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Effectiveness of "Priorix" Against Measles and Mumps Diseases in Children Born After 2004 in the United Kingdom

A Retrospective Case-control Study Using the Clinical Practice Research Datalink GOLD Database

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Background: Evidence on vaccine effectiveness (VE) may encourage vaccination and help fight the reemergence of measles and mumps in Europe. However, limited data exist on real-life effectiveness of individual measles, mumps and rubella (MMR) vaccines. This study evaluated VE of GSK's MMR vaccine ("Priorix") against measles and mumps.

Methods: This retrospective, case-control study used UK data from the Clinical Practice Research Datalink GOLD linked to the Hospital Episode Statistics database to identify children 1–13 years old diagnosed with measles or mumps from January 2006 to December 2018. Cases were matched to controls according to birth month/year and practice region. Cases were identified using clinical codes (without laboratory confirmation). "Priorix" exposure was identified using vaccine batch identifiers. Children exposed to other MMR vaccines were excluded. Adjusted VE was estimated for ≥1 vaccine dose in all children, and for 1 dose and ≥2 doses in children ≥4 years at diagnosis.

Results: Overall, 299 measles cases matched with 1196 controls (87.6% <4 years old), and 243 mumps cases matched with 970 controls (74.2% <4 years old) were considered. VE for ≥1 dose in all children was 78.0% (97.5% confidence interval: 67.2%–85.3%) for measles and 66.7% (48.1%–78.6%) for mumps. In children ≥4 years old, VE after 1 dose was 74.6% (–21.7% to 94.7%) for measles and 82.3% (32.7%–95.3%) for mumps, and VE after ≥2 doses was 94.4% (79.7%–98.5%) for measles and 86.5% (64.0%–94.9%) for mumps.

Conclusions: "Priorix" is effective in preventing measles and mumps in real-life settings.

Key Words: effectiveness, measles, mumps and rubella vaccine, measles, mumps, matched case-control

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The implementation of effective vaccination programs against measles and mumps in several countries has led to considerable decreases in the incidence of these diseases and the associated mortality.[1–3] Despite the beneficial impact of these programs, many regions, including Europe, have registered a reemergence in the number of measles cases and a notable increase in the frequency of large outbreaks,[4–6] in addition to regular mumps outbreaks.[7,8] For instance, in England and Wales—where 2 doses of measles, mumps and rubella (MMR) combined vaccine are recommended (at 12–13 and 40 months of age)—989 confirmed measles cases and 1088 confirmed mumps cases were reported in 2018.[9–11] Potential causes underlying disease resurgence include noncompliance with recommended vaccination schedules, vaccine hesitancy and potential waning of immunity over time (especially for mumps).[5,8,12]

Having high-quality, real-life evidence of the effectiveness of routinely used vaccines contributes to awareness of the importance of adherence to vaccination recommendations, which in turn increases the success of vaccination programs at the individual and population level.[13] Several studies in real-life settings have shown that MMR vaccines are effective in preventing MMR.[14–18] However, brand-specific effectiveness data are scarce, which limits the use of real-life evidence in making decisions regarding the inclusion of specific vaccines in recommended programs.

The present study therefore aimed to assess the effectiveness of GSK's MMR vaccine ("Priorix"; GSK, Rixensart, Belgium) against measles and mumps in children, using a large UK-based general practitioner database extensively used in pharmacoepidemiology studies.[19]

A plain language summary of the results is shown in Figure 1.

MATERIALS AND METHODS

Study Design

This observational, retrospective, matched case-control study analyzed de-identified patient data from January 2006 to

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This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

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All authors either participated in the design, implementation or analysis and interpretation of the study, as well as the development of this article. All authors had full access to the data and granted their final approval of the paper before submission.

Data availability statement: Access to data in Clinical Practice Research Datalink (CPRD) is provided by the CPRD for health research purposes depending on approval of the study protocol by the Medicines & Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (ISAC) (https://www.cprd.com/home/). The CPRD and Hospital Episode Statistics (HES) data used in this study cannot be shared directly with others due to contractual agreements.

