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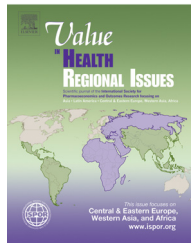

Children Hospitalized for Varicella: Complications and Cost Burden

Ozden Turel, MD[1,], Mustafa Bakir, MD[2], Ismail Gonen, MD[1,3], Nevin Hatipoglu, MD[3], Cigdem Aydogmus, MD[3], Emine Hosaf, MSc[4], Rengin Siraneci, MD[3]*

[1]*Department of Pediatrics, Bezmialem Vakif University Faculty of Medicine, Istanbul, Turkey;* [2]*Department of Pediatrics, Marmara University Faculty of Medicine, Istanbul, Turkey;* [3]*Department of Pediatrics, Bakirkoy Maternity and Children's Educational and Treatment Hospital, Istanbul, Turkey;* [4]*Department of Microbiology, Bakirkoy Maternity and Children's Educational and Treatment Hospital, Istanbul, Turkey*

ABSTRACT

Objective: To evaluate the direct medical cost of hospital admissions for patients with varicella (i.e., chickenpox) to assess the cost burden of varicella from a health care perspective for ultimate use in health economics studies in Turkey. **Methods:** Records of children hospitalized with varicella at the Bakirkoy Maternity and Children's Hospital between November of 2006 and June of 2011 were reviewed. Reasons for hospitalization, types of varicella-associated complications, and direct medical cost of hospitalization were noted. Patients with underlying risk factors were excluded. Data obtained from one hospital were used to estimate the national cost of the disease. **Results:** During the 4.5-year study period, 234 patients were hospitalized with varicella. Of these cases, 48 (20%) children previously ill with underlying cancers or chronic diseases were excluded from the study. Ultimately, 186 previously healthy children (age range: 14 days to 159 months, median age: 14 months) were included. The main reasons for hospitalization were complications related to varicella (79%), the most frequent of which was skin and soft tissue infections, followed by neurological complications and pneumonia. The median cost of hospitalization per patient was US $283, 50% of which was attributed to medication costs. The annual cost for varicella hospitalizations in Turkey was estimated at US $396,200. **Conclusions:** A significant number of healthy children are hospitalized for varicella and associated complications. Descriptions of these complications and their related costs provide important data for cost-effectiveness studies for decisions about the inclusion of the varicella vaccine in a childhood vaccination program.

Keywords: child, complications, cost, varicella.

Introduction

Varicella, otherwise known as chickenpox, that is, the primary manifestation of a varicella zoster virus (VZV) infection, is generally mild; indeed, severe complications are seldom reported in immunocompetent children [1]. Nevertheless, hospitalizations due to varicella do occur in otherwise healthy children, thereby producing an economic burden on the health care system [2]. Worldwide, the reported incidence of varicella-related hospitalizations involving children varies widely, that is, from 0.9 to 29.4/100,000, depending on the geographic setting and hospital admission policies [3–5]. In Turkey, the exact incidence is unknown because varicella is not on the list of tracked diseases; however, estimates indicate that the rate is 6.3/100,000 [6].

A safe and effective vaccine against varicella was developed in 1970 and has been made a recommended part of childhood vaccination programs in several countries. Countries with routine childhood varicella vaccinations have seen a positive effect on disease prevention and control [7–13]. In the United States, the annual varicella-related hospitalization rate decreased from 0.5 per 10,000 in 1993 to 0.13 per 10,000 in 2001. The incidence of varicella has also decreased in nonvaccinated groups, including adults and infants who are too young to be vaccinated, thereby suggesting a strong herd protection effect [7–10]. A widespread varicella vaccination program, however, has not yet been introduced everywhere, especially in developing countries.

The health economics of a VZV immunization program is vital for decisions on vaccine funding and has been studied in many countries [14–17]. To facilitate the decision-making process regarding the introduction of a vaccination program, each country needs to collect data on the incidence, complications, and cost due to hospitalizations associated with the particular disease under consideration. Surveillance of varicella complications is also important to assess the potential impact of a vaccination program. In Turkey, a few studies have evaluated complication rates; however, knowledge about the cost of varicella hospitalizations is quite limited. A more detailed investigation of the cost burden of varicella from a health care perspective can be accomplished by collecting data about the number and cost of hospitalizations in a tertiary care hospital in Istanbul, which can then be extrapolated to the whole country to estimate the national burden of this disease.

Conflict of interest: The authors report no conflict of interest.

* Address correspondence to: Ozden Turel, Department of Pediatrics, Division of Pediatric Infectious Diseases, School of Medicine, Bezmialem Vakıf University, Adnan Menderes Bulvarı Vatan caddesi 34093 Fatih, Istanbul, Turkey.

E-mail: barisbulent98@yahoo.com.

