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Varicella in French adolescents and adults: individual risk assessment and cost-effectiveness of routine vaccination

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Abstract

Age-specific force of varicella infection, hospitalisation and death rates in non-immune persons were calculated using an age-based mathematical model and national data for France. A cost-effectiveness model was then applied to hypothetical cohorts of persons aged 15–45 years with a negative or uncertain history of varicella. Vaccination strategies with and without prior serotesting, and healthcare payer perspective and societal perspective were considered. A sensitivity analysis was performed. Vaccination prevented more than one third of all varicella-related deaths. With serotesting, compared with no intervention, the cost per case avoided and per year of life saved for subjects aged 15 years were €335 and 55,100, respectively. When work-loss costs were also included, savings were associated with screening and vaccination of subjects less than 30 years old. Without serotesting, the costs raised markedly, with an almost identical effectiveness, resulting in an unfavourable incremental cost-effectiveness. Based on medical costs, routine serotesting and varicella vaccination for French adolescents and young adults with a negative or uncertain history of varicella affords health benefits at a cost comparable to those of other very expensive therapies considered worthwhile. From the societal perspective, such screening and vaccination might save costs.

Keywords: Varicella; Vaccination; Adult

1. Introduction

After a first peak during childhood, the incidence of varicella among non-immune individuals in France increases again in 30-year-old adults [17]. The mean age of acquisition of, or hospital admission for, varicella has risen recently in both the UK [1–4] and Italy [5]. Because varicella-related hospitalisation and mortality rates are known to increase significantly with age [6–8], reducing the number of varicella cases among adolescents and young adults is an important public health issue.

Although an effective varicella vaccine exists, there has been concern that routine childhood immunisation could create an adult population at risk for varicella in case of failure to reach high levels of vaccine coverage in the population, or a waning of vaccine-induced immunity [9,10]. This would increase the number of varicella cases with complications. Targeting non-immune adolescents or adults for vaccination therefore has a strong appeal, and may prevent a substantial proportion of complicated or lethal cases of varicella, while at the same time avoiding an increase in incidence among adolescents and adults.

Since most of the individuals who are hospitalised for, or die of varicella were previously healthy [1,6,7,11,12], routine screening with immunisation should be considered. Several screening strategies are possible, based on the patient's reported history, and on the availability of a serological test. However, the predictive values of the reported history and of the serological test may be imperfect, justifying a detailed analysis of the impact of classification errors on the vaccination strategies.

Informed decision-making for routine varicella vaccination in older individuals requires age-specific estimation of the risks and complications of primary varicella for these individuals. In order to allow comparison with other health-care programmes competing for the same resources, the

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cost-effectiveness of these strategies is also important. Each year in France, varicella-related disease was predicted to cause €16 million in discounted medical cost and more than 23,000 days in absence from work [15]. In the US, these costs were recently evaluated for varicella vaccination in adolescents and adults [13,16], although routine childhood immunisation has been recommended in this country since 1996.

Our objective was to evaluate the morbidity and mortality risks of varicella in older adolescents and adults in France, and to evaluate the cost-effectiveness of strategies for routine screening and vaccination.

2. Methods

We constructed an age-based mathematical model to evaluate the morbidity and mortality risks of varicella in French individuals aged 15 years or older. We then developed a cost-effectiveness model to estimate the clinical impact, cost, and cost-effectiveness of routine vaccination for older adolescents and adults reporting a negative or uncertain history of varicella.