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December 2018 from the UK Clinical Practice Research Datalink (CPRD) GOLD and the linked Hospital Episode Statistics (HES) databases. CPRD GOLD captures longitudinal medical records (including details of demographics, clinical events, prescriptions and preventive medicine including vaccinations) from a primary care network (including data from over 700 practices) representative of the UK population.[19,20] HES contains details of all admissions to National Health Service hospitals in England and is linked to approximately 50% of CPRD practices.[21,22]

Before conducting this study, a feasibility assessment was performed to ensure the suitability and adequacy of CPRD GOLD to address our research question. The aims were to determine MMR vaccination coverage (including "Priorix") in children <2 years old in the United Kingdom, develop algorithms for case finding and estimate the number of measles and mumps cases in subjects <25 years old from 2006 to 2016. Feasibility assessment results are summarized in the results section and presented in more detail in the Supplemental Digital Content 1 (http://links.lww.com/INF/E337), Figure, Supplemental Digital Content 3 (http://links.lww.com/INF/E339) and Figure, Supplemental Digital Content 4 (http://links.lww.com/INF/E340).

The study protocol (Independent Scientific Advisory Committee protocol number 19_094) was approved by the Independent Scientific Advisory Committee of the CPRD and made available to the journal reviewers. This study was carried out in accordance with the Guidelines for Good Pharmacoepidemiology Practices[23] and the guiding principles of the Declaration of Helsinki. Data extracted from CPRD are coded and do not include information that can identify patients.[19,20] In addition, linkage of CPRD with HES data is done by a trusted third party within National Health Service.[21,22] Therefore, the researchers could not make an association between the data and specific subjects, so informed consent was not required.

Study Objectives

Primary objectives were to assess the effectiveness of ≥1 dose of "Priorix" against measles and mumps in children born after 2004. Secondary objectives consisted in assessing the effectiveness of 1 and ≥2 doses of "Priorix" against measles and mumps in children ≥4 years of age at index date (an age at which children would have received a second MMR vaccine dose per UK recommendations [40 months]). Index date was defined as the date of first diagnosis within a case-control matched set.

Study Population

Two populations were considered: a "measles population" and a "mumps population." In each population, cases and controls were defined as children born after 31 December 2004, who were registered continuously in CPRD GOLD from the age of 10 months until the index date, and with at least 1 consultation recorded in the year preceding the index date (excluding a consultation for vaccination). Cases were all children with a first diagnosis of measles or mumps between January 2006 and December 2018 (based on Read codes in CPRD GOLD and International Classification of Diseases, 10th Revision codes in HES). Cases identified in HES were considered as severe due to their hospitalization status. Controls were children who had no code for a diagnosis or suspicion of measles (for measles controls) or mumps (for mumps controls) between January 2006 and December 2018. Disease-specific codes (listed in Supplemental Digital Content 1, http://links.lww.com/INF/E337 and Table [Supplemental Digital Content 2, http://links.lww.com/INF/E338]) were deemed appropriate based on the feasibility assessment.

Cases and controls were matched by month and year of birth, and practice region. Up to 4 randomly selected controls could be matched to 1 case. The choice of birth date after 2004 was based on results from the feasibility assessment, which showed that "Priorix" was reported in the database from 2003 (see Supplemental Digital Content 1, http://links.lww.com/INF/E337 and

