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Immunity to chickenpox among school adolescents in Lebanon and options for vaccination

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SUMMARY

Varicella infections cause substantial morbidity and mortality in adolescents and adults. The primary infection, chickenpox, results in lifelong immunity to chickenpox. A seroprevalence study carried on adolescents 15–18 years of age attending schools in Lebanon showed 96·6% immunity to varicella. The positive predictive value for immunity to chickenpox based on history alone was 97·4%, whereas the negative predictive value was 4·5%. Coming from a bigger family was a statistically significant predictor of immunity to chickenpox. In a developing country like Lebanon the merits and limitations of implementing universal varicella vaccination is discussed in relation to seroprevalence and socioeconomic factors.

INTRODUCTION

Varicella infections are an important source of morbidity and mortality in young adults [1]. It is a highly contagious disease caused by the varicella zoster virus (VZV). Chickenpox, the primary infection, is a self-limiting illness that produces long-lasting immunity. After the primary infection, VZV remains dormant in sensory nerve ganglia and may be reactivated at a later time causing herpes zoster. Chickenpox tends to be a moderate disease in childhood but may lead to significant complications especially in young adults [2]. These may include encephalitis, pneumonia, and even death. The risk of such complications increases after 15 years of age and is particularly high in those aged 20 years and above [1, 2] with a fatality rate up to 50 per 100 000 adults (25 times the childhood fatality rate) [3].

In temperate climates most people acquire the infection during childhood. Susceptibility to varicella in the United States is 34% for children aged 4–5 years, 18% for children aged 6–10 years, 6% for individuals aged 11–19 years, and only 4% for those aged 20–29 years [4]. Similar studies in Spain showed that antibody prevalence to varicella virus increases gradually with age from 20% at 1 year to 100% at 15 years [5]. In tropical areas, the incidence is lower among children and much higher among adolescents and adults [6]. Surveys carried out in Singapore and India revealed low herd immunity and higher susceptibility of the young adult population to varicella (42·8 and 68·2% respectively) compared to those in temperate climates [7, 8]. Likewise, Somali adult refugees in the United States were found to be highly susceptible to varicella [9]. Lebanon has a sub-tropical climate and no large-scale studies have been conducted to determine the true prevalence of varicella. It is believed that most people are immune by early adulthood [10]. The recent availability and licensing of the varicella vaccine in the country has prompted the need for larger, more representative seroprevalence studies in order to plan future immunization policy.

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The purpose of this study was to evaluate antibody prevalence to the varicella virus among Lebanese adolescents (15–18 years) attending school, to assess socioeconomic and demographic factors affecting rates of infection and to evaluate different vaccination strategies for Lebanon.

MATERIALS AND METHODS

Study sample

The target population was adolescents between 15 and 18 years of age attending schools in Lebanon. The study population was more than 85000 high school students enrolled in 575 public and private schools listed under the Ministry of Education in 1997–8 [11]. The study sample size was estimated at 1000 high school students with an 80% study power and a 5% chance error. A random sample of 30 high schools, stratified by the number of students, was selected from the national list of high schools [11].

School directors were approached for approval. The study objectives and protocol were explained to them in a letter, followed by a phone call and a personal visit. Letters of support for the study from the Ministries of Education and Public Health were sent to the directors encouraging them to participate. Upon the school director's approval, a random sample of 80 students (or all students if the total number was 80 or less) was selected from the list of students in the top three classes in each school, regardless of the size of student body. The next school on the national list replaced uncooperative or inaccessible schools.

