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Varicella in non-immune persons: incidence, hospitalization and mortality rates

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SUMMARY

This study was conducted to estimate the varicella morbidity and mortality rates per age group among the non-immune population in France. Morbidity and mortality data for the years 1990–9 were derived from nationwide databases and surveillance systems. An incidence/prevalence model was designed to quantify the non-immune population per age group. The incidence of varicella in the non-immune population peaks during childhood and again in the 25–35 years age group. For children aged 1–4 years, adults aged 25–34 years and those older than 65 years, the hospitalization rates are respectively 235, 1438 and 8154 per 100 000 cases, and the death rates are respectively 7, 104 and 5345 per million cases. Case fatality or case hospitalization rates were not evenly distributed among adults and increased dramatically with age.

INTRODUCTION

Varicella is usually a mild disease. Nevertheless, it may cause death, although rarely in adults, pregnant women and immunosuppressed patients [1–3]. An efficient live attenuated vaccine has been licensed in many countries, but few have adopted routine childhood immunization. Today, it is only practised in the United States (since 1995), and in Japan and Korea [1]. Widespread childhood immunization should greatly reduce the number of primary cases. However, it may also favour an increase in complications, as a result of the shift in the age distribution of the remaining cases towards older persons, because of the waning of vaccine-induced immunity or the reduction of exposure to infection [4]. This is all the more concerning since during the pre-vaccine period in the United States and United Kingdom, the average age of cases has already risen [5–7]. Targeting vaccination to non-immune adults or adolescents therefore has a strong appeal in countries where routine childhood immunization has not yet been considered. Such targeting may be expected to prevent a significant portion of complicated or lethal cases of varicella, while at the same time avoiding an increase in its incidence among adolescents and adults.

To assess the benefit of this strategy, it is necessary to determine the epidemiology of complications from primary varicella in the pre-vaccine era, and the frequency of severe and costly complications. Providing health professionals and the lay public with estimates of these factors before any vaccination programme is implemented may help to gain confidence and support for the programme. Estimates of the incidence of varicella and of its hospitalization and mortality rates in the general population have been reported in countries where the vaccine is not currently in use, and in the United States for the pre-vaccine era [2, 3,

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Table 1. *Average annual number of varicella-related deaths in France (1990–7) and hospitalizations (1997–9), by age group*

Age group (years)	<1	1–4	5–14	15–24	25–34	35–44	45–64	⩾65	⩾15 (% all ages)	All ages
Varicella related deaths	2·0	2·4	1·8	1·3	2·5	1·5	2·0	5·8	13·1 (69)	19·1
Varicella related hospitalization										
Varicella meningitis or encephalitis	12·3	35	30·7	9	6·7	5	8·3	7·7	36·7 (32)	114·7
Varicella pneumonia	17·9	10·3	3·7	13	51	20·7	14	9·7	108·4 (78)	139·7
Total number of hospitalization	1240	819	401	172	348	124	111	90	845 (26)	3306

5, 7–17]. However, none of these reports dealt directly with the risks for non-immune persons, which are crucial in deciding for or against the immunization of an adolescent or adult.

In France, the epidemiology of varicella has not been changed by the vaccine, as the latter is only licensed for children with leukaemia or cancer, for persons in household contact with immunocompromised persons and for their care-givers. Using a substantial database of varicella cases collected by a French national system of surveillance for communicable diseases over the last 10 years, and an age-specific incidence/prevalence model for varicella, we estimated its age-specific incidence rates in non-immune persons, and computed their varicella-related age-specific hospitalization and mortality rates.

METHODS

Available surveillance data for varicella consist of case descriptions that do not allow direct calculation of its incidence in non-immune individuals. To make this calculation possible, we constructed an incidence/prevalence mathematical model for the epidemiology of varicella, and applied it to a population similar to that of France. We first modelled the history of infection in a birth cohort in relation to ageing, and included 100 lagged birth cohorts, in order to re-create the age structure of the general French population. The age-specific risks were then obtained by dividing the numbers of incident cases, hospitalizations and deaths by the number of living non-immune individuals.

