MCV or subsequent varicella vaccine doses administered within 1–27 days. In addition, we built models which were either extended by the inclusion of variables for (i) type of vaccine (VAR, MMRV), (ii) age at first varicella vaccination (11–14 months; > 15 months of age), (iii) time to varicella vaccination following MCV (same day as MCV or > 27 days after MCV; incompliant spacing) excluding patients with incompliant spacing between varicella vaccinations, or (iv) time between first and second varicella vaccination (incompliant spacing; 28–365 days; > 1–3 years; > 3 years) excluding patients with incompliant spacing to MCV. We defined one group of outcome (no complications as failure and censored the patient in presence of the remaining outcome group (complications) and vice versa to estimate VE for the prevention of varicella-associated complications vs no complications. Using the Wald test, we tested for significant differences of coefficients and their interactions and applied a Bonferroni correction to the p values when multiple testing was performed.

The cumulative baseline hazards in the time-series analyses are the stratum-specific cumulative hazards in unvaccinated children. We used these to estimate morbidity among unvaccinated children stratified by sex, birth cohort and ASHIP. We used linear regression to summarise these cumulative hazards for both Saxony, an area with low VC, and the remaining ASHIP regions. The ratio of these mean cumulative hazards was used to compare the different degree of protection in regions with different VC. The risk R(t) of acquiring varicella up to time t can be derived from the cumulative hazard H(t) by applying the formula

\[ R(t) = 1 - e^{-H(t)} \]

In addition, we calculated attack rates from the observational data using probability weights (Pearson test statistics of the survey procedures in Stata) for Saxony and outside Saxony and compared them with each other in a rate ratio. We set the significance level to 0.05.

We calculated longitudinal VC both in Saxony and the remaining ASHIP regions as described previously by counting age-specific doses at an individual level by ASHIP/year of birth/sex and subsequent aggregation to VC by age within and outside Saxony [2,3].
Results
Between January 2006 and October 2013, a total of 5,294,301 live births were registered in Germany, of which 2,790,220 children (53%) were born in the investigated ASHIP regions and years of birth. Among those, 1,449,411 children (52%) were available for VE analysis (range over regions and years of birth: 35–69%). Their characteristics are given in Table 2.

Overall vaccine effectiveness
Over the total observation period and after exclusion of children with incompliant spacing between vaccine doses, VE for one dose (VE1) was 81.9% (95% confidence interval (CI): 81.4–82.5) and significantly lower (p < 0.0001) than VE2 with 94.4% (95% CI: 94.2–94.6) (Table 3). The incremental VE of adding a second dose to the first dose was 68.9% (95% CI: 67.5–70.1). Stratified by sex, the VE1 difference was less than 2 percentage points and slightly higher in females as compared with males (82.8% vs 81.1%, p = 0.0015); for VE2, the difference was even smaller (94.6% vs 94.2%, p = 0.0072). The inclusion of children with incompliant spacing had nearly no influence on VE (Table 3).

Vaccine effectiveness by time since vaccination and age
While VE1 increased over time from 79.4% (95% CI: 78.2–80.5) at >0.5–1.0 year TSV to 88.0% (95% CI: 76.6–93.8) at >7.0–8.0 years TSV, VE2 remained stable at >92.0% (Table 4).

Within the first year since vaccination, both VE1 and VE2 were slightly but significantly lower than in the following 3–5 time intervals. When stratifying by vaccine type, VE1 from VAR stayed in the same magnitude over time (80.6% (95% CI: 78.8–82.3) at >0.5–1.0 year TSV; 78.4% (95% CI: 47.7–91.1) at >7.0–8.0 years TSV) whereas VE1 from MMRV increased from 78.0% (95% CI: 76.4–79.5) to 92.0% (95% CI: 78.3–97.1). VE1 did not differ by age at first vaccination (82.1%; 95% CI: 81.4–82.8 in age group 11–14 months and 81.5%; 95% CI: 80.6–82.3 at ≥15 months; Table 3).

Effect of time between subsequent live attenuated vaccine doses
A single varicella vaccination given 1–27 days after MCV conferred significantly lower protection (VE1 = 32.2%, 95% CI: 10.4–48.6) than a single dose given simultaneously or >27 days after MCV (80.9%, 95% CI: 80.2–81.5) (Table 3). VE2 was not reduced when only one of the two doses was administered 1–27 days after MCV.

Two varicella vaccinations administered in an interval of 28–365 days gave statistically similar VE2 as vaccinations given 1–27 days, >1–3 years or >3 years apart. The VE2 estimate for varicella vaccinations 1–27 days apart was based on only 305 patients, was ca 8 percentage points lower than with any other time interval and had a wide 95% CI.

Vaccine effectiveness by vaccine type
We found similar VE1 for VAR and MMRV (82.0% (95% CI: 81.0–82.9) vs 81.7% (95% CI: 81.0–82.4), respectively) (Table 3). VE2 for all combinations of VAR and MMRV as first or second dose were also similar and

ASHIP: Association of Statutory Health Insurance Physicians.

Analysis time 0–0.5 years was omitted from hazard analysis. At time = 0, children are ca 11 months.

Linear fit (p < 0.001, R-squared = 0.94).
ranged between 94.3% (95% CI: 93.9–94.8) and 95.0% (95% CI: 94.3–95.5).

Protection against complicated vs non-complicated varicella

VE against varicella-associated complications (VE1 = 98.2%, 95% CI: 98.0–98.5; VE2 = 99.5%, 95% CI: 99.4–99.5) was significantly higher than against non-complicated varicella (VE1 = 65.3%, 95% CI: 64.2–66.4; VE2 = 89.3%, 95% CI: 89.0–89.7) with two doses being significantly more effective than a single dose.

Risk of acquiring varicella among unvaccinated children

VC in Saxony was lower than in other ASHIP regions over the whole age-range covered in the sample; e.g. at 24 months of age VC1 was 73.2% and VC2 was 25.3% in Saxony vs 90.1% and 68.3% outside Saxony (Figure 1). The attack rate of varicella in unvaccinated children was 12.6% (95% CI: 12.3–12.9) in Saxony vs 5.8% (95% CI: 5.7–5.9) in other regions translating into a rate ratio of 2.2 (95% CI: 2.1–2.2; p < 0.0001). The cumulative hazard and the risk of acquiring varicella among unvaccinated children were around two times higher in Saxony; e.g. after 4 years of analysis time we calculated a ratio of the cumulative hazards of 2.4, and a risk ratio of 2.2 corresponding to a cumulative hazard of 27.4% (95% CI: 27.4–27.5) in Saxony vs 11.3% (95% CI: 11.3–11.3) outside of Saxony, and after 7.5 years of analysis time the ratio of the cumulative hazards was 2.4 and the risk ratio 2.0, corresponding to a cumulative hazard of 58.3% (95% CI: 58.3–58.3) in Saxony vs 24.6% (95% CI: 24.6–24.6) in other regions (Figure 2).

Discussion

Starting from diagnoses and administered vaccinations as documented in health insurance claims and linked at the individual level, our analysis shows that the German IIS is a potent system for the continuous monitoring not only of VC but also of the effectiveness of vaccination and the impact of vaccination at the population level after widespread use. Our data confirm the additional effect of a second varicella vaccine dose and demonstrate indirect protection of unvaccinated individuals in areas with high VC.

Evidence on the loss of vaccine-induced protection after one dose has been inconclusive in previous studies [17–19]. Our data demonstrate the absence of waning of vaccine-induced protection by one and two doses over at least eight years. However, after the second dose, protection is much higher in each observed time interval after vaccination, with an overall incremental effectiveness of 68.9%. The result for VE1 is in line with data from a case–control study and a time-series approach in Germany where 86.4% and 83.2% were estimated [21,22]. Our findings are also comparable to the results of a recent German study based on the screening method and to international data from case–control studies where VE1 and VE2 were at 80–87% and 97–98%, respectively [13,14,15,23-26]. In addition, a 2016 meta-analysis of literature published between 1995 and 2014 on VE among healthy children reported similar results with a pooled VE1 of 81% (95% CI: 78–84) and a pooled VE2 of 92% (95% CI: 88–95) [27].

We found similar VE1 irrespective of young or older age at vaccination. Previously, evidence for vaccination at young age as a potential risk factor for vaccine failure has been reported inconclusively [28,29]. Our findings support the current national immunisation scheme recommending the first varicella dose at young age (from as early as 11 months) as recommended in the majority of countries that have adopted varicella vaccination [30].

VE1 was strongly reduced when the first varicella vaccination was administered with incompliant spacing to MCV. In contrast, VE2 estimates were not affected when one of the doses (first or second) were given with incompliant spacing to MCV. Due to small sample size, VE2 under the condition of both doses given with incompliant spacing could not be analysed. A higher risk for varicella due to a short spacing between the administration of MCV and a single varicella vaccine dose has been described previously [29]. Generally, a minimal time interval for the administration of live attenuated vaccines is recommended to avoid potential suppressive effects on the immune response. To our knowledge this has only been studied for vaccinations given up to 4 weeks after MMR vaccinations but not for successive varicella vaccinations [29,31,32]. In contrast to our result that two varicella vaccine doses may compensate the reduced VE of one dose given too early after MCV, the VE2 point estimate of the 1–27-day time interval between varicella vaccine doses was lower than for longer intervals. However, the sample size was small and the decrease was statistically non-significant. Still, this might indicate that a short spacing of subsequent varicella vaccinations negatively affects VE. This is of particular importance for accelerated schedules in situations like outbreaks, urgent catch-ups and for rapid immunisations before travelling. Overall, simultaneous administration of MCV and varicella vaccine or a time interval > 27 days between these vaccinations or between subsequent varicella vaccinations seemed to confer optimal protection against varicella. We found no significant difference in VE2 in all investigated time intervals > 27 days up to > 3 years between varicella doses, indicating that different national or regional recommendations regarding this interval will lead to similar VE2. This observation and our result that vaccine-induced protection is not waning, support the current recommendation in Germany for a second dose given early in childhood.

We found no statistical difference in VE from single-compound vs combined vaccines, neither for one dose nor in any two-dose combination. Also at the level of point estimates, VE was virtually similar. Although Spackova et al. identified differences in relative risk
point estimates for breakthrough infections by type of vaccine, their findings concerning the use of two single-compound vaccines and MMRV were non-significant [16]. Our finding shows that in particular the currently recommended combination of VAR followed by MMRV in Germany confers the same protection as any other combination.

Our results show that a single dose better protects against a more serious course of infection than against mild varicella. A second dose only adds a small additional benefit in this regard. Our results point towards the same direction as the results of previous observations, although the observed endpoints were different (recorded codes of diagnosis in our study vs observed symptoms or number of lesions in other studies) [27].

