A collaborative approach to investigating the risk of thrombocytopenic purpura after measles–mumps–rubella vaccination in England and Denmark

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A B S T R A C T

The assessment of rare adverse events following vaccination may not be possible within a single country due to an insufficiently large denominator population. In 2008 a European consortium (VAESCO) was funded to perform collaborative vaccine safety studies. To help assess the feasibility of multi-country collaboration England and Denmark, who have established vaccine safety research infrastructures, undertook to work to a common protocol and share results and data to estimate the risk of a known true adverse event, thrombocytopenic purpura (TP) following measles–mumps–rubella (MMR) vaccination. TP is a known rare reaction to MMR and therefore provided an opportunity to assess whether two countries would produce similar results when working collaboratively. Despite some initial problems with ensuring data were comparable, the two countries gave very similar estimates of the relative incidence in the 6 weeks after vaccination and a pooled relative incidence estimate of 2.13 (95% confidence interval 1.55–2.94) and attributable risk of 1 in 50,000 doses. Both countries used hospital admissions for TP and the analysis was performed using the self controlled case series method which is particularly suited to collaborative studies because of its implicit control for individual level confounding. The study therefore shows the potential for vaccine safety collaborations across Europe to detect true associations through use of common protocols and sharing of results or data.

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1. Introduction

Vaccine safety assessment post licensure is essential for maintaining public confidence in vaccines and recommended immunisation programs. Whilst clinical trials should identify common reactions to vaccination, rare events can only be investigated once a vaccine is licensed. New vaccines, such as the human papillomavirus vaccines, rotavirus vaccines, and varicella vaccines continue to be introduced in European Member States and require rapid safety assessment through pharmacovigilance reports as well as if needed epidemiological studies to investigate occurring signals. Safety issues may also arise for established vaccines such as the measles–mumps–rubella (MMR) vaccine for which studies looking at a variety of events including autism, gait disturbance, convulsions and thrombocytopenic purpura (TP) have been performed [1–4]. New combined vaccines may also be introduced such as the MMR-varicella vaccine for which established risks such as febrile convulsions need to be compared to those of existing vaccines [5].

Most vaccines are licensed in multiple countries and therefore vaccine safety is a global issue. A safety concern that arises in one
country is likely to be applicable to many other countries. In 2006 a meeting in Annecy, France took place to assess the feasibility of global safety assessment through the collaboration of many countries [6]. Following this in 2008 the European Centre for Disease Control funded a group of countries called the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium to establish a European vaccine safety datalink in which aggregated data on events linked to immunisations could be shared to investigate safety concerns for rare events [7]. This model has been established for over a decade across several states in the USA [8]. To help assess the feasibility of such studies across country-borders in the European Union, England and Denmark, who have established systems for performing epidemiological studies on vaccine safety [9,10], undertook to update the estimate of the risk of TP following MMR by working collaboratively.

TP is a condition of often unknown (idiopathic) cause, where a low platelet count causes symptoms such as bruising, petechiae and bleeding diathesis [11]. In children TP often requires hospitalisation and may be preceded by a viral illness which can include live virus vaccines [12,13]. Although TP can be a serious and possibly fatal condition, vaccine associated TP is usually mild and self-limiting [13]. Reports of TP following live measles have been published since the 1960s [14] and in 1993 a review by the Institute of Medicine concluded that there was a causal relationship between MMR and TP [15]. An epidemiological study in the UK showing a significant elevated risk was published in 1995 and updated in 2001 with an attributable risk of 1 in 32,000 doses [9,16]. These findings have since been confirmed in a vaccine safety datalink study in the US, and in a recent systematic review of 12 studies where the median risk was 1 in 38,500 doses (range 1 in 25,000 to 1 in 1.1 million) [4,17].

The main aim of this study was to evaluate the feasibility of performing collaborative studies across Europe by assessing a known vaccine associated event. The study would also enable calculation of a reasonably precise estimate for the risk of TP following MMR using data on hospital admissions linked to immunisation data from England and Denmark.

2. Methods

2.1. Collaborative issues

Prior to starting the study we identified the collaborative issues that may arise. These included scientific issues such as obtaining a common protocol with standard case-definitions and methods of analysis as well as practical issues such as identifying the principal investigator, timescales, data-sharing and study authorship. In the assessment we also took the opportunity to compare the results obtained from pooling the data with a meta-analysis of each country’s individual estimates and also to compare results in Denmark from using a cohort approach and a self-controlled case-series approach, two methods commonly used for association studies of vaccine safety signals. The study protocol was drawn up after one face to face meeting in England, two meetings within the VAESCO consortium and four teleconferences.