Data collection

Each student received a questionnaire to be completed by the parents at home. A cover letter introduced the study and assured confidentiality. Parents were asked to sign whether they permitted or not the drawing of blood from their children at school and were encouraged to complete the questionnaire even if they did not consent to blood sampling. The questionnaire (available upon request) inquired about the education and occupation of both parents, place of residence, history of immunization of students and their personal medical history. These questionnaires were collected in a follow-up visit to the school during which blood was drawn from those whose parents consented. Students not feeling well, those who refused to give blood or were absent were excluded. Trained medical laboratory technicians drew a sample of 5 cc of blood from the antecubital vein using vacutainers and sterile needles. Blood tubes were kept in an icebox and transferred to the serology laboratory at the American University of Beirut Medical Center. Blood was centrifuged and sera were kept in refrigerators at 4 °C until analysis. Sera were analysed and tested for VZV IgG using ELISA (Clarks Laboratories, inc. immunodiagnostics, Jamestown, NY). Data collection started in October 1999 and ended in June 2000. Information was entered and double-checked for errors and inconsistencies.

A total of 155 randomly selected parents were asked to identify the picture of chickenpox skin eruption out of the coloured pictures of six different diseases (measles, mumps, rubella, viral exanthema and rheumatic fever). The aim was to assess the ability of parents to recognize chickenpox rash, in comparison to other childhood disease.

The University Research Board approved the study and the Institutional Review Board cleared it ethically.

Data analysis

Statistical analysis included determining the prevalence of immunity (IgG positive) to varicella, the characteristics of the non-immune adolescents, and the accuracy of the parents reporting of a history of chickenpox in their children. Using presence of varicella IgG antibodies as the gold standard for immunity, the sensitivity [true positive/(true positive + false negative)], specificity [true negative/(true negative + false positive)], positive predictive value [true positive/(true positive + false positive)], negative predictive value [true negative/(true negative + false negative)], and accuracy [(true positive + true negative)/all tested] of reporting of chickenpox were computed.

SPSS for windows was used for data entry and analysis. Student's *t*-test was used to measure the statistical significance for continuous variables while χ^2 analysis was used for categorical variables. Logistic regression analyses were performed to adjust for multiple variables. Missing data were not replaced; instead, a 'missing' value was added for variables where the number of missing data was high. Statistical significance was set at a P value of 0·05.

RESULTS

School and parents' response participation

Thirty schools (12 public and 18 private) were approached. This ratio of public to private was the same

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Table 1. *Characteristics of students tested for varicella IgG. Child and family characteristics*

	Varicella test		
	IgG positive No. (row %)	IgG negative No. (row %)	Total No. (column %)
Child and family characteristics	754 (96·7)	26 (3·3)	780 (100)
School category			
Private	279 (96·5)	10 (3·5)	289 (37·1)
Public	475 (96·7)	16 (3·3)	491 (62·9)
Gender			
Male	285 (97·5)	8 (2·7)	293 (37·6)
Female	469 (96·3)	18 (3·7)	487 (62·4)
District			
Greater Beirut	138 (95·2)	7 (4·8)	145 (18·6)
Mount Lebanon	164 (96·5)	6 (3·5)	170 (21·8)
Bekaa	172 (96·1)	7 (3·9)	179 (22·9)
North	166 (98·2)	3 (1·8)	169 (21·7)
South	114 (97·4)	3 (2·6)	117 (15·0)
Current chronic disease*			
Yes	80 (96·4)	3 (3·6)	83 (10·6)
No	656 (97·0)	20 (3·0)	676 (86·7)
Missing	18 (85·7)	3 (14·3)	21 (2·7)

* $P<0·05$.

as for all schools in the country (2 : 3). All public schools ($n=12$) and 11 out of the 18 private schools were cooperative. One of the private schools was not accessible for security reasons (located in an occupied territory), another was relocated, and 5 refused to cooperate. Seven new private schools were approached. Of those, 4 were cooperative, 2 were not accessible, and 1 refused to cooperate. The final sample of schools included 12 public and 15 private for a total of 27 schools distributed over the different regions of Lebanon.

A total of 1957 questionnaires were distributed to eligible students: 930 in public schools and 1027 in private schools. The number of questionnaires returned was 978 (50%): 579 (59%) from public and 399 (41%) from private. Of these, 835 parents (85%) consented to blood drawing from their children: 491 from public and 289 from private. Out of those whose parents consented only 780 were available for blood withdrawal while the rest were either absent from school or refused.