The overall incidence of varicella was obtained from the French general practitioners' *Sentinelles* surveillance network [18]. The members of this network, about 500 voluntary unpaid Sentinel General Practitioners (1% of all GPs), report cases of communicable diseases every week. Incidence estimates for the whole country are produced by extrapolation of the cases reported. It was previously shown that the characteristics of the GPs in the Sentinel network are comparable to those of all French GPs as regards regional distribution, the proportion in rural practice, the type of practice and the distribution of the main clinical skills [19]. The age distribution of incident varicella cases in general practice was estimated on the basis of all the varicella cases reported and described between 1 January 1991 and 31 December 1998 ($n = 28\,453$).

All-causes age-specific mortality rates were obtained from the French National Mortality Database (INSERM SC8). Data concerning mortality for varicella were obtained from the French National Mortality Database, for deaths between 1 January 1990, and 31 December 1997, as were all deaths coded varicella (International Classification of Disease, 9th revision, code 052), and information on underlying medical conditions (Tables 1, 2).

Hospitalization data were obtained by reviewing all hospital discharge reports from 1 January 1997 to 31 December 1999 (PMSI Data Processing Centre). These reports constitute a national collection of all discharges from all short-stay/acute-care hospitals since 1997. The national hospital discharge register of information is abstracted by physicians from information found in the patient's medical record, using the International Classification of Diseases, 10th Revision. Varicella hospitalization was defined as hospital discharges with code B01.0-9 for varicella and its complications, and code P35.8 for congenital varicella. Information on underlying medical conditions known to increase the severity or risk of occurrence of

Table 2. *Percentage of deaths and cases hospitalized in France with underlying conditions known to increase the severity or risk of occurrence of varicella*

Underlying condition	International classification of diseases, 9th revision, codes used to determine underlying conditions	Percentage of hospitalizations for varicella	Percentage of deaths from varicella
Human immunodeficiency virus/AIDS	042·0–044·9, 795·8	1·5	9·8
Leukaemia and other malignancies	140·0–208·9	3·3	17·6
Other forms of blood dyscrasia	284·0–284·9	0·5	0·7
Immune deficiencies	279·0–279·9, 288·0–288·2	0·9	2
Pregnancy	634·0–634·9, 647·6, 647·9, 650·0–656·9	1·2	0
Total		7·5	30

varicella was also obtained (Tables 1, 2). The figures in the Results section include all hospitalizations and deaths of subjects with varicella-related diagnoses, either principal or associated.

Data gathered through the *Sentinelles* network makes possible the estimation of the number of new varicella cases per age group per year (denoted V_i, where i is the age class); it is the extrapolated total number of cases of varicella (V) in France, over 1 year, as derived from the *Sentinelles* data, apportioned to the observed age-distribution (f_i) of the varicella cases compiled through the *Sentinelles* network ($V_i = V * f_i$). Assuming the epidemiology of varicella has been stationary over time, the counts V_i are the age-specific incidence experienced by a birth cohort throughout life. The history of varicella in a birth cohort was therefore simulated as follows: starting from a totally susceptible birth cohort of size $L_0 = 720\,000$, counts of living individuals were calculated in relation to age by progressively discounting deaths ($L_i = L_{i-1} * (1 - d_{i-1})$, where L_i is the number of living individuals in age class i and d_i the all causes death rate in this age class). The age-specific number of living non-immune (denoted N_i) was calculated accordingly, by applying the age-specific incidence of varicella V_i to the counts of non-immune, starting from the first age class ($N_i = (N_{i-1} - V_{i-1}) * (1 - d_{i-1})$; $N_0 = L_0 =$ size of the birth cohort). We used 1-year age classes up to age 20 and 5 years age classes afterwards.

