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Two-dose measles vaccine effectiveness remains high over time: A French observational study, 2017–2019

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ABSTRACT

Background: From 2008 to 2019, France has experienced a resurgence of measles epidemics. Surveillance data have shown that the proportion of cases vaccinated with two doses of measles-containing vaccine (MCV) increased with age, raising concerns about the duration of vaccine protection. Our objectives were to investigate age-stratified vaccine effectiveness (VE) for the second dose of MCV (MCV2) and to quantify protection levels over time.

Methods: We analyzed data on measles cases aged 2–31 years, reported via mandatory notification to the French measles surveillance system from October 2017 to September 2019. We estimated an age-stratified VE for MCV2 using the screening method, which compares the vaccination status of cases with that of the general population. We improved this method by accounting for natural immunity, exploring four scenarios with four possible levels of natural immunity in the population. In addition, we quantified the decay rate of protection over time, by fitting an exponential decay model among individuals vaccinated in early life.

Results: In the baseline analysis (absence of natural immunity), VE estimates were high in all age groups and decreased with age, from 99.6 % (95 % confidence interval: 99.3–99.8) in 2–5 years old to 91.4 % (85.1–95.0) in 26–31 years old. Accounting for natural immunity increased VE in the older age group to 93.2–99.2 % depending on the scenario. We estimated that VE was slowly decreasing over time, with an exponential decay rate of 0.0022/year (0.0017–0.0028), leading to VE of 96.7 % (96.0–97.4) 16 years after MCV2 vaccination. This decline was most compatible with scenario 2, a scenario of 4.4 % naturally immunized, non-vaccinated individuals in the 26–31 years old.

Conclusion: Our study confirms the continued high effectiveness of two doses of MCV with only slight degradation, decades after immunization. These findings support the importance of achieving a very high vaccination coverage with 2 doses of MCV.

1. Introduction

Measles is an airborne, highly transmissible disease, caused by an RNA virus (genus *Morbillivirus*, Paramyxoviridae family). Complications such as pneumonia and various types of encephalitis may lead to fatal outcomes, pneumonia being a major cause of measles associated deaths [1] and acute encephalitis responsible for a case fatality rate (CFR) of up to 25 % [2–4].

Since the World Health Organization (WHO) established the Expanded Program on Immunization in 1974, the global measles incidence and mortality declined sharply: between 2000 and 2019, the numbers of cases and deaths respectively dropped by about 65 % and 62 % worldwide [5]. However, measles remains a major concern as the global incidence rate increased again in 2019 [5], although this dynamic was interrupted during the COVID-19 pandemic, at least in Western countries.

A solely human reservoir, no documented evidence of asymptomatic carriage and the availability of an effective and well tolerated vaccine mean that measles elimination (i.e. the absence of endemic measles virus transmission in a defined geographical area for at least 12 months) is possible, providing that a sufficiently high level of population immunity is achieved and maintained [6]. The 2012 WHO Global measles and rubella strategic plan identified measles elimination in five of the six WHO regions as a priority goal for 2020, with the objective of reaching

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and remaining at 95 % vaccine coverage (VC) for each of the two doses at the national and subnational level [7]. In Europe, measles elimination was first planned for 2010, and then for 2015 [7]. However, many European countries still experience measles outbreaks and no WHO region has achieved and maintained measles elimination [8,9]. Hence, WHO has extended the deadline for elimination to 2030 [10].

In France, measles-containing vaccines (MCV) were first introduced in the infant immunization schedule in 1983, with one dose at 12–15 months. The second dose was first implemented in 1996 at 11–12 years, then shifted at 3–6 years one year later. MCV2 was introduced to catch up vaccination in children missing MCV1 or to protect children with primary vaccination failure [11]. A National Plan for Measles Elimination was launched a few years after, in 2005, aiming to achieve VC above 95 % and 80 % in 2-year-old children, respectively for the first (MCV1) and second dose (MCV2) of MCV, and a VC above 90 % for MCV2 in 6-year-old children [12]. To meet its objectives, and since then, MCV1 administration has been scheduled at 12 months of age and MCV2 during the second year of life [13]. VC for MCV1 at 2 years of age has increased steadily up to 1991 but has since plateaued at around 90 %. Furthermore, immunizing unvaccinated individuals born since 1980 has been insufficiently implemented. Even though MCV1 VC for the 6 to 15 years old is above 95 % according to latest data available, MCV2 VC remains below 90 % for children aged 2, 6 and 15 years, thus below WHO target thresholds [14].

The failure to reach the national and international vaccination coverage targets has resulted in a resurgence of measles in France from 2008 to 2019, with more than 20,000 cases reported during the 2008–2011 outbreak [15], even though in 2020, in the context of the implementation of COVID-19 control measures, the number of measles cases decreased by a tenfold [16]. A seroprevalence survey conducted among French young adult blood donors in 2013, showed that 9 % of individuals aged 18–32 years remained nonimmune, representing around 1 million individuals susceptible to measles [17], despite the strengthening of the catch-up vaccine policy launched after the 2008–2011 outbreak.

