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MUMPS: BURDEN OF DISEASE IN FRANCE

Coffinières E [1,2], Turbelin C[1,2], Riblier D[1,3], Aouba A[4], Levy-Bruhl D[5], Arena C[1,2,6,7], Gonzalez Chiappe S[1,2,8], Ferry JP[1,2], Hanslik T[1,9,10], Blanchon T[1,2]

1. INSERM, U707, F-75012, Paris, France

2. UPMC Univ Paris 06, UMR S 707, F-75012, Paris, France

3. Université Henri Poincaré, Nancy, France

4. INSERM, CépiDc, Le Kremlin-Bicêtre, France

5. Département des maladies infectieuses, Institut de veille sanitaire, Saint-Maurice, France

6. Laboratoire de Virologie, Université de Corse, France

7. Observatoire Régionale de Santé de Corse, Ajaccio, France

8. Service de Gastroentérologie et de Médecine Interne, Centre hospitalier de Firminy, Firminy, France

9. UVSQ, Université de Versailles Saint Quentin, Versailles, France

10. Assistance Publique Hôpitaux de Paris, service de Médecine Interne, Hôpital Ambroise Paré, Boulogne Billancourt, France

Abstract

This article provides a review of the epidemiological data on mumps in France since 1986. The results of 26 years of monitoring in general practice by the Sentinel network are analysed, such as hospitalisation data between 2004 and 2010, as well as mortality data between 2000 and 2009. The annual incidence rate has plummeted between 1986 and 2011, from 859 cases per 100,000 inhabitants [95% CI: 798-920] to 9 cases per 100,000 inhabitants [95% CI: 4-14]. A change in the age distribution is significant with an increase of Relative Illness Ratio (RIR) for patients over 20 years. Since 2000, vaccine status has also changed, and the majority of recent mumps cases occur among previously vaccinated patients. The average annual hospitalisation rate is 3.2 per 1 million inhabitants. Mumps was identified as the initial cause of death in 1 case every 5 years. This study estimates the burden of mumps disease in France.

Keywords

Mumps, Epidemiology, General medicine, Hospitalisation, Mortality

GPs: General Practitioners

ICD-10: International Classification of Diseases-Tenth revision

1. Introduction

Although mumps is usually mild in children, the risk of complications increases in adults (including encephalitis, orchitis or pancreatitis) (1). Sequelae may also be seen such as deafness or testicular atrophy (2). On December 2007, 114 of 193 (57%) World Health Organization (WHO) member states began to include vaccination against mumps in their national immunisation programs (3). This large-scale vaccination has resulted in a sharp drop of the mumps incidence rate within a few years (4). In France, vaccination against mumps was recommended in 1986 as a single dose, and a second dose has been added in 1996.

In 2002-2003, French vaccination coverage for mumps in the last year of kindergarten was 92.6% for the first dose, and 24.4% for the second dose (5). Mathematical models indicate, that a vaccination rate of 85 to 90% would be required to prevent virus circulation (6). Insufficient coverage, limiting the circulation of the mumps virus in the population without eradicating it entirely and lowering exposure during childhood, might lead to a shift in the incidence of this disease to older age classes (4, 7-9) for whom complications are more important (10, 11). Indeed, several recent outbreaks have primarily affected the 15-24 years old age group (12-14) with a higher complication rate among patients over 15 years old (15).

The persistent occurrences of mumps cases, whilst the epidemiology of the disease is also changing (4, 7-9), requires careful monitoring to assess the burden of mumps disease and to adapt effective public health measures. Unlike the USA (16), the United Kingdom (17) or Greece (7), mumps is not a notifiable disease in France, and the monitoring is performed since 1985 by general practitioners (GPs) of the French GPs Sentinelles network. This network of research and surveillance, created in 1984, is incorporated into a mixed research unit of National Institute of Health and Medical Research (INSERM) and Pierre and Marie Curie University (UPMC) (18, 19). The network is developed in collaboration with the National Institute for Public Health Surveillance (InVS). This study presents the analysis of data collected by this network between 1986 and 2011. This work is supplemented by hospitalisations and deaths national data analysis sourced from the national databases of Program Medicalisation of Information Systems (PMSI) and French epidemiological center of medical causes of death (CépiDc). The disease's incidence in primary care, as well as hospitalisation and mortality are considered to assess the burden of mumps disease in France.

