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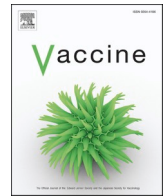
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What is the relevancy of a surveillance of mumps without a systematic laboratory confirmation in highly immunized populations? Epidemiology of suspected and biologically confirmed mumps cases seen in general practice in France between 2014 and 2020

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ABSTRACT

Background: In France, mumps surveillance is conducted in primary care by the *Sentinelles network*, the National Reference Centre for Measles, Mumps and Rubella and Santé publique France.

Aim: The objective of this study was to estimate the incidence of suspected mumps in general practice, the proportion of laboratory confirmed cases and the factors associated with a virological confirmation.

Methods: General practitioners (GPs) participating in the Sentinelles network should report all patients with suspected mumps according to a clinical definition in case of parotitis and a serological definition in case of clinical expression without parotitis. All suspected mumps cases reported between January 2014 and December 2020 were included. A sample of these cases were tested by real time reverse transcriptase polymerase chain reaction (RT-PCR) for mumps biological confirmation.

Results: A total of 252 individuals with suspected mumps were included in the study. The average annual incidence rate of suspected mumps in general practice in France between 2014 and 2020 was estimated at 11 cases per 100,000 population [CI95%: 6–17]. A mumps confirmation RT-PCR test was performed on 146 cases amongst which 17 (11.5 %) were positive. Age (between 20 and 29 years old), the presence of a clinical complication and an exposure to a suspected mumps case within the 21 days prior the current episode were associated with a mumps biological confirmation.

Conclusion: If these results confirm the circulation of mumps virus in France, they highlight the limits of a surveillance without a systematic laboratory confirmation in highly immunized populations.

1. Introduction

Mumps is a contagious respiratory disease caused by a Rubulavirus of the Paramyxovirus family. The most frequent clinical symptom is a unilateral or bilateral parotitis. Complications can occur such as

meningitis (15 %), orchitis (20 % of post-pubertal males), pancreatitis (4 %) and more rarely oophoritis and mastitis [1].

As recommended by the World Health Organization (WHO), the majority of industrialized countries and many countries in economic transition have integrated vaccine strategies to prevent the spread of

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disease [1]. These countries have seen the incidence of mumps cases drop drastically. In Finland, elimination was achieved by the mid-1990 s after the implementation of a vaccination program started in 1982 using two Measles, Mumps, and Rubella (MMR) shots and covering more than 95 % of the population [2]. In 1986, France implemented mumps immunization with a single dose of MMR vaccine in 1-year-old children. Ten years later, a second dose was added for children aged 11 to 13 years, now recommended between 16 and 18 months of age. Since 2018, the two doses of MMR vaccine have become mandatory in France for infants. After the implementation of vaccination, the annual incidence of mumps disease decreased from 859 to 9 cases per 100,000 population between 1986 and 2011 [3]. However, outbreaks are still reported with changes in the characteristics of people affected [4]. Mumps affects adolescents and young adults more frequently for whom the risk of complications and sequelae is higher [3,5], and predominantly individuals previously vaccinated according to recent studies [6,7].

To follow the effectiveness of vaccination campaigns and estimate the incidence of mumps infection in the general population, countries developed epidemiological surveillance systems based on mandatory declaration as in Canada [8] or sentinel surveillance as in France [9]. In France, a sentinel surveillance without a systematic laboratory confirmation was set up in general practice by the *Sentinelles network* in 1985 in partnership with the French national health authorities [9]. Sentinel general practitioners (GPs) must report all patients presenting with mumps-like symptoms in consultation according to a clinical definition in case of parotitis and a serological definition when no parotitis is observed (detailed definition presented in the “Methods” section). As parotitis could be caused by other infectious agents [5]), and mumps is rare in a highly immunized populations, the positive predictive value of parotitis for mumps diagnosis is low [10].

This seemingly low positive predictive value raises the question on whether cases diagnosed in general practice are actually mumps, and if there may be an overestimation of mumps incidence using a surveillance system without a laboratory confirmation. In this context, the *Sentinelles network* added a mumps virological surveillance in 2014. The objectives of this study are to estimate the incidence of suspected mumps seen in primary care according to the usual *Sentinelles* definition, the proportion of laboratory confirmed cases and the factors associated with this confirmation.

2. Methods

2.1. Data collection

The *Sentinelles network* is a French national surveillance system monitoring a set of diseases seen in primary care based on the voluntary participation of a sample of GPs. Between 0.7 and 1.2 % of French GPs actively contribute to the clinical surveillance of these diseases during the study period (between 394 GPs in 2014 and 685 GPs in 2020, the lowest and highest number of GPs participating per year over the study period) [9,11].