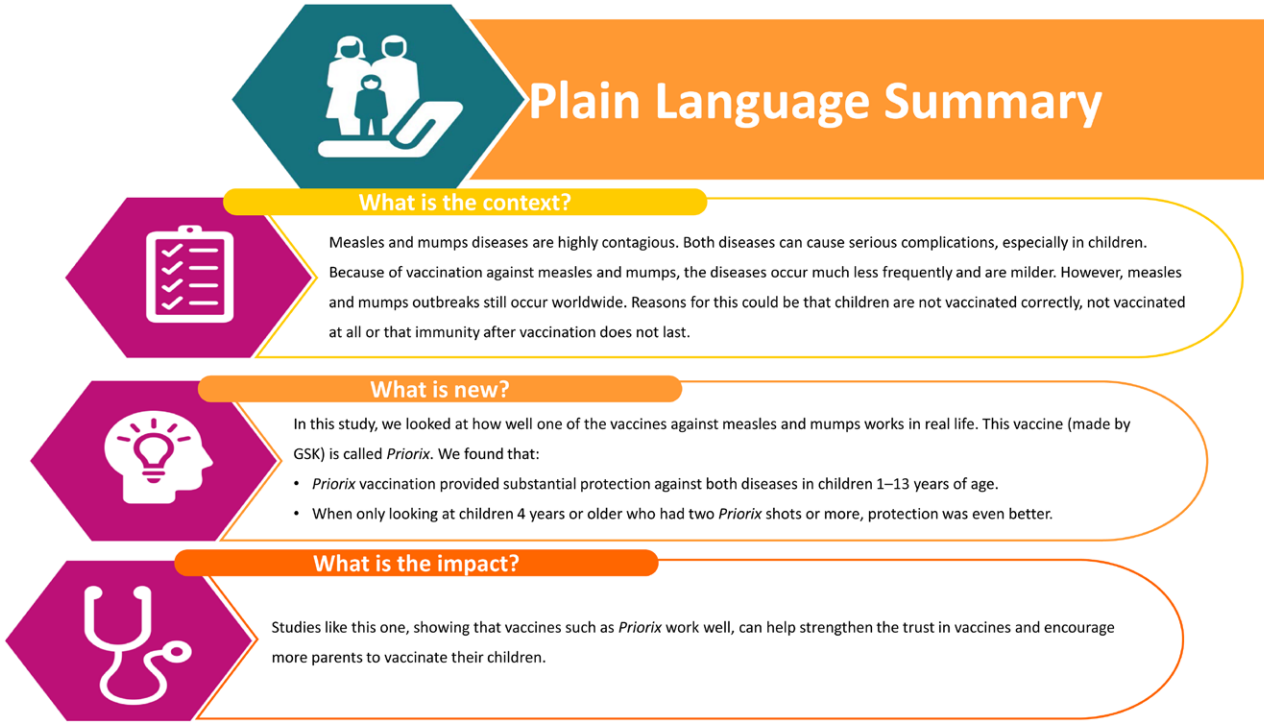

FIGURE 1. Plain language summary.

Figure [Supplemental Digital Content 3, http://links.lww.com/INF/E339]). Due to this choice of birth date and the defined study period, study population ages ranged from 1 to 13 years.

Children were excluded from the study if they met at least one of the following criteria: vaccination with an MMR vaccine other than "Priorix," onset of measles or mumps infection before their first birthday or database-linkage discrepancies (such as having several HES records, or several children being linked to the same HES record).

Variables

Exposure to "Priorix" was defined as a record of MMR vaccination with a batch number containing specific "Priorix" identifiers ("A69C," "A69D," "A69F," or "Priorix") in the child's vaccination records. Other MMR vaccination records were treated as exposure to a non-"Priorix" MMR vaccine.

Other data extracted from CPRD GOLD were birth month and year, gender, practice region, date of first diagnosis (for cases) and Index of Multiple Deprivation (IMD) quintile as linkage variable. Derived data included number of "Priorix" vaccinations, exposure to MMR vaccines other than "Priorix" and number of consultations not including vaccination in the 12 months preceding the index date.

Statistical Methods

All statistical analyses were performed using SAS (SAS Institute). Considering 4 controls for each case and assuming a 90% MMR vaccination coverage, including a vaccine uptake of 35% for "Priorix" (see Figure, Supplemental Digital Content 3, http://links.lww.com/INF/E339), and a 70% expected vaccine effectiveness (VE), a minimal sample size of 56 cases was needed to detect a statistically significant VE with 90% power and a 1.25% nominal type I error for each objective.

Analyses were performed separately on the measles and mumps populations. Gender, age at index date, history of "Priorix" vaccination (including number of doses received) and annual distribution of cases were summarized using descriptive statistics.

VE was computed as 1 minus the ratio between the odds of exposure among cases and the odds of exposure among controls. The 2-sided 97.5% confidence interval (CI) for VE resulted from an adjustment for multiplicity to account for the 2 study objectives (effectiveness of both the measles and mumps components of the vaccine). It was derived from the CI obtained for the odds ratio using a conditional logistic regression model adjusted for vaccination status, IMD quintile and number of consultations not including vaccination in the 12 months preceding the index date as covariates. For the primary objectives, VE was calculated in all children regardless of age, whereas the secondary objectives were based on the subset of children ≥4 years of age at index date.

Two additional, prespecified exploratory analyses were performed to estimate VE of ≥1 dose of "Priorix" against measles and mumps: by age stratum (1–3 years, 4–13 years) and in severe cases (ie, identified in HES).