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Methods

Study Design

In this retrospective cohort study, we reviewed the records of children with varicella who were admitted to the Bakirkoy Maternity and Children's Educational and Treatment Hospital (BEH) between November of 2006 and June of 2011. In Istanbul, a majority of patients are treated at secondary and tertiary care hospitals [18]. BEH is one of the main tertiary referral centers for pediatric patients in which 40,000 patients are hospitalized and over 500,000 patients are examined annually [19]. The population of children aged younger than 15 years in Istanbul is 3,455,049, that is, one-fifth of the population under 15 in Turkey [20].

Data Collection

Enrollment in this study required a discharge diagnosis of varicella or its associated complications as defined by the *International Classification of Disease* codes. Further detailed investigations of medical records of patients hospitalized with varicella were undertaken to avoid incorrect diagnoses. Data on the demographic features of the patients, their underlying conditions, reasons for hospitalization, types of varicella-related complications, blood culture results, length of hospital stay, outcomes, and costs were collected.

Hospital expenses noted in this study included the cost of the prescribed drugs, doctor visits, nursing care, laboratory and radiological diagnostic tests, bed stay, and other related charges. The records of the patients logged hospital costs in the Turkish lira and were converted into the US dollar.

Statistical Analysis

Version 16 of the Statistical Package for Social Sciences (SPSS for Windows) was used for all statistical analyses. One-way analysis of variance was used to compare continuous data among more than two groups. Multiple comparisons were analyzed by using Tukey's honestly significant difference post hoc test, while Pearson's correlation test was used to assess the relationships among continuous variables.

Results

Of the 684 children with varicella who were examined at BEH during the study time period, 234 were hospitalized. Of these cases, 48 patients (i.e., 20%) had an underlying illness and were thus excluded from the study (Table 1). Therefore, 186 previously healthy children (i.e., 55.9% males) were included in this study. Considering that BEH provides services to 15% of all children hospitalized in Istanbul and 3% of all children hospitalized in Turkey, the annual number of formerly healthy children younger than 15 years who are hospitalized because of varicella in Turkey was estimated at 1400.

The median age of the patients with varicella in our study was 14 months (i.e., ranging from 14 days to 159 months). The highest rate of hospitalization occurred in patients younger than age 3 years (i.e., 74.15%), of which 64.2% were younger than or equal to age 1 year. The median length of hospital stay for this population was 5 days. The majority of the cases were detected in the spring and early summer months, with a peak in May (Fig. 1). The main reasons for hospitalization were complications associated with varicella (i.e., accounted for 79% of the admissions). Bacterial superinfections involving the skin and soft tissues accounted for 32.6% of the admissions and were the most frequently observed complications; this was followed by neurological complications in 29.9% of the admissions and pneumonia in 21.7% of the admissions (Table 2). The children who were hospitalized for pneumonia were younger than those hospitalized with neurological complications ($P < 0.05$) (Fig. 2). Most outcomes were favorable with exception to one child needing thoracal tube insertion to treat empyema, one with abduscent nerve paralysis, and one with cellulitis that resulted in severe scarring.

Table 1 – Varicella-related hospitalized patients with underlying illnesses.

Underlying illness	n	%
Malignancy		
Acute lymphoblastic leukemia	14	29
Lymphoma	2	4.2
Rhabdomyosarcoma	1	2.1
Spinal tumor	1	2.1
Neuroblastoma	1	2.1
PNET	1	2.1
Metabolic		
Type 1 diabetes mellitus	5	10.4
Congenital adrenal hyperplasia	2	4.2
Cystic fibrosis	1	2.1
Graves' disease	1	2.1
Niemann Pick	1	2.1
Hematologic		
Hereditary spherocytosis	2	4.2
Diamond Blackfan anemia	1	2.1
Thalassemia major	1	2.1
Thrombasthenia	1	2.1
Factor 7 deficiency	1	2.1
Chronic ITP	2	4.2
Primary immunodeficiency		
SCID	1	2.1
IgA deficiency	1	2.1
CVID	1	2.1
Cyclic neutropenia	1	2.1
Other	2	4.2
Other		
Holoprosencephaly	1	2.1
CMV hepatitis, hyperphenylalaninemia	1	2.1
Echinococcal cyst	1	2.1
Total	48	100

CMV, cytomegalovirus; CVID, common variable immunodeficiency; IgA, immunoglobulin A; ITP, idiopathic thrombocytopenic purpura; PNET, primitive neuroectodermal tumor; SCID, severe combined immunodeficiency.

The median cost of hospitalization per patient was US $283, 50% of which was attributed to medication costs (Table 3). The costs for physician visits were lowest among the cost categories listed in Table 3 because revisits are not billed in accordance with current Turkish regulations. A positive correlation was observed between the total costs and the age of the patients ($r = 0.27$, $P < 0.001$). Costs for hematological complications were higher than the costs for any of the other complications. For the five patients with the highest total costs, three had hematological complications and received blood transfusions; for the remaining two, one had septicemia and the other child had severe cellulitis that necessitated 26 days of hospitalization. The direct annual cost for otherwise healthy children hospitalized with varicella in Turkey was estimated to be US $396,200.

