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We present 10 years of results from a paediatrician hospital network surveillance in France, set up in 1996 to monitor the trend of pertussis (whooping cough) in children and the impact of the vaccination strategies.

Microbiologists from 43 hospitals that participate in the network on a voluntary basis notify pertussis diagnosis, and paediatricians complete a questionnaire for the infants under 6 months that fulfil the microbiological, clinical or epidemiological case definition. The network covers about 30% of pertussis cases seen in French hospitals.

Around 300 cases of pertussis are notified in France annually. Two peaks occurred in 1997 and 2000. The estimated national incidence rate for the 0-2 months old children is 276/100 000 on average. Since March 1996, the network has described 1688 cases under-6 month. The male-female ratio was 1.0 and 63 % were less than 3 months of age. Most patients (96%) were hospitalised with 17% admitted in intensive care. The case fatality ratio was 2% with 32 deaths. Vaccination status was confirmed through medical records for 83% of children and 78% were not vaccinated. The source of contamination was identified for 53 % of cases and was in majority the parents.

The Renacoq data confirmed the risk for young children, the role of parents as source of infection and the need of a pertussis vaccination in time. Vaccination is now recommended to adults who hope to become parents, and this should help to reduce this burden.

Introduction

Because high vaccination coverage using a very effective vaccine has been maintained in children in France for the past 40 years, [1], the epidemiology of pertussis has changed, and the disease mainly affects children who are too young to be vaccinated and persons who are no longer protected by vaccine or disease-induced immunity [2]; these changes led to the introduction in 1998 of a fifth dose with acellular vaccines at 11-13 years old. Nowadays, the childhood vaccine schedule recommends primary course for children aged 2, 3 and 4 months and two boosters at 16-18 months and 11-13 years old respectively [3]. Since 2004, adults who are planning to become parents and health staff in charge of children under 6 months old are also included in pertussis vaccine recommendations [3]. Acellular vaccines have been available in France since 1998, and the whole cell vaccine was taken off the market in 2005.

To monitor the trend of severe pertussis in children and the impact of acellular vaccines and of the late booster, a hospital network surveillance was set up in March 1996. This article presents the results of 10 years of pertussis surveillance.

Material and methods

The surveillance system consists of 43 hospitals participating on a voluntary basis including 21 regional reference hospitals, located in 21 of the 22 French regions. Data are collected from children who present at the outpatient department or who are admitted to hospital.

General reporting

Whatever the age of the children, microbiologists list the results of pertussis culture or PCR performed. They send the isolates to the National Reference Laboratory, which validates the PCR, culture and serology results. This system of data collection has been unchanged since 1996 and is used to analyse data trends over time.

Enhanced surveillance

Paediatricians complete a standardised form for every child with paroxysmal cough lasting more than 8 days who fulfils one of the three following case definitions:

- A **laboratory confirmed case** defined as a positive culture, PCR or serology
- A **clinical case** if the cough lasts more than 21 days with at least one of the following symptoms: whoop, vomiting after paroxysms, apnoeas, cyanosis, lymphocytosis $>10\ 000/\text{mm}^3$
- An **epidemiological case** defined as a case with a link to a laboratory confirmed case.

Since 2004, paediatricians have collected data from children under 6 months only. The paediatric data were compared with data from children of the same age group from previous years. The paediatric form includes demographic, clinical and microbiological data and, vaccination status. Contact tracing is performed by interviewing the family and diagnosis of the person presumed to have infected the child is clinical only. The vaccination data analysed is that obtained from the child's "carnet de santé". This document is given to all children and records the main health events of the child, including immunisation. Children are considered to be correctly vaccinated according to age if at least, children aged 2 or 3 months have received 1 dose, those aged 4 months 2 doses and those aged 5 months 3 doses. Data from microbiologists and paediatricians are reconciled on a regular basis.

Virtually all cases of pertussis in children under 3 months old are admitted to hospital and it has been calculated from hospital admissions data that the network represents 27% to 29% of paediatric admissions according to the year.. Therefore, we assessed the national incidence in this age group from the total number of cases observed in the network.

Because some information was not available for all patients, denominators may differ in separate analysis.

A descriptive study was undertaken with the data from 1996 to 2005.