To comply with CPRD confidentiality policy, statistical outputs with cell counts <5 were not disclosed. In some tables, cell counts <10 were masked to mitigate the possibility of deriving the content from the total and from other unmasked cells.

Potential age- and region-related biases were addressed through the criteria applied for controls-to-case matching. In addition, statistical analyses were adjusted for IMD quintiles and the number of consultations not including vaccination in the 12 months preceding the index date to account for bias related to socioeconomic status and healthcare utilization, respectively. Missing data were not substituted except for birth month that was set to June of the birth year when missing.

RESULTS

Feasibility Assessment Results

The feasibility assessment showed that MMR vaccination coverage (any brand) in children <2 years reported in CPRD GOLD was aligned with Public Health England (PHE) data (87%–96% during 1992–2015; see Supplemental Digital Content 1, http://links.lww.com/INF/E337 and Figure [Supplemental Digital Content 3, http://links.lww.com/INF/E339]). Results showed that "Priorix" was reported in the database from 2003, and its use increased in subsequent years with a vaccine coverage oscillating between 15% and 47% (see Supplemental Digital Content 1, http://links.lww.com/INF/E337 and Figure [Supplemental Digital Content 3, http://links.lww.com/INF/E339]).

Several algorithms for case identification were developed by combining clinical codes and laboratory testing codes. However, as there are limited laboratory data in CPRD GOLD and based on previously published data,[14,16,24,25] the results of the feasibility assessment and the fact that measles and mumps are well-characterized diseases, only clinical codes (without further laboratory confirmation of cases) were used for case finding.

Using these codes, we identified annual numbers of measles and mumps cases ranging from 35–296 and 91–336, respectively, in subjects <25 years in CPRD GOLD (see Supplemental Digital Content 1, http://links.lww.com/INF/E337 and Figure [Supplemental Digital Content 4, http://links.lww.com/INF/E340]). Trends observed for both diseases in CPRD GOLD were similar to those from PHE (see Supplemental Digital Content 1, http://links.lww.com/INF/E337 and Figure [Supplemental Digital Content 4, http://links.lww.com/INF/E340]).

Study Population Characteristics

A flowchart of the study population is presented in Figure 2. A total of 2708 subjects were included: 299 cases and 1196 controls in the measles population, and 243 cases and 970 controls in the mumps population.

In the measles population, 87.6% of children were 1–3 years old, with a mean age at index date of 1.8 years; most had received no or 1 dose of "Priorix" (Table 1). The annual number of measles cases ranged between 55 in 2009 (18.4% of all cases) and <10 during the period 2015–2018. In the mumps population, 74.2% of children were 1–3 years old, with a mean age at index date of 2.7 years; most had received 1 or ≥2 doses of "Priorix" (Table 1). The annual number of mumps cases ranged between 29 in 2010 and <10 in 2006 and 2018. Most measles and mumps cases were identified from CPRD GOLD only.

Vaccine Effectiveness

In the measles population, 64.5% of cases and 41.9% of controls were unvaccinated (Table 2). The estimated VE of ≥1 dose of "Priorix" was 78.0% (97.5% CI: 67.2%–85.3%). In children ≥4 years of age at index date, VE of 1 dose was 74.6% (–21.7% to 94.7%) and VE of ≥2 doses was 94.4% (79.7%–98.5%) (Table 2). VE of ≥1 dose of "Priorix" was 92.3% (75.1%–97.6%) in the 4–13 years age group, 73.1% (58.5%–82.6%) in the 1–3 years age group and 91.6% (52.7%–98.5%) against severe measles disease (Table 2).

In the mumps population, 31.7% of cases and 17.6% of controls were unvaccinated (Table 2). VE for ≥1 dose of "Priorix" was 66.7% (48.1%–78.6%; Table 2). In children ≥4 years old at index date, VE of 1 dose against mumps was 82.3% (32.7%–95.3%) and VE of ≥2 doses was 86.5% (64.0%–94.9%) (Table 2). In age-stratified analyses, VE of ≥1 dose of "Priorix" was 85.7% (63.3%–94.4%) in the age group 4–13 years, and