Logistic regression analysis showed that consent to blood sampling was statistically significantly associated ($P<0·05$) with each of the following: public schooling, male gender, presence of a chronic disease, mother's education, and geographic district. Consent, however, was not associated with a history or severity of chickenpox among the children.

History of chickenpox

A total of 584 out of 978 parents (59%) reported that their children had had chickenpox; 50% of these children had chickenpox by age 5 and 75% by age 8. The mean age of the chickenpox attack was 68·2 months (S.D. 35·7). In two-thirds of the cases, a physician diagnosed chickenpox. In the remaining third, the parents relied on themselves, a family member or a relative. The contact source of the infection was not known in half of the cases. Of the 584 cases, 50 (8·6%) reported complications of which 90% were dermatological, while only 4 cases (0·7%) required hospitalization for an average of 4·5 days (S.D. 4·0).

In contrast to the parents' report, 754 out of the 780 students who gave blood (96·7%) were immune to chickenpox. Only 26 students (3·3%) had negative varicella zoster IgG antibodies. This difference was observed, although only 87·7% out of the 155 parents who were asked correctly identified the picture of chickenpox.

Immune versus non-immune students

Tables 1–3 show no statistically significant differences between IgG-positive and IgG-negative students regarding age, gender, district, parents' occupation and

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Table 2. *Family characteristics of students tested for Varicella IgG*

	Varicella test		
	IgG positive No. (row %)	IgG negative No. (row %)	Total No. (column %)
Father's occupation			
White collar	294 (96·1)	12 (3·9)	306 (39·2)
Blue collar	245 (97·2)	7 (2·8)	252 (32·3)
Missing	215 (96·8)	7 (3·2)	222 (28·5)
Father's education			
At least high school	305 (96·8)	10 (3·2)	315 (40·4)
Lower than high school	429 (97·2)	16 (3·6)	445 (57·1)
Missing	20 (100·0)	—	20 (2·6)
Mother's occupation*			
Working	135 (99·3)	1 (0·7)	135 (17·4)
Housewife	618 (96·1)	25 (3·9)	445 (57·1)
Missing	1 (100·0)	26 (3·3)	1 (0·1)
Mother's education			
At least high school	317 (96·4)	12 (3·6)	329 (42·2)
Lower than high school	413 (96·9)	13 (3·1)	426 (54·6)
Missing	24 (96·0)	1 (4·1)	25 (3·2)
Number of household members†			
Mean (standard deviation)	6·30 (1·78)	5·42 (1·39)†	6·16 (1·76)
Number of rooms†			
Mean (standard deviation)	4·61 (1·49)	3·92 (1·67)†	4·60 (1·49)

* 4 mothers dead; † $P<0·05$.

Table 3. *Characteristics of students tested for Varicella IgG. History of chickenpox as a child*

	Varicella test		
	IgG positive No. (row %)	IgG negative No. (row %)	Total No. (column %)
Ever had chickenpox			
Yes	451 (97·4)	12 (2·6)	463 (59·4)
No	299 (95·5)	14 (4·4)	313 (40·1)
Missing	4 (100·0)	—	4 (0·5)
Hospitalized because of chickenpox			
Yes	2 (100·0)	—	2 (0·4)
No	449 (97·4)	12 (2·6)	461 (99·6)
Any complications due to chickenpox			
Yes	42 (97·7)	1 (2·3)	43 (9·3)
No	405 (97·4)	11 (2·6)	416 (89·8)
Missing	4 (100·0)	—	4 (0·9)
Hospitalization due to complications			
Yes	1 (100·0)	—	1 (2·3)
No	41 (97·6)	1 (2·4)	42 (97·7)
Age in years			
Mean (standard deviation)	16·52 (0·96)	16·69 (0·93)	16·53 (0·96)

* $P<0·05$.

parents' education. Students with IgG-negative sera, however, came from smaller families ($P<0·01$) and homes with a smaller number of rooms ($P<0·02$). Logistic regression analysis revealed that lack of immunity (IgG-negative test) was associated with smaller families (OR 1·42 [95% CI 1·06–1·90], $P<0.02$) and homes with a smaller number of rooms (OR 1·37 [95% CI 1·02–1·83], $P<0·04$).