Using the model, we calculated age-specific incidence rates per population, per living non-immune (or 'force of infection') and determined the lifetime risk of varicella from the predicted percentage of immune in the uppermost age class. To assess the variability of the results due to random fluctuations, we replicated all calculations with source data (number of incident cases, hospitalization and deaths, and age distribution of cases) systematically varied over a range reflecting the degree of uncertainty of the original data. We performed 1000 independent simulations, each time using a different combination of resampled source data. We report the results as the mean and range obtained from the simulations, and also exhibit the special case where the lifetime risk of varicella is 100%. Source data were resampled as follows:

Using data from the *Sentinelles* network, the extrapolated annual incidence of varicella (V) diagnosed by GPs in France between 1991 and 1998 was estimated at 680 400 cases (http://www.u444.jussieu.fr/sentiweb). It led to a lifetime risk of 96% (we restate that the lifetime risk calculation is based on the percentage of immune individuals in the uppermost age class predicted by the model). To account for underestimation, this figure was considered the lower limit of the incidence. To explore the range of lifetime risk from 96 to 100% in the sensitivity analysis, we chose, in each simulation, the value of V at random between 680 400 and the annual incidence leading to a lifetime risk of 100%. This last figure was determined for each simulation because it was dependent on the resampled age distribution of cases; to study the special case of a 100% lifetime risk, the above-determined value was used for V.

The age distribution of cases (f_i) was resampled by creating, each time, a surrogate series of cases by resampling with replacement the original series of cases described to the *Sentinelles* network ($n = 28\,453$ over the period 1991–8), over which the age distribution was then calculated.

For varicella-related hospital and mortality counts, the original data were resampled, assuming that these

Table 3. *Average age-specific incidence rates of varicella per year in the general population and in non-immune persons, France, 1991–8. For the incidence in non-immune persons, the lifetime risk ranged from 96 to 100%, with a mean case corresponding to 98%. The special case of a 100% lifetime risk is reported in a separate column*

Age group (years)	Incidence per 100 000 general population	Incidence per 100 000 non-immune population	
	Mean (range)	Lifetime risk 96% – 100% Mean (range)	Lifetime risk 100% Mean (range)
<1	4 973 (4487–5521)	4 973 (4487–5521)	5 093 (4600–5552)
1–4	12 124 (11 702–12 534)	15 015 (14 383–15 676)	15 439 (15 092–15 802)
5–14	3 600 (3441–3764)	17 329 (15 311–19 991)	19 351 (18 621–20 058)
15–24	342 (305–377)	3 620 (2710–4936)	4 632 (4181–5087)
25–34	344 (309–386)	5 751 (3904–8860)	8 557 (7701–9330)
35–44	92 (72–110)	3 324 (1509–9121)	8 135 (6922–10 186)
45–64	12 (8–19)	691 (185–3378)	2 747 (1682–4768)
⩾65	10 (5–15)	769 (161–7567)	4 829 (2553–8936)
<15	5 974 (5826–6143)	14 168 (13 334–15 128)	14 953 (14 689–15 214)
⩾15	128 (119–138)	3 229 (1901–6185)	5 943 (5514–6836)
Total	1 255 (1228–1285)	10 866 (8965–13 497)	13 287 (12 982–13 643)

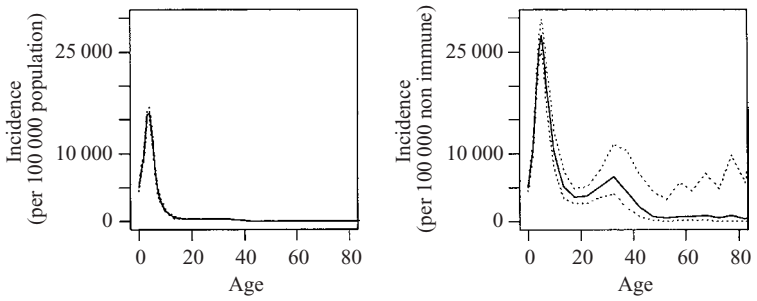

Fig. 1. Incidence in the general French population (left) and the non-immune population (right). Solid line corresponds to the mean case (lifetime risk of 98%), dotted lines to the minimum (lifetime risk 96%) and maximum (lifetime risk 100%) from the sensitivity analysis.

counts conformed to the Poisson distribution. For each age group, the original count was used as an estimate of the mean number of cases.

