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INVESTIGATIVE REPORT

Bacterial Skin Infections in Children Hospitalized with Varicella: A Possible Negative Impact of Non-steroidal Anti-inflammatory Drugs?

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This 1-year multicentre prospective study in northern France sought to evaluate the incidence of secondary bacterial skin complications related to varicella, describe these superinfections, and analyse risk factors for their onset. The study included every child admitted to a district paediatric unit with a varicella infection. Patients with varicella infection, with and without secondary bacterial skin complication, were compared. The study included 159 children, 43 of whom had a secondary bacterial skin complication on admission, 21 of them had a severe secondary bacterial skin complication (respective incidence: 7.5 and 3.7/100,000 children younger than 16 years old). Persistence or recurrence of fever ≥38.5ºC for ≥3 days after the beginning of varicella infection (adjusted odds ratio (aOR)=8.1; 95% confidence interval (CI): 2.3–28.4) and the use of non-steroidal anti-inflammatory drugs (aOR=4.8; 95%CI: 1.6–14.4) were independent factors associated with severe secondary bacterial skin complication. ***Key words: varicella; bacterial skin infection; hospitalization; children.***

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Varicella, a childhood disease affecting those younger than 20 years in 95% of cases (1), is generally relatively mild and common, but complications, sometimes quite severe, occur in 2–3% of cases (2–4), usually in healthy children. The hospitalization incidence rate in children before the vaccination era was estimated at 2.6–28/100,000 and varied according to age group (5–9). The reported death rate (all ages) then ranged from 1/33,000 to 1/40,000 (10, 11). Varicella thus has significant individual as well as collective consequences: high medical costs and parental work-days missed account for most of the sizable financial burden of this disease (12, 13).

Severe bacterial skin complications, mainly due to group A Streptococcus (GAS) and *Staphylococcus aureus* (*S. aureus*), have appeared more frequently in recent years. We showed previously (9), and others have confirmed (14), that the leading reason for hospitalization of children with varicella is a skin superinfection. Treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) are thought to play a role in the severity of these infections (15, 16).

The aims of this prospective multicentre study were to determine the incidence rate of hospitalization for patients with secondary bacterial skin complication related to varicella, to describe these superinfections and to identify their characteristics and potential risk factors.

PATIENTS AND METHODS

Study design and inclusion criteria

This study used data from our prospective multicentre cohort study, conducted in northern France in 2003, in the pre-varicella vaccine era. All 11 district hospitals with paediatric units participated in this study. The study included all children younger than 16 years admitted with a varicella infection during the study period. Children were included at any stage of the rash, from the vesicular stage to the end-stage of the scabs, or for any varicella-related event within 4 weeks of disease onset. Diagnosis was based on physical examination, as usual in daily practice. Children admitted more than once for any varicella-related events were not considered as new cases, but the new outcome data were added to the initial questionnaire form.

A paediatrician prospectively completed a standardized case report form when a patient with varicella met the inclusion criteria. Data collection was non-nominative. One paediatrician in each centre was the local co-ordinating investigator for the Inter-Hospital Network for Evaluating Management of Common Childhood Diseases. This co-ordinating investigator ensured that the case report forms were properly completed, validated each inclusion, and transmitted the completed case report forms to the principal investigators.

Definitions

Varicella infection was defined as a generalized pruritic vesicular rash, usually with mild fever and systemic symptoms, followed 5–6 days later by crusting of the vesicles, with shedding of the scabs in about 14 days (17). Consensual definitions of secondary bacterial skin complications came from textbooks and dictionaries (Table I). Thus, cellulitis, necrotizing fasciitis, staphylococcal or streptococcal toxin-mediated disease, skin abscess, ecthyma and varicella gangrenosa were all considered severe bacterial skin complications.