All statistical analyses were done using χ^2 test and a $p < 0.05$ was considered statistically significant.

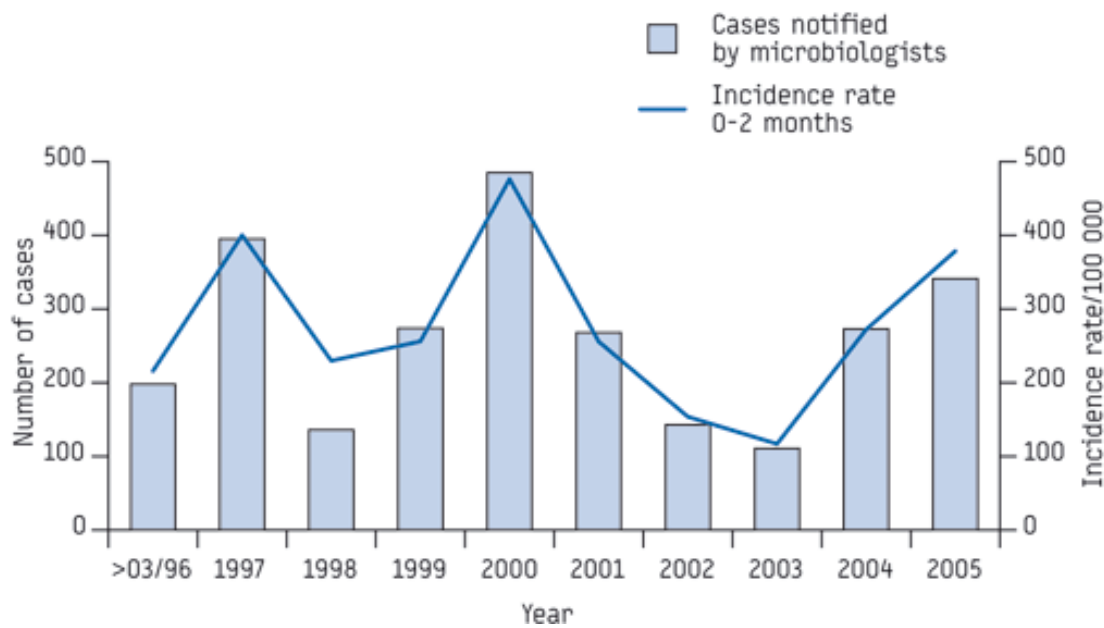
Results

General reporting

For the past 10 years, microbiologists have reported between 111 and 485 cases/year with an average of 262 cases/year. After two years of declining numbers following the 2000 peak, the overall number of laboratory confirmed cases reported by microbiologists increased again in 2005, but did not reach the peaks seen in 1997 and 2000 [FIGURE 1]. The proportion of infants under 3 months of age reported by microbiologists increased from 33% of all pertussis cases in 1996 to 50% in 2005 (??: 36.6, $p < 10^{-3}$). On average, the estimated national incidence in this age group is 276 /100 000 per year [CI 95%: 231-321/100 000]. The annual estimated national incidence followed the increasing trend observed by microbiologists [FIGURE 1].

FIGURE 1

Laboratory confirmed pertussis cases notified by microbiologists and national estimate of incidence rate in infants less than 3 months of age, Renacoq, France, 1996-2005



Enhanced surveillance

- Epidemiological characteristics [TABLE]

TABLE

General reporting and enhanced surveillance characteristics, Renacoq, France, 1996 to 2005