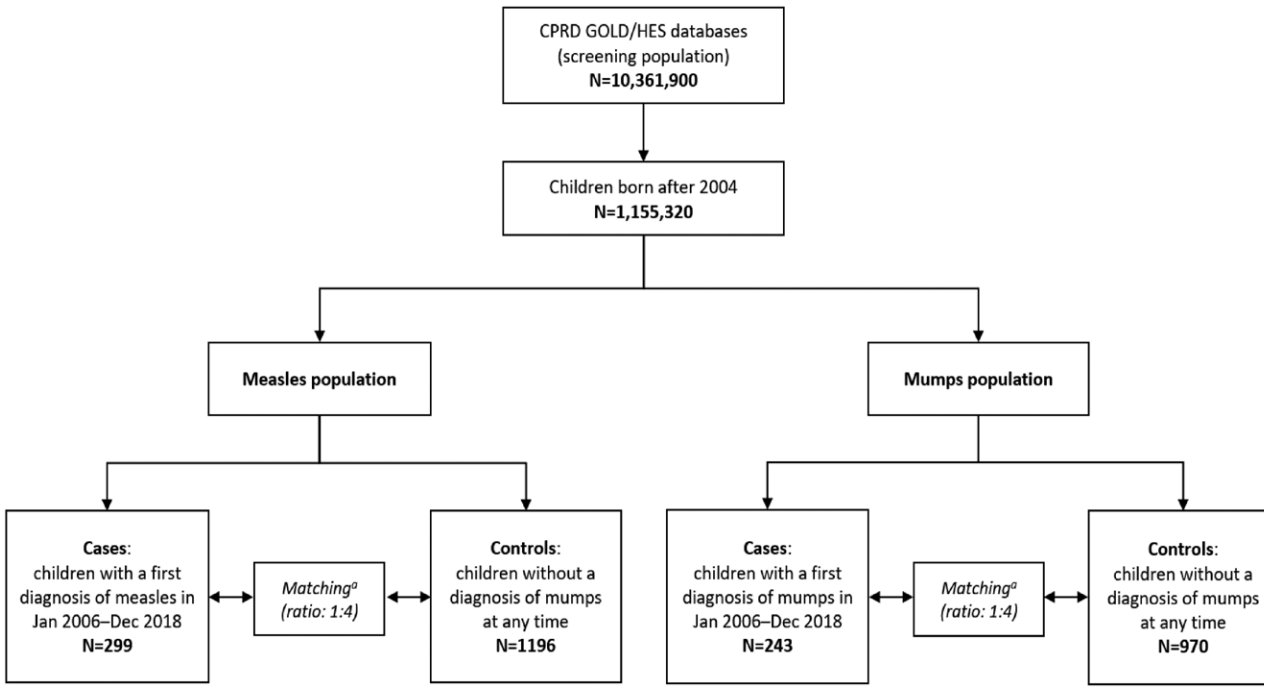

FIGURE 2. Disposition of study subjects. [a]Controls were matched to cases in a 4:1 ratio, according to month and year of birth and practice region. N indicates number of children.

TABLE 1. Demographic and Other Characteristics of the Study Populations

	Measles Population			Mumps Population		
Characteristic	Cases, N = 299	Controls, N = 1196	Total, N = 1495	Cases, N = 243	Controls, N = 970	Total, N = 1213
Male sex, n (%)	172 (57.5)	638 (53.3)	810 (54.2)	170 (70.0)	511 (52.7)	681 (56.1)
Age at index date, yr*, mean (SD)	1.8 (1.4)	1.8 (1.4)	1.8 (1.4)	2.7 (1.9)	2.7 (1.9)	2.7 (1.9)
Age category, n (%)						
1–3 yr	262 (87.6)	1048 (87.6)	1310 (87.6)	180 (74.1)	720 (74.2)	900 (74.2)
4–13 yr	37 (12.4)	148 (12.4)	185 (12.4)	63 (25.9)	250 (25.8)	313 (25.8)
Number of "Priorix" doses received, n (%)						
0	193 (64.5)	501 (41.9)	694 (46.4)	77 (31.7)	171 (17.6)	248 (20.4)
1	95 (31.8)	548 (45.8)	643 (43.0)	121 (49.8)	553 (57)	674 (55.6)
≥2	11 (3.7)	147 (12.3)	158 (10.6)	45 (18.5)	246 (25.4)	291 (24.0)
Primary diagnosis database, n (%)						
CPRD GOLD	278 (93.0)	NA	NA	235 (96.7)	NA	NA
HES	14 (4.7)	NA	NA	<10†	NA	NA
HES and CPRD GOLD	7 (2.3)	NA	NA	<10†	NA	NA
Cases per year, n (%)						
2006	17 (5.7)	NA	NA	<10†	NA	NA
2007	28 (9.4)	NA	NA	14 (5.8)	NA	NA
2008	32 (10.7)	NA	NA	27 (11.1)	NA	NA
2009	55 (18.4)	NA	NA	26 (10.7)	NA	NA
2010	31 (10.4)	NA	NA	29 (11.9)	NA	NA
2011	22 (7.4)	NA	NA	23 (9.5)	NA	NA
2012	31 (10.4)	NA	NA	25 (10.3)	NA	NA
2013	46 (15.4)	NA	NA	23 (9.5)	NA	NA
2014	11 (3.7)	NA	NA	24 (9.9)	NA	NA
2015	<10†	NA	NA	13 (5.3)	NA	NA
2016	<10†	NA	NA	15 (6.2)	NA	NA
2017	<10†	NA	NA	15 (6.2)	NA	NA
2018	<10†	NA	NA	<10†	NA	NA