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Data collection

Of the questions on the case report form, 81% required simple yes/no answers. The form asked about demographic data, suspected or identified risk factors for severe or complicated varicella infection (asthma, eczema, immunosuppressive disease or treatment, recent cases of varicella in the family) (15, 18, 19) and clinical features (fever, extent of rash, mucosal involvement and suspected complications). Attending physicians determined whether microbiological analyses were necessary for patients with suspected bacterial superinfection. Before the study began, each local co-ordinating investigator received an information guide that described the study objectives, recent data on varicella-zoster virus epidemiology, and definitions of varicella and its secondary bacterial skin complications. This guide was designed to ensure that all study centres and paediatricians used the same diagnostic criteria and reported data consistently. Principal investigators contacted local co-ordinating investigators by telephone every 2–3 weeks to monitor study progress. Epi–Data 2.1b software (Epidata Association, Odense, Denmark) was used for anonymized data entry, with a check-in control. At the end of the study, the data were compared with each hospital's discharge codes to assess the efficacy of case ascertainment. The ethics committee declared that its specific approval was not required since the study protocol did not include any investigation or treatment other than standard care.

Analysis

Statistical analyses used Epi–Info 6.04 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). The analysis described all varicella-related bacterial skin complications diagnosed at admission, determined the incidence rates of admissions for varicella-related bacterial skin complications (based on demographic data from the Institut National de Statistiques et des Etudes Economiques, INSEE: www.insee.fr), and described the characteristics of the patients with skin infections and compared them with patients without skin infections using a χ^2 statistical test to compare proportions or a Wilcoxon test for means comparisons.

All subsequent analyses concentrated on risk factors for severe varicella-related bacterial skin complications, which are the major concerns of physicians. A secondary case-control study permitted comparison of these "severe" patients with other patients admitted with varicella infection. The univariate analyses used the χ^2 statistical test and Fisher's exact test and calculated odds ratios (OR) and 95% confidence intervals (CI). To avoid over-fitting, the backward stepwise multivariate logistic regression analysis included only variables significantly associated with severe secondary bacterial skin complications in the univariate analysis (p <0.05). This multivariate analysis was performed with Statview software (SAS Institute, Cary, NC, USA) to determine the independent risk factors (p <0.05) for severe varicella-related bacterial skin complications.

RESULTS

During the study year, 44 patients were identified with secondary bacterial skin complications at admission. One was subsequently excluded because the lesions were not infective. The 43 subjects represented 27% of the 159 children admitted with varicella and 46% of the 93 patients with varicella-related complications. Twenty-one of the subjects had at least one severe secondary bacterial skin complication: 15 cellulitis, 3 staphylococcal epidermolytic toxin-mediated diseases, 2 abscesses, 5 ecthymas, one varicella gangrenosa and one scarlet fever. The other 22 patients with bacterial skin complications presented impetigo (n=21) or whitlow (n=1) (Table I). Compared with discharge codes (9), the case ascertainment rate was 94%. Based on this rate, and the estimated population of children younger than 16 years in 2003 in the Nord district, the incidence rate of children admitted with varicella-related bacterial skin complications was 7.5/100,000 and of children with severe bacterial skin complications 3.7/100,000.

The mean age of the 43 patients with bacterial skin complications was 28 months (median 27 months; range 1 month–7 years), not statistically different from the 116 patients admitted without bacterial skin complications (Table II). Bacterial skin complications were more frequent in boys (72% vs. 54%, p=0.04). An underlying condition (eczema (n=8) or asthma (n=3)) was present in 21% of the 43 subjects (Table II); none had immunosuppression. Nearly half (47%) had a sibling with recent varicella infection, and 81% had a fever (≥38ºC) on admission. The vesicular rash was extensive (>100 vesicles) for 54% and none had only a mild rash (<10 vesicles). Mucosal involvement was present in 65%. Micro-organisms were identified

Table I. *Details of varicella-related bacterial skin complications at admission (43 children)*