RESULTS

The incidence of varicella diagnosed by GPs for 1991–4, was not different from the incidence for 1995–8. There was no sex-related difference in this incidence. In the general population, the incidence of varicella cases seen by GPs peaked among children aged 4 years, and then decreased regularly (Table 3, Fig. 1). Among individuals aged more than 15 years, the overall incidence was 47 times lower than in children, and in addition, decreased markedly with age. An annual estimated average of 57 881 cases were diagnosed by French GPs in subjects aged 15 years and more (range: 53 987–62 221), i.e. 8·3% of the total annual number of cases of varicella (range: 7·7–8·9%). In a birth cohort, 10·8% of subjects remained susceptible at age 15 (range: 6·4–14·9%).

The force of infection of varicella, i.e. its incidence among non-immune persons, peaked during childhood, at age 5, and also displayed a second peak among subjects 30 years old. Thus, the incidence for the 25–29 years age group was 42% higher than for the 20–24 years age group, and the incidence in those aged 35–39 years was 36% less than in those aged 30–34 years. This feature was found regardless of the assumed lifetime risk of varicella. However, the risk starts increasing again in the old when 100% lifetime risk is assumed.

Table 4. *Average hospitalization and mortality rates for varicella per year, in the general French population and in non-immune persons by age group, France*

	Hospitalization (1997–9)			Mortality (1990–7)		
Age group (years)	per 100 000 population	per 100 000 non-immune	per 100 000 cases	per 1 000 000 population	per 1 000 000 non-immune	per 1 000 000 cases
<1 year	172 (156–189)	172 (156–189)	3467 (3075–4032)	2·86 (0–11·1)	2·86 (0–11·1)	57 (0–221)
1–4 years	28 (25–33)	35 (31–40)	235 (209–269)	0·83 (0–2·78)	1·03 (0–3·4)	7 (0–24)
5–14 years	5·6 (4·8–6·6)	27 (22–33)	156 (134–186)	0·24 (0–0·98)	1·17 (0–4·6)	7 (0–27)
15–24 years	2·4 (1·9–3·1)	25 (17–37)	707 (528–962)	0·18 (0–1·12)	1·92 (0–10·1)	53 (0–357)
25–34 years	4·9 (4·3–5·7)	82 (53–138)	1438 (1200–1751)	0·36 (0–1·14)	5·98 (0–24·2)	104 (0–338)
35–44 years	1·8 (1·3–2·2)	64 (26–184)	1945 (1225–2602)	0·22 (0–1·01)	7·81 (0–53·1)	235 (0–1072)
45–64 years	0·8 (0·6–1·2)	46 (14–194)	6902 (3804–12 233)	0·15 (0–0·61)	8·13 (0–93·9)	1219 (0–4971)
⩾65 years	0·8 (0·6–1·2)	60 (14–536)	8154 (4687–15 183)	0·54 (0–1·38)	40·2 (2·43–501)	5345 (0–15 395)
<15 years	23·0 (21·5–24·4)	54 (49–58)	383 (357–416)	0·58 (0–1·30)	1·37 (0·0–3·18)	10 (0–22)
⩾15 years	1·9 (1·7–2·1)	47 (17–92)	1464 (1264–1670)	0·29 (0·07–0·62)	7·32 (1·37–21·4)	228 (53–484)
Total	5·9 (5·6–6·3)	51 (33–63)	473 (441–504)	0·35 (0·20–0·66)	3·00 (1·22–5·54)	28 (11–54)

Each year, varicella and its complications were responsible for an average of 3306 hospitalizations, and 19 deaths (Table 1). About 78% of the varicella patients hospitalized for pneumonia and 70% of the deaths attributed to varicella concerned persons of 15 years or more (Table 1). Congenital varicella accounted for an average of 29 hospitalizations each year. Among non-immune persons, the risk of varicella-related hospitalization was highest among infants. It was lower and approximately constant in other age-groups, and exhibited a marked increase at 30 years (Table 4). The death rate was U-shaped, decreasing in childhood and increasing with age thereafter.