2. Materials and methods

2.1 Source of data

2.1.1 Mumps cases in general practice

On January 1st, 2012, there were approximately 1313 voluntary and unpaid general practitioners (GPs) (20) in the French GPs Sentinelles network, equivalent to 2.2% of all GPs in France (60,963 GPs at December 31, 2010 according to the French National fund of health insurance for employees (CNAMTS) (21)). Mumps Cases are reported every week in a standardised and automated manner by 359 of these GPs. The characteristics of the GPs of the Sentinelles network are comparable to those of all French GPs regarding regional distribution, proportion in rural practice, type of practice and distribution of main clinical skills (22). A case of mumps is defined either by a unilateral or bilateral parotid swelling, painful and developed recently often associated with testicular, pancreatic, brain damage, or meningitis, or - in the absence of parotitis - by orchitis, meningitis or pancreatitis with a mumps laboratory confirmation. For each case, GPs have to report age, sex and vaccine status. If the patient has been vaccinated, the date of vaccination as well as the number of doses received (item collected since 2009) and the source of this information (patient's immunization registry or statement from patients or parents) is required. An exposure to another case of mumps disease during the 21 days before illness, and a complication (orchitis, meningitis, pancreatitis, other) are collected since 1997. Laboratory confirmation (presence of IgM and / or multiplication of the IgG by a factor of 4) is collected since 2011. Data recovered for mumps are collected from January 1, 1986 to December 31, 2011.

2.1.2. Mumps hospitalisations

Hospitalisation data are collected by reviewing all hospital discharge reports containing a mumps code from January 1, 2004 to December 31, 2010 (last available data at the time of writing this paper). The data is obtained through the PMSI Data Processing Centre (23), which is a national register of all discharges from all short-stay to acute-care stays. It collects data described by the physicians who took care of the patients during the hospitalisation. Diagnoses are coded using the International Classification of Diseases, Tenth Revision (ICD-10), either as primary or associated diagnosis. For this study we select all hospital discharge reports between January 1, 2004 and December 31, 2010. Mumps hospitalisations were defined as an hospital discharge report with a primary or an associated

mumps diagnosis specific code (B26 *: B260 - B261 - B262 - B263 - B268 - B269, respectively encoding mumps orchitis, mumps meningitis, mumps encephalitis, and mumps (24)). Information on age, sex, and duration of hospitalisation was also obtained from the hospital discharge reports.

2.1.3. Mumps mortality

Mumps mortality is assessed through the French National Mortality Database (INSERM CépiDc) for deaths between January 1, 2000, and December 31, 2009 (the last available data at the time of writing this paper) (25). Mumps deaths are defined as any death certificate with an International Classification of Disease code for mumps and its complications (ICD-10 codes B26 *) as underlying cause in accordance with WHO rules. Information on age and sex is also obtained.

2.2. Analysis

To obtain the yearly national incidence rate, the mean number of cases per Sentinelles GP (standardised according to their participation and their geographical distribution) is multiplied by the total number of GPs in France and the result is then divided by the population of that year, using the French population included in national censuses as a reference (21). These estimates are based on one assumption: the Sentinelles GPs are a random sample representative of all French doctors (26). Age-specific incidences rates are also estimated for the following age groups: <4 years, 5-9yrs, 10-14years, 15-19, 20-24, 25-29 and> 30 years, comparable to age structure used by the European Centre for Disease prevention and Control (ECDC) for European Health Surveillance (8). Calculation of the 95% confidence interval (IC 95%) is based on the hypothesis that the number of reported cases followed a Poisson distribution. In order to develop a better understanding with regards to the burden of mumps disease in a given age group, the Relative Illness Ratio (RIR) is also calculated as the ratio between the percentage of cases in a given age group and the percentage of the general population belonging to the same age (formula below). The latter of these ratios is estimated for each year by the French National Institute of Statistics and economic studies (INSEE) (27).

$RIR = (Ci / Ci\ \Sigma) / (Ni / Ni\ \Sigma)$

Ci: number of mumps cases for a given age

Σ Ci: sum of mumps cases all age groups combined

Ni: population for a given age,

Ni Σ: sum of all populations of different ages (30)

Hospitalisation and mortality rates are calculated in a similar way.

3. Results

3.1. In general practice

Between the first week of 1986 and the last week of 2011, 6,141 mumps cases were reported by GPs of the French Sentinelles network, including 5,597 cases (91.1%) individually described. During the entire study period, the estimated yearly incidence decreased from 475,671 cases (95% CI: 441,867-509,475) in 1986, which corresponds to 859 cases per 100,000 inhabitants [95%: 798-920], to 5,841 cases (95% CI: 2,817-8,865) in 2011, which corresponds to 9 cases per 100,000 inhabitants [95% CI, 4-14]. An initial sharp decrease was observed in 1988, followed by a second in 1993. Between 1997 and 2011, a low but continuous decrease was observed (Figure 1 and Table 1).