*Index date is defined as date of first diagnosis within a case/controls matched subset.
†Exact number of cases (and percentage) is not explicitly reported if inferior to 10 (see Materials and Methods).
N indicates number of children in the population; n (%), number (percentage) of children in a given category; NA, not applicable.

56.2% (26.1%–74.0%) in the age group 1–3 years (Table 2). The estimated VE of ≥1 dose of "Priorix" against severe mumps was –30.1% (–1731.0% to 90.8%) (Table 2).

Hazard ratios for the different covariates used in the models are shown in Table 3.

DISCUSSION

This study generated real-life evidence of the effectiveness of "Priorix" against measles and mumps by retrospectively analyzing UK healthcare data from general practices (CPRD GOLD) and hospitals (HES) using a matched case-control design. VE estimates for ≥1 "Priorix" dose in children 1–13 years of age were 78.0% against measles and 66.7% against mumps, while estimates for ≥2 "Priorix" doses in children ≥4 years were 94.4% and 86.5%, respectively.

Most cases in this study were in children <4 years old, reflecting the higher incidence of measles and mumps reported in this age group in the United Kingdom,[26,27] where a second dose of MMR vaccine at 40 months (3.33 years) is recommended.[9] Due to this fact, the VE estimates for ≥1 "Priorix" dose were probably mostly determined by a population that received only 1 dose, which may provide less protection than the 2-dose regimen recommended for "Priorix" (as shown by the higher estimates of VE against measles for ≥2 "Priorix" doses compared with VE for 1 "Priorix" dose; Table 2). The VE for ≥1 "Priorix" dose estimated from the population of this study might therefore be lower than what could be expected with a population consisting of a larger proportion of older children (>40 months of age) who would have received 2 doses of the vaccine.

In a prespecified exploratory analysis, we observed higher values of VE of ≥1 dose in children 4–13 years of age (92.3% against measles and 85.7% against mumps) than children 1–3 years of age (73.1% and 56.2%, respectively). However, these results are subject to cautious interpretation due to the wide CIs observed. Given the MMR vaccination schedule recommended in the United Kingdom, the higher VE estimates observed in the age group 4–13 years might be the result of a higher proportion of children in this group having received 2 doses, compared with the 1–3-year group. This could be further assessed by exploring dose distribution by age, however, such an analysis would require unmasking of personal data (cell counts <5) and thus cannot be conducted due to CPRD confidentiality policy.

The results of the prespecified exploratory analysis based on disease severity showed that "Priorix" was effective in reducing the number of severe measles cases. Conversely, the VE against severe mumps could not be reliably assessed in our study (the CI was very wide and included 0) due to the limited number of cases identified

TABLE 2. Vaccine Effectiveness Against Measles and Mumps Diseases of At Least 1 Dose of "Priorix" (Primary Objectives), of 1 and At Least 2 Doses of "Priorix" (Secondary Objectives) and of At Least 1 Dose of "Priorix" by Age Stratum and Disease Severity (Prespecified Exploratory Analyses)