The hospitalization and case fatality rates for varicella were highest among adults, and then infants, and the lowest rates were for children. The risk of hospitalization was 4–50 times higher in adults than in children 5–14 years old. The case fatality rate showed a risk of death 7·5 times higher in subjects aged from 15 to 24 years than in children of 5–14 years, and was more than 174 times higher in adults aged 45 years or more. There was a higher risk of death and hospitalization in infants than in children aged 1–4 years. Underlying conditions known to increase the severity or risk of occurrence of varicella accounted for 30% of varicella-related deaths and for 7·5% of varicella-related hospitalizations (Table 2).

Ranges for incidence rates among the general population were narrow. On the contrary, estimates of the force of infection spanned a wide range around the mean value for those over 15. For younger individuals however, a 10% range around the mean value was observed (Table 3). These variations were mainly a consequence of the assumed lifetime risk, and indeed the force of infection increased with the lifetime risk. Nevertheless, even with a lifetime risk of 100%, there were substantial variations resulting from the age distribution of cases. These increases accounted in turn for much of the variability in the hospitalization and mortality rates for non-immune persons. The hospitalization and mortality rates in the general population and among varicella cases were not sensitive to the overall incidence of varicella. For these rates, the main source of variability was in the counts of hospitalizations or deaths by age group, which were modelled on the basis of the Poisson distribution. The lowest bound estimates for mortality were indeed 0, because with this distribution, a 0 death count in an age group was common in the replicated samples.

DISCUSSION

This work provided estimates of the force of infection of varicella, and of varicella-related hospitalization and death rates according to age in France, a country where no mass immunization has been implemented. It showed that the force of infection increased in 30-year-old adults, and that although the incidence of varicella among non-immune individuals decreased with age, the hospitalization and fatality rates increased exponentially with age.

Estimates of the age-related force of varicella infection, hospitalization and death rate in non-immune

persons were obtained on a nationwide level. Certain previously published estimates of the force of infection were obtained by dividing the yearly incidence of varicella by the percentage of susceptible adults [20], with results similar to those reported here. However, their estimates were limited to young adults. The prevaccination force of varicella infection estimated in Canada [21] was based on mathematical modelling, data for antibody prevalence, and billings. This procedure yielded higher rates than those we obtained, except when the lifetime risk was set to 100%. For example, the force of infection in subjects 25–44 years old ranged from 2 to 8% in this work for a lifetime risk increasing from 96 to 100%; the upper limit compared to the 8% of the Canadian study. Likewise, the force of infection ranged from 0·1 to 7% in individuals older than 65, and the special case of 100% lifetime risk yielded an average value of 4%, in accordance with the Canadian study.

One surprising feature of the force of infection reported here is that besides the expected peak during childhood, a second peak appeared in the 25–35 years age group. The occurrence of this peak had previously been postulated [22], but never actually observed. Presumably, individuals in this age group are naturally in contact with young children through parenthood, and are therefore likely to be infected if they are not already immune. This implies that the risk of varicella may be very heterogeneous among adults, and that familial or occupational exposure must be taken into account in the individual risk/benefit analysis of vaccination. On the whole, the 30-year incidence peak provides a strong justification for screening young adults before they have their first child.

The age-specific yearly incidence rates of varicella observed in France in the general population and reported here correspond to those previously published for the United States [1, 3, 20, 23, 24], and so do the French mortality and hospitalization rates, per population and per number of cases [1, 3, 10, 11, 23].