Males represented 54.6% of mumps cases (3,010 cases) without significant modification of the sex ratio during the study period. The median age was 6 years [4-10] and the mean age 9.4 years old. The median age increased from 5 years old in 1986 to 16.5 years old in 2011, such that the mean age increased from 8.2 years old to 21.9 years old. Whilst between 1986 and 1998 incidence rates declined steadily for all age groups, after the year 1998 they ceased to decline for patients under 20 years old. However, the incidence rate for patients over 20 years old did not change, from a rate of incidence of 10 per 100,000 in 1998 to 11 per 100,000 in 2011 for the 20-24 year old patients. Over the entire monitoring period, the trend observed for RIR by age group was a decrease for patients under 10 years old, stable for 10-14 years old, and rising for patients over15 years old (Figure 2).

The overall percentage of reported mumps cases vaccinated was 18.3% (n=945 of 5,171 cases described for this item). Since 2009, and the need for specifications regarding the number of vaccine doses received, 52.7% cases of mumps received two doses of vaccine (n=19 of 36 cases described in this item). The distribution of cases according to the vaccine status changed between 1986 and 2011, ranging from a majority of cases among unvaccinated patients (735 cases were not vaccinated in 1986, corresponding to 98.1% of cases for that

year) to a majority of cases among previously vaccinated patients since 2000 (11 cases are vaccinated in 2011, corresponding to 68.8% of cases) (Figure 3). Vaccine status was determined by GPs according to the patient's immunization registry in 72.6% of cases, and according to statements from patients or their relatives in 27.4% of cases. An exposure was reported in 26.6% of cases (n=72 of 271 cases described in this item). The place of exposure was specified for 25% of these cases (n=68): most of them were exposed at school (30.9%, n=21).

Since 1997, after which time data collection begins, 18.5% of declared mumps cases presented a complication according to the GP (n=57 of 308 cases described in this item). But only 8 of them were described (4 orchitis, 1 meningitis, 1 pancreatitis, and 2 pharyngitis-bronchitis). The proportion of mumps cases described with a complication decreased significantly, ranging from 42.6% in 1998 cases (20/47) to 0% in 2011 (0/20). Complicated cases were seen predominantly in 10-14 year old age groups (17 cases corresponding to 29.8% of complicated mumps).

From January 1, 2011, GPs have the opportunity to specify whether or not their clinical diagnosis was completed by a laboratory confirmation. Of the 22 reported mumps cases in 2011, two cases had a laboratory confirmation while 15 were not laboratory investigated. In 5 cases this information was not specified by the GP.

3.2. Mumps hospitalisations

Over the seven-year study period, 1,377 hospitalisations with a primary or associated mumps diagnosis, corresponding to 1331 patients, were identified. These cases included 597 hospitalisations / 592 patients with a primary mumps diagnosis. Among these patients with a primary mumps diagnosis, 99.2% (n = 587) were hospitalised once for this reason, and 0.8% (n=5) were hospitalised twice for mumps orchitis. A mean of 85.3 hospitalisations with a primary mumps diagnosis was identified each year, corresponding to 84.6 patients per year. The average rate of hospitalisation for mumps per year was 1.4 per 1 million inhabitants for the period spanning 2004-2010. The annual number of hospitalisations increased from 75 to 111 between 2004 and 2010 (Table 2).

Males represented 55% of hospitalised cases for mumps (n=325). Patients older than 30 years represented 37% of patients (n=220) hospitalised for mumps (Figure 4). The reasons of hospitalisation were mumps parotitis for 78.6% of cases (n = 465), orchitis for 9.3% of

cases (n=55), meningitis for 3.2% of cases (n= 19), pancreatitis for 2% of cases (n=12) and encephalitis for 0.8% of cases (n=5). 10% of patients (n=59) were hospitalised for mumps parotitis described as "complicated" but without further explanation. The average length of stay was 2 days per hospitalisation (median 6 days ± 0 days), with the same holding for the different complications.