We found an around twofold higher attack rate and risk of acquiring varicella in unvaccinated children in Saxony vs other ASHIP regions. Saxony has a much lower VC for both first and second dose varicella vaccination than any other ASHIP region in Germany. Similar findings are annually published based on cross-sectional analyses from nationwide school entrance examinations [33]. Having its own state level advisory committee on immunisation, Saxony recommended until the end of 2014 the second varicella dose from five years of age [34]. The lower risk of acquiring varicella in the unprotected population in regions of Germany that have higher varicella VC than Saxony is a strong indication for the presence of herd effects. Varicella herd protection was described previously based on health insurance claims data showing a decline in varicella outpatient visits and hospitalisations among infants

### Table 1

Database content relevant to varicella disease and vaccination in the German Associations of Statutory Health Insurance Physicians vaccination monitoring project

<table>
<thead>
<tr>
<th>Patient information</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymised unique identifier</td>
<td></td>
</tr>
<tr>
<td>Month/year of birth</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>County of residence</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Vaccination information</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claim codes of all recommended vaccinations (antigen or antigen combination specific)</td>
<td></td>
</tr>
<tr>
<td>Date of vaccination</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis information</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella-specific ICD-10 codes [38]</td>
<td></td>
</tr>
<tr>
<td>B01. Varicella [chickenpox]</td>
<td></td>
</tr>
<tr>
<td>B01.0 Varicella meningitis</td>
<td></td>
</tr>
<tr>
<td>B01.1 Varicella encephalitis</td>
<td></td>
</tr>
<tr>
<td>B01.2 Varicella pneumonia</td>
<td></td>
</tr>
<tr>
<td>B01.8 Varicella with other complications</td>
<td></td>
</tr>
<tr>
<td>B01.9 Varicella without complication</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis type</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current state</td>
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</tr>
<tr>
<td>Previous state</td>
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</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Not provided</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis reliability</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Excluded</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quarter and year of diagnosis</th>
<th>Measure</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physician contact information</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s ASHIP</td>
<td></td>
</tr>
<tr>
<td>Date of patients’ first contact per quarter and medical specialisation</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10: International Classification of Diseases, 10th revision [38]; ASHIP: Associations of Statutory Health Insurance Physicians.

### Table 2

Data characteristics of individuals analysed in the time-series models for varicella vaccine effectiveness estimates, Germany, 2006–2015

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (%)</td>
<td>1,449,411 (100)</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>704,036 (48.6)</td>
</tr>
<tr>
<td>Number of varicella cases (%)</td>
<td>29,404 (2.0)</td>
</tr>
<tr>
<td>Mean years of age at diagnosis</td>
<td>3.6</td>
</tr>
<tr>
<td>Number of cases with complications (%) among cases</td>
<td>1,213 (4.13)</td>
</tr>
<tr>
<td>Encephalitis (%) among cases</td>
<td>33 (0.11)</td>
</tr>
<tr>
<td>Meningitis (%) among cases</td>
<td>129 (0.44)</td>
</tr>
<tr>
<td>Pneumonia (%) among cases</td>
<td>9 (0.03)</td>
</tr>
<tr>
<td>Other (%) among cases</td>
<td>1,042 (3.54)</td>
</tr>
<tr>
<td>Mean years of individual diagnosis time (total personyears)</td>
<td>3.0 (4,332,641)</td>
</tr>
<tr>
<td>Number of individuals receiving varicella vaccination (%)</td>
<td></td>
</tr>
<tr>
<td>No vaccination</td>
<td>92,712 (6.4)</td>
</tr>
<tr>
<td>1st dose</td>
<td>1,298,697 (89.6)</td>
</tr>
<tr>
<td>2nd dose</td>
<td>1,090,969 (75.3)</td>
</tr>
<tr>
<td>Number of administered vaccine type (%)</td>
<td></td>
</tr>
<tr>
<td>1st VAR</td>
<td>490,002 (33.8)</td>
</tr>
<tr>
<td>1st MMRV</td>
<td>808,695 (55.8)</td>
</tr>
<tr>
<td>2nd VAR</td>
<td>87,504 (6.0)</td>
</tr>
<tr>
<td>2nd MMRV</td>
<td>1,003,465 (69.2)</td>
</tr>
<tr>
<td>Mean months of age at vaccination</td>
<td></td>
</tr>
<tr>
<td>1st dose</td>
<td>15</td>
</tr>
<tr>
<td>2nd dose</td>
<td>22</td>
</tr>
<tr>
<td>Number of individuals receiving 1st vaccination by age (%) among 1st doses</td>
<td></td>
</tr>
<tr>
<td>11–14 months</td>
<td>1,030,331 (79.3)</td>
</tr>
<tr>
<td>≥ 15 months</td>
<td>268,366 (20.7)</td>
</tr>
<tr>
<td>Number of subjects with varicella vaccination after MCV (%)</td>
<td></td>
</tr>
<tr>
<td>At least one dose 1–27 days</td>
<td>5,434 (0.4)</td>
</tr>
<tr>
<td>All doses same day 01–27 days</td>
<td>1,293,263 (89.2)</td>
</tr>
<tr>
<td>Number of 2nd vaccinations by distance to 1st dose (%) among 2nd doses</td>
<td></td>
</tr>
<tr>
<td>1–27 days</td>
<td>2,862 (0.3)</td>
</tr>
<tr>
<td>28–365 days</td>
<td>919,711 (84.3)</td>
</tr>
<tr>
<td>&gt;1 year–3 years</td>
<td>148,198 (13.6)</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>20,198 (1.9)</td>
</tr>
</tbody>
</table>

MCV: measles containing vaccine; MMRV: measles-mumps-rubella-varicella vaccine; VAR: single-compound varicella vaccine.
and adults not targeted for vaccination in the United States [35].

The basis for our analyses are health insurance claims data primarily generated for the reimbursement of medical services provided by physicians. They have not been created for the purpose of answering epidemiological questions in secondary data analyses. However, reimbursement for vaccinations is directly linked to correct code usage. Hence, validity of vaccination data can be expected to be very high as we have previously shown [3]. Still, several MMRV claim code changes occurred soon after its availability.

Wrong usage will have led to misclassification of a second MMRV dose as the first dose in our IIS, which was more likely in the early years of the programme. This explains the increase of VE1 over higher intervals of TSV from MMRV but not VAR. Therefore, VE1 estimated from VAR may be a more accurate representation of VE over TSV. VE1 measured from both VAR and MMRV in the overall analysis, however, is nearly similar to VE1 measured from VAR alone suggesting that the potential misclassification is of minor consequence.

Our IIS covers all individuals in Germany with statutory health insurance. Between 2006 and 2015, an

### Table 3

Varicella vaccine effectiveness from > 0.5 to 8.0 years since vaccination based on estimates from time-series analysis, Germany, 2006–2015 (n = 1,449,411)

<table>
<thead>
<tr>
<th>Overall (excluding patients receiving varicella vaccinations 1–27 days after MCV or 1st and 2nd dose varicella 1–27 days apart)</th>
<th>VE1 (95% CI)</th>
<th>VE2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>81.9 (81.4–82.5)</td>
<td>94.4 (94.2–94.6)</td>
</tr>
<tr>
<td>Overall</td>
<td>81.8 (81.2–82.4)</td>
<td>94.4 (94.2–94.6)</td>
</tr>
<tr>
<td>Age at 1st vaccination&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11–14 months</td>
<td>82.1 (81.4–82.8)</td>
<td></td>
</tr>
<tr>
<td>≥15 months</td>
<td>81.5 (80.6–82.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Varicella vaccination after MCV (excluding patients receiving 1st and 2nd dose varicella 1–27 days apart)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st dose 1–27 days</td>
<td>32.2 (10.4–48.6)</td>
<td>No meaningful estimate (n = 261 varicella case)</td>
</tr>
<tr>
<td>1st dose same day or &gt;27 days</td>
<td>92.8 (84.8–96.6)</td>
<td></td>
</tr>
<tr>
<td>Time interval 1st to 2nd dose (excluding patients receiving varicella vaccinations 1–27 days after MCV)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–27 days</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>28–365 days</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;1–3 years</td>
<td>94.8 (94.4–95.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>95.0 (93.6–96.1)</td>
<td></td>
</tr>
<tr>
<td>Vaccine type&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st dose VAR</td>
<td>82.0 (81.0–82.9)</td>
<td>95.0 (94.3–95.5)</td>
</tr>
<tr>
<td>1st dose MMRV</td>
<td>81.7 (81.0–82.4)</td>
<td>94.4 (93.4–95.2)</td>
</tr>
<tr>
<td>Prevention of uncomplicated/complicated cases&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complication</td>
<td>65.3 (64.2–66.4)</td>
<td>89.3 (89.0–89.7)</td>
</tr>
<tr>
<td>All complications</td>
<td>98.2 (98.0–98.5)</td>
<td>99.5 (99.4–99.9)</td>
</tr>
</tbody>
</table>

CI: confidence interval; MCV: measles containing vaccine; MMRV: measles-mumps-rubella-varicella combination vaccine; NA: not applicable; VAR: single-compound varicella vaccine; VE: vaccine effectiveness; VE1: vaccine effectiveness for one dose; VE2: vaccine effectiveness for two doses.

<sup>a</sup> VE1 difference not significant.

<sup>b</sup> Within VE1, VE is significantly different (p < 0.0001); within VE2 and where applicable, no combination with VE from both doses administered 0 / >27 days apart significantly different.

<sup>c</sup> No combination with VE at 28–365 days significantly different.

<sup>d</sup> Within VE1 and VE2, no combination significantly different.

<sup>e</sup> In contrast to the outcome ‘varicella’ in the majority of models, here we defined ‘varicella without complications’ as failure and censored the patient in presence of ‘varicella with associated complications’ and vice versa to estimate VE.

<sup>f</sup> Within VE1 and VE2 and between VE1 and VE2 difference significant (all p < 0.0001).

All given VE estimates are significant.
average of 83% among 0–14 year-olds (range between ASHIP regions: 81–89%) were statutory health insured (statistics of statutory health insurers by the German Ministry of Health; population statistics by the Federal Statistics Office). Both statutory and private health insurances fully reimburse recommended vaccinations. The authors of a large population-based cross-sectional study found no difference in the proportions of undervaccinated children when comparing children from parents with statutory and private health insurance [36]. Thus, we assume comparable VC and VE in children not covered by the IIS.