Varicella-related bacterial skin complication	Definition	*n*
Impetigo	Superficial skin infection caused by bacteria, characterized by small pus-filled blisters that form honey-yellow crusts	21
Cellulitis	Inflammation of the soft or connective tissue with fever, swelling and tenderness	15
Ecthyma	Type of impetigo, with a deep and hard base, rounded by inflammation, followed by scarring	5
Staphylococcal epidermolytic toxin-mediated disease	Superficial blistering skin disorders caused by the epidermolytic toxins of *S. aureus*, with bullae rupture, tenderness fever and irritability	3
Abscess	Localized collection of pus in a tissue, cavity or confined area	2
Varicella gangrenosa	Deep necrotic lesions with an erythematous base	1
Whitlow	Inflamed or abscessed end of finger or toe with pus formation	1
Scarlet fever	Red rash and fever, caused by *Streptococcus pyogenes*	1
Total		49[a]

[a]Number of events, in 43 children. Two patients had both cellulitis and impetigo, 2 had impetigo and ecthyma, one had cellulitis and ecthyma, one had cellulitis and Staphylococcal epidermolytic toxin-mediated disease.

Table II. *Characteristics of patients admitted with varicella disease (n=159)*

Characteristics	Patients admitted without skin infection (*n*=116)	Patients admitted with skin infection (*n*=43)	*p**
Mean age, months (range)	24 (2–83)	28 (3–115)	0.17
Male gender, %	54	72	0.04
Underlying condition, %	20	21	0.86
Recent sibling case, %	51	47	0.70
Previous advice, %	75	91	0.03
Fever ≥38.5°C, ≥3 days, %	39	64	0.006
Vesicles >100, %	26	54	0.002
Mucous involvement, %	33	65	$<10^{-3}$
Mean length of stay, days (range)	4.1 (1–78)	4.6 (1–16)	$<10^{-3}$

*χ^2 or Wilcoxon tests.

for only 6 patients (*S. aureus* for 3 and GAS for 3). The mean length of stay for patients with bacterial skin complications was 4.6 days (median 3.5; range 1–16 days). Antibiotic and antiviral treatments were necessary in 93% and 44% of cases, respectively. No sequelae were expected at discharge and no patients died.

Further analyses concentrated on potential risk factors for severe varicella-related bacterial skin complications. In the univariate analysis (Table III), extensive vesicular rash (>100 blisters), mucous involvement, and persistence or recurrence of fever were the clinical signs associated with severe varicella-related bacterial skin complications. Extreme youth (<24 months) appeared to be protective in our population. Neither recent varicella in siblings nor underlying conditions (eczema, asthma) were associated with these complications. After multivariate analysis, only the persistence or recurrence

Table III. *Univariate analysis of risk factors for severe varicella-related bacterial skin complications (except medication)*

	Severe bacterial skin complications						
	Yes (*n*=21)		No (*n*=138)				
Variables	*n*	%	*n*	%	OR	95% CI	*p*
General data							
Age <12 months	5	25	50	36	0.6	0.2–1.8	0.26
Age <24 months	6	29	86	62	0.2	0.1–0.7	0.004
Boy	16	76	78	57	2.5	0.8–8.3	0.09
Lives in Nord district	18	86	125	91	0.6	0.1–3.1	0.36
Admission on duty	16	76	87	66	1.7	0.5–5.6	0.35
Recent sibling case	8	42	60	51	0.7	0.2–2.0	0.46
Previous advice	19	91	104	78	2.7	0.6–18	0.18
Underlying conditions							
Eczema	3	14	20	15	1.0	0.2–3.9	0.62
Asthma	2	10	7	5	1.9	0.0–11	0.35
Immunosuppression	0	0	3	2	0.0	0.0–16	0.64
Clinical data							
Fever ≥38.5 ≥3 days	17	81	54	41	6.2	1.8–24	$<10^{-3}$
Mucous lesions	12	63	51	38	2.8	0.9–8.4	0.04
Vesicles >100	12	57	37	27	3.6	1.3–10	0.005

OR: odds ratio; CI: confidence interval.