3.3. Mumps mortality

During the period of 2000–2009, mumps as the initial or associated diagnosis was coded in 82 death certificates. After analysis of the death certificates, mumps was selected as the initial cause of death in 2 cases (2.4%), and as an associated cause in 3 cases (3.7%). In total, 33 cases of "bacterial parotitis" (40.2%) and 44 cases of unspecified "infectious parotitis" (53.6%) were excluded. Selected death certificates concerned 3 men and 2 women. The median age was 67 years (50 years - 84 years), and the mean age 71.8 years. For both certificates for which mumps was selected as the initial cause of death, the associated causes were “cardiopulmonary arrest” for one and “encephalopathy” for the second.

4. Discussion

This work provides, through public national databases, an estimate of the morbidity and mortality for mumps in France since 1986. The main results detail the fall in the incidence of mumps, as well as the change in the age structure and in the vaccine status of patients.

The decrease of mumps incidence in France immediately follows the 1986 onset of mumps vaccination in France. Identical decreases in incidence rates are found in countries recommending vaccination against mumps: ECDC describes a fall of the mean incidence rate from 62 per 100,000 in 1995 (28) to 3.2 per 100,000 in 2009 in 27 European Union countries (7). In U.S.A., mumps incidence decreased from 90 per 100,000 in 1967 to 0.7 per 100,000 in 1993 (29). Finland did not report any indigenous cases of mumps, 16 years after the establishment in 1982 of a two-dose vaccination schedule against mumps (30). However in France, mumps cases are diagnosed and hospitalised each year, as shown in this manuscript. Mumps vaccine coverage have to be increased, especially for the second dose (5). GPs, who are in favour of this vaccination for 96.8% of them (31), have a major role on this point.

The number of mumps cases in adults is not increasing, but an increase of the median and mean ages is observed. An increase of the Relative Illness Ratio for patients over 20 years

old is confirmed, such as that observed in outbreaks which occur in other countries. In Ireland, Gee & Al describe epidemics which occur between 2004 and 2008 as primarily affecting the 15-19 and 20-24 years old age groups (14). In the USA in 2006, Dayan & Al also find an incidence rate of 31.1 cases per 100,000 among 18-24 years old against 8.4 per 100,000 for all other age groups together (13). Shmid & Al report that in Austria, the age group of 21-25 years old is the most affected in 2006 (42% of cases) (32). This shift in age groups affected can be explained by an insufficient level of the mumps herd immunity for unvaccinated persons, in a context of a low circulation of mumps virus (33).

As expected, the majority of recent mumps cases occur among previously vaccinated patients. Such results have been published concerning some recent outbreaks in western countries: during 2006 in the United States, 77% to 97% of mumps cases were previously vaccinated with two doses (1), such as 69% of cases during Canadian outbreaks in 2005(4). This change is expected because of vaccination rate increases, and does not mean that vaccination policies have failed. However, it suggests that mumps vaccination clinical efficiency measured during outbreaks seems less effective than serological efficiency measured during clinical trials. For Jeryl Lynn strain, the serological efficiency is estimated to 95% (34), against 64 to 66% for clinical efficiency with a single dose, and 83 to 88% with two doses (35). Moreover, vaccination immunity may last for a shorter period of time than expected (36). This issue should be better analysed, as in a recent article on seroepidemiology of mumps in Europe, which presents ways to improve the mumps vaccination schedule (37).

This work also confirms the mild aspect of mumps. If 18.5% of cases seen in general practice present a complication, only a few of these complications are described by the GPs, suggesting a possible overestimation of this number. Moreover, according to PMSI data, 3% of mumps cases only are hospitalised. This result corroborates international findings which estimate that, among mumps cases, 4% are hospitalised (8). Patients hospitalised for mumps are mostly over 30 years of age, following the trend of hospitalised cases in Europe (8). Finally, it is important to note that only 2 deaths are attributable to mumps in 10 years of surveillance in France. There are no published international data on mumps mortality. Most of hospitalised mumps cases in Europe corresponding to 23% of cases are between 20 and 24 years of age in 2009 (8).

This study has both strengths and limitations. GPs from the GPs Sentinelles network appear representative of all French GPs, given their demographic characteristics (22, 26) and practices (work in progress at Inserm Unit in collaboration with CNAMTS). The incidence of mumps cases could be underestimated, due to asymptomatic patients who are not identified (approximately 30% to 40% of cases according to Hviid & Al (2), and may be more among previously vaccinated patients (38)). There are several limitations associated with using hospitalisation and death records, as inadvertent omissions and coding errors. It is important to notice that B26 code includes all infectious parotitis (24), and that the death certificates analysis shows that the main part of B269 codes are used for bacterial parotidis and not for mumps parotidis. These potential errors, induced by an imprecise ICD-10 definition, may have happened also for hospitalisations. Conversely, mumps incidence could be overestimated; because of the laboratory confirmation is not required to report a case. Davidkin & Al show that 831 mumps laboratory tests are negative on 848 clinical mumps cases during a study led in Finland between 1983 and 1998. Another viral etiology is found in 14% of cases (EBV, parainfluenza virus types 1 and 3, enterovirus, adenovirus, parvovirus B19, HHV-6) (39).