In addition, 2019 French notification data showed that the proportion of fully vaccinated cases increased with age, from 3 % among the 1–4 years old to 21 % among the 20–29 years old [18]. This high proportion of fully vaccinated cases among young adults has also been highlighted in several countries [19,20], and could reflect a higher coverage than in young children. Indeed, it is expected that, for a similar level of vaccine effectiveness, the proportion of vaccinated cases increases with vaccine coverage (Figure S1). However, it could also reflect the waning of protection with time, in the absence of circulating virus acting as natural boosters before the measles upsurge period. Several authors referred to a potential waning protection or immunity after MCV2, depicted by reduced vaccine effectiveness (VE) in older ages [20] or decreasing antibody titers over time [21,22]. If lack of vaccination has been shown to be mostly responsible for measles acquisition [23], some studies suggested that, due to waning immunity, fully vaccinated patients could get infected and transmit the disease [24,25]. However, the contribution of waning immunity to measles outbreaks remains insufficiently understood.

The first objective of our study was to estimate MCV2 VE for different age groups (2 to 31 years old) in 2017–2019 in France using the screening method [26], and improving it by accounting for natural immunity, especially in young adults who may have been exposed to the virus in their childhood due to higher measles incidence in the 1980s [27]. Our second objective was to quantify the decay rate of waning protection over time, by applying the same method. Although VE by age is specific to the French context, our estimates of waning protection over time can be generalized to other settings.

2. Materials and methods

2.1. Measles surveillance data (including vaccination status of cases)

The French measles surveillance system is based on mandatory notification. Measles was introduced in the list of mandatory reportable diseases in 2005 [12]. Notification of cases is made by physicians and/or biologists to the Regional Health Agencies, using specific case notification forms (available at https://www.formulaires.service-public.fr/gf/cerfa_12554.do). The forms are sent to the French National Public Health Agency and collated into a database. Notification criteria follow the case definition adopted by the European Commission [28]. Based on these definitions, we classified cases as clinical, confirmed, post-vaccine or non-cases. Clinical cases corresponded to ECDC's possible cases, and confirmed cases combined both ECDC's probable and confirmed cases. Clinical cases must meet the following criteria: fever $\geq$38,5 °C, maculopapular rash and at least one of the following signs: conjunctivitis, coryza, cough, Koplik's sign. Confirmed cases are defined as clinical cases with serum or saliva sample positive to measles by Enzyme Linked Immunosorbent Assay (ELISA) and/or by PCR (biologically confirmed cases) or clinical cases who had contact with a confirmed case within 7–18 days before symptom's onset (epidemiologically confirmed cases). Post-vaccine cases are defined as a rash occurring 5–20 days after vaccination in the absence of exposure to a measles case. Non-cases are suspected cases that tested negative or did not meet the clinical criteria. The database contains information on date of birth, gender, date of symptom onset, classification of either an imported or indigenous case, geographical information, vaccination status at the time of symptom onset, number of doses of MCV received, date of last vaccination, and the source of information for the vaccination status (i.e., verbally or written in medical records).

We included clinical and confirmed measles cases reported from October 1, 2017, to September 30, 2019, in metropolitan France (i.e., mainland France and Corsica, excluding overseas departments and territories). This period corresponded to an upsurge of measles cases in France [18]. Non-cases and post-vaccination cases (as defined previously) were discarded. We restricted the analysis to individuals aged 2–31 years, for which VC data in the general population were available (see 2.2), and considered the age groups 2–5, 6–10, 11–15, 16–20, 21–25 and 26–31 years. In our main analysis, we only included confirmed cases whose vaccination status was written in the medical record. We performed 3 sensitivity analyses (SA), by varying the case definition and the source of information for the vaccination status. In these analyses, we included: (i) confirmed cases where vaccination status was obtained from any source of information (written or verbally or unknown) (SA1), (ii) all cases (confirmed and clinical) where vaccination status was obtained from a written medical record (SA2), and (iii) all cases (confirmed and clinical) where vaccination status was obtained from any source of information (written or verbally or unknown) (SA3).

2.2. Vaccine coverage data

As a central vaccine registry was not available in France, we reconstructed VC by age between 1988 and 2017, combining data from three datasets, assuming VC was constant over the study period. For 2-year-old children, VC was obtained from estimates based on the mandatory medical certificates completed at 24 months of age, available since 1986. The certificates are filled in based on the doctor medical record or the childhood health booklet. They are sent by physicians to the district Maternal and Child Health Offices, then aggregated at a national level and analysed by Santé publique France. For children aged 3–15 years, we used the results of school-based surveys regularly conducted from 2000 to 2017 on large samples of pupils [14,29]. Participants were selected using a two-stage cluster sampling. The surveys were based on a medical exam conducted by a physician or a nurse, during which vaccination data were collected from the child's health booklet. For

catch-up vaccination in individuals aged >15 years, VC was estimated by Santé Publique France using the Social Security Inter-Scheme Consumption Database (Datamart de consommation inter-régimes, DCIR) [30], which includes French reimbursed health expenditures (hence data on purchased vaccines) since 2006. These data are individual, anonymized and cover 99 % of the population. The first cohort for which we had reliable VC data was individuals born in 1986; thus, the maximum age of the studied population in 2017 was 31 years.

2.3. Population data

We used the 2017, 2018 and 2019 population data for individuals aged 2 to 31 years from the National Institute for Statistics and Economic Studies (INSEE, https://www.insee.fr/fr/accueil) records.