Table IV. *Univariate analysis of treatments administered before admission to patients with or without severe varicella-related bacterial skin complications*

	Severe bacterial skin complications						
	Yes (*n*=21)		No (*n*=138)				
Medication	*n*	%	*n*	%	OR	95% CI	*p*
Oral							
Paracetamol	19	91%	93	69%	4.3	0.9–28	0.04
NSAID	13	62%	39	28%	4.1	1.4–12	0.002
Aspirin	1	5%	2	1%	3.4	0.0–52	0.35
Steroids	1	5%	5	4%	1.3	0.0–13	0.58
Antibiotics	3	14%	27	20%	0.7	0.2–2.8	0.41
Antivirals	0	0%	4	3%	0.0	0.0–11	0.56
Local							
Antiseptics	21	100%	131	95%	n.c.	n.c.	0.36
Colorants	13	62%	67	49%	1.7	0.6–4.9	0.25
Powders	7	33%	37	27%	1.4	0.5–4.0	0.53
Creams	3	14%	10	7%	2.1	0.4–9.8	0.24

NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; CI: confidence interval; n.c.: not calculable.

of fever ≥38.5ºC for 3 or more days after the onset of varicella infection (adjusted OR (aOR) = 8.1; 95% CI: 2.3–28.4) independently predicted severe varicella-related bacterial skin complication.

NSAIDs and paracetamol were the medications associated with these superinfections in the univariate analysis (Table IV). After multivariate analysis, however, only NSAID use (aOR=4.8; 95%CI: 1.6–14.4) was independently associated with their onset (Table V). Children younger than 2 years of age had a significantly and independently lower risk than our overall population (Table V).

DISCUSSION

Bacterial skin complications were seen in 27% of the children hospitalized with varicella infection (and 46% of those admitted with a varicella complication), and almost half were either severe bacterial skin complications, mainly cellulitis and staphylococcal epidermolytic toxin-mediated disease. The incidence of bacterial skin complications was high (7.5/100,000 children younger than 16 years). The persistence or recurrence of fever ≥38.5ºC for 3 or more days after the beginning of varicella infection was an important sign

Table V. *Multivariate analysis of risk factors for severe varicella-related bacterial skin complications*

	Multivariate analysis		
Variables	aOR	95% CI	*p*
Age <24 months	0.2	0.05–0.5	0.001
Fever ≥38.5ºC ≥3 days	8.1	2.3–28.4	0.001
NSAID	4.8	1.6–14.4	0.005

aOR, adjusted odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

of any varicella-related bacterial skin complications. Treatments administered for varicella before admission were suspected to play a role in these infections, and NSAID intake, in particular, significantly increased the likelihood of severe bacterial skin complications (aOR=4.8; 95% CI: 1.6–14.4; p=0.005). Young age was protective among our population, probably because young infants with varicella disease without skin complication were more easily admitted because of their young age and the parents' and doctor's fear of a complication.

Bacterial skin complications are the leading reason for hospital admission of children with varicella (9). They were responsible for 73% of the infectious diseases in patients with varicella-related hospitalizations in an American study (20) and 26% of hospitalizations for varicella-related complications in a German survey (21). Our high incidence of these superinfections is probably consistent with the high attack rate of GAS disease in children with varicella infection in Canada (relative risk=58) (22), since GAS is one of the principal pathogens in skin infections.

One weakness of our study is the absence of systematic bacterial identification for patients with severe bacterial skin complications, since microbiological analyses were performed at the discretion of each attending physician. Our study was conducted in a large and populous geographic area (>2.5 million people) and recorded consecutive children hospitalized in the area with a varicella infection for one year. Selection bias seems unlikely, since the case ascertainment rate was high: comparison with discharge codes (9) showed it to be 94%. The rate of missing data for most case report form items was lower than 5%, except for recent varicella in siblings (8%) and history of atopic dermatitis or asthma (7%). Because the study design was constructed retrospectively from this prospective cohort, potential confounding factors about indications for NSAID administration may have interfered in the analysis.

Although previous reports suggest that NSAIDs play a role in varicella-related bacterial skin complications, this hypothesis remains controversial (16, 18, 23, 24). Trends, but not definite significant correlations, have been identified. Because of the small size of these studies, they lack power. In 1998, the American Academy of Pediatrics determined that insufficient data were available for a clinical decision about the use or restriction of NSAIDs in children with varicella (25). Lesko et al. (15) later showed a significant association between ibuprofen use and invasive skin or soft-tissue GAS infections, although they could not rule out a potential confounding association with paracetamol use. In another study, however, they did not confirm any association between ibuprofen use and invasive GAS infection in children with varicella, although they identified an association with persistent high fever (26). Our results reinforce the hypothesis that NSAIDs are associated with these superinfections.