2.2. Case definition

In England and Denmark vaccine safety assessment is performed using routinely collected data where health outcomes are linked to immunisation data. For the TP study both countries used national TP coded hospital discharge data linked to immunisation registry data. The case definition for TP was based only on the presence of a relevant ICD10 code (D69.3) or ICD8 code (287.10) in one of the diagnostic discharge fields. First episodes were defined as the earliest record found for an individual, further episodes were initially required to be at least 14 days since a previous episode (to prevent double counting of episodes). This was later amended to 50 days after evidence that this interval was too short in Denmark. Validation was not sought for these codes as they had been used in a previous study where the MMR-TP association had been seen and where case-note validation had confirmed the TP admission in 21/24 cases (87%) [16].

2.3. Study populations

In England and Denmark the first MMR dose is scheduled during the second year of life. In this study the aim was to look at the risk of TP following this first dose, so the study population was chosen as children aged 12–23 months of age (365–732 days).

In England cases (based on ICD10) occurring between 1st April 1996 and 31st March 2007 were linked using NHS number or gender/date of birth/postcode to immunisation records. As there is no national immunisation database in England, regional immunisation registers, where ethical and data custodian permissions had been obtained for linkage, were used which cover a birth cohort of about 60,000. Only cases where a link to an immunisation record was successful were retained. For these cases any episodes occurring prior to 12 months were also obtained.

In Denmark the Central Person Registry (CPR) was used to construct a nationwide cohort consisting of all Danish children born in the period January 1st 1990 to December 31st 2007 (~1.2 million children) [18]. The unique CPR-number was used to link individual level information on childhood vaccinations, hospitalised TP cases (ICD8 from 1990 to 1993, then ICD10), and possible demographic confounders to the children in the cohort. Childhood vaccines in Denmark are administered by general practitioners who are reimbursed by the National Board of Health for the vaccinations. Based on these reimbursement reports a database has been constructed on all childhood vaccinations since 1990 [10]. In Denmark it is therefore possible to perform a cohort study during children’s second year of life as well as to select cases aged 12–23 months for combining with the case only data from England.

2.4. Sample size

Prior to the study the approximate number of episodes in the databases was obtained. This was 343 and, based on MMR vaccine coverage, would be sufficient to detect a relative incidence of 1.5 in the 6 week period following vaccination with 80% power at a 5% significance level.

2.5. Statistical methods

Our primary analysis was to use the case only data from England and Denmark to perform a self controlled case series (SCCS) study. This is now an established method for vaccine safety evaluation [19]. The method can have similar power to a cohort study and also enables control for individual level confounding. For comparison, a supplementary analysis of the Danish data was conducted using the cohort method, based on the same cases used in the case only analysis.

2.6. Self-controlled case series analysis

Each country created a dataset of TP episodes with variables for age at the study entry and exit date (usually 365 and 732 days, respectively), age at hospital admission, age at MMR if given (otherwise set to 9999 – i.e. outside study period) and a unique patient identifier. Adjustments for age were carried out in 1 month periods. The risk periods examined were 0–13, 14–27, 28–42 and 0–42
days post MMR and a pre-vaccination 'low' period: −7 to −1 days to allow for a vaccination being delayed if the child was ill. Each country performed the analysis themselves to produce estimates that could be combined by meta-analysis, the data were then pooled to enable a combined analysis in which differences between countries in the age and vaccine effects could be assessed using a likelihood ratio test. Analyses were performed using all episodes and using first episodes only. The analysis was performed in Stata version 10 (Stata Corp, College Station, Texas).

2.7. Cohort analysis

From the nationwide cohort all children born in Denmark from January 1st, 1990 to December 31st, 2006 were included. Study entry was defined as January 1st, 1992 or 1 year of age, whichever came last. Study exit was defined as the date of death, disappearance, emigration, TP (only for the cohort first episode analysis), 2 years of age or December 31st, 2007, whichever came first. Poisson regression was performed using person time and events summed across categories of exposure (0–13, 14–27, 28–42 days post MMR) confounding variables. Models were fitted just adjusting for age (1-month intervals) and calendar period (1 year intervals), and also adjusting for other covariates: child’s gender, place of birth (classified according to degree of urbanization), ethnicity of mother (Danish or not), mother’s age at birth (using age categories: <19, 20–24, 25–29, 30–34, 35–39, ≥40). The analysis was performed using Stata version 9.1.3 (SAS Institute, Cary, NC).

3. Results

3.1. Collaborative issues

With only two countries involved development of a joint protocol and agreement on timescales and the principal investigator was reasonably straightforward. The similar ICD coding of events and potential to use the SCCS method for both countries also helped standardise methods. Study periods, case selection and vaccine risk periods were all defined in the protocol. Nevertheless unforeseen issues did arise regarding data management and methodology as outlined in Table 1. These issues were addressed as they arose, but did delay the production of final analyses.