Subgroup	Cases, n (%)	Controls, n (%)	Total, n (%)	VE (97.5% CI)*
Measles population				
All children (299 cases; 1196 controls)				
≥1 dose	106 (35.5)	695 (58.1)	801 (53.6)	78.0 (67.2–85.3)
0 doses	193 (64.5)	501 (41.9)	694 (46.4)	
Children ≥4 yr at index date (37 cases; 148 controls)				
1 dose	5 (13.5)	15 (10.1)	20 (10.8)	74.6 (-21.7–94.7)
≥2 doses	8 (21.6)	111 (75.0)	119 (64.3)	94.4 (79.7–98.5)
0 doses	24 (64.9)	22 (14.9)	46 (24.9)	
Children 1–3 yr at index date (262 cases; 1048 controls)				
≥1 dose	93 (35.5)	569 (54.3)	662 (50.5)	73.1 (58.5–82.6)
0 doses	169 (64.5)	479 (45.7)	648 (49.5)	
Children 4–13 yr at index date (37 cases; 148 controls)				
≥1 dose	13 (35.1)	126 (85.1)	139 (75.1)	92.3 (75.1–97.6)
0 doses	24 (64.9)	22 (14.9)	46 (24.9)	
Severe disease (HES) (21 cases; 84 controls)				
≥1 dose	5 (23.8)	52 (61.9)	57 (54.3)	91.6 (52.7–98.5)
0 doses	16 (76.2)	32 (38.1)	48 (45.7)	
Mumps population				
All children (243 cases; 970 controls)				
≥1 dose	166 (68.3)	799 (82.4)	965 (79.6)	66.7 (48.1–78.6)
0 doses	77 (31.7)	171 (17.6)	248 (20.4)	
Children ≥4 yr at index date (63 cases; 250 controls)				
1 dose	5 (7.9)	31 (12.4)	36 (11.5)	82.3 (32.7–95.3)
≥2 doses	35 (55.6)	194 (77.6)	229 (73.2)	86.5 (64.0–94.9)
0 doses	23 (36.5)	25 (10.0)	48 (15.3)	
Children 1–3 yr at index date (180 cases; 720 controls)				
≥1 dose	126 (70.0)	574 (79.7)	700 (77.8)	56.2 (26.1–74.0)
0 doses	54 (30.0)	146 (20.3)	200 (22.2)	
Children 4–13 yr at index date (63 cases; 250 controls)				
≥1 dose	40 (63.5)	225 (90.0)	265 (84.7)	85.7 (63.3–94.4)
0 doses	23 (36.5)	25 (10.0)	48 (15.3)	
Severe disease (HES) (8 cases; 32 controls)†				
≥1 dose	<10‡	<10‡	<10‡	-30.1 (-1731.0–90.8)
0 doses	<10‡	<10‡	<10‡	

*VE was estimated using conditional logistic regression adjusted for vaccination status, IMD and the number of consultations not including vaccination during the year before index date (see Table 3 and Materials and Methods).

†In the analysis of VE against severe mumps cases, the conditional logistic regression model was overfitted when adjusting for IMD quintile and number of previous consultations not including vaccinations, so both covariates were removed from the model.

‡Exact number of cases (and percentage) is not explicitly reported if inferior to 10 (see Materials and Methods).

n (%) indicates number (percentage) of children in a given category.

TABLE 3. Estimates From the Adjusted Model for Calculation of Vaccine Effectiveness of At Least 1 Dose (Measles and Mumps Populations)

Subgroup	Measles Population, Hazard Ratio (97.5% CI)	Mumps Population, Hazard Ratio (97.5% CI)
Vaccination status		
≥1 dose vs. 0 doses	0.220 (0.147–0.328)	0.333 (0.214–0.519)
IMD		
1st quintile vs. 5th quintile	0.851 (0.515–1.406)	0.566 (0.313–1.022)
2nd quintile vs. 5th quintile	0.640 (0.383–1.070)	1.039 (0.634–1.705)
3rd quintile vs. 5th quintile	0.980 (0.617–1.556)	0.899 (0.546–1.481)
4th quintile vs. 5th quintile	0.757 (0.473–1.211)	0.734 (0.444–1.212)
Previous consultations*		
≥10 vs. <10	0.705 (0.508–0.977)	0.654 (0.465–0.920)

*Consultations not including vaccinations.

(only 8 cases). A possible explanation underlying the small number of severe mumps cases is that the disease is generally not severe enough to require hospitalization and can be managed at the general practitioner's level.