Some pathophysiological mechanisms may explain the potential role of these drugs in promoting bacterial skin complications: NSAIDs can impair granulocyte function, thereby reducing leukocyte recruitment, increasing cytokine production and facilitating Staphylococcus and Streptococcus infections (27). In addition, NSAIDs may mask signs of disease progression by relieving pain, reducing swelling and suppressing fever, all of which can help delay diagnosis and treatment (25). A particular or newly virulent bacterial strain may also be involved. One report suggests that a special GAS clone may be responsible for the severe bacterial skin complications (28), whereas others suggest that clonal variations among strains of a given serotype are not related to disease severity (29, 30). Severe bacterial skin complications may be related to the virulence of superantigen exotoxins (31).

In conclusion, our study suggests that the incidence of varicella-related bacterial skin complications was high in the pre-vaccine era and that it may be preventable by reducing prescriptions for oral NSAID treatment for patients with varicella. A recent study in our district showed that NSAIDs were prescribed for patients with varicella in 14–16% of cases (32). A programme of generalized vaccination for children may reduce the incidence of varicella and thus varicella-related complications, but only if the coverage rate is sufficiently high (33). Combining this vaccine with the measles-mumps-rubella vaccine could increase the coverage rate (34). Until then, physicians must be informed, and inform their patients, that some medications, including NSAIDs, should be avoided for patients with varicella, in order to reduce the number of varicella-related bacterial skin complications.

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REFERENCES

1. Centers for Disease Control and Prevention. Evaluation of varicella reporting to the National Notificable Disease Surveillance System – United States, 1972–1997. MMWR Morb Mortal Wkly Rep 1999; 48: 55–58.
2. Deguen S, Chau NP, Flahault A. Epidemiology of chickenpox in France (1991–1995). J Epidemiol Community Health 1998; 52 Suppl 1: 46–49.