2.4. Vaccine effectiveness estimation

2.4.1. Screening method

First, we estimated the MCV2 VE by age group using the screening method [26]. This method has been described previously [20,26,31]. Briefly, it compares the proportion of vaccinated people among cases (proportion of cases vaccinated (PCV)) and VC in the general population (proportion of population vaccinated (PPV)). In settings where only case data are available and the precise population at risk is unknown, the screening method allows taking external estimates of VC in the general population as a reference. We used the following VE formula for MCV2:

$$VE = 1 - \frac{PCV}{1-PCV} * \frac{1-PPV}{PPV} \quad (1)$$

with

$$PCV\ for\ MCV2 = \frac{number\ of\ cases\ vaccinated\ with\ 2\ doses}{number\ of\ cases\ vaccinated\ with\ 2\ doses\ +\ number\ of\ cases\ not\ vaccinated} \quad (2)$$

and

$$PPV\ for\ MCV2 = \frac{population\ vaccinated\ with\ 2\ doses}{population\ vaccinated\ with\ 2\ doses + population\ not\ vaccinated} \quad (3)$$

Cases and population who received only MCV1 were excluded from the denominators.

Let $RR_i = 1 - VE_i$ denote the relative risk of disease in vaccinated individuals compared to unvaccinated individuals in an age group *i*. It is equal to the odds ratio of vaccination in cases over the odds of vaccinated population:

$$RR_i = \frac{PCV_i}{1-PCV_i} * \frac{1-PPV_i}{PPV_i} \quad (4)$$

Therefore, one can derive the following equation for PCV_i in age group i:

$$logit(PCV_i) = \log(RR_i) + logit(PPV_i) \quad (5)$$

with $logit(x) = \log(\frac{x}{1-x})$

Following Farrington [26], the linear model can be formulated:

$$\log(RR_i) = \alpha + \beta_i \quad (6)$$

where α is an intercept and the coefficients β_i represent the variation in the relative risk over the age groups.

Eq. (5) can then be rewritten as a logistic regression model for PCV_i, with $logit(PPV_i)$ as an offset:

$$logit(PCV_i) = \alpha + \beta_i + logit(PPV_i) \quad (7)$$

We fitted this model to estimate the regression coefficients and obtain VE by age group using the following formula, derived from Eq. (6):

$$VE_i = 1 - RR_i = 1 - e^{\alpha+\beta_i} \quad (7)$$

Standard errors given by the model were used to compute 95 % confidence intervals (95% CI).

2.4.2. Scenarios accounting for natural immunity

In the baseline analysis, we applied the standard screening method, assuming absence of natural immunity. However, ignoring natural immunity among the non-vaccinated population can under-estimate PPV and subsequently VE. Indeed, a proportion of the non-vaccinated population may be naturally immune due to prior infection, and no longer susceptible to measles. In particular, as measles virus was widely circulating in the 1980 s in France (Figure S2), young adults may have been exposed to the virus in their childhood and developed immunity. To account for natural immunity, we modified the formula of PPV as follows:

$$PPV\ for\ MCV2 = \frac{population\ vaccinated\ with\ 2\ doses}{population\ vaccinated\ with\ 2\ doses + population\ not\ vaccinated - population\ not\ vaccinated\ but\ naturally\ immune} \quad (8)$$

Natural immunity in a population is difficult to quantify. We therefore built four scenarios describing possible proportions of naturally immunized, non-vaccinated individuals in the population, and estimated VE in each scenario. For scenario 1, we summed up the estimated number of non-vaccinated cases reported from 1986 to 2017, considering a reporting rate of 100 % for the period 1986–2005 (surveillance performed through a sentinel network) and 45 % for the period 2006–2017 (surveillance performed through mandatory notification) (details in Supplementary Text 1 and Figure S2). We considered that natural immunity was lifelong. This gave us an estimate of the proportion of naturally immunized, non-vaccinated individuals in each age group in 2017. This estimation, used to define scenario 1, was considered as an upper bound for the proportion of naturally immunized, non-vaccinated individuals. Indeed, among these non-vaccinated cases, an unknown proportion might have been vaccinated later (i.e., after developing measles), since the triple measles-mumps-rubella (MMR) vaccine is recommended in France even in case of a measles history, to protect against the two other diseases. The cases that were vaccinated later should be removed from our estimates. We therefore considered 3 other scenarios in which the proportion of naturally immunized, non-vaccinated individuals was reduced by 40 % (i.e., 40 % of the non-vaccinated cases were vaccinated later - scenario 2), 60 % (scenario 3) and 80 % (scenario 4) compared to scenario 1.

2.4.3. Waning protection over time

Estimating vaccine effectiveness by age group gives a snapshot of the level of protection in a population for a given time period (here 2017–2019) but does not tell us about the waning of protection over time, since older people have been vaccinated at a later age than younger people (Figure S3). To quantify the waning of protection over time, we applied the screening method to a sub-sample of the population vaccinated before 3 years old. For these individuals, since the mean age at vaccination was about 2 years (Figure S3), we could estimate the time

elapsed since vaccination as *age - 2* and translate estimates of VE by age into VE by time since vaccination. We performed this sub-analysis on individuals aged 3 to 14 years during the period 2017–2019, i.e., those vaccinated 1 to 12 years ago (we did not have enough power to go beyond 12 years) and unlikely to have natural immunity. For the PCV in the screening method formula, we included cases vaccinated before 3 years of age only; for the PPV, we used VC data at 3 years old. We then fitted an exponential decay model to estimate the decay rate of waning protection over time, assuming the decay was constant over time (details in Supplementary Text 2).