2.1. Morbidity and mortality risks of primary varicella

We calculated the risks of primary varicella and the related hospitalisation and death rates from data for the years 1990–1999. These were obtained from French national databases, including the French general practitioners' *Sentinelles* network for the surveillance of varicella [17], the French National Hospitalisation Database for hospitalisation [18], and the French National Mortality Database for death rates [19]. On the basis of these data, we constructed an age-specific mathematical model for varicella. The average size of a birth cohort in France is about 720,000. The history of varicella in a given birth cohort was simulated as follows: starting from an all-susceptible birth cohort, the number of living individuals was calculated by age by subtracting the number of deaths, indicated by the age-specific all-cause mortality rate. The number of living non-immune individuals was calculated by subtracting the age-specific incidence of varicella from this number. Age-specific incidence was estimated by apportioning the overall annual incidence according to the age distribution of cases obtained from the *Sentinelles* network. The values of four parameters were derived from this mathematical model: the proportion of non-immune subjects or percent susceptible; the lifetime expected probability of varicella among these subjects in the absence of vaccination; expected age at the occurrence of primary varicella in the absence of vaccination; and the expected lifetime hospitalisation and case fatality rates among individuals ≥15 years of age. Calculation of the mean age-related duration of hospitalisation was based on data supplied by the French National Hospitalisation Database [18]. To assess the variability of the results, we performed 1000 independent simulations, using, for each one, a different combination of resampled source data. We report results as the mean, 2.5th and 97.5th percentiles obtained in the simulations.

2.2. Cost-effectiveness model

We then constructed a cost-effectiveness model using a decision analysis tree to evaluate two distinct strategies for routine screening and vaccination in subjects with a negative or uncertain history of varicella (Fig. 1): (a) antibody testing in subjects reporting a negative or uncertain history of varicella, and vaccination of only those with negative tests (the "Ab test, Vax negative" strategy), and (b) vaccination of all subjects reporting a negative or uncertain history of varicella, without serological testing (the "Vax all" strategy). The strategies were compared in an incremental analysis, versus no screening or immunisation, which is the current standard of care in France. We assumed that the threshold age for screening and vaccination was 15. However, we also did sensitivity analyses using age thresholds of 20, 25, 30, 35, 40 and 45 years, and the effect of the age threshold on the results is reported. The time horizon of the analysis was from each age threshold until death.

2.2.1. Clinical risks

The clinical risks used in the cost-effectiveness model were derived from the literature (Table 1), and from estimates of age-specific risks of varicella calculated from our age-based mathematical model (Table 2).

2.2.2. Costs

Both the healthcare payer perspective, including only medical costs, and the societal perspective, which include work-loss costs and medical costs, were considered. Costs were reported in 2001 Euros (€). All future costs and health benefits were discounted at their present values, using an annual discount rate of 3% [20]. Costs were not adjusted for inflation.

The direct medical costs of varicella included physician consultation, medication and hospitalisation (Table 1). The number of consultations and the cost of varicella treatment were based on current data for adult varicella in France [15]. The cost of antiviral treatment was also considered, as recommended for adults [14]. Hospitalisation costs were computed on the basis of the daily charge in a general internal medicine ward (as established by the French Social Security System). Societal cost of varicella was estimated as the cost of work loss. The productivity loss associated with work stoppage was calculated as the daily median salary [21] multiplied by the mean number of days of work stoppage for a varicella case in an adult, and by the proportion of adults who stop working in case of varicella [15].

We used a vaccination price of €71.65 (two doses), based on US data where the vaccine is widely used [13,16]. We obtained a range of prices from other European studies [15,22]