Diagnoses from health insurance claims data have been exploited for measles incidence estimation and showed trends and variation similar to outpatient notification data estimates supporting their usefulness for epidemiological analyses [7]. However, there are no standardised guidelines for coding and updating diagnoses as ‘confirmed’ or ‘suspected’ disease. The physician does not require laboratory confirmation for this classification and may solely rely on clinical symptoms. Since we used only confirmed cases, our sampling approach for cases might have been rather conservative. Nonetheless, physicians may feel more confident in classifying a diagnosis as confirmed in unvaccinated cases. Because patients with mild disease are less likely to present at their physician while the probability of a mild course of the disease is higher for vaccinated cases, a bias might have been introduced in our study population which would result in an overestimation of overall VE but not VE for the prevention of severe varicella. We identified 4.13% of complications among all cases. This is in line with previous reports of 2–6% of cases with complications attending a general practice [37]. However, since health insurance claims data only cover outpatient data and complicated cases are more likely to be hospitalised and less likely to (at least initially) present as outpatient case, these cases are possibly underrepresented in our sample and therefore not included in the analysis. In 2004, a total of 2,316 hospitalised varicella cases were recorded in the statistics of hospital diagnoses followed by a decreasing trend to around 1,000 cases from 2008 until 2014 and an increase to 1,504 cases in 2015 (Federal Statistics Office). The decrease was especially prominent in children below 5 years of age, ranging from 1,139 cases in 2004 to 159 and 207 cases in 2014 and 2015, respectively. Since severity is associated with not being vaccinated, hospitalised cases among unvaccinated children may be disproportionately underrepresented in our sample. This bias may have led to a slight underestimation of our calculated VE.

Our IIS was implemented in 2004 and – after successful validations and extensive piloting – serves as a unique source to monitor and evaluate vaccination recommendations and strategies in Germany. The system provides VC data for the international reporting to the World Health Organization and informs the National Verification Committee for Measles and Rubella Elimination on the elimination progress in Germany, since it currently offers the only nationwide data source to estimate VC in various age groups. In
addition, since vaccination claims and disease codes can be linked at an individual level and the IIS captures a large proportion of the total population, it provides the opportunity to assess VE and vaccination programme impact at a population level. When the German Standing Committee on Vaccination initially endorsed the two-dose recommendation for varicella vaccination, it requested an evaluation by 2013. The IIS was one of four surveillance data sources that contributed to this evaluation [20]. There were some remaining questions that we were able to address in the present study, namely the duration of varicella vaccine-induced protection after two doses, the optimal age for the second dose, and potential differences in VE between the available varicella vaccine types.

By demonstrating that we were able to answer important questions related to the national varicella vaccination programme, we conclude that our IIS is an indispensable system not only for the assessment of VC in various age groups and geographical regions in Germany, but also for the monitoring and in-depth evaluation of national vaccination recommendations and strategies.

Acknowledgements

We thank all Associations of Statutory Health Insurance Physicians for providing claims data. This work was supported by the German Ministry of Health (grant number: IIA-2511NIK001/321-4533-06). The funding source was not involved in study design or collection, analysis and interpretation of data.

Conflict of interest

None declared.

Authors’ contributions

Mr Rieck conceptualised and designed the study, analysed and interpreted data, and drafted the article.

Mr Feig built and managed the database.

Dr an der Heiden provided statistical support.

Drs Siedler and Wichmann provided important intellectual input in the various steps of the study and revised the manuscript critically.

All authors approved the final manuscript.

References


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Written reminders increase vaccine coverage in Danish children - evaluation of a nationwide intervention using The Danish Vaccination Register, 2014 to 2015

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We evaluated a national intervention of sending written reminders to parents of children lacking childhood vaccinations, using the Danish Vaccination Register (DDV). The intervention cohort included the full birth cohort of 124,389 children born in Denmark who reached the age of 2 and 6.5 years from 15 May 2014 to 14 May 2015. The reference cohort comprised 124,427 children who reached the age of 2 and 6.5 years from 15 May 2013 to 14 May 2014. Vaccination coverage was higher in the intervention cohort at 2.5 and 7 years of age. The differences were most pronounced for the second dose of the measles-mumps-rubella vaccine (MMR2) and the diphtheria-tetanus-pertussis-polio vaccine DTaP-IPV4 among the 7-year-olds, with 5.0 percentage points (95% confidence interval (CI): 4.5–5.4) and 6.4 percentage points (95% CI: 6.0–6.9), respectively. Among the 2.5 and 7-year-olds, the proportion of vaccinations in the preceding 6 months was 46% and three times higher, respectively, in the intervention cohort than the reference cohort. This study indicates a marked effect of personalised written reminders, highest for the vaccines given later in the schedule in the older cohort. In addition, the reminders increased awareness about correct registration of vaccinations in DDV.

Introduction
Immunisation is one of the most successful and cost-effective [1] primary prevention tools in both low- [2] and high-income settings [3]. It is a public health priority to obtain a high vaccination coverage in the population to reduce the burden of vaccine-preventable diseases (VPD) [4]. However, in many high-income countries, the coverage rates are still below the target levels established by international [4] and national advisory committees [5]. The ongoing transmission of measles in Europe shows the consequences of the low coverage rates [6,7], missing the World Health Organization (WHO) goal of elimination [8].

In Denmark, all recommended childhood vaccinations are administered free of charge by the general practitioners (GPs). Still, Danish coverage rates for the second measles-mumps-rubella vaccination (MMR2) and the diphtheria-tetanus-pertussis-polio vaccine DTaP-IPV4 among the 7-year-olds, with 5.0 percentage points (95% confidence interval (CI): 4.5–5.4) and 6.4 percentage points (95% CI: 6.0–6.9), respectively. Among the 2.5 and 7-year-olds, the proportion of vaccinations in the preceding 6 months was 46% and three times higher, respectively, in the intervention cohort than the reference cohort. This study indicates a marked effect of personalised written reminders, highest for the vaccines given later in the schedule in the older cohort. In addition, the reminders increased awareness about correct registration of vaccinations in DDV.

A Cochrane review from 2005 of patient-reminder studies in Australia, Canada, Denmark, New Zealand, the United Kingdom and the United States (US) concluded that reminder and recall interventions increased the proportion of children being vaccinated [11]. Current evidence supports the use of postal reminders as part of a standard management of childhood immunisations [12].

The recommended childhood vaccination schedule for children from birth to five years is shown in Table 1 [13].

In Denmark, a national electronic Immunisation Information System (the Danish Vaccination Register (DDV)) contains information on all vaccinations given in the childhood vaccination programme since 1996 [14]. Linkage of data from DDV with other administrative registers using the Danish personal identification number provides a unique opportunity to implement a national intervention aimed at parents of children with missing vaccinations.
In 2014, a change in the health legislation allowed Statens Serum Institut (SSI) to use the DDV to send written reminders to parents with missing childhood vaccinations at 2, at 6.5, and at 14 years of age [15]. Implementation of the intervention began on 14 May 2014. The time points for sending out reminders were selected based on the Danish childhood vaccination schedule and manageable administrative practices [16].

The aim of the present study was to assess the effect of the first year of this nation-wide intervention on the vaccination coverage in Denmark.

Methods

Design and population
This study focused on an intervention caused by a policy change. The intervention cohort comprised children who turned 2 and 6.5 years and lived in Denmark between 15 May 2014 and 14 May 2015 and the reference cohort comprised children who turned 2 and 6.5 years of age between 15 May 2013 and 14 May 2014, the year before the national intervention was implemented. The vaccination coverage by vaccine type was compared for the intervention and the reference cohort at 2.5 and 7 years of age, so that the follow-up period was 6 months for every child in the study.

Civil registry system
In Denmark, all residents are assigned a unique personal identification number (CPR number) that is recorded in the civil registry system. The system includes information on date and place of birth, date of immigration and emigration, previous and present place of residence and links to family relations including siblings, parents, and parent custody information. The birth cohorts were identified in the civil registry system.

The Danish Vaccination Register
The Danish Vaccination Register (DDV) is a national immunisation system comprising all citizens in Denmark. The DDV contains information on all vaccinations given in the childhood vaccination programme from 1996 onwards, including the CPR number of the recipient, date of vaccination, name and Anatomical Therapeutic Chemical (ATC) classification group of the vaccine and identification on the vaccine provider. In Denmark, vaccines are administered by general practitioners (GPs). Since 2013, citizens have had online access to their own and their children’s vaccinations status and health professionals can access the patients’ vaccination status. In case registration of previous vaccinations was missed, both patients and doctors can register historical vaccinations online. Data registered by parents are validated by the GP [14]. Effective from 15 November 2015, real-time reporting of all vaccinations administered by medical doctors and their assistants has become mandatory.

The reminder database
The reminder system was implemented on 15 May 2014. All children who turn 2, 6.5 and 14 years lacking at least one vaccination in the childhood vaccination programme are identified in the DDV. Reminders concern all vaccinations in the childhood programme except for the pneumococcal conjugate vaccine, which is not recommended in the Danish childhood vaccination programme for children older than 2 years, and the Haemophilus influenzae b vaccine, which is combined with the DTaP-IPV and recommended for children younger than 6 years. For 2- and 6.5-year-old children, the reminder is sent to the parent in custody of the child. If the parents have joint custody but do not share the same address, the reminder is sent to both parents [16]. Information on all written reminders is saved in a database.

Main outcome measures
The number of administered vaccinations was calculated on an individual level as the number of vaccines in the ATC groups used in the Danish childhood vaccination programme that contain MMR (J07BD52, J07BD53, J07BD54, J07BD01 and J07BE01) and DT (J07AF01, J07CA06, J07CA09, J07CA11, J07CA02, J07CA12, J07AI52 and J07CA01). Timing of vaccinations and minimum intervals between vaccinations were not taken into account.

To compare the time–response relationship between receiving reminders and registered vaccinations in the intervention with the reference cohort, the numbers of vaccines registered where calculated for a 6-month period after the children turned 2 and 6.5 years.

Statistical methods
Data analysis was conducted using Stata (Version 12, StataCorp, College Station, Texas) and SAS software version 9.4 (SAS Institute Inc., Cary).

### Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>DTaPHib-IPV1 + PCV1</td>
</tr>
<tr>
<td>5 months</td>
<td>DTaPHib-IPV2 + PCV2</td>
</tr>
<tr>
<td>12 months</td>
<td>DTaPHib-IPV3 + PCV3</td>
</tr>
<tr>
<td>15 months</td>
<td>MMR1</td>
</tr>
<tr>
<td>4 years</td>
<td>MMR2</td>
</tr>
<tr>
<td>5 years</td>
<td>DTaP-IPV4</td>
</tr>
</tbody>
</table>

Vaccines are offered free of charge and administered by general practitioners. Reminders were issued for all vaccines except Hib and PCV.

DTaPHib-IPV: vaccine against diphtheria, tetanus, acellular pertussis, Haemophilus influenzae b, inactivated poliovirus; MMR: measles-mumps-rubella vaccine; PCV: pneumococcal conjugate vaccine.
For each cohort, vaccination coverage was calculated as the percentage of children alive and living in Denmark who had received a vaccine registered in the DDV. We counted all vaccines without considering the reported dose, as the dose number is often incorrect. The change in vaccination coverage after receiving a written reminder was calculated as the differences in vaccination coverage between the intervention and the reference cohorts among children aged 2.5 and 7 years (vaccine coverage difference measured in percentage points).

Ethical considerations
The study was purely register-based and was notified to the Danish Data Protection Agency with record number 2008–54–0474. Parents of children who were not fully vaccinated were contacted as part of the intervention [15].