2.4.4. Reconciling VE by age and waning protection over time

Finally, we reconciled the first (VE by age) and the second analyses (waning protection over time). For each age group in the first analysis, we calculated the mean age at MCV2 vaccination using VC data (Figure S3). We were thus able to estimate, for each age group, the average time elapsed since MCV2 (*mean age - mean age at MCV2 vaccination*) and to plot VE according to the mean time elapsed since MCV2. We could then overlay the two analyses (i.e., estimates of VE by time elapsed since vaccination in the first *vs* second analyses) and compare their consistency. We assumed that the exponential decay model could be extrapolated beyond 12 years. Based on this extrapolation, we identified which scenario of natural immunity was the most plausible.

All data analyses were performed with R software (version 4.0.3, October 2020).

3. Results

3.1. Measles cases and vaccine coverage data

Between October 1, 2017, and September 30, 2019, France received 5513 clinical or confirmed measles case notifications, of which 3396 were aged 2–31 years and lived in metropolitan France. Among these 3396 cases, 2855 (84 % had a known vaccination status and were included in our study. Seventy-two percent of these were confirmed cases (2016/2855) and 36 % (1030/2855) had their vaccination status written within a medical record.

Among the 1030 cases whose vaccination status was written in a medical record, 715 were confirmed cases and therefore included in our main analysis, with a mean age of 12.4 years, and a ratio m/f of 1.09. Among these 715 cases, 527 were unvaccinated (73.7 %, 62 (8.7 % had been vaccinated with MCV1 only and 126 (17.6 % with MCV2 (Table 1). The proportion of cases vaccinated with MCV2 increased with age, from 5.3 % in individuals aged 2–5 years to 29.5 % in individuals aged 26–31 years. When excluding MCV1 cases from the denominator (see definition in Methods), PCV for MCV2 increased from 5.5 % in individuals aged 2–5 years to 43.4 % in individuals aged 26–31 years.

In the general population, MCV2 VC increased from 86.0 % in individuals aged 2–5 years to 91.7 % in individuals aged 11–15 years, then decreased to 62.6 % in individuals aged 26–31 years (Table 2). The PPV for MCV2 (excluding MCV1 from the denominator as defined previously) increased from 94.0 % in individuals aged 2–5 years to 97.4 % in individuals aged 11–15 years, then decreased to 89.9 % in individuals aged 26–31 years.

Table 2
Vaccine coverage (VC) and proportion of population vaccinated (PPV) for MCV2 (second dose of measles-containing vaccine), by age group, in 2017 in France.

Age group (years)	Unvaccinated population (%)	Vaccine coverage for at least 1 dose (%)	Vaccine coverage for MCV2 (%)	Proportion of the population vaccinated (PPV) for MCV2 (%)*
2–5	5.4	94.6	86.0	94.0
6–10	2.4	97.6	91.6	97.5
11–15	2.5	97.5	91.7	97.4
16–20	3.3	96.7	88.9	96.5
21–25	4.2	95.8	86.0	95.4
26–31	7.1	92.9	62.6	89.9

*PPV for MCV2 differs from VC for MCV2 due to different denominators (for VC, the denominator is the total population, while for PPV the population vaccinated with 1 dose is excluded from the denominator (see definition in methods)).

3.2. Vaccine effectiveness estimation

3.2.1. Vaccine effectiveness by age group – Baseline analysis without natural immunity

In the baseline analysis (not accounting for natural immunity), the VE estimates were high in all age groups and decreased with age (Table 3, Fig. 1A): VE was above 99 % in individuals aged 2–5, 6–10 and 11–15 years and above 98 % in individuals aged 16–20 and 21–25 years. VE was lower in the 26–31 years age group with an estimate of 91.4 % (95%CI 85.1–95.0).

3.2.2. Scenarios accounting for natural immunity

In all scenarios, the proportion of naturally immunized, non-vaccinated individuals increased with age, older people having been more exposed to the virus than younger people (Fig. 1B). In the older age group (26–31 years old), the estimated proportion of naturally immunized, non-vaccinated individuals was 7.4 % in scenario 1 (upper bound) and decreased to 4.4 % in scenario 2, 3.0 % in scenario 3 and 1.5 % in

Table 3
Estimated vaccine effectiveness by age group and 95 % confidence interval (95%CI), in metropolitan France, between October 2017 and September 2019, in the baseline analysis (not accounting for natural immunity).

Age group (years)	Vaccine effectiveness % [95% Cl]
2–5	99.6 [99.3–99.8]
6–10	99.5 [99.2–99.7]
11–15	99.3 [98.9–99.5]
16–20	98.3 [97.3–98.9]
21–25	98.1 [96.5–98.9]
26–31	91.4 [85.1–95.0]

Table 1
Number of measles cases by vaccination status and age group, notified between October 2017 and September 2019 in metropolitan France, and included in the main analysis (confirmed cases whose vaccination status was obtained from a written medical record).