Since 1985, suspected cases of mumps are reported by sentinel GPs on a weekly basis according to the following definition: “recent unilateral or bilateral painful swelling of the parotid gland, isolated or associated with testicular, pancreatic, meningeal or cerebral damage”, or “in absence of parotitis, the combination of orchitis, meningitis or pancreatitis and a serological confirmation (presence of IgM or IgG increased by at least a factor of 4). For each case, the sentinel GPs report age, sex, clinical symptoms, hospitalization, vaccine status and potential exposure to another suspected mumps case during the 21 days prior to the onset of the disease. If the patient is vaccinated, the number of doses and the date of the last injection are collected.

Since 2014, a complementary virological surveillance has been implemented. Among sentinel GPs, volunteers received salivary swabs to collect a salivary sample from each suspected case of mumps according to the previous definition. These samples were analysed by the

French National Reference Center for Measles, Rubella and Mumps viruses for laboratory confirmation, based on detection of mumps viral RNA using real time reverse transcriptase polymerase chain reaction (RT-PCR) with primers and probes targeting the nucleoprotein gene [12].

2.2. Study population

All suspected mumps cases reported by sentinel GPs between January 1st, 2014 and December 31st, 2020 were included in our study.

2.3. Statistical analysis

Yearly national suspected mumps incidence per 100,000 population was estimated by multiplying the mean number of suspected mumps cases per sentinel GPs (adjusted according to their participation and their geographical distribution) by the total number of GPs in France and then dividing by the population of that year. Confidence intervals (CI95%) were calculated under the hypothesis that reported cases followed a Poisson distribution.

Suspected mumps cases reported by sentinel GPs were described. Due to the gradual shift of mumps from children to young adults in the last decades, age was classified by ranges of ten years between 0 and 40 years old and over 40. For sampled individuals, proportions laboratory confirmation of mumps were calculated. The characteristics of sampled and non-sampled cases and of mumps-positive and mumps-negative cases were compared by using a Fischer test. All analyses were performed using R software version 3.4.4 [13].

3. Results

During the study period, 252 suspected mumps cases were reported by sentinel GPs and included in the study. The average annual incidence rate of suspected mumps cases in general practice in France between 2014 and 2020 was estimated at 11 cases per 100,000 population [CI95%: 6–17], varying from 17 [CI95%: 10–24] in 2014 to 6 cases per 100,000 population [CI95%: 3–9] in 2017 (Fig. 1, Table 1).

3.1. Clinical data

The median age of the reported cases was 17 years [Inter-quartile range 6–32] and men accounted for 52.8 % (n = 132). A total of 79.0 % (n = 154 over 195) were vaccinated against mumps with 56.6 % (n = 110) vaccinated with at least two doses. All cases had a parotitis. Complications occurred in 4.1 % (n = 10) and included six orchitis, one meningitis, one encephalitis, one conjunctivitis and one diffuse adenopathy (Table 2).

3.2. Virological data

Out of the 252 cases included in this study, 148 (58.7 %) of them were sampled by sentinel GPs. Sampled and non-sampled cases had similar clinical characteristics, with the exception of the vaccination status, with a higher proportion of vaccinated cases observed in the sampled group (p = 0.002) (Table 3).

Out of the 148 sampled cases, 146 were tested and 11.6 % (n = 17) had a laboratory confirmation of mumps, which is an estimate of the positive predictive value of the clinical definition followed by the French GPs Sentinel network. Age (between 20 and 29 years old), presence of complications and an exposure to a suspected mumps case within the 21 days prior the current episode were significantly associated with mumps virological confirmation (Table 4).