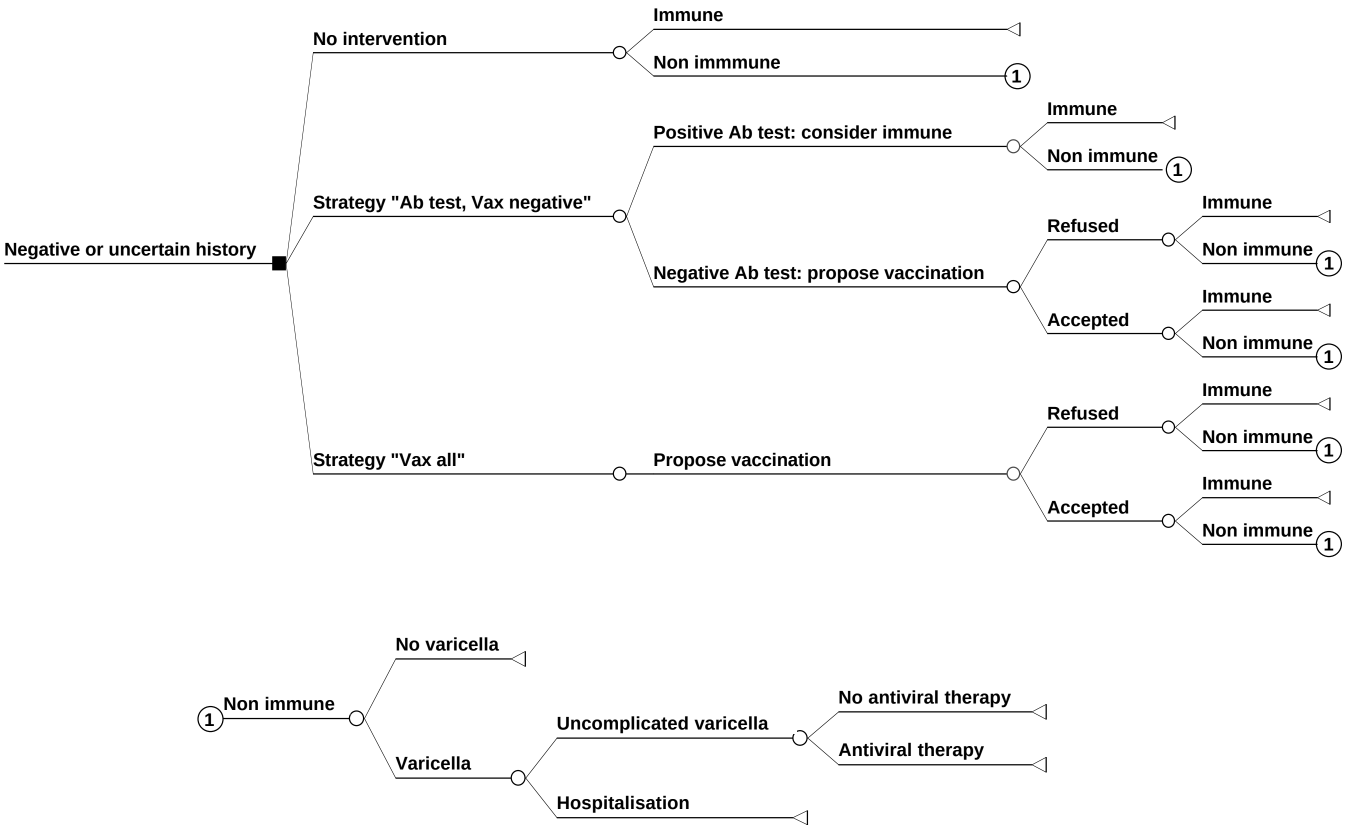

Fig. 1. Flowchart of the no intervention and screening and vaccination strategies for varicella proposed for adolescents and adults who have a negative or uncertain history of varicella. Subtree shows outcome for the non-immune patients. See Section 2 for details.

and included those in sensitivity analysis. The cost of administering the vaccine was derived from the French Social Security System tariff for a consultation with a general practitioner in France (17.65 €). Persons aged over 15 years require two doses of vaccine [14]. As testing and vaccination were assumed to occur incidentally in relation to a routine medical visit, the cost of only one outpatient visit was considered in the baseline analysis. We postulated that 1% of vaccinations (range: 0.31–2%) lead to a consultation, due to mild side effects [23,24]. This percentage was applied to the national tariff for the consultation of a general practitioner in order to calculate the cost of side effects of varicella vaccination.

2.2.3. *Effectiveness*

We assumed that the vaccine provided 80% protection against varicella infection (range: 70–90%), based on expert summary [14]. We also assumed that it conferred lifelong immunity, based on the observation that in vaccinated adults, the incidence and severity of varicella have not increased with time 13 years after vaccination [25]. For vaccinated persons who subsequently contracted varicella, we assumed that the costs of consulting a physician, medication, and work loss equalled those incurred by unvaccinated persons with varicella. However, we considered that in vaccinated persons, varicella would not lead to either major complications [26] or hospitalisation. The proportion of eligible subjects accepting vaccination was assumed to be 70% (range: 50–90%).