VE results presented here are consistent with previous studies demonstrating the effectiveness of MMR vaccines. A study using UK CPRD data estimated the VE against measles to be 51% and 61% (odds ratio: 0.49 and 0.39) for 1- and 2-dose MMR vaccination in 1–19-year-olds, respectively.[16] Another study using CPRD data estimated the VE against mumps to be 62% and 84% (odds ratio: 0.38 and 0.16) for 1- and 2-dose MMR vaccination, respectively, in children <10 years old.[14] A VE against measles of 99.7% after 2 doses of MMR vaccine was reported in Australia,[18] and reductions in measles- and mumps-associated hospitalizations were shown following MMR vaccination in Italy (hazard ratio: 0.10).[17]

This study presents some limitations, most of them inherent to the data sources. First, our analyses were dependent on the amount and quality of data available. There are limited laboratory data in CPRD GOLD, and all identified cases were therefore considered as confirmed cases for the present study. While some studies highlight the high positive predictive value of various outcomes, to our knowledge, there is no published validation study on the positive predictive value of measles and mumps disease codes in the CPRD.[28] Due to this lack of laboratory confirmation of cases and data regarding the positive predictive value of measles and mumps disease codes in the CPRD, the risk of misclassification of the diseases cannot be excluded and appears as an important limitation of this study. To mitigate the misclassification risk, the approach used in this study was based on previously published literature[14,16,24,25] and comparisons with data reported by PHE (see feasibility assessment in the Supplemental Digital Content 1, http://links.lww.com/INF/E337, Figure, Supplemental Digital Content 3, http://links.lww.com/INF/E339 and Figure, Supplemental Digital Content 4, http://links.lww.com/INF/E340.). Although measles and mumps are clinically well-characterized notifiable diseases, and suspicions of measles generally lead to laboratory testing, a degree of disease misdiagnosis cannot be excluded and may explain the differences between the VE estimated for "Priorix" in this study versus previously published VE estimates for MMR vaccines.[29] As a potential bias associated to disease misclassification would result in lower VE estimates than the same analysis performed on confirmed cases, our current assessment of the effectiveness of "Priorix" can be seen as conservative.

Second, while CPRD GOLD is highly representative of the UK population, a decline in the number of measles and mumps cases was observed over the 2015–2018 period, possibly due to a decrease in the number of subjects registered in the database after 2015. In addition to contributing to a degree of uncertainty in the estimated VE, this small number of cases precluded conducting analyses per year and assessing potential waning of immunity over time.

Third, the analysis cannot account for mild cases that did not require healthcare involvement. Since vaccination is known to reduce symptom severity during outbreaks, the number of unreported cases could be higher in vaccinated than in unvaccinated children, which may potentially result in an overestimation of the VE.[30,31]

Other parameters that may have impacted VE results and were not factored into the analyses performed in this study include delayed effects of vaccination. While the normal delay for protection after the first "Priorix" dose is estimated to be 42 days,[32] this study considered measles and mumps cases occurring at any time postvaccination, including those diagnosed in the first 42 days. This approach, although conservative, may have led to a slight underestimation of the true VE of "Priorix." Finally, children with underlying conditions such as immunodeficiency may be unvaccinated, and therefore at a higher risk of developing measles or mumps diseases, however, controlling for these underlying conditions was beyond the scope of this analysis.

The study also presents several strengths. First, the matched case-control design is a robust method conventionally used to measure VE in real-life settings.[33] We matched controls with cases according to their month and year of birth and the practice region. Such matching highly improves the robustness of the estimates, as these factors are known confounders and "Priorix" exposure may have varied in time and with regards to practice regions. Furthermore, the logistic regression used to calculate VE was conditional on the month and year of birth, practice region and the number of months from birth to the index date, which contributed to the robustness of the results together with the covariates that were factored into the analyses (IMD and number of consultations in 12 months preceding index date). Another strength of this study lied in the use of valid "Priorix" exposure data, which resulted in a limited risk of exposure misclassification. "Priorix" vaccination was identified in the database using the batch number variable and prespecified string characters specific for "Priorix" vaccine batches.

In conclusion, this study generated key data on the effectiveness of "Priorix" against measles and mumps in children born after 2004 in the United Kingdom. It provides the first evidence of the real-life impact of "Priorix" and may support efforts to increase MMR vaccine coverage that, in turn, can further support disease control programs. Additional studies in other settings or using prospective designs will be necessary to expand on these findings and further support public health messages and efforts to increase vaccine confidence.

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