Results
A total of 124,189 children were included in the intervention cohort. In the study period, reminder letters were sent to parents of 43,288 children (22,621 boys and 20,667 girls). Among the 2-year-olds, 27% (15,628/57,770) missed at least one vaccination and among the 6.5-year-olds, it was 42% (27,660/66,419). For 6,970 children, letters were sent to two parents because of divorce and joint child custody. A total of 423 letters were returned to sender unopened, and 56 parents made a request by either letter or encrypted email to opt out of the vaccination notification service.

In general, the vaccination coverage was highest for the first vaccinations in the schedule, with coverages reaching 90% and above for the two first DTaP-IPV vaccines, and the largest effect of the reminder letters was seen among the older children, Table 2. For the 2.5-year-olds, we saw for all vaccines in the intervention group a statistically significantly higher vaccination coverage of 1–2 percentage points for DTaP-IPV and 3.9 for MMR1. For the 7-year-olds, the difference was most pronounced for MMR2 and DTaP-IPV4: 5.0 percentage points (95% confidence interval: 4.5–5.4) and 6.4 percentage points (95% CI: 6.0–6.9), respectively. Stratifying by sex did not change the estimates.

Vaccine registration in a 6-month follow-up period
Table 3 displays the number of vaccines registered in the 6-month period after the child turned 2 or 6.5 years for the intervention and reference cohorts. Overall, among the 2.5-year-olds, the proportion of registered vaccines in the 6-month follow-up period was 46% higher in the intervention cohort compared with the reference cohort. In the 7-year-olds, this proportion was three times higher in the intervention compared with the reference cohort.

In the intervention cohorts, 15,061 DTaP-IPV and MMR vaccines were registered in the following 6 months. In the reference cohort a markedly smaller number of 7,010 vaccines where registered in the 6-month period. Most vaccines were administered within the follow-up period, but 9.3% of vaccines among 2-year-olds and 20.7% among 6.5-year-olds where registered directly in

---

**Table 2**

<table>
<thead>
<tr>
<th>Number of vaccine doses received</th>
<th>2.5 years</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>7 years</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>DTaP-IPV 1</td>
<td></td>
<td></td>
<td>56,890</td>
<td>96.5</td>
<td>56,337</td>
<td>97.5</td>
<td>1.0</td>
<td>(0.8–1.2)</td>
<td>63,555</td>
<td>97.1</td>
<td>64,996</td>
</tr>
<tr>
<td>DTaP-IPV 2</td>
<td></td>
<td></td>
<td>55,759</td>
<td>94.6</td>
<td>55,210</td>
<td>95.6</td>
<td>1.0</td>
<td>(0.7–1.2)</td>
<td>61,793</td>
<td>94.4</td>
<td>63,308</td>
</tr>
<tr>
<td>DTaP-IPV 3</td>
<td></td>
<td></td>
<td>49,869</td>
<td>84.6</td>
<td>50,019</td>
<td>86.6</td>
<td>2.0</td>
<td>(1.6–2.4)</td>
<td>58,562</td>
<td>89.4</td>
<td>60,806</td>
</tr>
<tr>
<td>MMR1</td>
<td></td>
<td></td>
<td>50,640</td>
<td>85.9</td>
<td>51,879</td>
<td>89.8</td>
<td>3.9</td>
<td>(3.5–4.3)</td>
<td>61,684</td>
<td>94.2</td>
<td>63,525</td>
</tr>
<tr>
<td>MMR2</td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>50,108</td>
<td>76.5</td>
<td>54,133</td>
</tr>
<tr>
<td>DTaP-IPV 4</td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>44,556</td>
<td>68.0</td>
<td>49,462</td>
</tr>
</tbody>
</table>

CI: confidence intervals; DTaP-IPV: diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine; MMR: measles-mumps,-rubella vaccine. NA: not applicable; VCD: vaccination coverage difference.

We calculated the ratio of children who received the vaccination per number of children in the birth cohort, alive and living in Denmark. Coverage was assessed at 6 months after the child turned 2 or 6.5 years in the period from 15 May 2014 to 14 May 2015 for both the reminder and the intervention cohort. The vaccination coverage by vaccine type was compared for the intervention and the reference cohort at 2.5 and 7 years of age, so that the follow-up period was 6 months for every child in the study.
the DDV by a doctor or a parent with a vaccination date that was before receiving the reminder.

Table 4 shows the total number of vaccines registered in the 6-month follow-up period. Of these, some were previously given vaccines now registered by citizens or doctors in the DDV. In the intervention cohort, a proportion of vaccines (9% and 21%) had been administered before the intervention and reflects registration of historic vaccinations that had not previously been registered in the DDV. This was mainly seen for the intervention cohort because information on the possibility to register historic vaccinations was included in the reminder letter.

Discussion
A simple intervention of sending out written reminders increased the vaccination coverage. The effect was higher for the children at 6.5 years than 2 years of age and the strongest effect was observed for the DTaP-IPV4 vaccine. Here, the coverage was 6.4 percentage points higher in the intervention group than in the reference group. The increase in coverage was mostly due to administration of vaccines but also due to increased compliance with registering previously given vaccines in the DDV. This study showed that it is feasible to use a national immunisation register for sending out written reminders to parents of children who lack vaccines in the childhood vaccination programme.

The uptake was highest for the first vaccines in the schedule. Participation in well-child visits decreases after the child has turned 1 year and parents may therefore not be reminded of the importance of adhering to the childhood vaccination programme. In addition, parents’ lack of time after having re-entered work after the 12-month parent leave customary in Denmark may have an impact. During maternal/paternal leave there is higher flexibility for immunisation appointments without having to accommodate a work schedule [9]. Another hypothesis is that parents may assume that a delayed vaccination cannot be caught up after a substantial period of time has passed and therefore disregard the importance of fulfilling a vaccination series. An official reminder may affect this notion.

Among the two and 6.5-year-olds in the intervention groups, we saw a significantly increased coverage 6 months after the intervention for all the vaccines. The increase was most pronounced for the two latest vaccines in the schedule. A possible explanation why the effect in the youngest age group was smaller could be that the children lacking vaccinations are delayed in their schedule and would have received the vaccinations later, regardless of the reminder. These results indicate that it may be inefficient to distribute reminders close to the scheduled date for each vaccine and that the optimal age in this study was in the older children. The larger number of vaccines registered in the intervention cohort in the first 6 months after reminder, compared with the reference cohort, supports the fact that the effect we experience is an actual increase in vaccines administered and not just a persistent difference between the two cohorts.

### Table 3
Vaccine doses registered in the 6-month follow-up at ages 2 and 6.5 in reference (n = 124,427) vs intervention cohort (n = 124,189), and the ratio (intervention vs reference), Denmark, 15 May 2013–14 May 2015

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vaccine doses received in 2.5 years</td>
<td>N = 58,943</td>
<td>N = 57,770</td>
<td>Δn (Δn(95% CI))</td>
<td>N = 65,484</td>
<td>N = 66,419</td>
<td>Δn (Δn(95% CI))</td>
</tr>
<tr>
<td>DTaP-IPV 1</td>
<td>61</td>
<td>155</td>
<td>2.59 (1.93–3.48)</td>
<td>95</td>
<td>247</td>
<td>2.56 (2.02–3.24)</td>
</tr>
<tr>
<td>DTaP-IPV 2</td>
<td>123</td>
<td>289</td>
<td>2.39 (1.94–2.95)</td>
<td>57</td>
<td>241</td>
<td>4.16 (3.12–5.55)</td>
</tr>
<tr>
<td>DTaP-IPV 3</td>
<td>642</td>
<td>1,319</td>
<td>2.07 (1.89–2.28)</td>
<td>222</td>
<td>745</td>
<td>3.28 (2.83–3.81)</td>
</tr>
<tr>
<td>MMR1</td>
<td>3,884</td>
<td>5,211</td>
<td>1.34 (1.29–1.39)</td>
<td>416</td>
<td>523</td>
<td>1.24 (1.09–1.41)</td>
</tr>
<tr>
<td>MMR2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>558</td>
<td>2,405</td>
<td>4.41 (3.77–4.53)</td>
</tr>
<tr>
<td>DTaP-IPV 4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>952</td>
<td>3,926</td>
<td>3.89 (3.63–4.18)</td>
</tr>
<tr>
<td>Total</td>
<td>4,710</td>
<td>6,974</td>
<td>1.46 (1.41–1.51)</td>
<td>2,300</td>
<td>8,087</td>
<td>3.20 (3.06–3.35)</td>
</tr>
</tbody>
</table>

CI: confidence intervals; DTaP-IPV: diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine; MMR: measles-mumps-rubella vaccine. NA: not applicable.

We calculated Δn as the number of vaccines administered during the study period, and the ratio of intervention vs reference cohort.
In an era of increasing complexity of immunisation schedules, it is important to understand and promote interventions that work. Studies have shown that patient reminder and recall systems in primary care settings are effective in improving immunisation rates in developed countries [11]. Our findings support the review by Harvey et al. who concluded that postal reminders are an effective measure [12]. Our national reminder system based on data linkage with an immunisation register is, to our knowledge, unique to Denmark, although immunisation registers are currently in place or under development in several other countries.

Beyond improving immunisation rates, reminders have additional benefits for the patient and practice. Studies have shown that patients who do not comply with immunisation programmes are likely not to comply with other measures of preventive care either [17], and that immunisation reminder or recall systems also improve other preventive care measures [18].

A study from 2007 showed that forgetfulness or oversights was the most frequent explanation for missing vaccines in Danish children [9]. A written reminder intervention may target this group of parents, while this type of intervention will not be effective in parents who do not want to vaccinate their children. The finding of the present study corroborates that the majority of lacking vaccines is explained by oversights [9,10,19]. We experienced only a small number of parents who actively opted out of the programme (n = 56, corresponding to a frequency of 0.001%), but this does of course not take into consideration parents ignoring the reminder letter. In agreement with previous findings in Denmark [9], Smith et al. found in a US study that reasons other than negative vaccine-related beliefs accounted for the vast majority of unvaccinated children and adolescents [20].

**Strength and limitations**

To our knowledge, this is the first evaluation of a written reminder service based on a national immunisation information system that covered complete birth cohorts. The study was large and nationwide and included all Danish children who turned 2 and 6.5 years in a 2-year period. The major strength of our study was the use of individual data from population-based registries covering the total population with complete follow-up. Further, children included in the analyses were from adjacent birth cohorts, minimising the risk of bias do to time-dependent factors.

Childhood vaccinations reimbursed by the Danish healthcare regions to the GPs are registered in the DDV. We recognise that there may be missing vaccine registrations. In 2013, Wójcik et al. validated the Danish childhood vaccination database in regards to the coverage of the DTaP-IPV4 and identified under-reporting estimated to 3–4 percentage points, mainly due to GPs not registering given vaccinations [10]. Our findings that at least 15% of the registered vaccinations in the follow-up period were administered before the reminder was received can be regarded as a measure of under-registration in the DDV. An additional positive effect of the reminder intervention was raised awareness about registration of vaccinations among GPs and the general population and led to an improvement of the immunisation register data.