2.2.4. *Outcome measures*

Primary outcome measures included the residual age-specific probability of the occurrence of varicella, the number of varicella cases, hospitalisations and deaths avoided, and the number of years of life saved per 100,000 subjects aged 15, 20, 25, 30, 35, 40 and 45 years who reported a negative or uncertain history of varicella, for each strategy compared with no intervention. We also calculated by what percentage each strategy would reduce the risk of varicella compared with no intervention, regardless of the history of varicella, i.e. for the whole population. Incremental cost-effectiveness is calculated as medical and total costs per case of varicella avoided and per life-year saved. The mean age at occurrence of varicella (a_{V}) for a susceptible individual screened at a given age threshold ($a_{\mathrm{T}} = 15, 20, \dots$) was obtained from the mathematical model described earlier. The number of life-years saved was calculated as the difference between the individual's life expectancy (a_{L}) and the mean age at occurrence of lethal varicella, and was discounted using the formula: $0.03^{-1}(1-0.03)^{a_{\mathrm{V}}-a_{\mathrm{T}}}(1-(1-0.03)^{a_{\mathrm{L}}-a_{\mathrm{V}}})$. Other future quantities (cases, hospitalisations, deaths, costs) were discounted at a rate of 3% for $a_{\mathrm{V}} - a_{\mathrm{T}}$ years.

Table 1
Clinical risks and costs of varicella in adolescents and adults derived from the literature

Parameter	Baseline	Range	Reference
Reported history of varicella (%)			
Sensitivity in relation to actual immunity	67.5	55.5–72.4	[40,41], estimates
Specificity in relation to actual immunity	86.8	80.1–87.8	[40,41], estimates
Varicella antibody testing (%)			
Sensitivity	97	86–97	[14]
Specificity	99	82–99	[14]
Cost (€)			
Blood collection	1.72	–	French Social Security System
ELISA	19.21	–	French Social Security System
Varicella vaccination efficacy (%)			
Protection against chickenpox 10 years after vaccination	80	70–90	[14]
Vaccination costs (€)			
Price of vaccine (two doses)	71.65	42.68–99.09	[15,16,22,24]
Administration of the vaccine	17.53	0–35.06	French Social Security System, estimates
Cost of vaccine side effect	0.18	0.05–0.35	[14,23,24,38], estimates
Varicella costs in persons ≥15 years			
Medical costs (€)			
Without antiviral treatment	94.11	50.00–144.06	[15]
Price of oral antiviral treatment (1 week)	103.51	–	French Social Security System
Percentage of receiving antiviral therapy	50	0–100	[14], estimates
Price of 1 day in hospital	502.78	–	French Social Security System
Work loss costs			
Incidence of work stoppage (proportion of cases) (%)	51.9	–	[15]
Mean duration of work stoppage (days)	10.9	–	[15]
Daily cost associated with work stoppage (€)	96.77	63.31–207.81	[21], National Institute of Statistics and Economic Studies, estimates

Costs are given in 2001 Euros (€).

Table 2
Estimated risks of varicella in adolescents and adults derived from an age-based mathematical model

Age (years)	Susceptibility rate for the whole population (%)	Expected lifetime proportion of occurrence of varicella in non-immune subjects (%)	Expected age at occurrence of varicella in non-immune subjects (years)	Expected lifetime case hospitalisation rate (per 10000 varicella cases)	Expected lifetime case fatality rate (per 10000 varicella cases)
15	10.3 (8.5–12.0)	79 (66–98)	28 (15–58)	146 (135–158)	2.3 (1.1–3.6)
20	8.4 (6.6–10.2)	74 (60–97)	31 (20–63)	174 (159–190)	2.8 (1.3–4.4)
25	6.9 (5.0–8.7)	69 (53–96)	34 (25–66)	201 (182–222)	3.5 (1.5–5.7)
30	5.1 (3.2–6.9)	57 (41–94)	39 (30–74)	234 (207–263)	5.0 (2.0–8.2)
35	3.4 (1.5–5.3)	37 (23–88)	46 (35–85)	354 (304–412)	9.9 (4.1–16.8)
40	2.7 (0.8–4.6)	21 (12–77)	55 (40–87)	547 (444–679)	19.1 (7.0–34.3)
45	2.5 (0.5–4.4)	13 (7–65)	63 (45–90)	736 (581–951)	28.1 (10.0–51.5)

Results are shown as the mean (2.5th and 97.5th percentiles) of the distribution obtained from the sensitivity analysis of the model. The age-specific susceptibility rate for the whole French population, the expected lifetime proportion of non-immune subjects contracting varicella, expected age at occurrence of varicella in these subjects, and the expected lifetime case hospitalisation and case fatality rates among individuals ≥15 years old were derived from the age-based mathematical model (data for the years 1991–1999, France, in the absence of vaccination).