In conclusion the risk of clustered cases of mumps in France seems to be a combination of several factors: an insufficient vaccination rate for the second dose, the assumption of a loss of immunity over time even after two vaccine doses, and the existence of cohorts of young adults not enough vaccinated in the context of a significant reduction of the virus circulation. According to these results, the question regarding the reality of mumps estimation based on a clinical cases declaration should be discussed. As a monitoring strategy, biological testing included in mumps case definition seems necessary in order to establish whether or not the mumps virus remains in circulation.

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Figure 1: Annual mumps incidence rate per 100,000 inhabitants in France, and confidence interval 95%, from 1986 to 2011.

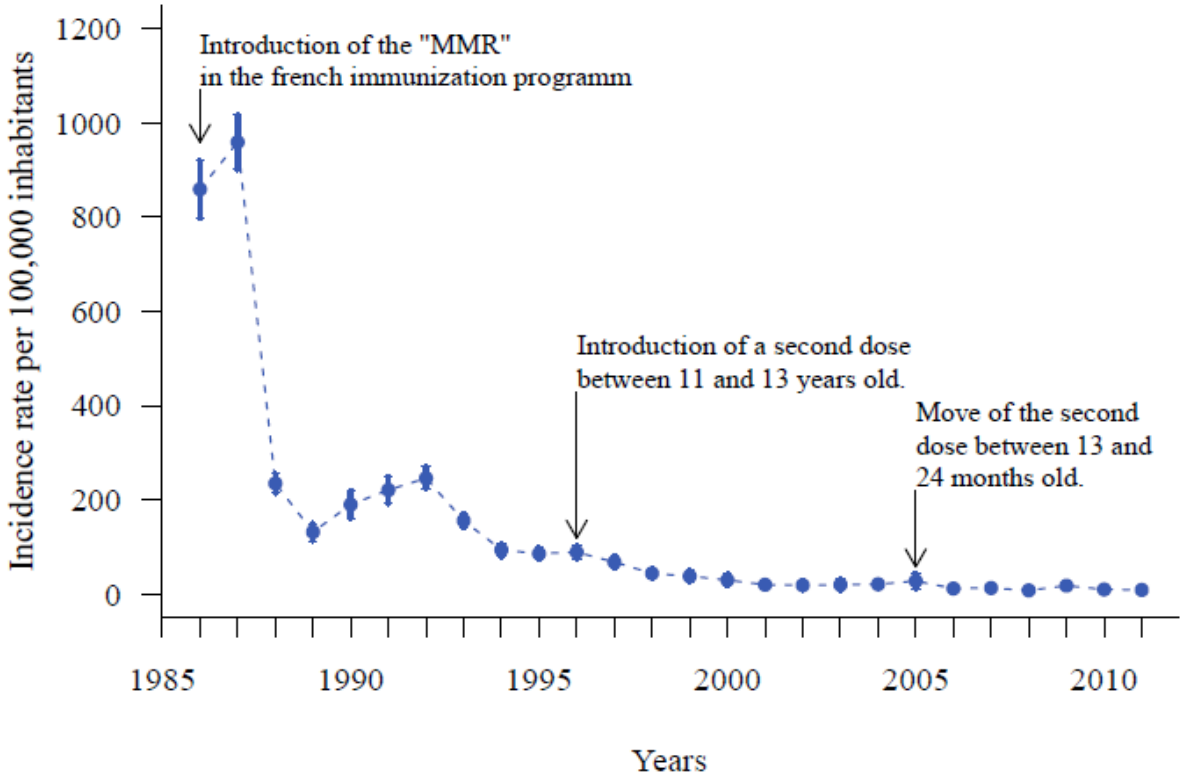

Figure 2: Relative Illness Ratio of mumps cases according to age between 1986 and 2011 in France