For calculation of vaccination coverage, we counted all vaccines without considering the reported dose, as the dose number is often incorrect. In case of missing registrations of vaccines, this method leads to a ‘false’ low coverage for the later vaccines in a series and possibly an underestimation of the effect of the reminder on the first vaccines in a series. The false low coverage is, however, the case for both the intervention and reference cohorts. The vaccine type-specific vaccination coverages presented in this study may differ from nationally reported coverage data, which calculates coverage including dose code.

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**Table 4**

| Vaccines registered by parents or doctors in the Danish Vaccination Register in the 6 month follow-up period in the intervention and reference cohorts, Denmark, 15 May 2013–14 May 2014 (reference) and 15 May 2014–14 May 2015 (intervention) |
|-------------------------------|-----------------|-----------------|-----------------|-------------------|
|                               | Total number of vaccines registered in 6 months after reminder date | Vaccines registered by parents with vaccination date before reminder date | Vaccines registered by GP’s with vaccination date before reminder date | Delayed vaccine registration |
|                               | N | n | n | % |
| **2.5 years**                 |   |   |   |   |
| Intervention cohort           | 6,974 | 487 | 159 | 9.3 |
| Reference cohort              | 4,710 | 0  | 3  | 0.1 |
| **7 years**                   |   |   |   |   |
| Intervention cohort           | 8,087 | 1,323 | 354 | 20.7 |
| Reference cohort              | 2,300 | 0  | 0  | 0.0 |

GP: general practitioner.
We are not aware of recommendations or previous studies on the most appropriate time for follow-up after sending written reminders. As it may take some time from receipt of reminder until the parents make a vaccination appointment, we evaluated a possible effect after six months.

Natural experimental studies enable us to study effects in a whole population or, in this case, a whole subgroup of the population [21]. Due to the applied design of a reference consisting of a pre-intervention cohort, any time-dependent factors affecting the coverage may complicate conclusions of causality. A randomised controlled trial would have been the strongest evaluation strategy, but the nature of the nationwide policy change evaluated in this study precluded this possibility. We cannot rule out the possibility that differences in our intervention cohort and the previous year’s cohort could be due to other factors, as we cannot fully disclose all possible measures of effect on the vaccination coverage. It is possible that the media attention given to measles outbreaks as in the US [22,23] and in Germany [6,24] had a positive influence on the awareness of communicable infectious diseases and subsequently on the vaccination coverage in the childhood vaccination programmes. However, this attention should have had a similar impact on both the intervention and reference groups. On the other hand, there has been heated parallel debate in the Danish media on perceived adverse events to the human papillomavirus vaccine and a dramatic drop in HPV vaccination coverages among 12–14-year-old girls in Denmark, with only 16% of girls born in 2003 finishing the vaccination programme compared with 79% of girls born in 2000 [25]. This may have affected the vaccination coverage of other childhood vaccinations negatively. In addition, several healthcare regions in Denmark have implemented different reminder systems where GPs are informed about unvaccinated children connected to their practice. However, to our knowledge, these interventions have been the same for the two cohorts and we therefore assume that they did not seriously affect the interpretation of our results. That more vaccines were administered in the follow-up period in the intervention cohort than in the reference cohort leads us to believe that this was true effect of the intervention.

As the reminders were send out as a national policy, various stakeholders reviewed the wording, and due to legal constraints, it is currently not possible to test wording in an RCT approach. Therefore, the effect of any changes in the reminder system can only be followed in the target groups at the national level.

Our data were generated by sending out letters to parents of a 43,288 children registered with missing vaccines in the DDV. Denmark is a country with a high level of both interpersonal trust and trust in the authorities [26] and it is therefore plausible that a large percentage of the letters where in fact opened and acted on, which is not necessarily true for other countries with lower levels of trust.

**Implications**

A reminder is just one of the tools that can be used to raise the coverage. The WHO Regional Office for Europe has developed The Guide to Tailoring Immunisation Programmes (TIP) which aims to provide methods and tools to identify susceptible populations, determine barriers to vaccination and implement evidence-based interventions [27]. This approach has already been applied in Sweden [28].

The current intervention only comprised sending written catch-up reminders to certain age groups. We have not reached the target vaccination coverage and could have hoped for a better response. More research is needed to understand how wording, format, timing of sending out the reminders as well as resending reminders affect the response. However, it is clear from the current study that reminders cannot stand alone in the efforts to increase vaccination coverage. On the other hand, the costs of the reminder system have been low, with DKK 1.7 million (EUR 229,000) in the developmental stage and a yearly operational cost of DKK 1 million (EUR 134,000). Since November 2016, we have been sending electronic reminders at the same time points as described in the study, which is an even cheaper solution. How this will affect the coverage is of great importance and must be evaluated in the coming years. Technically, it would also be feasible to send out electronic reminders both before and after scheduled vaccination, and more advanced reminder systems are currently under development. Odene et al. concluded that although the use of other communication channels such as websites and mobile phone apps has great potential, the data are scant for now [29]. The change to mandatory registration of vaccines by doctors may lead to more timely and complete registration in the register, which also needs to be further evaluated. Several countries are currently developing IIS and may have an opportunity to implement similar reminder interventions. However, the effect may be influenced by cultural settings and organizational practices that differ from country to country.

**Conclusions**

Our evaluation showed that written reminders increased vaccination coverage. The reminders are also likely to have an indirect effect by increasing awareness about correct registration of vaccines in the immunisation register. Immunisation registers have already proven extremely useful in providing reliable information on vaccination coverage and supporting studies on vaccine effectiveness and safety. The study presented here showed that the immunisation register can also be used for reminder services, which may have the potential to improve coverage in national vaccination programmes.
Acknowledgements

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Conflict of interest

None declared.

Authors' contributions

The idea for this study was conceived by Camilla Hiul Suppli and Tyra Grove Krause. Camilla Hiul Suppli performed the literature search, conducted statistical analysis and produced the first draft manuscript. All co-authors participated in the preparation of the paper and the various revisions of the manuscript.

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Perspective

Suboptimal MMR2 vaccine coverage in six counties in Norway detected through the national immunisation registry, April 2014 to April 2017

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In 2014, Norway became aware of potential low vaccination coverage for the second dose of measles-mumps-rubella vaccine (MMR2) in six of 19 counties. This was detected by comparing the national coverage (NC) for 16-year-olds extracted from the national immunisation registry SYSVAK with the annual status update for elimination of measles and rubella (ASU) reported to the World Health Organization (WHO). The existing method for calculating NC in 2014 did not show MMR2 coverage. ASU reporting on MMR2 was significantly lower then the NC and below the WHO-recommended 95% coverage. SYSVAK is based on the Norwegian personal identification numbers, which allows monitoring of vaccinations at aggregated as well as individual level. It is an important tool for active surveillance of the performance of the Norwegian Childhood Immunisation Programme (NCIP). The method for calculating NC was improved in 2015 to reflect MMR2 coverage for 16-year-olds. As a result, Norway has improved its real-time surveillance and monitoring of the actual MMR2 coverage also through SYSVAK (the annual publication of NC). Vaccinators receive feedback for follow-up if 15-year-olds are missing MMR2. In 2017, only three counties had an MMR2 coverage below 90%.

Background

The Norwegian national immunisation registry
The Norwegian immunisation registry SYSVAK is a national Immunisation Information System (IIS) administered by the Norwegian Institute of Public Health (NIPH) [1]. SYSVAK is legally anchored in the Norwegian law for Health Registries [2] and the SYSVAK regulation [3]. It has been nationwide since 1995 and covers all vaccinations in all age groups. Registrations of vaccinations in SYSVAK are based on the unique personal identification numbers assigned to people registered in the National Registry (population registry of Norway [4]). Since November 2015, SYSVAK has also covered persons applying for asylum in Norway. The population of Norway was 5.2 million people on 1 January 2017 [5]. It is mandatory for health personnel to report all vaccinations offered through the Norwegian Childhood Immunisation Programme (NCIP) [6] to SYSVAK [3]; consent from the vaccinee is not required. On 31 December 2016, SYSVAK contained more than 34 million vaccine entries for more than 4.1 million persons. SYSVAK offers the possibility to produce a snapshot status of the vaccination coverage against a disease at any given time. This can be done for the Norwegian population in general, for targeted geographical areas (at national, county, municipality and district level) and at an individual level. For further details on SYSVAK see Trogstad et al. [1].

The Norwegian childhood immunisation programme
Measles vaccine was introduced in the NCIP in 1969. Rubella vaccine has been offered to girls since 1978. In 1983, two doses of the measles-mumps-rubella combination vaccine (MMR) was introduced to both sexes and replaced the monovalent vaccines. The current NCIP foresees MMR1 at age 15 months and MMR2 at age 11–12 years. It is primarily public healthcare stations and school healthcare services who offer NCIP vaccinations in Norway. All services, including vaccinations, are voluntary and free of charge.

All countries in the World Health Organization (WHO) European Region have committed to eliminate measles and rubella by 2015. One of the strategies is to achieve and sustain a very high coverage of at least 95% with two doses of measles and at least one dose of rubella vaccine.
Vaccination coverage in Norway

National coverage (NC) for MMR in Norway is published for ages 2, 9 and 16 years. During the past decade, NC for MMR at age 16 years varied between 91% and 95%. NC for 16 year-olds as reported from SYSVAK before 2015 did not specifically show MMR2 coverage because 16-year-olds would also appear as fully vaccinated if they had only received MMR1 in the past 9 years. However, MMR2 coverage is required in the annual status updates for elimination of measles and rubella (ASU) sent to the WHO Regional Office for Europe (WHO/Europe). In 2015, Norway received feedback from the WHO/Europe Regional Verification Commission for measles and rubella elimination (RVC) that the population immunity was considered alarmingly low in parts of the country, based on ASU reporting (sent in April 2014 for 2013) [7]. The ASU report for 2013 showed low MMR2 vaccination coverage of below 90% in six of 19 counties (range: 87–89%).

We aim here to describe corrective actions taken as a result of the RVC conclusions, in particular changes in the method for assessing MMR2 coverage. Figure 1 shows the main events from the relevant timeperiod 2014–2017.

Method for assessment of vaccination coverage in SYSVAK

Vaccination coverage in SYSVAK aims to represent actual protection against disease, based on the NCIP. To be considered fully protected, a person needs to have received the vaccine at recommended age and with recommended intervals between doses, according to the NCIP or alternative immunisation schedules (e.g. children who followed a vaccination schedule in another country before residing in Norway).
The coverage is calculated for a given birth cohort and represents the percentage of persons in that cohort who are fully protected against disease. Vaccination coverage can be calculated at any time, for any given cohort and by sex for residents registered in the National Registry in Norway.