We used cost-effectiveness analysis and not cost-utility or cost–benefit analyses because of the limited time frame of the quality of life impact of varicella, and of the lack of data on economic valuation of these outcomes. One-way threshold sensitivity analyses were performed for all parameters, to calculate the change in cost-effectiveness over a plausible range of variation for these parameters. We also calculated a "worst case" scenario, where the effect of vaccination on the reduction of both risk and cost was the smallest.

3. Results

3.1. Projection of morbidity and mortality from varicella (Table 2)

We found that subjects ≥15 years old represent 8.3% of the total projected number of cases of varicella (2.5th and 97.5th percentiles: 7.9–8.6%), 26% of varicella-related hospitalisations (24–27%) and 69% of all varicella-related deaths (56–76%). Table 2 shows the age-related susceptibility rate for the whole population, the lifetime proportion of non-immune subjects expected to contract varicella, the expected age at occurrence of varicella in these subjects and the expected lifetime case hospitalisation and case fatality rates among individuals ≥15 years old. The risks of varicella are not uniformly distributed among adults, and are dependent on age. The lifetime proportion of non-immune subjects expected to contract varicella decreased from 79% in 15-year-old subjects (66–98%) to 13% in 45-year-old subjects (7–65%). Hospitalisation rates rose from about 146 per 10,000 at 15 years, to 736 per 10,000 at 45 years. The case fatality rate rose from 2.3 per 10,000 to 28.1 per 10,000, respectively.

3.2. Clinical effects of vaccination strategies (Table 3)

Health benefits were similar for strategies "Ab test, Vax negative" and "Vax all". For subjects reporting a negative or uncertain history of varicella, we found that either strategy would prevent about 55% of the projected varicella cases (about 32% in the worst case).

Table 3 shows the age-related probability of being vaccinated among subjects reporting a negative or uncertain history of varicella. Serotesting always reduced this proportion, e.g. from 70 to 18% when performed at age 15. As the numbers of varicella cases decrease with age, the absolute health benefits of vaccination also decreases with age. With the "Ab test, Vax negative" strategy, the number of varicella cases avoided decreased from 6712 in 15-year-old subjects (2785 in the worst case scenario) to 333 per 100,000 in 45-year-old subjects (131 in the worst case) among subjects reporting a negative or uncertain history of varicella. The number of hospitalisations avoided decreased from 98 in 15-year-old subjects to 25 per 100,000 in 45-year-old subjects (38 to 9 in the worst case). The number of deaths avoided decreased from 1.57 to 0.92 per 100,000, respectively (0.65 to 0.36 in the worst case). The number of years of life saved decreased from 41 in 15-year-old subjects to 12 in 45-year-old subjects (17 to 5 in the worst case). The figures were similar in the "Vax all" strategy.

For the entire population, the two strategies would reduce the risk of varicella by about 49% (28% in the worst case). In each age group, less than 27% of individuals would be vaccinated on the basis of their medical history alone, and less than 5% on the basis of this history and the results of serotesting.

3.3. Costs of screening and vaccination strategies (Table 4)

Compared with no intervention, vaccination raised medical costs by €23 per 15-year-old person according to the strategy "Ab test, Vax negative", and by €48 according to the strategy "Vax all". When work loss costs were added to medical costs, there was an estimated average net benefit of €12 per 15-year-old person with the strategy "Ab test, Vax negative", compared with no intervention, and vaccination raised total costs by €13 according to the strategy "Vax all".