Age group (years)	Unvaccinated		Vaccinated with only 1 dose (MCV1)*		Vaccinated with 2 doses (MCV2)*		Proportion of cases vaccinated (PCV) for MCV2 (%)**	Total number of cases
	n	%	n	%	n	%		
2–5	190	90.9	8	3.8	11	5.3	5.5	209
6–10	112	80.0	6	4.3	22	15.7	16.4	140
11–15	91	76.5	4	3.4	24	20.2	20.9	119
16–20	64	61.5	10	9.6	30	28.8	31.9	104
21–25	40	61.5	9	13.8	16	24.6	28.6	65
26–31	30	38.5	25	32.0	23	29.5	43.4	78
Total	527	73.7	62	8.7	126	17.6	19.3	715

* MCV1 and MCV2: first and second doses of measles-containing vaccines.
** PCV for MCV2 was computed by excluding MCV1 cases from the denominator (see definition in Methods).

scenario 4. Under all scenarios assuming natural immunity, VE estimates among the younger age groups were unchanged compared to the baseline analysis (Fig. 1A), since they have very low levels of natural immunity. However, accounting for natural immunity had a substantial impact on VE among older age groups, especially in individuals aged 26–31 years, having the highest levels of natural immunity: in this age group, VE increased from 91.4 % (baseline analysis) to 93.2 % (88.2–96.0) in scenario 4, 95.0 % (91.4–97.1) in scenario 3, 96.8 % (94.4–98.1) in scenario 2 and 99.2 % (98.7–99.6) in scenario 1.

3.2.3. *Waning protection over time*

In the analysis of waning protection over time, VE was above 99 % up to 4 years after MCV2 vaccination (i.e., for children aged 6 years and vaccinated around 2 years), and slowly decreased to 97.8 % (97.2–98.3) 11–12 years after vaccination (i.e., for children aged 13–14 years and vaccinated around 2 years) (Fig. 1C). The results for all scenarios of natural immunity were similar (Figure S4) since only individuals below 14 years old, unlikely to have natural immunity, were included in this analysis. We estimated that the exponential decay rate was 0.0022/year (95%CI 0.0017–0.0028), meaning that the yearly decline rate was 0.22 %.

3.2.4. *Reconciling VE by age and waning protection over time*

Fig. 1D overlays the data shown in Fig. 1C and 1A after replacing the x-axis by the mean time since vaccination (*age - mean age at vaccination*), instead of age. For instance, for individuals aged 26–31 years, the mean time since last vaccination was 16.4 years. We found that the results of the two analyses were consistent. When extrapolating the exponential decay model up to 16.4 years, we found that the scenario of natural immunity most compatible with the estimated decay rate was scenario 2, in which the proportion of naturally immunized, non-vaccinated individuals was 4.4 % in 26–31 years old. Under this scenario, VE in individuals aged 26–31 years was estimated at 96.8 % (94.4–98.1), compared to 91.4 % when natural immunity was not accounted for.

3.2.5. *Sensitivity analyses*

We performed three sensitivity analyses, under the most plausible scenario for natural immunity (i.e., scenario 2). Age-specific VE