3. Yawn BP, Yawn RA, Lydick E. Community impact of childhood varicella infections. J Pediatr 1997; 130: 759–765.
4. Levrat V, Floret D. Caractéristiques cliniques des varicelles hospitalisées en réanimation pédiatrique de 1998 à 2001 en France. Bull Epidemiol Hebdom 2003; 9: 51–52.
5. Coplan P, Black S, Rojas C, Shinefield H, Ray P, Lewis E, et al. Incidence and hospitalization rates of varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease. Pediatr Infect Dis J 2001; 20: 641–645.
6. Lin F, Hadler JL. Epidemiology of primary varicella and herpes zoster hospitalizations: the pre-varicella vaccine era. J Infect Dis 2000; 181: 1897–1905.
7. Gil A, Oyaguez I, Carrasco P, Gonzalez A. Epidemiology of primary varicella hospitalizations in Spain. Vaccine 2001; 20: 295–298.
8. Boelle PY, Hanslik T. Varicella in non-immune persons: incidence, hospitalization and mortality rates. Epidemiol Infect 2002; 129: 599–606.
9. Dubos F, Hue V, Grandbastien B, the Hospital Network for Evaluating the Management of Common Childhood Diseases, Martinot A. Epidemiology of hospital admissions for paediatric varicella infections: a one-year prospective survey in the pre-vaccine era. Epidemiol Infect 2007; 135: 131–138.
10. Varughese PV. Chickenpox in Canada, 1924–87. CMAJ 1988; 138: 133–134.
11. Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970–1994. J Infect Dis 2000; 182: 383–390.
12. Saddier P, Floret D, Guess HA, Durr F, Peyrieux JC, Weber DJ, et al. Cost of varicella in France: a study in day care centers. J Infect Dis 1998; 178 Suppl 1: 58–63.
13. Law B, Fitzsimon C, Ford-Jones L, McCormick J, Riviere M. Cost of chickenpox in Canada: part II. Cost of complicated cases and total economic impact. The Immunization Monitoring Program – Active (IMPACT). Pediatrics 1999; 104: 7–14.
14. Grimprel E, Levy C, de La Rocque F, Cohen R, Soubeyrand B, Caulin E, et al. Paediatric varicella hospitalisations in France: a nationwide survey. Clin Microbiol Infect. 2007; 13: 546-549.
15. Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001; 107: 1108–1115.
16. Zerr DM, Alexander R, Duchin JS, Koutsky LA, Rubens CE. A case-control study of necrotizing fasciitis during primary varicella. Pediatrics 1999; 103: 783–790.
17. Whitley RJ. Varicella-zoster virus. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 6th edn. Philadelphia: Elsevier, Inc., 2004: p. 1780–1786.
18. Peterson CL, Vugia DJ, Meyers HB, Chao SM, Vogt J, Lanson J, et al. Risk factors for invasive group A streptococcal infections in children with varicella: a case-control study. Pediatr Infect Dis J 1996; 15: 151–156.
19. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. J Infect Dis 1985; 152: 1172–1181.
20. Aebi C, Ahmed A, Ramilo O. Bacterial complications of primary varicella in children. Clin Infect Dis 1996; 23: 698–705.
21. Ziebold C, von Kries R, Lang R, Weigl J, Schmitt HJ. Severe complications of varicella in previously healthy children in Germany: a 1-year survey. Pediatrics 2001; 108: e79.
22. Laupland KB, Davies HD, Low DE, Schwartz B, Green K, McGeer A. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group. Pediatrics 2000; 105: e60.
23. Choo PW, Donahue JG, Platt R. Ibuprofen and skin and soft tissue superinfections in children with varicella. Ann Epidemiol 1997; 7: 440–445.
24. Brogan TV, Nizet V, Waldhausen JH, Rubens CE, Clarke WR. Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients. Pediatr Infect Dis J 1995; 14: 588–594.
25. American Academy of Pediatrics. Committee on Infectious Diseases. Severe invasive group A streptococcal infections: a subject review. Pediatrics 1998; 101: 136–140.
26. Lesko SM. The safety of ibuprofen suspension in children. Int J Clin Pract Suppl 2003; 135: 50–53.
27. Stevens DL. Could nonsteroidal antiinflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome? Clin Infect Dis 1995; 21: 977–980.
28. Cockerill FR 3rd, MacDonald KL, Thompson RL, Roberson F, Kohner PC, Besser-Wiek J, et al. An outbreak of invasive group A streptococcal disease associated with high carriage rates of the invasive clone among school-aged children. JAMA 1997; 277: 38–43.
29. Chaussee MS, Liu J, Stevens DL, Ferretti JJ. Genetic and phenotypic diversity among isolates of Streptococcus pyogenes from invasive infections. J Infect Dis 1996; 173: 901–908.
30. Descheemaeker P, Van Loock F, Hauchecorne M, Vandamme P, Goossens H. Molecular characterisation of group A streptococci from invasive and non-invasive disease episodes in Belgium during 1993–1994. J Med Microbiol 2000; 49: 467–471.
31. Norrby-Teglund A, Thulin P, Gan BS, Kotb M, McGeer A, Andersson J, et al. Evidence for superantigen involvement in severe group A streptococcal tissue infections. J Infect Dis 2001; 184: 853–860.
32. Dubos F, Langlois-Meurinne HB, Hue V, Grandbastien B, Martinot A. Assessment of out-patient treatment of varicella in children. Presse Med 2004; 33: 992–996.
33. Rentier B, Gershon AA, European Working Group on Varicella. Consensus: varicella vaccination of healthy children – a challenge for Europe. Pediatr Infect Dis J 2004; 23: 379–389.
34. Coudeville L, Paree F, Lebrun T, Sailly J. The value of varicella vaccination in healthy children: costbenefit analysis of the situation in France. Vaccine 1999; 17: 142–151.