Table 3
Health benefits of two strategies of routine screening for vaccination against varicella, applied to individuals aged ≥15 years reporting a negative or uncertain history of varicella, as determined by the decision–analysis model

Age (years)	Strategy	Probability of being vaccinated (%)	Varicella cases avoided[a] (per 100000)	Hospitalisations avoided[a] (per 100000)	Deaths avoided[a] (per 100000)	Years of life saved[a] (per 100000)
15	Ab test, Vax negative	18	6712	98	1.57	40.8
	Vax all	70	6780	99	1.58	41.2
20	Ab test, Vax negative	15	5820	102	1.61	41.2
	Vax all	70	5879	102	1.62	41.5
25	Ab test, Vax negative	13	4781	96	1.67	41.6
	Vax all	70	4830	97	1.69	42.0
30	Ab test, Vax negative	11	3374	79	1.70	41.4
	Vax all	70	3408	80	1.72	41.8
35	Ab test, Vax negative	8	1320	46	1.29	27.4
	Vax all	70	1334	47	1.30	27.5
40	Ab test, Vax negative	7	581	32	1.10	19.0
	Vax all	70	587	32	1.11	19.2
45	Ab test, Vax negative	6	333	24	0.92	11.9
	Vax all	70	336	25	0.94	12.0

Results are shown for the baseline hypotheses and for the "worst case" hypotheses, i.e. when the effect of vaccination on risk reduction was the smallest. All results are averages per 100,000 persons of the French population reporting a negative or uncertain history of varicella. For the cases avoided, the reference is "no intervention". Strategy "Ab test, Vax negative": antibody testing in case of negative or uncertain history of varicella, and immunisation of subjects with a negative test. Strategy "Vax all": immunisation in case of negative or uncertain history of varicella, without antibody testing.

[a] Discounted to present value (3%).

Table 4
Costs and cost-effectiveness of two strategies of routine screening for and vaccination against varicella for individuals ≥15 years reporting a negative or uncertain history of varicella

Age (years)	Strategy	Cost of strategy per person (€)[a]		Incremental cost effectiveness per varicella case avoided (€)		Incremental cost effectiveness per year of life saved (€)	
		Direct	Total	Direct	Total	Direct	Total
15	No intervention	24	87	–	–	–	–
	Ab test, Vax negative	47	75	335	Savings[b]	55100	Savings[b]
	Vax all	72	100	37900	37400	7494800	7391200
20	No intervention	22	76	–	–	–	–
	Ab test, Vax negative	43	68	369	Savings[b]	52100	Savings[b]
	Vax all	71	95	47400	46900	7588000	7505200
25	No intervention	20	65	–	–	–	–
	Ab test, Vax negative	41	61	428	Savings[b]	49200	Savings[b]
	Vax all	70	90	61000	60500	7854400	7787700
30	No intervention	15	46	–	–	–	–
	Ab test, Vax negative	36	50	617	108	50300	8800
	Vax all	68	82	94000	93500	7920300	7877500
35	No intervention	8	19	–	–	–	–
	Ab test, Vax negative	31	36	1752	1255	84500	60600
	Vax all	65	71	254100	253600	22846400	22802600
40	No intervention	5	9	–	–	–	–
	Ab test, Vax negative	29	31	4127	3672	126000	112100
	Vax all	64	66	624200	623700	32496600	32472300
45	No intervention	3	5	–	–	–	–
	Ab test, Vax negative	28	29	7419	7000	207700	196000
	Vax all	64	65	1241500	1241000	24138700	24129300

Results are given in 2001 Euros (€). Costs of strategies are expressed per person reporting a negative or uncertain history of varicella in the whole French population. Strategy "Ab test, Vax negative": antibody testing when negative or unsure varicella history, and immunisation of subject with a negative test. Strategy "Vax all": immunisation when negative or unsure varicella history, without antibody testing.

[a] Discounted to present value (3%).

[b] Cost-saving interventions ("savings") are those that result in both health benefits and financial savings.

Strategies for subjects aged more than 15 years cost more than for those aged 15 years (Table 4). With regard to total costs, only strategy "Ab test, Vax negative", when applied to 20- and 25-year-old subjects, was cost-saving (€ 7 and 4 with the baseline parameter values, respectively).

3.4. Cost-effectiveness of strategies (Table 4)

With baseline assumptions in 15-year-old persons, vaccination according to strategy "Ab test, Vax negative" avoided varicella cases and saved lives at an average incremental medical cost of € 335 per varicella case avoided and € 55,100 per life-year saved, versus no intervention. When work loss costs were added to medical costs in persons less than 30-year-old, the "Ab test, Vax negative" strategy was cost saving compared to "no intervention", i.e. it resulted in both health benefits and financial saving. Incremental cost-effectiveness raised sharply in subjects aged more than 30 years. The cost-effectiveness of vaccination without antibody testing is much less favourable economically compared with testing then vaccination.