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Table 4. *Immunity to chickenpox in relation to clinical history*

History of varicella	Serology					
	Positive		Negative		Total	
	No.	% row	No.	% row	No.	% column
Positive	451	97·4	12	2·6	463	59·6
Negative	299	95·5	14	4·4	313	40·4
Total	750	96·6	26	3·4	776	100·0

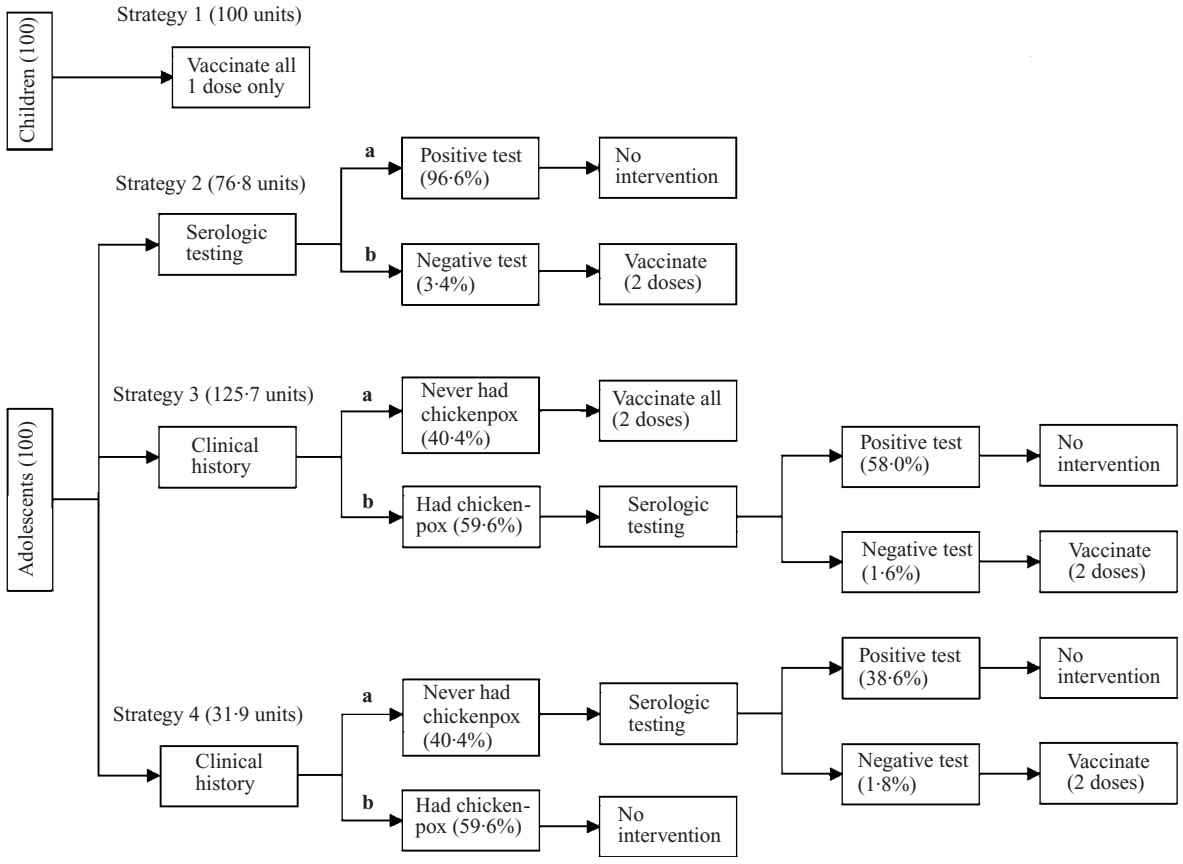

Fig. 1. Algorithm of various vaccination strategies suggested

Accuracy of reporting history of chickenpox

A history of chickenpox and the results of the blood test (varicella IgG) were concurrently available for 776 children. Of the 776 who tested positive, only 58% ($n=451$) were reported to have had chickenpox by their parents. Of the 26 who tested negative, 46% ($n=12$) were reported to have had a history of chickenpox (Table 4). Asking parents about the occurrence of chickenpox in their children had 60% sensitivity, 54% specificity and 60% accuracy. Variables enhancing the accuracy of reporting a history of chickenpox increased among parents of female students, those with higher education, those whose fathers had a white-collar job, whose mothers worked outside the house or whose families resided in the capital and its suburbs (Greater Beirut Region).

Vaccination approach model

Based on the results of this study various decision scenarios were constructed to outline alternative policies and project possible outcomes for varicella vaccination. They may serve as potential models for future plans related to varicella vaccination (Fig. 1).

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The cost assessment included the price of the serological test and the vaccine. The cost of vaccine administration was not included. Cost of medical visits also was not included, as inquiries about varicella history occur during routine visits for non-related matters, and follow-up services do not require direct physician involvement [12].

Each strategy was evaluated based on a group of 100 individuals for the convenience of calculation and analysis. Total charges were calculated in units, in order to avoid fluctuations and discrepancies in currency exchange rates. The vaccine retail fee was considered as one unit and the charge of serological testing for varicella was calculated relative to the cost of the vaccine. The cost of the serological test (including laboratory material used) was derived from the median cost of the ten busiest laboratories in the country, which turned out to be equivalent to 0·7 units.