Foundation: the rule engine

To calculate the real-time vaccination coverage and the extent to which NCIP recommendations are followed, SYSVAK uses a built-in rule engine. Any changes in the NCIP require updates in the rule engine. In order to calculate coverage as accurately as possible, the rule engine takes into account on an individual basis the age at vaccination, intervals between doses and number of doses. It is adjusted to take into account individual deviations from the recommended NCIP, such as age of vaccination and/or type of vaccine.

Vaccines administered within the time range and age limitations accepted in the Summary of Product Characteristics (SmPC) are counted as valid doses in SYSVAK. The rule engine is evaluated on a regular basis and follows the rules below for any of the vaccination schemes in NCIP:

- the minimum age at which the first dose can be counted as a valid dose,
- the minimum age at which a later dose can be counted as a valid dose,
- the minimum interval between a new dose and the previous dose, in order for the new dose to be counted as valid, and
- the period of a vaccination’s validity with respect to the date at which it is administered (i.e. the period of protection offered by the dose).

It is a complex system developed over many years and allows adjustments to improve accuracy in calculating coverage, identify unvaccinated individuals and hence improve vaccination coverage over time.

Practical use of the rule engine

The rule engine is a tool that makes the health registry useful on a daily basis as well as in active surveillance during outbreaks. Vaccination coverage can be calculated at any given time using this tool. Coverage can be calculated on a national, regional, municipality or district level using of the National Registry’s information on residency.

National and regional level coverage is published annually for 2-, 9- and 16-year-olds [8] for all NCIP diseases. These data are also reported to WHO through the United Nations Children’s Fund (UNICEF)/WHO joint reporting form. Owing to Norwegian data protection regulations, complete coverage data are published only on county level to avoid identifying individuals. Coverage data on municipality and district level for the same age groups are sent to the responsible health personnel in each municipality and district in the major cities in Norway. In addition these data are presented in the Municipal Public Health Statistics Bank [9] in accordance with data protection regulations.

The rule engine was developed to improve the quality of data in SYSVAK. Quality lists can be produced on municipality and district level. The quality lists identify unvaccinated children as well as children who are not fully vaccinated according to age and NCIP. All registered vaccine doses for the selected diseases are listed. The NIPH produces such quality lists for children aged 2, 8 and 15 years once a year in the autumn. In addition, lists for children aged 15 years are produced annually in the spring. The lists are sent to the responsible health personnel in all municipalities and districts for attention and further follow-up of children resident in their municipality. The quality lists are a tool to monitor and verify the local efforts on immunisation.

The main purpose of the quality lists is to help health personnel ensure that all children are offered the recommended vaccinations according to the NCIP. Furthermore the lists provide quality control of the data reported to SYSVAK and ensure that errors in the registry are rectified. The lists do not give recommendations on further vaccinations. Health personnel may contact counselling services at the NIPH for advice on further immunisation and/or registrations to SYSVAK.

Codes are used to indicate why the persons listed are defined as not fully vaccinated, e.g. minimum age not fulfilled or interval between doses too short. Reported vaccine refusal is also included in the quality lists, but SYSVAK does not have the legal authority to document the reason for refusal.

Figure 2
National coverage for MMR and MMR1 coverage for 16-year-olds, Norway, 2007–2016
Assessing MMR coverage for 16 year-olds

As seen in the timeline in Figure 1, the method for assessing MMR coverage in 16-year-olds was changed in November 2015. Table 1 illustrates how vaccination coverage was calculated in SYSVAK before November 2015. The table includes practical examples of the impact of the method on whether persons appear fully vaccinated or not.

Implementing a new method for assessment of MMR2 coverage

A new method for assessing MMR2 coverage in SYSVAK was implemented in November 2015. The new method also gives a snapshot of coverage at any moment, and secures in addition the previously missing alignment between NCIP and WHO elimination recommendations for MMR2 at the age of 16 years. Table 1 presents the new method and gives practical examples of its impact on individuals.

Figure 2 shows the drop in MMR NC for 16-year-olds following the introduction of the new method (from 94% 2014 to 91% 2015) and the continuously high MMR1 coverage of 97% for the same age group.

Table 2 shows that ASU MMR2 coverage at national level remained unchanged at 91% from 2013 to 2016. However, ASU MMR2 coverage on county level shows a decrease in the number of counties with a coverage below 90% (from six in 2013 to three in 2016).

Additional efforts to improve MMR2 coverage

In addition to the change in method in the IIS, the RVC feedback in 2015 also led to other efforts at the NIPH to secure high MMR2 coverage. The NIPH improved the advice to health professionals on the importance of giving two doses of MMR vaccine to all children. All children 16 years or younger should have two MMR vaccinations, even if the first dose is received later than recommended. Communication efforts were made mainly through the NIPH webpages [10], the Norwegian vaccination guidelines [11], seminars and presentations, as well as different counselling services at the NIPH.

In addition, the NIPH and the Norwegian Directorate of Health initiated an activity mapping local challenges to maintain a high vaccination coverage in June 2015 (Figure 1). A questionnaire was sent to all counties and municipalities to clarify whether the data in SYSVAK showed under-reporting and to highlight the main challenges for improving local vaccination coverage. The questionnaire covered all NCIP vaccines but had a particular focus on MMR2 at age 16 years.

<table>
<thead>
<tr>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
<th>ExamplesFully vaccinated at age 16 years</th>
<th>ExamplesNot fully vaccinated at age 16 years</th>
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<tr>
<td><strong>Old method valid until October 2015</strong></td>
<td></td>
<td></td>
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<tr>
<td>MMR1: - Minimum age 12 months - Valid 9 years from date of vaccination</td>
<td>Gives snapshot of coverage at any moment.</td>
<td>For late starters, receiving MMR1 after age 7 years: no alert of missing MMR2.</td>
<td>A person who received MMR1 and MMR2 vaccinations according to NCIP.</td>
<td>A person who received MMR1 at age 6 years.</td>
</tr>
<tr>
<td>MMR2: - Minimum age 3 years - Valid 20 years from date of vaccination</td>
<td>Reflects NCIP recommendations when MMR1 is given according to NCIP.</td>
<td>High vaccination coverage does not necessarily mean that MMR2 has been received.</td>
<td>A person with MMR1 at age 7 years (or later) and no MMR2.</td>
<td>A person who received MMR1 at age 4 years and MMR2 at age 4 years and 1 month.</td>
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<tr>
<td>Minimum interval between MMR1 and MMR2: 90 days</td>
<td></td>
<td></td>
<td>A person who received MMR1 at age 12 years</td>
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<tr>
<td><strong>New method valid from November 2015</strong></td>
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<tr>
<td>MMR1: - Minimum age 12 months - Valid until 13 years of age</td>
<td>Gives snapshot of coverage at any moment.</td>
<td>New method was quick to implement in the system, but implementation of new practice amongst vaccinators takes time to change.</td>
<td>A person who received MMR1 and MMR2 vaccinations according to NCIP.</td>
<td>A person with MMR1 at age 7 years (or later) and no MMR2.</td>
</tr>
<tr>
<td>MMR2: - Minimum age 3 years - Valid 20 years from date of vaccination</td>
<td>Secures alignment with NCIP and WHO elimination recommendations for MMR2 (2 doses MMR all children by age 16 years).</td>
<td>The new method is therefore expected to cause a false decrease in vaccination coverage compared with previous years.</td>
<td>A person who received MMR1 at age 12 years and MMR2 at age 14 years.</td>
<td>A person who received MMR1 at age 12 years.</td>
</tr>
<tr>
<td>Minimum interval between MMR1 and MMR2: 90 days</td>
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NCIP: Norwegian Childhood Immunisation Programme; WHO: World Health Organization.

* NCIP recommends: MMR1 at age 15 months and MMR2 at age 11–12 years.
Dicussion

We have shown here that SYSVAK detected low MMR2 coverage in six counties (in 2014) and describe actions that were taken to improve this, such as a new method for measuring NC. The new method, which requires a person to have received MMR2 to be considered fully vaccinated at age 16 years, was quick to implement. However, NC published April 2017 still showed low MMR2 coverage in three counties [8].

SYSVAK and its rule engine is unique and based on the NCIP and the vaccine recommendations for Norway. It takes into account other vaccination regimes that have been followed to secure the individual’s vaccination coverage against disease. Before we started ASU reporting on MMR2, we were not aware of the deviation between the NC and MMR2 coverage in the ASU for 16-year-olds. The new method is particularly important in securing MMR2 for individuals that have not had their MMR1 according to the NCIP.

The new method caused a false drop from 2015 to 2016 in published NC because the old method did not show MMR2 coverage for 16-year-olds. It was not a real drop in coverage per se, but it indicated that NC before 2016 had counted 16-year-olds as fully vaccinated even though some had only received MMR1. The drop does not reflect the actual uptake of the MMR vaccination offer in Norway; NC for MMR1 remains high in this age group (97%).

The support for the NCIP is high in the population. Therefore, we believe it may rather be a result of MMR2 not being offered to those who were outside of the regular NCIP MMR regime. The old method was very well adjusted to the NCIP, but not as good for deviations from the NCIP regarding long-term protection against disease secured by two doses of MMR vaccine. The goal of using the new method in combination with other efforts is to ensure that all children receive two doses of MMR. There is currently no system to actively follow up on individual vaccinations after a person has left school and the healthcare services provided by municipality/school, so it is important to catch missing vaccinations before age 16.

So far, we have not seen pockets of unvaccinated children in smaller geographical areas of Norway. By ensuring that the IIS measures vaccination coverage in the best possible way, we should be able to detect such pockets and target them in case of an outbreak where it is important to identify unvaccinated individuals or groups of individuals.

Future plans and challenges

SYSVAK is considered a complete system offering the basic requirements of an IIS. However, there is potential for further development. Collaboration with expert groups on immunisation registries initiated by the European Centre for Disease Prevention and Control (ECDC) and WHO provides important information on immunisation registries in other countries. The MesVaccines.net service in France [12] has functions that could benefit the Norwegian Immunisation registry. Particularly the vaccination recommendations to individuals offered through an online service based on questions and answers are interesting. A similar

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<td>Old method</td>
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<td>National level</td>
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</table>

ASU: annual status updates for elimination of measles and rubella sent to the World Health Organization; NC: Norwegian national coverage.

The table shows MMR2 coverage reported in the ASU and in parenthesis the reported NC in the same year. Since 2015, ASU and NC coverage have been equal. All vaccination coverage below 90% is marked in italics. Vaccine coverage is calculated per disease. Here, the percentages for measles are shown. Coverage for mumps and rubella can be considered close to equal.
service on NIPH’s public website, without the need for authentication, could strengthen the current service My vaccines [13]. This could have a positive impact on the vaccination coverage of the older population born before the establishment of SYSVAK.

**Conclusion**

We have shown how a national IIS could be used to identify and handle low sub-national vaccination coverage. Through a rapid change of the method for assessing MMR2 vaccination coverage, the IIS monitored the measures put in place to improve coverage and thereby contributed to reaching WHO vaccination coverage targets. MMR2 coverage is still below the 95% WHO target, so efforts to secure two doses of MMR vaccine for all children must continue. Further efforts to increase coverage will be monitored through SYSVAK.