In the one-way sensitivity analyses, when only direct costs were considered, none of the parameters presented a threshold that could reverse the cost effectiveness ratios, i.e. that could result in savings, whatever the age. In 15-year-old persons for the "Ab test, Vax negative" strategy, the costs per case avoided ranged between € 220 and 460. Cost-effectiveness ratios ranged between € 36,700 and 75,900 per year of life saved. The parameters leading to the largest change in cost-effectiveness were the vaccination cost, followed by the cost of hospitalisation and the probability of reporting a negative history among immune persons. For subjects aged more than 15 years, most of the variability was related to hospitalisation costs, followed by the susceptibility rate for the whole population and the expected lifetime proportion of occurrence of varicella in non-immune subjects at a given age. When total costs were considered, the findings were less robust: one-way sensitivity analysis showed that the "Ab test, Vax negative" strategy in persons less than 30-year-old was no longer cost saving when the total costs of treating a case of varicella (i.e. medical cost and work loss costs) were less than € 280, when the total costs of hospitalisation were less than € 960, when the susceptibility rate for the whole population was less than 6% and when the expected lifetime proportion of occurrence of varicella in non-immune subjects was less than 60%. In the worst case scenario, savings were not possible with vaccination, for either direct medical or total costs. With the worst case assumptions, cost-effectiveness ratios were increased by three-fold for subjects aged 15–34 years, and by four-fold for subjects aged over 35 years.

4. Discussion

We found that routine vaccination targeted to 15-year-old subjects would reduce projected varicella-related morbidity and mortality by half. Since more than two thirds of all varicella-related deaths occur after age 15 (even though only 8.3% of all varicella cases occur in subjects of that age), more than one-third of all varicella-related deaths in France could be prevented by vaccinating 70% of subjects with a negative or uncertain history of varicella of age 15 (18% after serotesting). The selection of subjects to vaccinate on the basis of negative serotesting (strategy "Ab test, Vax negative") was markedly less costly than vaccination based solely on reported history (strategy "Vax all"). From the healthcare payer's point of view, including only medical costs, the routine varicella vaccination of older adolescents and adults with a negative or uncertain history of varicella increased health benefits at an incremental cost above €55,100 per year of live saved. In a broader societal perspective, i.e. when work-loss costs are added to medical costs, a vaccination program based on the testing than vaccination strategy may yield savings in subjects aged less than 30 years with the baseline estimates, but could remain very costly with the "worst case" hypothesis.

Previous cost-effectiveness studies of routine varicella vaccination mainly focused on children [15,22–24,27,28]. They showed that childhood vaccination would avoid expenditure from the societal perspective, at low cost to the healthcare payer. For example, the cost for pre-school-age children would be ≈€2.3 (US$ 2) per varicella case prevented and ≈€2800 (US$ 2500) per life-year saved [24], compared to €335 and 55,100 respectively for 15-year-old subjects in our study.

Varicella vaccination of adults has been previously studied in specific populations including non pregnant women of childbearing age [29], military recruits [30], and health care workers [31]. For the first two categories, vaccination costs were very high. The cost-effectiveness of the routine vaccination in older adolescents or adults without a history of varicella has only been evaluated in two American studies by Lieu et al. [13] and by Smith and Roberts [16]. In both studies serotesting before vaccination proved to be the least costly strategy, as we found. For the health-care payer, the cost-effectiveness ratios per varicella case prevented in our study are in agreement with those reported in these two studies. However, when work-loss costs are added to medical costs, vaccination versus no intervention was found to be cost-saving by Smith and Roberts [16] but not by Lieu et al. [13]. The present cost-effectiveness analysis of routine varicella vaccination in adults, the first to be conducted in Europe, includes detailed estimates of the age-specific force of varicella infection, hospitalisation and death rates for non-immune individuals obtained on a nation wide level, based on an age-structured mathematical model. We made non conservative assumptions regarding testing and vaccination strategies in the baseline analysis, in contrast to the authors cited above, particularly as regards compliance with vaccination and vaccine efficacy [13,16]. The "worst case" hypothesis may be helpful for policy makers, as it indicates the situation which would be least favourable if the vaccination strategy were implemented, although it is improbable that all uncertain parameters would be so pessimistic at the same time.