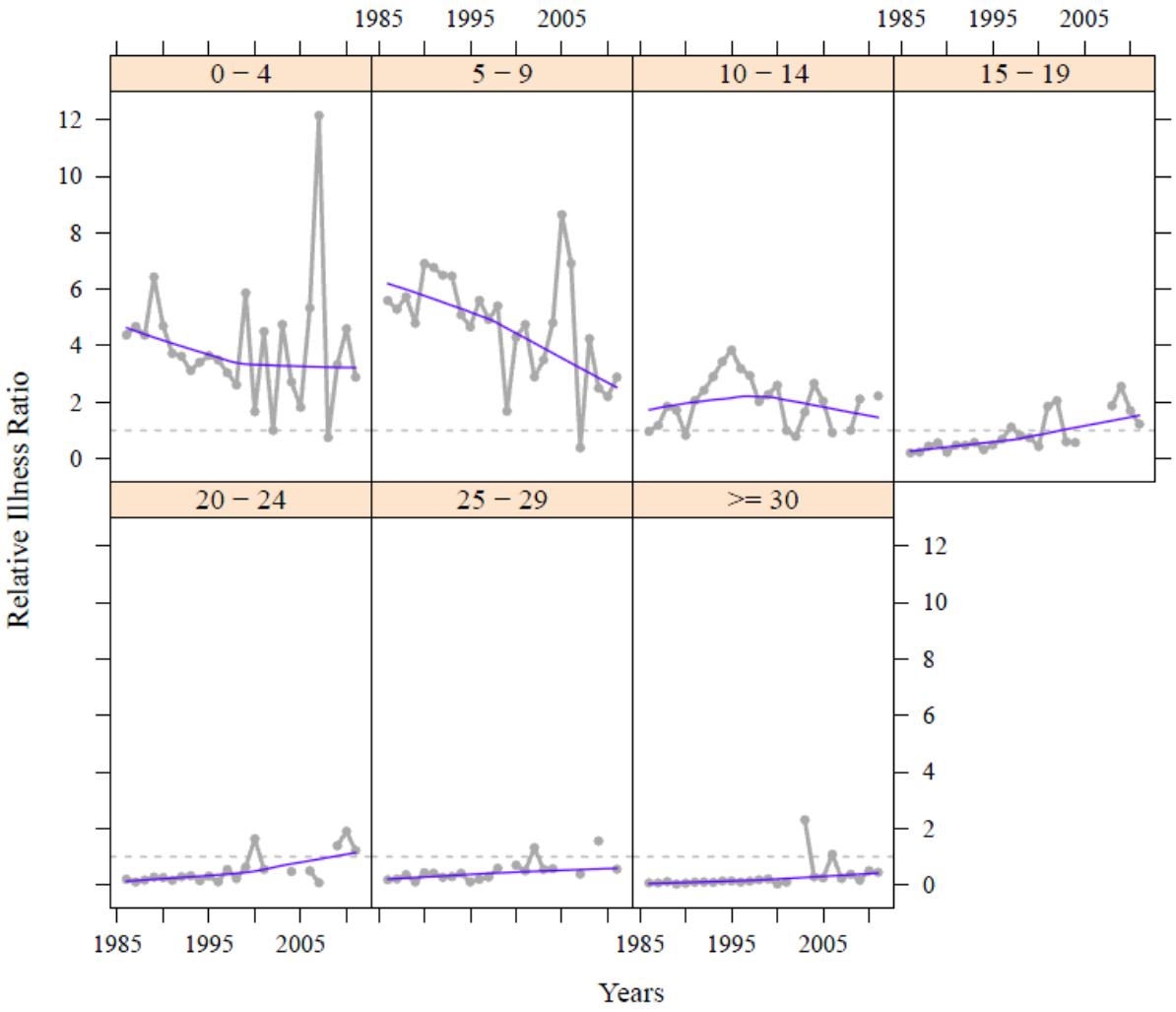

Figure 3: Percentage of mumps cases seen in consultation of general practice in France according to vaccine status between 1986 and 2011