It is well known that the complications of varicella tend to be more severe in adults than in children. Thus, in previous studies conducted in the United States, the risks of hospitalization and death were highest among those aged 20 years or more [1, 3, 8, 10, 23]. For instance, the risk of dying of varicella was 25 times greater in adults than in children aged 1–4 years [1, 10], and the risk of hospitalization 14 times greater [3, 23]. Our estimates show a similar trend, as the risk of death was 30 times greater in subjects over 15 years than in children aged 1–4 years, but the risk of hospitalization was only 7 times greater. Note that in previous studies all subjects aged 20 years or more were considered as adults for the calculation of varicella-related risks of death and hospitalization [3, 10, 23]. However, our results show that case fatality or case hospitalization rates, far from being uniformly distributed in adults, are greatly dependent on age.

Adults $\geqslant$25 years old accounted for 62% of all varicella deaths in France, a higher proportion than in the United States, where this figure was estimated at about 54% [1, 10]. Most of those who died of, or were hospitalized for, varicella were previously healthy individuals. We found that an underlying condition, often immunosuppression, was a factor contributing to death in 30% of our adult cases, as reported in other countries [9, 10, 25]. In two studies, 15% of the persons hospitalized for varicella were reported to have had an underlying condition known to increase the severity or risk of occurrence of varicella [2, 11]. The rate we calculated was lower, despite a comparable case hospitalization rate.

In temperate countries, it is often admitted that the annual incidence of varicella almost equals the size of the birth cohort. Seroprevalence studies, which are the gold standard for establishing previous infection by varicella, showed that the lifetime risk of varicella was indeed close to 100%, but published estimates have generally yielded smaller values: for example, the lifetime risk was estimated at 97·8% in a recent study from Spain [26]. The *Sentinelles* network estimates that there are approximately 680400 cases of varicella per year, which leads to a lifetime risk of 96%. This is likely underestimated, because data is reported by GPs only, hence patients who consulted a paediatrician, or dermatologist, or went to a hospital emergency unit were not accounted for. Furthermore, parents may seek medical advice for the index case in the family but less frequently for subsequent cases. Nevertheless, the estimated lifetime risk of acquiring varicella was over 95%, indicating that only a small percentage of patients are likely to be missed by the *Sentinelles* network. We investigated this underestimation in two ways: first, the sensitivity analysis took into account the fact that the lifetime risk could be between 96 and 100%, and we also investigated the special case of a 100% lifetime risk. This analysis showed that there was strong uncertainty regarding the actual level of the force of infection after age 50,

due to the small percentage of the population still vulnerable beyond that age.

Our hospitalization and mortality data were certainly closer to reality than those in certain other reports, because they were obtained from the full set of hospital discharge reports and death certificates. Although hospitalization data, unlike those concerning mortality, describe episodes of care and thus are not person-based, varicella is not a recurrent disease, and repeated hospitalization seems improbable [27]. The retrospective nature of the present study might raise the question of the accuracy of the mortality and hospital discharge data, and of the actual nature of the cases diagnosed as varicella during a visit with a physician. Nevertheless, the clinical definition of varicella is simple enough for it to be diagnosed with precision in clinical practice, and it is unlikely to be confused with other conditions causing vesicles. At the same time, we cannot completely rule out the possibility that certain cases of disseminated herpes zoster in elderly adults might have been misclassified as primary varicella. We also admit that adult cases may have been more likely to have received medical attention than milder cases in children.

In conclusion, the estimates provided by our study show that the force of infection of varicella increases in 30-year-old adults, and confirm the strong dependence of varicella-related mortality and hospitalization rates on age. In countries where no routine childhood immunization is implemented, targeted vaccination of non-immune adolescents and adults could still reduce the current medical and financial burden constituted by varicella. Medicoeconomic evaluation of the benefit of such vaccination is therefore needed for decision making.

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