General reporting (microbiologists' notification)	>03/96	1997	1998	1999	2000	2001	2002	2003	2004	2005
Lab confirmed cases (n)	198	395	136	274	485	268	143	111	273	341
Age 0-2 months	33%	32%	40%	36%	40%	40%	43%	43%	47%	50%
Enhanced surveillance (for the <6 months of age)	>03/96	1997	1998	1999	2000	2001	2002	2003	2004	2005
Total (n)	185	337	181	192	277	121	63	59	100	173
Clinical cases	31%	25%	31%	13%	7%	6%	11%	5%	4%	1%
Lab confirmed cases	66%	70%	66%	85%	92%	93%	89%	95%	96%	99%
Epidemiological cases	3%	6%	3%	2%	1%	1%	0%	0%	0%	0%
Biology										
Culture performed	86%	85%	77%	66%	55%	56%	44%	63%	64%	66%
positive (n/performed)	35%	40%	35%	35%	38%	34%	43%	43%	67%	64%
PCR performed	47%	50%	61%	81%	89%	90%	90%	97%	97%	90%
positive (n/performed)	93%	88%	79%	95%	93%	96%	95%	96%	96%	98%
Serology performed	27%	23%	24%	16%	12%	14%	19%	12%	27%	2%
positive (n/performed)	58%	59%	68%	48%	76%	85%	25%	80%	0%	0%
Clinical description										
Age 0-2 months	59%	58%	60%	59%	65%	64%	65%	66%	79%	74%
Sex (% males)	45%	49%	51%	53%	53%	45%	46%	51%	54%	45%
Cough lasting more than 21 days	91%	90%	90%	87%	88%	86%	86%	73%	77%	74%
Hospitalisation	92%	96%	94%	95%	96%	98%	98%	98%	94%	98%
ICU among hospitalised patients	16%	17%	18%	17%	24%	14%	16%	13%	12%	16%
Death	1%	1%	1%	2%	3%	2%	0%	7%	1%	3%
Contact tracing to find source of infection										
Unknown	18%	20%	18%	25%	15%	22%	14%	29%	35%	47%

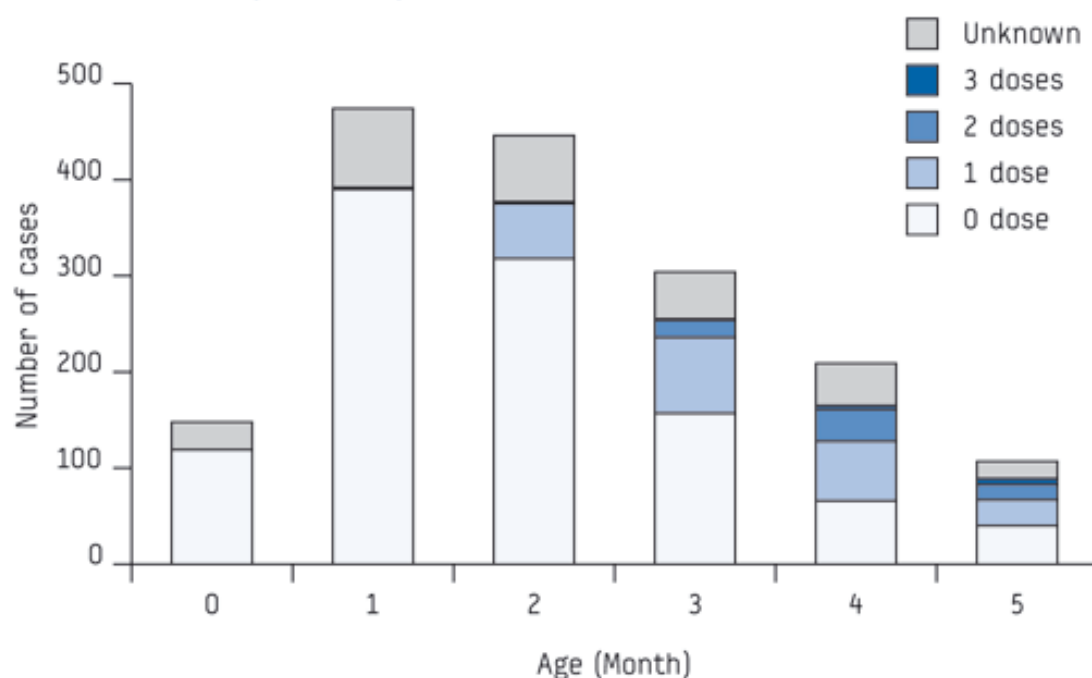
Unknown	18%	20%	18%	25%	15%	22%	14%	29%	35%	47%
Negative	28%	28%	34%	20%	32%	28%	29%	29%	1%	0%
Positive	55%	53%	48%	55%	53%	50%	57%	42%	64%	53%
Type of contaminators (n)	101	177	87	105	146	60	36	25	64	91
Parents	44%	53%	52%	55%	52%	60%	53%	72%	67%	58%
Sibling	34%	26%	26%	22%	31%	22%	25%	4%	17%	23%
Others	21%	16%	20%	18%	14%	18%	19%	24%	16%	19%
Unknown	2%	5%	2%	5%	3%	0%	3%	0%	0%	0%
Immunisation status (n)	161	294	159	156	236	101	51	42	87	117
0 dose	73%	77%	74%	76%	81%	81%	86%	74%	77%	81%
1 dose	20%	17%	19%	19%	14%	14%	14%	14%	11%	11%
2 doses	6%	5%	3%	5%	4%	5%	0%	10%	7%	6%
3 doses	1%	0%	2%	0%	1%	0%	0%	2%	1%	1%