4. Discussion

The results highlight the limits of an epidemiological surveillance of

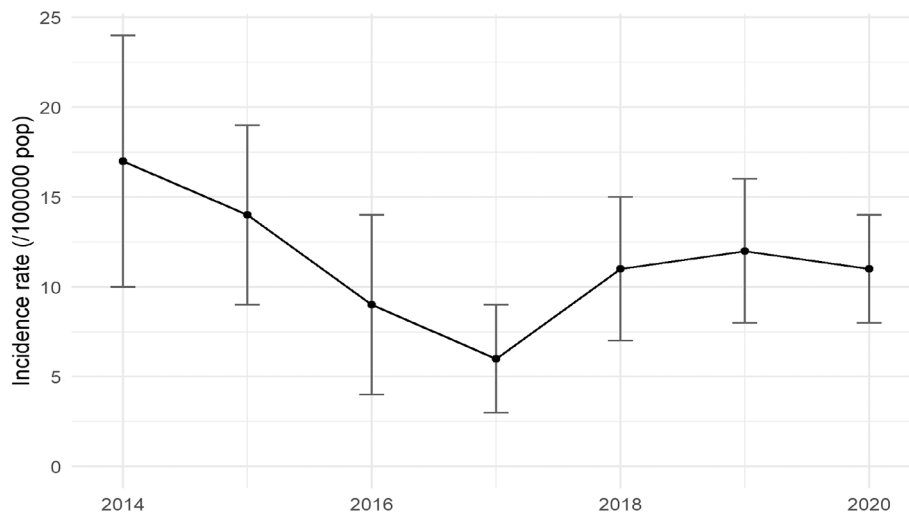


Fig. 1. Yearly incidence estimates and 95% confidence intervals of suspected mumps seen in general practice, France, 2014–2020, French Sentinelles network.

Table 1

Number of suspected mumps cases included in the study per year, estimates of the incidence and the incidence rate of suspected mumps cases seen in general practice in France per year and 95% confidence intervals, France, 2014–2020.

Year	Reported cases (n)	Estimates of suspected mumps cases annual incidence	Confidence interval 95 % of annual incidence [CI95%]	Estimates of suspected mumps cases annual incidence rate per 100,000 population	Confidence interval 95 % of annual incidence rate per 100,000 population [CI95%]
2014	38	10,960	6,750 – 15,170	17	10 – 24
2015	39	8,959	5,512 – 12,406	14	9 – 19
2016	23	6,176	3,062 – 9,290	9	4 – 14
2017	21	4,026	1,900 – 6,152	6	3 – 9
2018	36	7,017	4,351 – 9,683	11	7 – 15
2019	41	7,994	5,350 – 10,638	12	8 – 16
2020	54	7,514	5,255 – 9,773	11	8 – 14

mumps without laboratory confirmation in highly immunized populations. They show a low laboratory confirmation rate among the suspected mumps seen in GPs’ consultation and underline factors associated with this confirmation.

The low proportion of laboratory confirmed cases demonstrate a discrepancy between clinical suspicion and the confirmation of mumps. This is consistent with other studies equally supporting low laboratory confirmation rates for clinically suspected cases of mumps [3,14,15]. The rate of confirmed cases was 9 % in an Australian study (serology confirmation) and 14 % in a Canadian study (RT-PCR confirmation) [14,15]. This contrast between suspected and laboratory confirmed cases could be linked to the differential diagnosis of parotitis, especially infectious diseases caused by other viruses (such as Epstein Barr Virus (EBV), parainfluenza or adenovirus) [14,16]. In a Korean study on viral etiologies of parotitis, EBV was the most frequently found virus (20.7 %), followed by HHV 6 (8.0 %) while mumps were only found in 5.5 % of cases [16]. These elements reveal the fragility of a diagnosis strategy based solely on clinical arguments. Other findings convey the limitations of clinically based diagnosis, suggesting that the positive predictive value of clinical diagnosis decreases when there is a low disease prevalence, as observed in highly immunized populations with mumps [3,14]. Accordingly, reinforcing laboratory confirmation would increase considerably the accuracy of mumps surveillance, in order to improve public health strategies for mumps control and/or elimination.

Several factors not associated with clinical expression were significantly associated with laboratory confirmation of mumps cases. Exposure to a suspected mumps case within the 21 days prior to the current episode and the presence of a clinical complication reflect the course of mumps disease, beginning with the transmission and having different clinical presentations from parotitis to more severe case [5]. Ages

between 20 and 29 years is also associated with a laboratory confirmed cases. This gradual shift of cases from children to young adults in the last decades is supported by the last Santé publique France report on mumps [17] and by the most recent epidemics [18–20]. This could be due to a residual but significant rate of non-vaccinated people. In highly immunized populations with a low level of mumps virus circulation, the probability of infection among unimmunized people decreases and the fewer people getting the disease are actually infected at an older average age [5,21]. The median age of mumps infection might keep climbing until the level of immune population needed to stop spread of mumps has been achieved [22]. The increase in age for mumps confirmed cases may also be due to the waning immunity after MMR vaccination. Waning immunity [23,24], combined with a viral circulation too low to work as a natural immunity booster may also support the age distribution of cases. Suggesting that two doses of MMR vaccine, used with the current schedule, could in fact not be adequate in providing a lifelong immunity [19,23,24].