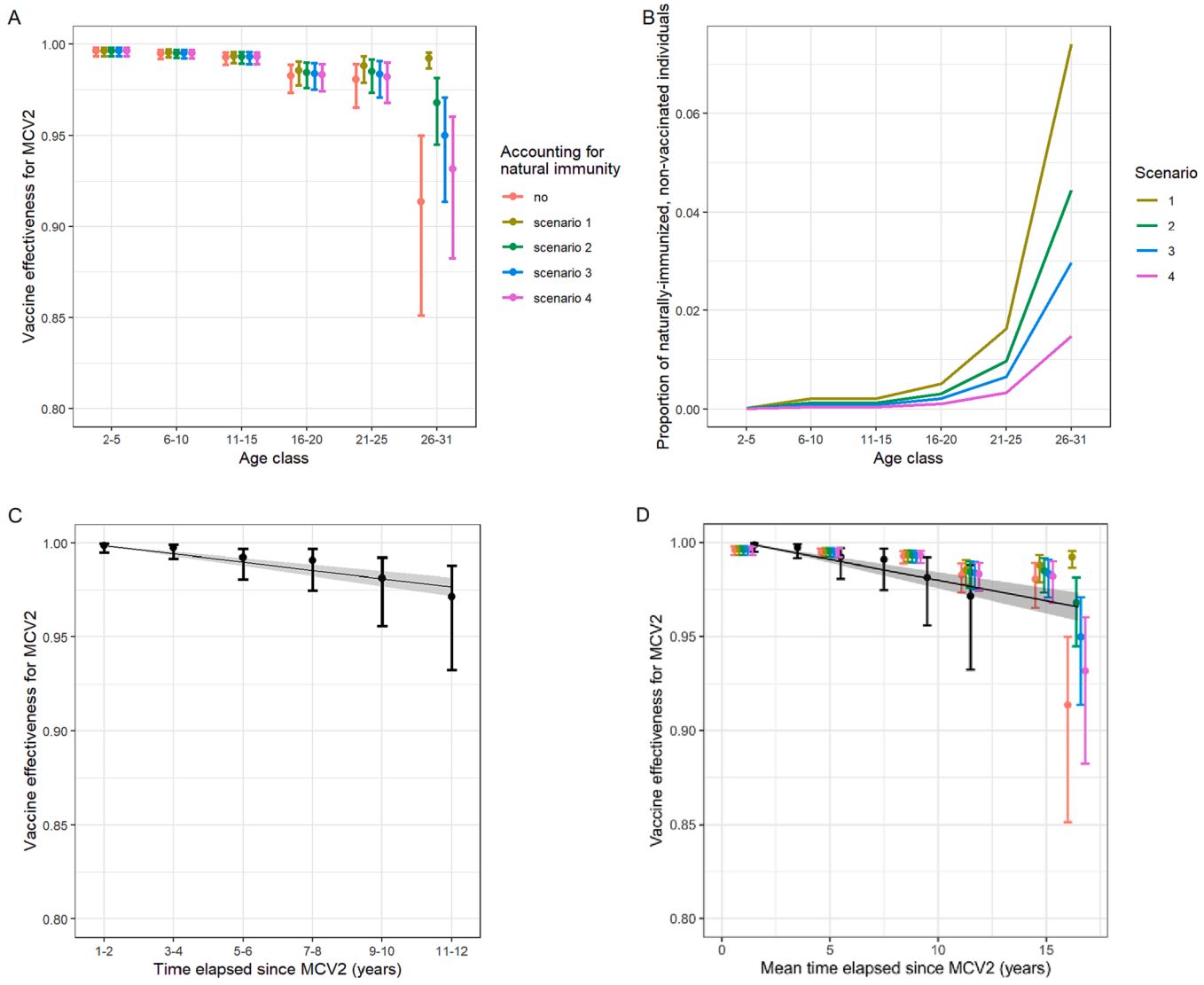

Fig. 1. Estimated vaccine effectiveness (VE) for 2 doses of measles-containing vaccine (MCV2) in metropolitan France between October 2017 and September 2019. A: VE estimates by age group, not accounting for natural immunity (baseline analysis) or accounting for natural immunity (4 scenarios). B: Definitions of the four scenarios in terms of estimated proportion of naturally immunized, non-vaccinated individuals in each age group. C: Evolution of VE as a function of the time elapsed since MCV2 vaccination, only including individuals aged 3 to 14 years and vaccinated by MCV2 in early life (before 3 years old); the mean age at vaccination was around 2 years (Figure S3), so the time elapsed since vaccination varied from 1 to 12 years. D: Superimposition of panel A (translated into VE by mean time elapsed since MCV2) and panel C, keeping the same color scheme. In all panels, the points and segments show the point estimates and their 95 % confidence intervals. In panels C and D, the line and shaded area show the model fit and the 95 % confidence interval. In panels A and D, colored points were separated to avoid overlap.