Strategy 1. Vaccination of all children as recommended by the Advisory Committee on Immunization Practices (ACIP) [13] (estimated cost per 100 children = 100 × 1 unit).

Strategy 2. Testing all adolescents age between 15 and 18 years for varicella IgG. Children are assumed not to have received any testing or vaccination in childhood. Those with positive tests would receive no further intervention (2a). Those with negative tests would be notified to receive two doses of the varicella vaccine (2b) [13] (approximate cost per 100 = 2a + 2b = 100 × 0·7 + 3·4 × 2 = 76·8 units).

Strategy 3. Obtaining history of prior varicella infection from adolescents or their parents. Those with negative or unsure history will be immunized with two doses (3a). Meanwhile individuals with positive history will be tested and two doses of the vaccine will be administered only to those with negative serology (3b) (approximate cost per 100 = 3a + 3b = [40·4 × 2] + [59·6 × 0·7 + 1·6 × 2] = 125·7 units).

Strategy 4. Obtaining history of prior varicella infection from adolescents or their parents. Those with negative or unsure history will be tested and immunized accordingly (3a) while those admitting positive history will receive no further intervention (3b) (estimated cost per 100 = 4a + 4b = [40·4 × 0·7 + 1·8 × 2] = 31·5 units).

DISCUSSION

Our target population was adolescents and young adults who are at high risk of acquiring severe disease if they contract the primary infection. It is representative of the age groups of the Lebanese population; however, it does not include out-of-school children who may have different prevalence of disease for socioeconomic reasons.

The low response rate is consistent with the literature. Determinants of willingnesss to participate in medical research vary and could be affected by several factors: having a relative or friend who have an illness, being middle-aged, prior experience with participation in a medical research study, and favourable attitude toward use of human subjects in medical research [14]. Another important contributing factor was the length of the questionnaire (three pages) [15]. The remarkably low response rate in private schools may reflect an attitude issue towards medical surveys, which is an area that should be looked into.