The following are several examples of benchmarks against which to measure the cost-effectiveness ratio, in terms of the direct medical cost of routine varicella vaccination in 15-year-old subjects (€55,100 ≈ US$ 50,700 per year of life saved): US$ 54,500 per year of life saved for universal hepatitis B virus vaccination in the general American adult population, US$ 32,700 per year of life saved by thrombolytic therapy with tissue plasminogen activator versus streptokinase for acute myocardial infarction, US$ 20,000 per year of life saved by medical therapy versus no therapy for severe hypertension, US$ 35,000 per year of life saved by hemodialysis versus no dialysis for chronic renal failure, or US$ 19,000 per year of life saved for the median medical intervention cost in 1995 [32–34]. The upper limit of an acceptable cost-effectiveness ratio remains controversial, but values of more than US$ 100,000 per year of life saved are generally considered very high [34].

This study has several limitations. As in previous studies, we made the simplifying assumption that vaccination confers lifelong immunity [29]. It is possible that immunity could wane over time. However, the persistence of immunity for more than 20 years after vaccination has been demonstrated [35]. As in previous studies, our screening for vaccination was based primarily on a negative or uncertain history of varicella. The age-specific reliability of this parameter has not yet been determined. In 18–21-year-old American trainees, the positive predictive value of a history of varicella was found to be 98.5%, whereas the negative predictive value was 23.0% [36]. When calculated with our decision analysis model for 20-year-old subjects, the results were almost identical, 97.7 and 24.6%, respectively. In our analyses, we did not include the potential impact of vaccination on the incidence of herpes zoster. Vaccinated adults may have a lower rate of zoster than unvaccinated adults [14]. Therefore, vaccination strategies would be even more cost-effective if they prevented herpes zoster or reduced its risk or severity. Similarly, we also did not include any assumptions regarding the beneficial effects of vaccination on the congenital varicella syndrome [29]. An important problem concerning vaccination of older adolescents and adults is the difficulty of implementation, although high coverage of these age groups has proven feasible in France, where 80% of 16–20-year olds were vaccinated against hepatitis B in 1997. The reaction of physicians to the recommendation for routine varicella vaccination is also difficult to predict [37].

The one-way sensitivity analysis showed that our findings were robust with respect to variation in all model parameters including only direct costs, but this was not the case when including total costs. Societal cost of illness is a controversial area. We measured the opportunity cost of time as the average wage among persons in the labour force. This may not adequately reflect the value of time for persons engaged primarily in leisure—such as retired persons—or in activities for which they are not compensated—such as household activities. Therefore, including all time lost from work in the calculation could overestimate illness costs and cost savings due to vaccination. The impact of varying this parameter was tested in the sensitivity analysis. This showed that when the lower end values of varicella total costs were included in the model, the average net saving obtained with the strategy “Ab test, Vax negative” in a 15-year-old person disappeared when compared with no intervention.

The side effects of varicella vaccine must also be considered in the informed decision making process. Postlicensure safety surveillance for varicella vaccine shows that serious risks are rare when the vaccine is appropriately used, and that for most of the serious events reported, a vaccine aetiology could not be confirmed [38,39]. Although healthy vaccinated persons have minimal risk of transmitting a vaccine virus to their contacts, this risk may be higher when a varicella-like rash develops after vaccination [14]. In clinical trials, a non-localised rash developed in 3.8% of children and 5.5% of adolescents and adults (median: five lesions) after the first injection, and 0.9% of adolescents and adults after the second injection [14].

In summary, although routine childhood immunisation for varicella remains the most effective and cost-effective strategy [24], targeted vaccination of non-immune adolescents and adults could still reduce the current medical and financial burden of varicella in countries where no routine childhood immunisation is implemented. We found that routine varicella vaccination of adolescents and adults aged up to 25 years increases health benefits at a cost comparable to those of other expensive therapies routinely considered worthwhile. From a societal perspective, such vaccination is likely to be cost saving.

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