5. Limits

A limitation of our study is the focus on primary care since only cases reported by GPs were considered, excluding patients consulting elsewhere. These cases could differ from those seen in GPs’ consultation with more severe clinical presentations and a higher laboratory confirmation rate. Using a sentinel network in primary care, built with a small fraction of the French GPs, to monitor a rare disease impose a cautious interpretation of the results. The higher vaccination coverage in the laboratory-tested samples could have partly biased our results here, by reducing artificially the rate of confirmed cases in the sampled group. However, the vaccination does not appear to be linked to mumps

Table 2

Characteristics of suspected mumps cases seen in general practice included in the study, France, 2014–2020, French Sentinelles network.

Characteristics	N (%)
Total	252 (100 %)
Sex (m. d. = 2)	
Male	132 (52.8 %)
Female	118 (47.2 %)
Age groups (years) (m. d. = 1)	
0–9	85 (33.8 %)
10–19	52 (20.8 %)
20–29	42 (16.8 %)
30–39	29 (11.6 %)
≥40	43 (17.1 %)
Delay between symptoms onset and consultation (m. d. = 68)	
<2 days	91 (49.5 %)
Between 2 and 4 days	73 (39.7 %)
>4 days	20 (10.9 %)
Parotitis (m. d. = 1)	251 (100 %)
Complications (m. d. = 9)	
Yes	10 (4.1 %)
No	233 (95.9 %)
Vaccination (m. d. = 57)	
No	41 (21.0 %)
Yes (1 dose)	31 (15.9 %)
Yes (2 dose or more)	110 (56.4 %)
Yes (unknown number of doses)	13 (6.7 %)
Contact with another suspected mumps case (up to 21 days previous disease) (m. d. = 102)	
Yes	12 (8.0 %)
No	138 (92.0 %)
Hospitalization (m. d. = 38)	
Yes	4 (1.9 %)
No	210 (98.1 %)

Abbreviation: m. d. = missing data.

† Complications: 6 orchitis, 1 meningitis, 1 encephalitis, 2 other types.

positivity in our study, which is corroborated by recent epidemiological reports [25,26]. This difference could be explained by the fact that GPs, faced with a suspected mumps case who has been vaccinated, would like to check more systematically that the symptoms presented by the patient are indeed due to mumps.

6. Conclusion

The WHO recommendation for countries with high mumps control, making compulsory to report cases and systematic the biological exploration for every suspected case [27], should be taken into consideration. The generalization of laboratory confirmation, however, encounters practical obstacles. There are notable challenges in engaging GPs due to the limited impact of laboratory confirmation on therapeutic strategies. Feasibility issues arise, especially concerning the specific constraints associated with swabbing. This includes the necessity for a swab to be conducted within 4 days of the onset of symptoms for clear interpretability and the requirement for sample storage at cold

Table 3

Comparison of characteristics between sampled and unsampled suspected mumps cases seen in GPs' consultations between 2014 and 2020, France, French Sentinelles network.

	Sampled cases n = 148 (58.7 %)	Unsampled cases n = 104 (41.3 %)	p-value
Sex (m. d. = 2)			0.16
Male	72 (49.0 %)	60 (58.3 %)	
Female	75 (51 %)	43 (41.7 %)	
Age groups (years) (m. d. = 1)			0.82
0–9	47 (31.8 %)	38 (36.9 %)	
10–19	29 (19.6 %)	23 (22.3 %)	
20–29	27 (18.2 %)	15 (14.6 %)	
30–39	18 (12.2 %)	11 (10.7 %)	
≥40	27 (18.2 %)	16 (15.5 %)	
Delay between symptoms onset and consultation (m. d. = 68)			0.42
<2 days	53 (49.5 %)	38 (49.4 %)	
Between 2 and 4 days	46 (43 %)	27 (35.1 %)	
>4 days	8 (7.4 %)	12 (15.6 %)	
Parotitis (m. d. = 1)	148 (100 %)	103 (100 %)	
Complications † (m. d. = 9)			0.74
Yes	7 (4.9 %)	3 (3.0 %)	
No	137 (95.1 %)	96 (97.0 %)	
Vaccination ‡ (m. d. = 57)			0.002
No	18 (16.1 %)	23 (27.7 %)	
Yes (1 dose)	16 (14.3 %)	15 (18.1 %)	
Yes (2 dose or more)	76 (67.9 %)	34 (41 %)	
Yes (unknown number of doses)	2 (1.8 %)	11 (13.3 %)	
Contact with another suspected mumps case (up to 21 days previous disease) (m. d. = 102)			0.37
Yes	5 (5.9 %)	7 (10.8 %)	
No	80 (94.1 %)	58 (89.2 %)	
Hospitalization (m. d. = 37)			0.36
Yes	1 (0.9 %)	3 (2.9 %)	
No	111 (99.1 %)	100 (97.1 %)	

Abbreviation: m. d. = missing data.