Despite the low response in both public and private, bias resulting from this difference is unlikely to affect our results. Results revealed 96·6% immunity to varicella in the study population. One previous small-scale study reported 97% immunity in a selected group of Lebanese nurses in 1986 [10]. This finding was similar to figures obtained from countries with temperate climates where immunity to chickenpox ranged between 85 and 98% by the age of 10 [16, 17] and reached 100% by 15 years of age [5].

Most of the participants had acquired chickenpox by the age of 8, a finding previously reported in countries with a similar climate to Lebanon [18]. The complication rate was 8·6%, with skin-related problems being the most common, as reported by others [19]. Hospitalization rate due to varicella was 0·4%, as compared to Whartson et al. who reported rates ranging between 0·27 and 0·43% [20].

Most demographic variables did not help predict varicella antibody status, except for a lower immunity in those who grow up in households with smaller families ($P < 0·001$). This finding is consistent with the decreased risk of exposure during childhood for those with few or no siblings [21]. Although children from lower socioeconomic strata schools were relatively more represented in the study, bias from this disparity is unlikely because IgG positive rates did not differ between the two socioeconomic groups.

Reporting a history of chickenpox was helpful. The PPV for immunity to chickenpox with a positive history was 97·4%, whereas the negative predictive value was 4·5%. The high PPV for a history of chickenpox has also been noted by Struewing et al. [22] who reported a PPV of more than 95%. In our study, 12 students out of 26 seronegative (46·1%) reported

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having had the disease. Unless immunization is universal or serological screening is mandatory, this group may be missed and will be difficult to identify if clinical history was the only screening tool. More confusing are those who gave negative history but were serologically immune. Of this group, 299 out of 313 (95·58%) had positive serology, and only 14 (4·4%) were negative. Thus most with a negative history are immune. This finding is in agreement with previous reports where 71–93% of adults who did not have a reliable or negative history were immune [23–25].

The high percentage of parents familiar with chickenpox rash was not compatible with the sizable number of parents reporting erroneous histories in their children. We tend to attribute this to failure of recall due to the length of time since their child acquired the disease, and not to a subclinical form of the disease which is rare in chickenpox. When obtaining history of chickenpox, it is important to know the number of siblings and family members, as well as the parental level of education, socioeconomic status, and place of residence. Henninger et al. found that only the number of siblings influenced the presence of antibodies whereas place of residence and parental education did not [21].

Several alternative approaches are suggested to help determine the relative cost effectiveness of various vaccination strategies. Vaccinating all children is a good option if eradication is desired but would entail a prohibitively high cost for a developing country like Lebanon. According to Lieu et al., mass vaccination was the most effective strategy in children, while serological testing prior to vaccination in adolescents was found to be more economically reasonable [25]. In the current study, on economic factors alone, the best immunization strategy favoured the history-based approach, where adolescents are screened for history of disease and those with negative or unsure chickenpox history are vaccinated. Based on this study and data from countries with similar climatic conditions, the best age for screening by history is 8–9 years [18]. Studies from the United States showed that in young adults a positive varicella history accurately predicted immunity, but verification of a negative history with antibody testing was recommended before vaccination. This strategy will miss those with erroneous positive histories, but the small number of those who would be missed would be protected by an ever-growing herd immunity [26]. Serological screening for all and vaccinating the non-immune would seem a reasonable second option if policy makers are willing to tolerate a slightly higher cost for a small increase in the number of cases prevented or if the test can be obtained at a cost lower than the current price. Studies from the United States showed that testing prior to vaccination saved 38% of the cost of routinely vaccinating all children [12].

Pursuing a cost-effective module regarding varicella vaccination has many shortcomings and may underrepresent many factors. The costing is roughly estimated and many charges are not accounted for, e.g. indirect cost resulting from loss of work days by parents, price of over-the-counter medications given to children, the side effects of the vaccine, management of breakthrough illness and hospitalization charges. Thus, results should be interpreted with caution.