Since March 1996, paediatricians have documented 1688 cases in infants under 6 months of age. Most of cases (82%) were laboratory confirmed, 15% were clinical cases and 3% were epidemiological cases. The proportion of laboratory confirmed cases was increasing over time from 66% in 1996 to 99% in 2005 (χ^2 : 183.8, $p < 10^{-3}$).

The male:female ratio was 1.0 and 63% of cases were under 3 months of age [FIGURE 2]. The proportion of cases in this age group increased over time (χ^2 : 28,6; $p < 10^{-3}$).

FIGURE 2

Number of cases (n=1688) according to age and pertussis vaccine status, France, 1996-2005



A cough lasting more than 21 days was observed for 86% of cases (n=1217). Most of the patients (96%) were admitted to hospital with 17% (n=277) admitted to intensive care. These data were stable over time.

Contact tracing was positive for 53% of patients (n=892), negative for 24% (n=405) and unknown for 23% (n=391). Source of infection was parents (55%), sibling (25%) or outside the household (17%). The type of infection source was not given for 3%. Of the 892 people thought to be a source of infection, age was known for 587 (66%), and the average age was 23 years old with a median of 25 years. The mean age increased over time from 19.6 in 1996 to 25.3 years in 2005 but the difference was not statistically significant. Of the children for whom a source of infection was identified, the proportion of children infected by their parents increased from 44% in 1996 to 72% in 2003, followed by a slight decrease in 2004 and 2005 ($p=0.12$). The trend is the same for the 0-2 months age group, with an increase from 47% in 1996 to 85% in 2003 and 66% in 2005 ($p=0.07$) but there was no increase for the 3/5 months age group ($p=0.8$).

Vaccination status was checked by looking at the "carnet de santé" for 83% of the children [FIGURE 2].

Of these, 78% had received no vaccination at all, of whom 47% were under 2 months of age and only 1% of children received 3 doses: these proportions were stable over time. Among infants aged 2-5 months, only 24% (n=96) had received a correct number of doses according to age.

Thirty two deaths (2%) occurred. Among them, 28 (88%) were in children under 3 months of age and 19 (59%) were boys. Most of them (91%) were laboratory confirmed. Only one was in a vaccinated child, a 3 month old infant who had been vaccinated with one dose, one month before the onset of the disease. Contact tracing was yielded results for 22 children and parents were the source of contamination for 17 of them.

- Microbiological description

During the 10 years under study, 82% positive cultures found *Bordetella pertussis*, 1% *B. parapertussis* and the isolate was unknown for 17%. The proportion of culture performed declined, from 75% in 1996 to 64% in 2005. During the same period, the proportion of PCR requested increased from 51% to 92%, and the proportion of serology test performed decreased from 26% to 1%.

Discussion

Since March 1996, the Renacoq network has not shown any resurgence of pertussis. However, since 2004, the number of pertussis cases has increased, although it did not reach the peaks seen in 1997 and 2000. This 2004-2005 increase cannot be due to a surveillance bias as the information comes from the microbiologists, whose rate of participation has remained high and stable since 1997 (>93% each quarter). Pertussis cycles are observed every 3 to 5 years in populations with high vaccine coverage and the three last peaks occurred in France in 1993, 1997 and 2000. Therefore, the 2005 data could be the peak expected since 2000 but with low amplitude.