† Complications: 6 orchitis, 1 meningitis, 1 encephalitis, 2 other types.

temperatures, necessitating access to a refrigerator [28]. The availability of biological tests in current practice of any standard lab should be monitored, as well as the financial responsibility of the biological analysis. On the other hand, the current sentinel surveillance is useful in identifying trends or outbreaks, and permit to equip, teach and follow-up rigorously a representative part of the GPs in a territory [29,30]. However, its effectiveness is diminished as disease prevalence decreases. Indeed, the size of the sample of GPs needed to compensate the low occurrence of the disease would have to be so big that it would contradict the epidemiological model of the sentinel surveillance system. If further research should be done to examine the most adequate surveillance system for ensuring the monitoring of mumps, these results support the addition of systematic laboratory confirmation to mumps surveillance systems in highly vaccinated populations. The answer matters on a national scale but also on the European stage to harmonize the reporting systems, still heterogeneous [31], and improve the representativeness of the mumps surveillance.

7. Ethical statement.

The protocol was conducted in agreement with the Helsinki declaration. We obtained authorization from the French Data Protection Agency (CNIL#471393) and the French ethical research committee (Comité de protection des personnes). All participating physicians consent to publication of the results from the surveillance.

Table 4

Comparison between mumps positive and mumps negative sampled cases seen in GPs' consultations between 2014 and 2020, France, French Sentinelles network.

	Positive for mumps n = 17 (11.6 %)	Negative for mumps n = 129 (88.4 %)	p-value
Sex (<i>m. d. = 1</i>)			0.80
Male	9 (52.9 %)	62 (48.4 %)	
Female	8 (47.1 %)	66 (51.6 %)	
Age groups (years) (<i>m. d. = 0</i>)			<0.001
0–9	2 (11.8 %)	45 (34.9 %)	
10–19	3 (17.6 %)	26 (20.2 %)	
20–29	10 (58.8 %)	16 (12.4 %)	
30–39	2 (11.8 %)	15 (11.6 %)	
≥40	0 (0.0 %)	27 (20.9 %)	
Delay between symptoms onset and consultation (<i>m. d. = 40</i>)			0.93
<2 days	7 (50 %)	46 (50.0 %)	
Between 2 et 4 days	7 (50.0 %)	38 (41.3 %)	
>4 days	0 (0.0 %)	8 (8.7 %)	
Parotitis (<i>m. d. = 0</i>)	17 (100.0 %)	129 (100.0 %)	1
Complications (<i>m. d. = 3</i>)			0.04
Yes	3 (17.6 %)	4 (3.2 %)	
No	14 (82.4 %)	122 (96.8 %)	
Vaccination \ddagger (<i>m. d. = 36</i>)			0.62
No	3 (21.4 %)	15 (15.6 %)	
Yes (1 dose)	3 (21.4 %)	13 (13.5 %)	
Yes (2 dose or more)	8 (57.1 %)	66 (68.8 %)	
Yes (unknown number of doses)	0 (0.0 %)	2 (2.1 %)	
Contact with another suspected mumps case (up to 21 days previous disease) (<i>m. d. = 62</i>)			0.02
Yes	3 (25.0 %)	2 (2.8 %)	
No	9 (75.0 %)	70 (97.2 %)	
Hospitalization (<i>m. d. = 36</i>)			1
Yes	0 (0.0 %)	1 (1.0 %)	
No	14 (100.0 %)	95 (99 %)	

Abbreviation: *m. d.* = missing data.

8. Funding statement

The primary care surveillance of mumps coordinated by the French Sentinelles network is funded by the French public health agency, Santé Publique France.

9. Authors' contributions

PPM, FHD et TB designed the study. PPM, FHD and CS undertook the statistical analysis. JH and JD were responsible for the virological analyses and prepared the virological databases. PPM, FHD, OG, SM and TM were responsible for the management of the epidemiological and the virological databases. PPM, FHD et TB wrote the draft manuscript and all authors participated in the enhanced mumps surveillance, revised and approved the final version.

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

The data can be available upon request on the Sentinelles website: <https://www.sentiweb.fr/france/en/?page=request>.

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