It is important to remember that developing countries have different health perspectives in comparison to developed nations. Decision-making depends largely on urgent health priorities and the ability to cope. Recommendations and guidelines originating from industrialized countries related to implementation of new vaccines should not be blindly accepted, because of dissimilarities in epidemiology [11]. The cost effectiveness of immunizing all children in the United States was based not only on health outcomes, but on social and economic factors also. These cost-effectiveness studies took into consideration lost worktime and other socioeconomic aspects [18, 23]. Our study showed, in accordance with the national data [27], that the percentage of working women in Lebanon does not exceed 17·4%. This percentage is significantly lower than that in the United States where women constitute a higher percentage of the working labour force reaching up to 46% [28]. The low rate of hospitalization encountered in the study population is supported by even lower incidence of serious complications in countries with similar epidemiology [29]. Meanwhile, a recent report from the England and Wales re-emphasized the seriousness of chickenpox and the increasing incidence of adult death in their population compared to other classical childhood diseases [30].

In Lebanon, despite scarcity of studies, local projects showed under-immunization in some remote areas in the country. Follow-up vaccination rates were only 61·7% for oral polio vaccine, and 49·5% for measles in children less than 1 year of age [31]. Besides under-immunization, the recent licensing of the varicella vaccine in Lebanon has led to sporadic vaccination of those who can afford it (private sector), leaving those who are economically unprivileged and

depend on governmental facilities for immunization, unprotected. Thus, fractional vaccination uptake, with disproportionate levels of coverage in different areas, will place an unacceptable number of older children at risk of complications from varicella [32, 33]. This assertion is further supported by reports from the United States showing that being covered by private insurance plan was one of the predictors for varicella vaccine administration by physicians [34].

From the public point of view the clamour for protection against varicella is not exciting because the danger is not sufficient to satisfy such an intervention [35] and preferences for vaccination are to be accounted for. Chickenpox disease is considered as a natural rite of passage and a 'must' that children should go through [36]. Add to that the emergence of recent reports of latent complications associated with some vaccines, has made the population at large more hesitant to accept newer vaccines [37, 38].

From the clinicians' perspective, there is no rush to implement varicella vaccination in childhood, since concerns regarding vaccine efficacy, duration of vaccine immunity, as well as subsequent changes in epidemiology are awaiting further clarification. In the United States, there is still some evidence of poor adherence to varicella vaccination, and about one-third of pediatricians are not recommending the varicella vaccine currently, with vaccination coverage below the expected levels in many states [39]. Although studies have established the cost effectiveness of the varicella immunization programme, most projected varicella-related costs were not due to medical care but rather to carers' missed workdays [40–43]. Some physicians feel this is not a justifiable reason for immunization.

Public health officials on the other hand, favour giving all children a uniform basket of subsidized vaccinations, and 'not encouraging well-off parents to give their offspring shots that poor families cannot afford' [44].

Lebanon has not yet been declared as polio free despite active surveillance and immunization efforts by the government and the related UN agencies, and is currently instigating the anti-measles campaign. Committing the limited resources of the public health system to embark on another crusade to eradicate a relatively benign childhood disease, such as varicella, is at present a low health priority. Any future policy should take into consideration the following: prevalence of the disease, rate of complications, incidence of hospitalization, efficacy of the vaccine and its long term protection, effect on zoster in later life, cost effectiveness in relation to the anatomy of the society and its economical outlook, the health care system and medical insurance coverage, public enthusiasm and acceptance, compliance and rate of follow-up, parental accuracy of disease recognition, and the ability of the system for appropriate handling, storing and administering the vaccine. A recent study from United States has raised concern about adequate preservation of vaccine material in private practice and adherence to recommendations, a crucial issue anywhere and even more so in developing countries [45].

Whatever immunization strategy the policy makers wish to adopt, they should first establish a clear goal for their programme [26]. We hope that the current study and implementing similar large-scale epidemiological surveys will help establish an appropriate strategy that will best achieve their goal.

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