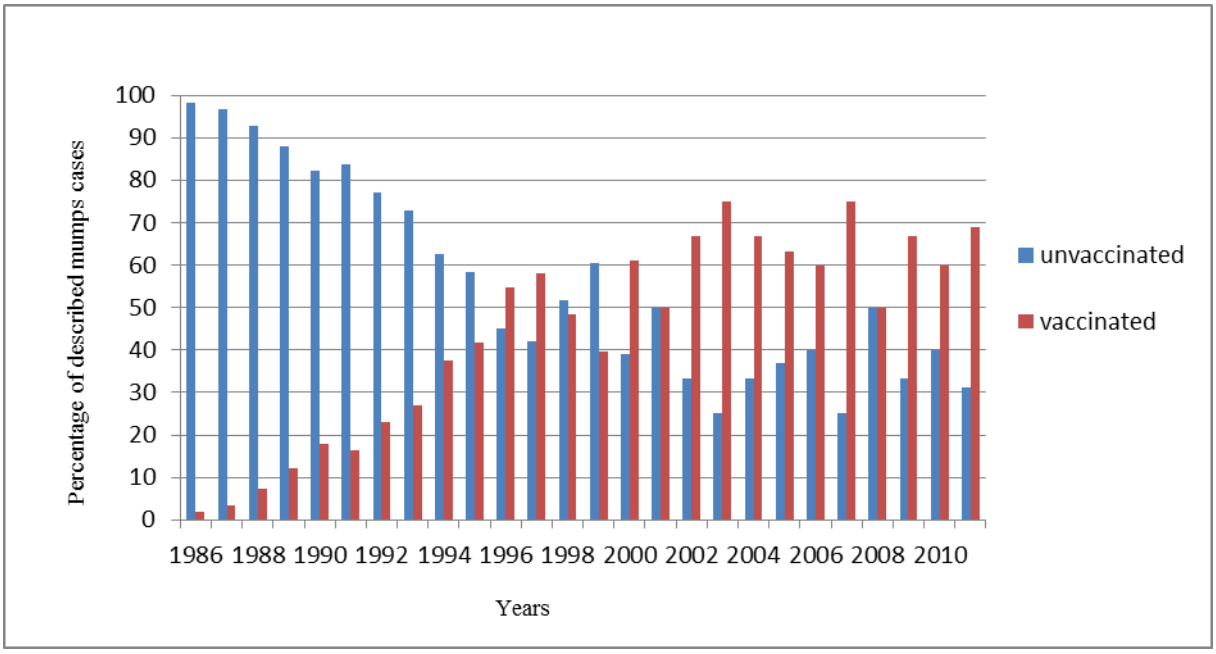

Figure 4: Number of hospitalised cases for mumps in France according to age between 2004 and 2010

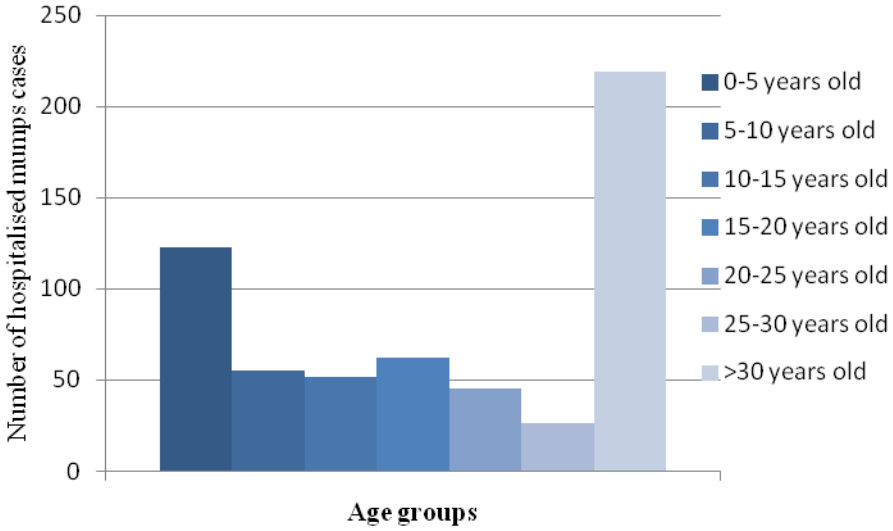

Table 1: Annual mumps incidence rate per 100,000 inhabitants in France, and confidence interval 95%, according to age groups between 1986 and 2011.