3.2. Self-controlled case series analysis

In the English dataset there were 73 admissions for TP in 67 individuals (66 of whom had a first event aged >12 m), 6 had two episodes whilst aged 12–23 m. All but 2 individuals had an MMR date recorded. In the Danish dataset there were 208 TP admissions in 181 individuals (167 with a first event aged >12 m), 15 individuals had 2 episodes whilst aged 12–23 m, 3 had 3 episodes, and 2 had 4 episodes. All but 18 individuals had a date of MMR.

Fig. 1 shows the timing in weeks of TP around MMR and Table 2 shows the relative incidence estimates by individual country using all episodes. Results are similar in Denmark and England with a 2 fold excess in the 6 weeks post vaccination peaking in days 14–27 at a 3 fold excess. There was no evidence of any difference between the estimates in the two countries (p = 0.70 for the 0–42 day period estimates, all episodes analysis). Table 3 gives the results of pooling data and of performing a meta-analysis of the individual country estimates. The results are very similar, and almost identical if a different age-effect is allowed in each country. The age effect is not significantly different between countries (p = 0.81) so the analysis with the common age effect is preferable since it gives slightly narrower 95% confidence intervals (CI). In the pooled analysis the 7 day pre-vaccination low period had a RI of 0.47 (95% CI: 0.12–1.91), suggesting delayed vaccination in children admitted to hospital with ITP. The analysis using first episodes gave pooled RI estimates of 1.48 (95% CI: 0.79–2.78), 3.59 (2.32–5.59), 2.45 (1.46–4.13) and 2.48 (1.77–3.48) for the 0–13, 14–27, 28–42 and 0–42 day periods respectively.

3.3. Cohort analysis

A total of 1,121,204 children contributed 1,055,050 person-years of follow-up. Follow-up was terminated prematurely for 3829 children because of death (n = 465), loss to follow up, (n = 89) or emigration (n = 3275). As with the SCCS analysis there were a total of 208 events in 167 children. A total of 886,036 children received the first dose of MMR vaccine before the end of follow-up. Table 2 shows that the results of this analysis adjusting for age and period were similar or slightly lower compared to the SCCS estimates. The cohort analysis with full adjustment for covariates gave RI estimates that were very similar (less than 1% different). Interestingly the 95% CIs were slightly narrower (standard errors slightly lower) for the SCCS analysis than the cohort analysis indicating no loss of power from just using the cases.

3.4. Attributable risk

The number of cases in the 6 week post vaccination period estimated to be attributable to vaccine is (1.13/2.13) × 55 = 29.2. These cases are estimated to have arisen from a total population of 1.12 million + 60,000 * 11 = 1.78 million children given
Table 2
Relative incidence of TP after MMR vaccination in children aged 12–23 months in England using the self controlled case series method (SCCS) and in Denmark using the SCCS and cohort methods.

<table>
<thead>
<tr>
<th>Country/analysis</th>
<th>Period after MMR (days)</th>
<th>0–13 RI (95% CI) [n]</th>
<th>14–27 RI (95% CI) [n]</th>
<th>28–42 RI (95% CI) [n]</th>
<th>0–42 RI (95% CI) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>England/SCCS(\text{a})</td>
<td></td>
<td>1.10 (0.33–3.71) [3]</td>
<td>3.13 (1.44–6.79) [9]</td>
<td>1.53 (0.58–4.03) [5]</td>
<td>1.92 (1.02–3.59) [17]</td>
</tr>
<tr>
<td>Denmark/SCCS(\text{b})</td>
<td></td>
<td>1.38 (0.68–2.78) [9]</td>
<td>2.75 (1.61–4.69) [17]</td>
<td>1.94 (1.04–3.62) [12]</td>
<td>2.01 (1.34–2.99) [38]</td>
</tr>
<tr>
<td>Denmark/Cohort(\text{c})</td>
<td></td>
<td>1.32 (0.65–2.68) [9]</td>
<td>2.54 (1.47–4.37) [17]</td>
<td>1.72 (0.92–3.22) [12]</td>
<td>1.85 (1.23–2.78) [38]</td>
</tr>
</tbody>
</table>

\(\text{a}\) Adjusting for age and period.
\(\text{b}\) \(n\) = number of episodes in the period.