The incidence among the infant cases aged 2 months or younger (276/100 000) was particularly high compared with the incidence 107/100 000 seen in the United States in the 1990s []. The incidence of laboratory confirmed cases in this age group in 2003 and 2004 in England and Wales [] was four times smaller than the incidence calculated from Renacoq data in France. This is probably not due to a better detection rate or a better reporting rate in France; however, community surveillance systems, such as those used in the US and in England and Wales, may underestimate the incidence of infant pertussis compared with data provided by a hospital based surveillance system such as Renacoq. Young children are mainly protected through active detection and rapid treatment of pertussis cases in their household, associated with prophylaxis for contacts and the vaccination of siblings. The infant pertussis vaccination coverage is almost the same in France and in England and Wales and there is not enough data on control measures around pertussis cases in the two areas to explain the differences in incidence.

The proportion of laboratory confirmed cases is increasing over time, probably because of the increasing use of PCR. Serology is barely used any more at the hospital, and we suggest that this test should now be abandoned for pertussis diagnosis in children as it takes a minimum of three years for the acellular vaccine-induced antitoxin antibodies to disappear. In France an interval of 3 years after the last dose is recommended before serology results can be used for diagnostic purposes.

The lethality has not changed over time, and remained especially high in 2005. This confirms that infants are particularly at risk and must be protected from contact with pertussis, which calls for the protection of their household. The case fatality rate over the 10 year period (2%) is in the upper value of what has been documented in the literature [,]. Most of the participating hospitals are regional reference centres. The most severe pertussis cases are probably transferred to these units, which would explain the high case fatality rate. The high rate of hospital admission reflects the fact that Renacoq is a hospital surveillance system. In Europe overall, between 1998 and 2002, the proportion of cases in children under one year of age admitted to hospital varied between 8% and 100% with a median around 65% when it was for the same period 95% in France []. As observed for infants under one year of age admitted to hospital in the US, boys and girls were represented equally and the 17% admitted to intensive care was comparable to the 14% seen in the US [6].

Even after the introduction of acellular vaccines in 1998 and the progressive replacement since then of whole cell vaccines, the proportion of cases immunised with 3 doses has been the same since 1996. This suggests a comparable vaccine effectiveness for acellular and whole cell vaccine. Most of the children were not correctly vaccinated according to age and parents and physicians should be encouraged to start childhood vaccinations without delay. Although the difference was not statistically significant, the age of the presumed source of infection is increasing, and the proportion of parents identified as the source of infection is increasing. These results could indicate a positive effect of the late booster strategy.

According to IMS Health data concerning vaccine sales, late booster coverage in 2005 was estimated to be around 50% in the age group 11-13 years in France. This coverage must be improved so that the impact of the late booster strategy impact on infants can be better assessed.

We did not study risk factors according to the number of vaccine doses received but such a study is currently being carried out using Renacoq data, and will be published soon. It confirms the protective effect of an increasing number of doses of vaccine for infants against the risk of severe pertussis defined as death, assisted ventilation or admission to intensive care, the protective effect starting with the first dose [].

As described previously, the source of infection was most often found to be the parents. The proportion of parents identified as supposed source of contamination is probably biased as contact tracing is done through family interview and as immunised siblings are more likely to have mild or asymptomatic pertussis which cannot be detected []. Nevertheless, this result supports the immunisation strategy which has recommended a pertussis booster for future or new parents [3] since 2004 and the updated recommendations concerning control measures for people exposed to pertussis cases []. Unfortunately, a survey has recently showed that pertussis vaccination of new or future parents is rarely carried out [] and much work remains to be done to promote this strategy.

It is difficult to compare the Renacoq data with data from other European countries. There is heterogeneity of surveillance systems with different case definitions, and the vaccination background varies from country to country []. Nevertheless, Renacoq and other European data confirm that young children are particularly at risk of infection and even death.

Pertussis is far from being controlled in France. The Renacoq data confirmed what has been previously published concerning the risk for young children, the role of parents as source of infection and the need pertussis vaccination to be given in accordance with the schedule. Due to poor coverage, the late booster strategy is difficult to assess. If put into practice, the new vaccine recommendations and information for health workers and parents should help to reduce infections in infants. The Renacoq network originated these new strategies and would help us to assess them.

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