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**Conflict of interest**

None declared.

**Authors’ contributions**

All authors have contributed to conception and design, analyses and interpretation of data and approval of the version to be published.

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Computerised, population-based vaccination registers are valuable tools for assessing the vaccine uptake and impact in populations. However, reliable impact assessment is only possible if the data quality can be reviewed and monitored continuously. This report describes the establishment and maintenance of the National Vaccination Register (NVR) in Finland. Currently, the NVR covers nationwide records of vaccinations given within the frame of the National Vaccination Programme since 2009. All vaccinations registered in the NVR contain a record of the personal identity code, the administered vaccine, and the date of vaccination. The vaccine lot number is the key component for recording and identifying vaccinations, because of its broad availability across patient information systems and its importance in vaccine safety monitoring. Vaccination records are accumulated and updated daily into the NVR, and their completeness is monitored monthly to assess deficiencies in data entry and data collection. Additionally, an alert system reports unexpected changes in data accumulation prompting the validation of observed changes in vaccination coverage. The presented process documentation may serve as a basis to improve the design and quality of other vaccination or healthcare registers and aims to inspire the set-up of vaccination registers in those countries which still do not have one.

Introduction
Computerised, population-based vaccination registers are valuable tools for assessing the vaccine uptake in populations in real-time. The performance of dynamic vaccination programmes can be evaluated, time trends monitored, and sub-populations with low vaccination coverage identified. Most importantly, by linking individual-level vaccination records with other medical records and health outcome databases, the impact of vaccines – both effectiveness and safety – can be studied comprehensively. This in turn will aid in formulating the best possible vaccination programmes.

The need for a National Vaccination Register (NVR) was recognised in Finland already in the late 1990’s and the Finnish vaccination decree of 2004 [1] requires all administered vaccinations to be recorded (Figure 1). In 2009, Finland introduced its NVR. Already before that, several countries in Europe had established vaccination registers on a regional and national level, e.g. Norway in 1995 [2], Denmark in 2000 [3], and the Netherlands in 2005 [4].

This report describes how the National Institute for Health and Welfare (THL) established the NVR in Finland. The presented process documentation may serve as a basis to improve the design and the quality of other vaccination or healthcare registers. Moreover, the aim is to inspire the set-up of vaccination registers in those countries which still do not have one.

Structure of public primary healthcare delivery in Finland
Finland has a population of 5.5 million and an annual birth cohort of ca 55,000 [5]. All vaccinations within the National Vaccination Programme (NVP) [6] are purchased centrally and paid by the state. They are given free of charge and on a voluntary basis. Municipalities (local governments) are responsible for the primary healthcare of their citizens, including NVP vaccinations. Changes in municipality borders and municipality mergers have occurred continuously in Finland during the last two decades. At the end of 2015, the population size of municipalities ranged from 99 in Sottunga, an island municipality of Åland, to 628,208 in the capital Helsinki [5]. In order to rationalise the organisation of public primary healthcare, some small municipalities have joined forces to form shared healthcare centres (HCCs), while other municipalities maintain their own. A map of Finnish administrative areas (317 municipalities and 153 healthcare centres in 2015) is presented in Figure 2.
After an update to one patient information system software, all vaccination records of newly and recently born children were accidentally omitted from real-time data submissions in the healthcare centres using that particular software.

Finnish HCCs have adopted computer-based recording of patient files since the early 2000s. In the mid-2000s, nearly all HCCs were using electronic patient information systems (Figure 1). However, both the versions of the systems, and the systems themselves varied between HCCs. Today, five commercial software programmes are in use, but the commercial ownership of the software programmes has changed frequently.

**Standardisation and coding**

As part of the nationwide eHealth information architecture [7] developed in the mid-2000s, a nationwide service for classification, coding, and terminology of health information was established. The providers of the patient information systems’ software generally apply the respective classifications, codes, and terminologies when implementing structured fields in their systems. In spring 2010, the nationwide coding of vaccination information was added to the National Code Server (Figure 1), where it is publicly available as reference [8]. It currently covers service providers, vaccines’ trade and generic names, vaccine preventable diseases, vaccination route, and vaccination site. Vaccines also appear in the Finnish Medicinal Products Database [9], which additionally covers the Anatomical Therapeutic Chemical code [10] and the Nordic Article Number [11].

**Vaccine lot number**

Both the Finnish and the European Medicines Agency mandate a lot-level traceability for purposes of vaccine safety monitoring [12]. The importance of being able to trace vaccinations on a lot level was highlighted in a vaccine safety study conducted by THL, regarding the pandemic influenza vaccine and narcolepsy, a rare sleep disorder, in children and adolescents [13,14] (Figure 3), where one of the questions posed was whether the onset of narcolepsy was due to manufacturing error confined to certain lots of the vaccine.

In this study, nationwide vaccination data collected from the HCCs’ patient information systems were linked to information from patient files collected from Finnish hospitals and reviewed by sleep disorder experts. Certain lot numbers occurred more frequently in patients who had developed narcolepsy (Figure 3). However, when comparing the relative frequency of lot numbers to the corresponding population, the lot number distributions did not differ, suggesting that the occurrence of the disease was not associated with certain lot numbers.

Based on these experiences, the vaccine lot number was recognised as the key content for identifying vaccinations in the NVR.

**Data entry and data collection**

The implementation of the NVR was guided by two principles: (i) to avoid double entry of data and (ii) to avoid double collection of data. The vaccination records in the NVR were therefore designed to be collected directly from the patient information systems and as part of other pre-existing nationwide register collections (Figure 4).

In the late 2000s, in order to expand the accessibility of nationwide health-related information, THL initiated a project to collect nationwide information about primary healthcare visits and subsequently established the Register of Primary Health Care Visits (Avohilmo) as part of its statutory duties [15]. The first pilot to collect real-time data of primary healthcare visits was conducted in 2009. The fields describing vaccinations were included to the Avohilmo data content in spring 2010. This formed a basis for collecting the records of vaccinations given during any primary healthcare visit in real-time. The HCCs, which are responsible for the
administration and computer-based recording of NVP vaccinations, joined the Avohilmo data collection gradually: the majority of HCCs (105/150) started submitting real-time data in 2012 and by autumn 2015 all operational HCCs (153/153) had joined Avohilmo (Figure 1).

The definition of Avohilmo’s data content has been evolving over time and all vaccinations given within the public primary healthcare system are covered. Table 1 shows the 2017 vaccination data content in Avohilmo.

Each software company designs the data entry into its patient information system software following its own guidelines concerning the use of coding and field validation rules. The process of extracting the data from the patient information systems and submitting them to Avohilmo at THL is fully automated and instructed to be dispatched every night, comprising new primary healthcare visit records and updates to existing primary healthcare visit records each time. The submission pace, i.e. the time interval between the day of submission and the day of vaccination varies between HCCs. In 2015, 84% (129/153) of the HCCs were submitting vaccination records in near real-time, which was defined as a median submission pace of 7 days or less.

**Record linkage**

Avohilmo receives the patient information in batches. With regard to vaccinations, these batches contain new and updated records as well as duplicates of old records, i.e. records previously received from another HCC. At THL, the vaccination records (Table 1) are extracted from Avohilmo, pseudonymised and transformed into the NVR with the objectives to identify (i) the administered vaccine and (ii) the vaccination event.

The default variable for identifying the administered vaccine is the lot number, because of its importance in vaccine safety monitoring (Figure 3) and its broad availability regardless of the different patient information systems in use. THL is responsible for the distribution of the vaccines given within the NVP. The list of those vaccines’ lot numbers is continuously updated and incorporated into the NVR for identification purposes. In addition, a contract has been set up with the Finnish Medicines Agency to retrieve bi-annually all lot numbers that are used in Finland but not distributed in the frame of the NVP. All the known lot numbers are used to check against lot numbers that are entered into the patient information systems and submitted to Avohilmo and the NVR by means of exact and approximate string matching, i.e. the comparison of character sequences. Potential spelling mistakes are accounted for by using data cleansing rules and the Levenshtein string similarity metric [16] against the known lot numbers (Table 2).

Matches over a certain level (data-driven set to 0.7) that unambiguously match against the known lot numbers of one vaccine are interpreted as successfully identified. If this identification process fails, the record of the trade name is used and evaluated by exact string matching including common spelling variations.

Vaccination events are defined as unique combinations of three key variables: (i) personal identity code, (ii) identified administered vaccine, and (iii) date of vaccination. The record describing the vaccination event that was received first is kept for further processing and analysis.

![Map of administrative areas, municipalities and healthcare centres, Finland, 2015 (n=317 municipalities and 153 healthcare centres)](image)
Alignment with commercial patient information systems

In addition to establishing nationwide coding standards, collaboration with the patient information systems’ software companies is pivotal, since they are responsible for designing the data retrieval based on their patient information systems, and for creating the data format for data transfers. In spring 2010, the collaboration was initiated by reviewing the data entry in each of the patient information systems. In autumn 2010, THL piloted a retrospective data collection of vaccination records as part of a planned nationwide collection of pandemic influenza vaccination records via the patient information systems’ software companies. This data collection was also used by THL to assess the availability, completeness, and quality of the available information. Subsequently, three additional retrospective data collections have been conducted in 2011, 2014, and 2015, respectively, covering all vaccinations, but limited to certain HCCs and time periods. By incorporating the retrospective data collections through the same record linkage steps that are applied to the Avohilmo data, the NVR currently covers nationwide records of vaccinations given in Finnish HCCs since 2009 (Figure 1).

Education and centralised guidance for healthcare professionals

Guidelines for recording vaccinations are available online [17]. The recording of lot numbers is emphasised because of the lot level traceability requirements. When the majority of HCCs started submitting real-time data, in spring 2012, a two-day educational workshop was held for HCCs’ staff responsible for the guidance of the patient information recording, as well as representatives of the patient information systems’ software companies (Figure 1). The purpose of the workshop was to alert the healthcare providers about the creation of the NVR, to standardise recording conventions,

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*Confirmed cases diagnosed by the end of 2012 [14].

The distribution of vaccine lots in those who developed narcolepsy does not differ from the distribution in the general population (chi-squared test for independence: \( p \text{ value} = 0.315 \)).
and to learn about the practical challenges in everyday work when it comes to computer-based recording.

Currently, for any feedback from the HCCs or staff involved in the patient information systems, a NVR contact person can be reached via phone and email. Thus, feedback can be evaluated promptly and questions may even be answered immediately. Feedback is also exchanged during four to 12 annual field visits in the HCCs by teams composed of experts from the NVR, Avohilmo, and THL's Vaccination Programme Unit. These visits are used for both education and guidance of healthcare professionals and investigation of deficiencies in data quality. Often including also representatives of the software companies, these joint dialogues have led to HCC-specific modifications in the recording conventions, as well as to software interface changes that have made the recording of vaccinations easier, more complete, and less error-prone.