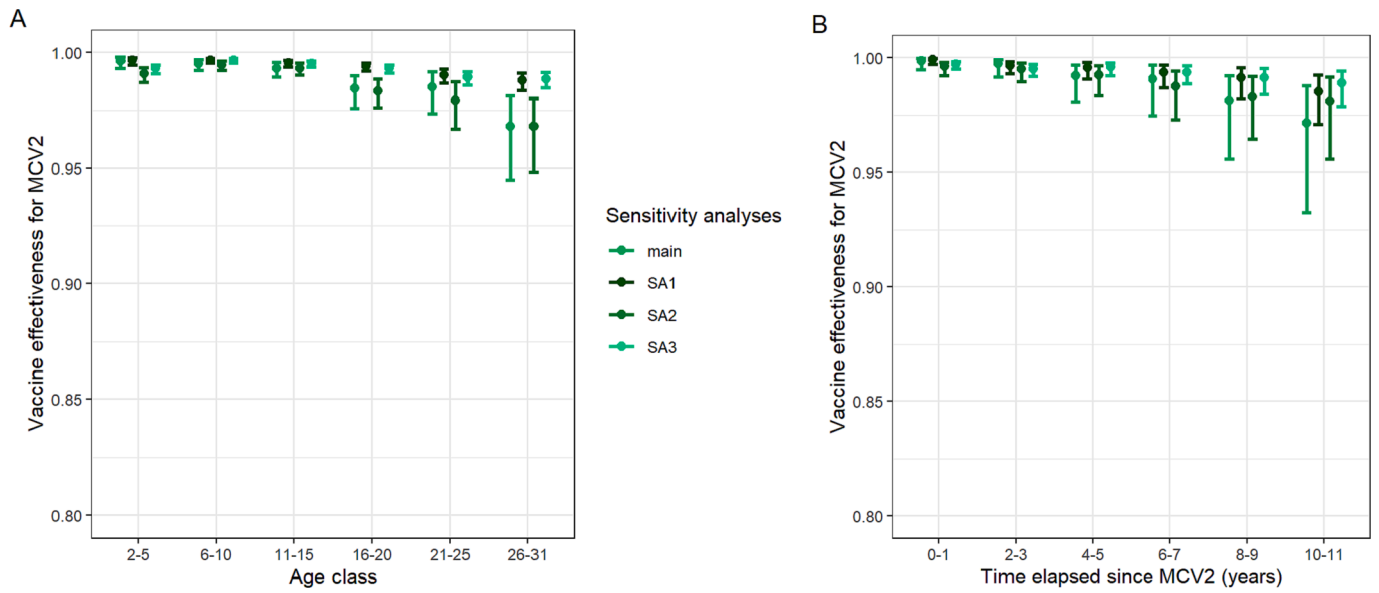

Fig. 2. Estimated vaccine effectiveness for 2 doses of measles-containing vaccine (MCV2), by age group (A) and by time elapsed since MCV2 (B), in metropolitan France between October 2017 and September 2019, in the 3 sensitivity analyses (SA) compared to the main analysis, using scenario 2 of natural immunity for all analyses. SA1: confirmed cases whose vaccination status was obtained from any source of information (written medical record or verbally or unknown); SA2: all cases (confirmed and clinical) whose vaccination status was obtained from a written medical record; SA3: all cases (confirmed and clinical) whose vaccination status was obtained from any source of information (written medical record or verbally or unknown). Numbers of cases included in each sensitivity analysis are given in Table S1.

estimates from SA2 (including confirmed and clinical cases) were close to those found in the main analysis, showing that case definition had negligible impact on VE estimates (Fig. 2). Estimates from SA1 (confirmed cases whose vaccination status was obtained from any source of information) and SA3 (confirmed and clinical cases whose vaccination status was obtained from any source of information) were higher in older age groups: VE reached 96.8 % (95.5–97.6) and 96.9 % (95.9–97.7) in SA1 and SA3, respectively, in individuals aged 26–31 years, due to a lower PCV in this age group compared to the main analysis. In the three sensitivity analyses, VE estimates according to the time elapsed since vaccination were not different from the main analysis, although the estimated waning of protection was slower: the yearly exponential decay rate was 0.0011 (0.0009–0.0013), 0.0015 (0.0013–0.0017) and 0.0007 (0.0006–0.009) in SA1, SA2 and SA3, respectively, compared to 0.0022 in the main analysis. The fitted exponential decay models for each sensitivity analysis are shown in Figure S5.

4. Discussion

The resurgence of measles in France in 2008 and the presence of fully vaccinated cases raised the question of the contribution of decreasing protection following vaccination. In this study relying on French measles surveillance and vaccine coverage data, we estimated the age-stratified VE for MCV2 and quantified the decay of protection over time following early vaccination.

In the baseline analysis (assuming absence of natural immunity), estimates of MCV2 VE were high (>90 % in all age groups: VE was above 99 % for children below 15 years old, around 98 % for 16–25 years old and decreased to 91.4 % for 26–31 years old. These results are consistent with those of a German study using the screening method, although their estimate was higher in the 24–30 years group (98.5 % and the decline was observed later, with VE decreasing to 90.9 % for individuals >30 years old [20].

Our baseline analysis was performed using the standard screening method, assuming absence of natural immunity among non-vaccinated individuals. To account for natural immunity in the population (particularly in young adults exposed to measles in their childhood due to high circulation of the virus in the 1980s), we improved the screening method by removing naturally immunized, non-vaccinated individuals from the PPV. We showed that natural immunity had a substantial impact on VE estimates in the 26–31 years old, yielding an estimate of VE of 96.8 % in the most plausible scenario for this age group, compared to 91.4 % when natural immunity was ignored. Our results show that natural immunity should be accounted for, especially for older individuals. If natural immunity is present but cannot be accounted for, then VE estimates based on the standard screening method should be considered as lower bound estimates, with bias increasing with age.

To assess the robustness of our results, we performed several sensitivity analyses. In the main analysis, we only relied on confirmed cases and written vaccination status information. This may have reduced the power of the study, especially in the older age groups, but it provided the least biased estimates. We showed that using a broader case definition (including clinical cases) had little influence on estimates. However, we found higher VE estimates when cases' vaccination status was obtained from any source of information (either written, verbal or unknown source). This may be due to a recall bias in cases regarding their vaccination history, leading to underestimate PCV and overestimate VE. Overall, our choice in the main analysis therefore appears to be conservative.

Importantly, if one wants to investigate the waning of protection over time, VE estimates by age group can be misleading in settings where older people have been vaccinated at a later age than younger people. For instance, in our studied population, the mean age at MCV2 vaccination varied from 2 to 14 years depending on the age group. Therefore, we also estimated VE according to the time elapsed since MCV2 vaccination, to quantify the waning of protection over time, by restricting the analysis to individuals vaccinated around 2 years old. We found that VE slowly decayed at a rate of 0.22 % per year, declining to 97.7 % 11–12 years after vaccination. Data were too scarce to estimate VE more than 12 years after vaccination. However, by assuming a constant decay rate, we found that extrapolated VE would be equal to 96.7 % (96.0–97.4) 16 years after MCV2 vaccination. In another study, 20 years after measles immunization, after one or two doses, 92 % of individuals still had protective antibody titers [32]. Two meta-analyses estimated a faster decline, with an exponential waning rate of 0.8–0.9 %

after the second dose [33,34]. The difference could be explained by the fact that they included studies of antibody persistence, while immunological protection against measles is also mediated by cellular immunity [11]. Thus, a proportion of individuals who have undetectable antibodies might still be protected against the disease.