Years	All age together	0-4 years old	5-9 years old	10-14 years old	15-19 years old	20-24 years old	25-29 years old	>30 years old
1986	**859 [798-920]**	3762 [3345-4179]	4810 [4147-5473]	831 [635-1027]	177 [92-262]	169 [84-254]	157 [72-241]	60 [30-90]
1987	**959 [901-1018]**	4488 [4028-4947]	5076 [4553-5598]	1129 [866-1392]	220 [95-345]	100 [46-154]	200 [99-300]	65 [33-97]
1988	**235 [514-256]**	1028 [855-1201]	1347 [1161-1533]	435 [320-550]	104 [52-156]	40 [13-68]	84 [36-131]	27 [9-45]
1989	**132 [113-150]**	849 [661-1037]	633 [472-794]	226 [149-303]	74 [24-124]	36 [3-69]	14 [0-33]	4 [0-10]
1990	**190 [160-220]**	893 [600-1187]	1313 [1032-1594]	157 [74-240]	43 [1-84]	49 [0-99]	82 [2-162]	12 [0-26]
1991	**221 [192-250]**	823 [603-1043]	1497 [1200-1794]	454 [314-594]	106 [37-175]	36 [0-74]	91 [5-176]	21 [7-37]
1992	**246 [223-270]**	892 [712-1073]	1598 [1368-1827]	596 [464-728]	116 [55-177]	71 [25-116]	66 [22-110]	25 [7-42]
1993	**156 [140-172**	487 [381-594]	1009 [852-1167]	453 [348-558]	89 [43-135]	51 [18-84]	46 [12-80]	14 [4-25]
1994	**94 [80-107]**	321 [216-425]	479 [365-594]	323 [228-417]	30 [6-53]	14 [0-28]	39 [7-70]	13 [3-24]
1995	**86 [74-99]**	314 [213-416]	401 [301-501]	331 [239-424]	42 [3-82]	27 [2-51]	9 [0-20]	12 [1-24]
1996	**89 [74-103]**	311 [209-414]	499 [344-653]	284 [192-376]	61 [23-100]	10 [0-25]	18 [0-38]	9 [2-16]
1997	**68 [55-82]**	207 [119-295]	335 [216-455]	200 [116-285]	76 [10-141]	37 [0-76]	19 [0-48]	9 [0-20]
1998	**44 [33-54]**	115 [37-193]	238 [145-331]	89 [37-142]	36 [6-66]	10 [0-29]	26 [0-52]	8 [0-19]
1999	**38 [27-50]**	223 [108-338]	64 [2-126]	86 [17-156]	28 [0-62]	24 [0-59]	0	8 [0-19]
2000	**30 [17-43]**	50 [1-99]	129 [2-257]	78 [2-153]	13 [0-38]	49 [4-94]	21 [0-62]	1 [0-3]
2001	**20 [11-29]**	90 [19-162]	95 [0-191]	20 [0-47]	37 [0-82]	11 [0-33]	10 [0-31]	2 [0-7]
2002	**19 [9-29]**	19 [0-55]	55 [1-110]	15 [0-35]	39 [0-97]	0	25 [0-60]	0
2003	**20 [9-32]**	95 [1-189]	70 [0-149]	33 [0-81]	12 [0-35]	0	11 [0-33]	46 [0-115]
2004	**21 [13-30]**	57 [0-115]	101 [27-175]	56 [0-116]	12 [0-35]	10 [0-30]	12 [0-37]	6 [0-15]
2005	**28 [11-45]**	51 [0-109]	242 [0-489]	57 [0-141]	0	0	0	7 [0-15]
2006	**12 [6-18]**	64 [4-125]	83 [20-145]	11 [0-33]	0	6 [0-19]	0	13 [0-32]
2007	**13 [5-21]**	158 [36-281]	5 [0-15]	0	0	1 [0-2]	5 [0-16]	3 [0-9]
2008	**8 [4-12]**	6 [0-18]	34 [0-69]	8 [0-24]	15 [0-36]	0	0	3 [0-6]
2009	**18 [11-24]**	60 [1-118]	45 [5-84]	38 [6-71]	46 [0-94]	25 [0-55]	28 [0-59]	3 [0-8]
2010	**10 [5-14]**	46 [8-83]	22 [0-50]	NA	17 [0-36]	19 [0-46]	0	5 [0-12]
2011	**9 [4-14]**	26 [0-58]	26 [0-57]	20 [0-45]	11 [0-26]	11 [0-32]	5 [0-14]	4 [0-11]

Table 2 : Number of hospitalised cases and number of hospitalisations* per year in France between 2004 and 2010, according primary or associated mumps diagnosis

	Primary mumps diagnosis + Associated mumps diagnosis		**Primary mumps diagnosis only**	
Year	**Number of hospitalised cases (n)**	**Number of hospitalisations* (n)**	**Number of hospitalised cases (n)**	**Number of hospitalisations* (n)**
2004	199	206	73	75
2005	190	199	73	73
2006	155	163	80	80
2007	170	177	75	78
2008	185	187	83	83
2009	211	216	97	97
2010	221	229	111	111

* Some cases have been hospitalised more than one time.