Table 3
Relative incidence of TP after MMR vaccination in children aged 12–23 months using SCCS analysis of pooled data from Denmark and England and using meta-analysis of each individual SCCS RI estimates.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Period after MMR (days)</th>
<th>0–13 RI (95% CI) [n]</th>
<th>14–27 RI (95% CI) [n]</th>
<th>28–42 RI (95% CI) [n]</th>
<th>0–42 RI (95% CI) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled data with common age effect(\text{a})</td>
<td></td>
<td>1.38 (0.76–2.50) [12]</td>
<td>2.09 (2.02–4.73) [26]</td>
<td>1.97 (1.18–3.28) [17]</td>
<td>2.13 (1.55–2.94) [55]</td>
</tr>
<tr>
<td>Pooled data with country specific age effects(\text{b})</td>
<td></td>
<td>1.30 (0.71–2.38) [12]</td>
<td>2.87 (1.85–4.46) [26]</td>
<td>1.81 (1.07–3.05) [17]</td>
<td>1.98 (1.41–2.78) [55]</td>
</tr>
<tr>
<td>Meta-analysis(\text{c})</td>
<td></td>
<td>1.30 (0.71–2.38) [12]</td>
<td>2.84 (1.82–4.43) [26]</td>
<td>1.83 (1.08–3.09) [17]</td>
<td>1.98 (1.41–2.78) [55]</td>
</tr>
</tbody>
</table>

\(\text{a}\) Adjusting for age, period and country.
\(\text{b}\) Adjusting for age, period, country and country-age interaction.
\(\text{c}\) Adjusting for age and period, fixed effect meta-analysis.
\(\text{d}\) \(n\) = number of episodes in the period.

886,038 \times 60,000 \times 11 \times 0.86 = 1.45 million doses, a risk of 1 in 50,000. Note that this assumes an average MMR coverage of 86% in England and Wales over the study period. The 95% CI for the risk can be calculated based on the 95% CI for the RI and gives an interval of 1 in 74,000 to 1 in 40,000.

4. Discussion

This collaborative study between centres in Denmark and England was carried out in the frame of the VAESCO project (http://vaesco.net). It aimed to explore the potential for vaccine safety studies involving health care databases from different European countries to detect true associations through use of common protocols and sharing of results or data. This study gave consistent estimates of the relative incidence of TP following MMR vaccination in one year olds. It demonstrates that by using a common protocol with a similar case definition based on ICD coding, the risk of a known rare adverse reaction to MMR can be estimated with improved precision by pooling data or estimates. The pooled RI estimates and attributable risk are a little lower but have greater precision than those seen in the previous study in England where the RI was 3.27 (95% CI; 1.49–7.16) for the 6 week period [16]. The RI was also lower than that reported is the US study of 5.38 (2.72–10.62) but the attributable risk of 1 in 50,000 was similar to the 1 in 39,500 reported [17]. This lower RI may be explained by the chart review carried out in the US study whereby a more specific case-definition was applied resulting in exclusions where other causes were identified. Our use of ICD coded events without further validation may reduce the RI, but this does not bias the estimate of the attributable risk as long as specificity is not differential in the vaccine and non-vaccine risk periods. Furthermore, it is possible that a highly specific case definition may result in a loss of sensitivity which, whilst not biasing the RI estimate will give under estimate the attributable risk.

The study also confirmed the fact that the SCCS method produces similar results with the same precision to a cohort approach for this acute and clinically well-defined adverse event. The SCCS method is particularly suited to studies across several countries due to the implicit adjustment for all non-time varying confounders. Other methods may require capture of many other confounders to provide unbiased estimates, and these may not be available in
all countries or have the same effects in different countries. Time varying confounders such as age or period must still be allowed for with the SCCS method, and an advantage of pooling data between countries is that such confounders can be estimated with better precision. The advantage of this pooling approach needs to be offset against potential difficulties with countries being able to share data. In our study the results were only slightly less precise based on pooling estimates rather than data, however ensuring exactly the same analysis was performed in both countries was challenging, and would be more difficult if many countries were involved. Approaches to standardizing local data collection and entry, classification and transmission would be useful for efficient multinational collaborations.

Part of the VAESCO project involves establishing a European vaccine safety data link in which countries provide data in a common format to a central hub for analysis [7]. To ensure anonymity the data shared are aggregated over individuals or over person time within individuals (for the SCCS method). This approach has the advantage that exactly the same analysis can be applied to data from all countries and data can be pooled. Clearly it is still important that the data being pooled have been obtained using a common protocol and that each participating country has ensured that the data are carefully validated, as this is not possible with aggregated data. This study between Denmark and England highlighted that even with careful planning; data issues such as the definition of first episodes, intervals between episodes and post vaccination risk periods will arise.

In conclusion, this study demonstrates that when using a common protocol and analysis two countries give consistent estimates of an established vaccine risk and suggest that, with care and standardized approaches, pooling data or results over multiple countries could enable the investigations of rare events not possible in any one country.

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