Moreover, THL organises monthly web-based seminars for those working with vaccinations. Depending on the topic, reminders on the need for accurate data entry and the different ways of using the data are covered during these seminars.

**Data quality assessment**

From the start of the NVR, completeness of vaccination data has been investigated in order to assess deficiencies in data entry and data collection. Nowadays, the completeness of vaccination data is routinely monitored every month for each HCC [18] (i) for the population as a whole to control whether the HCC has been submitting vaccination records at all and (ii) for children younger than 2 years, who are recommended to follow a tight vaccination schedule of 10 or more vaccinations in the first 2 years of life [5]. For the whole population, the ratio of the monthly number of vaccination events other than seasonal influenza vaccination and the yearly count of residents living in the municipalities served by the HCC is calculated. For children
younger than 2 years, the ratio of the monthly number of diphtheria, tetanus, acellular pertussis, inactivated polio, and *Haemophilus influenzae* type b (five-in-one) and measles, mumps, and rubella (three-in-one) vaccination visits and the number of children younger than 2 years living in the municipalities served by the HCC is calculated. The rolling 6-month average of these ratios is compared with a fixed cut-off, one for each ratio [18]. The choice of the two cut-offs is data driven and aimed at identifying notable temporal changes in the data flow from the HCCs. These changes are assumed to be caused, among others, by modifications in software programmes, recording conventions, or data submission.

Additionally, an alert system has been deployed that reports monthly unexpected changes in the HCCs’ reporting behaviour based on those ratios. Taking into account each HCC’s median submission pace of the last 30 days, it checks the data completeness of the last month and produces a list of HCCs with an insufficient amount of documented vaccination events. This system is devised to react early to systematic data entry and data dispatch problems. The development of the alert system has largely been guided through experience.

In autumn 2012, after an update to one patient information system software, all vaccination records of newly and recently born children were accidentally omitted from real-time data submissions in the HCCs using that particular software. At this time, only one general indicator for vaccination data completeness similar to the first one described above (i) was available, but not regularly checked. Since records were still accumulating for the rest of the population served by these HCCs, it took several months to detect this deficiency, which led to the implementation of a more elaborate alert system including the indicator for childhood vaccination data completeness (ii) and automated, monthly alert reports. In spring 2014, a similar situation occurred affecting adolescent human papillomavirus (HPV) vaccinations after an update to another patient information system software. This time, the alert system was able to point out the anomaly in less than two months. After both incidents, the respective software companies were contacted and retrospective data collections were conducted in order to fill the identified NVR’s gaps.

### Reporting

Starting with autumn 2013, THL has been reporting annual nationwide and HCC-specific vaccination coverage figures of the Finnish childhood vaccination programme, adolescent HPV vaccination programme and seasonal influenza vaccination programme [6] (Figure 1). These are also available in a form of interactive maps, providing user-friendly access to aggregated nationwide vaccination data. Only HCCs meeting the criterion for data completeness for all the months covered by the observation period of interest, e.g. from birth until the age of 2 years in the case of early-childhood vaccinations, are included in nationwide reports, which are online available [19]. The same quality control process is applied for any vaccine impact analysis using the NVR: in a recent effectiveness study of the live attenuated and the inactivated influenza vaccine in 2-year-olds, the individuals covered by the HCCs that did not meet the data completeness criterion, i.e. 5% of the study population, were omitted from the population-based analysis [20].

### Table 1

<table>
<thead>
<tr>
<th>Field</th>
<th>Coding of content</th>
<th>Currently used to identify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client’s personal identity number</td>
<td>Personal identity code</td>
<td>Vaccinee</td>
</tr>
<tr>
<td>Service provider</td>
<td>National health service provider code</td>
<td>Healthcare centre</td>
</tr>
<tr>
<td>Date and time of contact</td>
<td>Timestamp with minute precision</td>
<td>Date of vaccination</td>
</tr>
<tr>
<td>Vaccine administration date</td>
<td>Timestamp with minute precision</td>
<td>NU</td>
</tr>
<tr>
<td>Lot number of vaccine</td>
<td>Free text</td>
<td>Administered vaccine</td>
</tr>
<tr>
<td>Trade name of vaccine</td>
<td>THL vaccine trade names code</td>
<td>Administered vaccine</td>
</tr>
<tr>
<td>Generic name of vaccine</td>
<td>THL vaccine generic names code</td>
<td>NU</td>
</tr>
<tr>
<td>Vaccine preventable disease</td>
<td>THL vaccine preventable disease code</td>
<td>NU</td>
</tr>
<tr>
<td>Anatomical Therapeutic Chemical code of vaccine</td>
<td>Anatomical Therapeutic Chemical code [10]</td>
<td>NU</td>
</tr>
<tr>
<td>Article number of package</td>
<td>Nordic Article Number [11]</td>
<td>NU</td>
</tr>
<tr>
<td>Vaccination route</td>
<td>National vaccination route code</td>
<td>NU</td>
</tr>
<tr>
<td>Vaccination site</td>
<td>National vaccination site code</td>
<td>NU</td>
</tr>
</tbody>
</table>

NU: not used for identification purposes; THL: National Institute for Health and Welfare.

a Since 2017.
b Since 2017, previously free text.
Data on the absolute count of vaccinations are included in the reports as well, allowing a direct comparison with the HCCs’ own records. In addition, summaries of the vaccine identification process (Table 2) are shared with the HCCs. After continuous efforts emphasising the importance of the lot number, both through education and by means of periodical reports, the quality of these data entries has improved from 94% (1,570,169/1,674,905) identified by lot number in 2012 to 97% (2,063,669/2,121,646) in 2015 and from 1% (21,675/1,674,905) unidentified in 2012 to 0% (6,257/2,121,646) in 2015.

Moreover, the amount of incoming vaccination data is monitored weekly and internal online follow-ups provide near real-time vaccination coverage information for all vaccines and age groups.

### Challenges and future perspectives

The constantly reshaping administrative areas (Figure 2) and the variety of patient information system software programmes and their versions have made the establishment of the NVR in Finland particularly challenging. The current mechanisms constantly required for maintaining the NVR are (i) methods for record linkage, (ii) education of healthcare workers, (iii) data quality assessment, and (iv) continuous reporting.

The vaccine lot number is used as the key variable for identifying the vaccine. From the coding point-of-view, the lot number is a suboptimal choice for vaccine identification, because it is not feasible to develop a pre-coded data entry for the lot number in the patient information systems. Instead, free text is required. A potential improvement would be to use barcode readers, but unfortunately vaccine manufacturers do currently not include the lot number in the vaccines’ barcodes in Europe. However, with the listed four quality control mechanisms in place, the quality of computer-based recording of NVP vaccinations in Finland has improved to a degree that almost all vaccines are currently identified on a lot level [18].

When collecting a large amount of real-time data in an automated fashion, and from several data providers and software systems, special attention is required to detect any anomalies in data. Any unexpected changes in the process of data entry and data dispatch can lead to inadvertent omission of records, as exemplified by the problems experienced during the first years of the NVR. In order to detect these changes, an alert system has been deployed. However, since it is not possible to anticipate all possible anomalies, developing and maintaining the alert system based on previous experience, is a continuous process.

Maintaining the NVR also requires continuous interaction and dialogue with the HCCs. A pivotal tool for such interaction is permanent provision of reports that summarise vaccination records at HCC-level. Due to regional and temporal gaps in the completeness of the data, only periodical (annual) reporting has been employed so far. However, the plan is to gradually move towards continuous reporting. Continuous reporting was piloted during the influenza season 2015/16, when the accumulation of influenza vaccinations documented in the NVR was reported weekly on a public THL webpage [21], and is continued in 2016/17 [22].

At the moment, the NVR contains vaccinations given within the public primary healthcare system. However, Avohilmo is currently being expanded also to the private primary healthcare. Furthermore, other national registers like the Hospital Discharge Register and the Medical Birth register are being prepared to include also vaccination information into their data content and collection. The purpose of these additions is to include also vaccinations given in hospitals and at birth clinics into the NVR.

In parallel with the efforts to add the collection of vaccination records into other national registers, a project has been initiated, which explores the possibility to utilise the recently established Finnish National Patient Archive (Kanta) [23]. Kanta is a nationwide archive impossible.

<table>
<thead>
<tr>
<th>Lot number</th>
<th>Cleansed lot number</th>
<th>Similarity value</th>
<th>Trade name</th>
<th>Vaccine identified by</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT FJ2098C</td>
<td>FJ2098C</td>
<td>(not evaluated)</td>
<td>(not evaluated)</td>
<td>Lot number, exact match</td>
</tr>
<tr>
<td>FJ2098C</td>
<td>FJ2098C</td>
<td>0.857</td>
<td>(not evaluated)</td>
<td>Lot number, fuzzy match</td>
</tr>
<tr>
<td>FJ2098</td>
<td>FJ2098</td>
<td>(not evaluated)</td>
<td>(not evaluated)</td>
<td>Lot number, fuzzy match</td>
</tr>
<tr>
<td>FJ2098</td>
<td>FJ2098</td>
<td>0.714</td>
<td>(not evaluated)</td>
<td>Lot number, fuzzy match</td>
</tr>
<tr>
<td>FJ20</td>
<td>FJ20</td>
<td>0.571</td>
<td>FLUENZTETRA</td>
<td>Trade name, exact match</td>
</tr>
<tr>
<td>Fluenz Tetra</td>
<td>FLUENZTETRA</td>
<td>0.091</td>
<td>(missing value)</td>
<td>(not identified)</td>
</tr>
</tbody>
</table>

The default variable for identifying the administered vaccine is the lot number, cleansed for potential spelling mistakes. If this identification process fails, the trade name is evaluated. Having valuable information, e.g. the trade name, entered in the wrong field and other fields, e.g. the actual field for the trade name, empty or also with the wrong kind of information, can make the vaccine identification as part of the record linkage impossible.
system developed for nationwide access to patient information for both healthcare workers and citizens themselves. Through Kanta, citizens can browse personal vaccination records via an online server. Parallel efforts to expand data collections and utilise already collected data for register purposes is especially topical now, when Finland is introducing a health, social services and regional government reform, one of the biggest ever administrative and operational overhauls in Finland [24].

Conclusion
Constant monitoring of the quality of a population-based vaccination register is a prerequisite for a continuous and reliable evaluation of both the vaccine uptake and impact on a national level. The presented quality control measures developed to monitor the validity of NVR data in Finland have proven useful to improve the quality and completeness of the register. Thus, this process documentation may serve as a basis to improve the design and the quality of other vaccination or healthcare registers.

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Conflict of interest
None declared.

Authors’ contributions
UB, JS, SJ, MN, TP, and JJ contributed to the conception and design of the manuscript. UB and JS performed the analyses and all authors interpreted the results. UB wrote the first draft. All authors reviewed, provided comments and approved the final version of the manuscript.

References


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