To estimate VE, the screening method is convenient when the population at risk is unknown (here population susceptible to measles). We used available estimates of age-dependent VC, without having to select random samples of non-measles cases (as in VE case-control studies) or unvaccinated individuals (as in VE cohort studies). The relative risk calculation or "screening odds"- in cases related to standard population - is based on similar principles than for a case-control study. However, it has limitations, mainly the need for stratification on confounding factors such as age and the requirement of stratified and high-accuracy external estimates for the PPV, which are not always available. Here, availability of good-quality data on vaccine coverage in France allowed us to stratify by age, the main factor influencing VE. VC estimates were based on three reliable sources of information. First, at two years of age, we used the national database of the health certificates completed for every child at 24 months. Second, estimates for older children up to 15 years of age were obtained from school surveys of large random samples of pupils. The main limitation of these data is their insufficient power, hindering the estimation of reliable subnational VC [35], which prevented us from stratifying the analysis by geographic regions. However, even though MMR vaccine coverage is not homogenous throughout the country, regional differences remain small and the impact of the absence of geographical stratification in the analysis should be minor. Third, catch-up activities above 15 years of age were estimated through the National Social Security Inter-Scheme Consumption Database. It may slightly overestimate the actual coverage since it counts purchased (not administered) vaccines (in France patients are usually required to purchase a vaccine and then return to the general practitioner for administration). Yet, the MCV vaccine has been exceptionally provided free-of-charge in the public sector, meaning that the database may also underestimate coverage. For all data sources, we used available data up to 2017 and, based on observed trends, assumed VC was constant over the study period. A slight increase of VC from 2017 to 2019 would yield a slightly higher VE.

Our study has other limitations. First, regarding mandatory notification data, an absence of vaccination on the medical record of measles cases was considered by the reporting clinician as non-vaccination, which could have overestimated VE. Another limitation is that the mandatory notification database used to identify measles cases suffer from underreporting: a 45 % under-notification rate was previously estimated [15]. However, it remains unclear whether notification of a case is associated with vaccination status. If not, we do not expect any impact of underreporting on our VE estimates. In addition, our study mainly captures typical measles presentation meeting the European Commission's case definition. Several studies showed that the clinical presentation in secondary vaccine failure after MCV could be mild or atypical. This could have led to underestimating PCV and overestimating VE against any type of presentation but does not call into question our estimates of VE against typical measles and its complications. Furthermore, transmission from such mild breakthrough infections is considered very uncommon, probably due to lower viral loads and the limited presence of cough [24,36,37].

Finally, estimating the proportion of naturally immunized individuals in a population is challenging. We defined four hypothetical scenarios accounting for realistic levels of natural immunity in the French population, based on measles cases captured by the sentinel surveillance system before 2005 and reported by the mandatory notification system after 2005. Sentinel surveillance is subject to biases, that we could not explicitly correct for, such as under-reporting (i.e., only including GPs, therefore cases seen by pediatricians were not included) or over-reporting (e.g., cases were reported based on clinical criteria, which led to falsely notify measles-like illnesses as measles cases, especially during a low incidence period). These two types of biases could have led to under- and overestimate, respectively, the amount of natural immunity in scenario 1. Moreover, among the non-vaccinated cases, a proportion might have been vaccinated later, since the triple MMR vaccine was also recommended in case of a measles history to provide protection against mumps and rubella. Hence, we included scenarios 2 to 4 to have a reduction in the proportion of naturally immunized people compared to scenario 1. We did not consider scenarios with natural immunity higher than in scenario 1, because PPV would then have become larger than 1 in the oldest age group. Nonetheless, the uncertainty on the actual proportion of natural immunity only affects VE for older age groups, notably the 26–31 years old, which we found to be between 91.4 % and 99.2 %. Interestingly, by reconciling VE by age and waning protection over time, and assuming a constant exponential decay rate of vaccine protection, we were able to narrow down this uncertainty and identify scenario 2 as the most plausible one, yielding a VE of 96.8 % in this age group.

5. Conclusions

Our results demonstrate that MCV2 VE remains high until 31 years of age, and that protection wanes slowly over time. Yet, the proportion of vaccinated cases increases with age, but this increase more likely reflects the increase in vaccine coverage, as illustrated in Figure S1. Importantly, most notified cases are still non-vaccinated. Therefore, increasing MCV2 coverage in age groups targeted by measles vaccination is necessary to maintain the population immunity at a sufficiently high level to achieve measles elimination. The introduction in January 2018 of a mandate for the two doses of MCV in the first two years of life will impact only the long-term susceptibility profile of the French population and is insufficient to prevent measles resurgence in the near future [38]. Catch-up vaccinations for older children and young adults are urgently needed to fill the immunity gap in those age groups with insufficient VC.

Ethical statement

The study was based on pseudonymised data whose collection and analysis by Santé publique France is a legal obligation. The legal provisions allowing access to these data were subject to the prior opinion of the Commission Nationale Informatique et Libertés. Anonymous data from public statistics surveys were used as well. The study based on existing data does not constitute research involving the human person requiring the opinion of an ethics committee.

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CRediT authorship contribution statement

Léa Franconeri: Writing – original draft, Writing – review & editing. **Denise Antona:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Simon Cauchemez:** Methodology, Writing – review & editing. **Daniel Lévy-Bruhl:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Juliette Paireau:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.018.

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