Discussion

Although varicella complications are believed to be rare in immunologically healthy children, related hospitalizations have

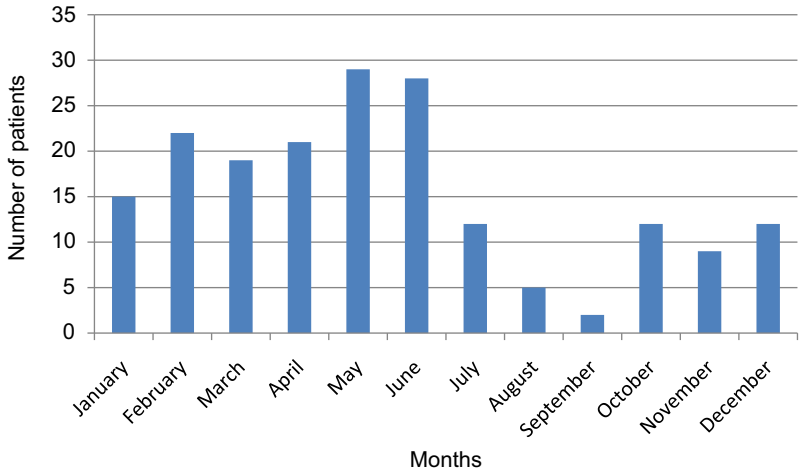

Fig. 1 – Number of hospitalized varicella cases according to months of the year.

been reported in children without any identified risk factors [2,21]. Of the 24,488 varicella-related hospitalizations during 2000-2006 in the United States, 70% were among healthy persons with no contraindications for vaccination [22]. Similarly, we noted that 80% of the children with varicella who were hospitalized during the study period at BEH had no underlying diseases. Carapetis et al. [2] reported that immunocompromised patients with varicella were admitted earlier in their illness and had lower complication rates than did otherwise healthy patients. For this reason, we conducted a detailed examination of hospitalizations for varicella only in previously healthy children. We estimated that hospitalizations due to varicella in otherwise healthy children have an incidence of 7.7/100,000. A multicenter study in Turkey also showed that 73.3% of hospitalized patients were previously healthy [23]. The estimated overall incidence was 5.29 to 6.89/100,000 in all children aged 0 to 15 years; therefore, considering that hospitalized patients constitute 1% of all cases of varicella, the overall incidence of varicella was estimated as 466 to 768/100,000 [23].

Table 2 – Reasons for hospitalization in children with varicella.

Cause	n (%)
Complications	147 (79)
Skin, mucosa and soft tissue infections	48 (25.8)
Pyoderma	25
Cellulitis	12
Abscess	5
Cervical lymphadenitis	2
Stomatitis	4
Neurologic	44 (23.7)
Cerebellar ataxia	19
Convulsion	17
Meningoencephalitis	5
Papilloedema, optic neuritis	1
Pneumonia	32 (17.2)
Other	23 (12.3)
Hematologic (thrombocytopenia)	7
Sepsis	8
Upper respiratory tract infection	4
Arthritis	2
Gastrointestinal	2
Other causes	39 (21)
Age < 2 months	21
Fever	8
Generalized skin lesions	3
Poor feeding	3
Poor general appearance	2
Total	186 (100)

The median age of children hospitalized with varicella-related complications in the United Kingdom and Ireland was reported as 3 years [5]. In our study, children hospitalized for varicella tended to be younger; indeed, 47.6% of the patients in our study were 1 year or younger. Seroprevalence studies in Turkey have shown that after the decline in maternal antibodies present in the bloodstream at birth, seropositivity rates for VZV were low until the end of the first year (i.e., 16.6%) and gradually increased to 41.2% at age 5 years [24,25]. Protection of children younger than 1 year, however, can be achieved only by increased herd immunity that is established via a widespread vaccination program because the vaccine is not recommended in children younger than 1 year.

A multicenter study in France demonstrated a strong inverse correlation between levels of circulating anti-VZV maternal antibodies in full-term infants and the occurrence of varicella complications in children who contract the disease at age younger than 1 year [26]. During the first 3 months of life, maternal antibodies against VZV protect most infants, and unless this immunity is absent, newborns with mild chickenpox should not require antiviral therapy [27]. In our study population, we identified 21 patients aged 14 days to 2 months who were hospitalized solely for varicella without any complications, and most of them received antiviral therapy. This indicates that many physicians still view the disease as a serious illness during early infancy.

The majority of varicella complications identified in our study were bacterial superinfections, which is similar to the findings of previous studies [6,21]. *Staphylococcus aureus* and group A β-hemolytic streptococci are the main pathogens responsible for bacterial complications related to varicella [28,29]. Pathogens were isolated from cultures of tissue samples in only five of our study patients (i.e., two had coagulase-negative staphylococci and one had α-hemolytic streptococci from blood cultures, whereas one had methicillin-sensitive *S. aureus* from abscess material, respectively). The low yield of microorganisms in our study is likely caused by insufficient culturing practices that must be improved in future studies and treatment of patients with varicella.

Neurological complications were the second most common complication in patients who were hospitalized for varicella in

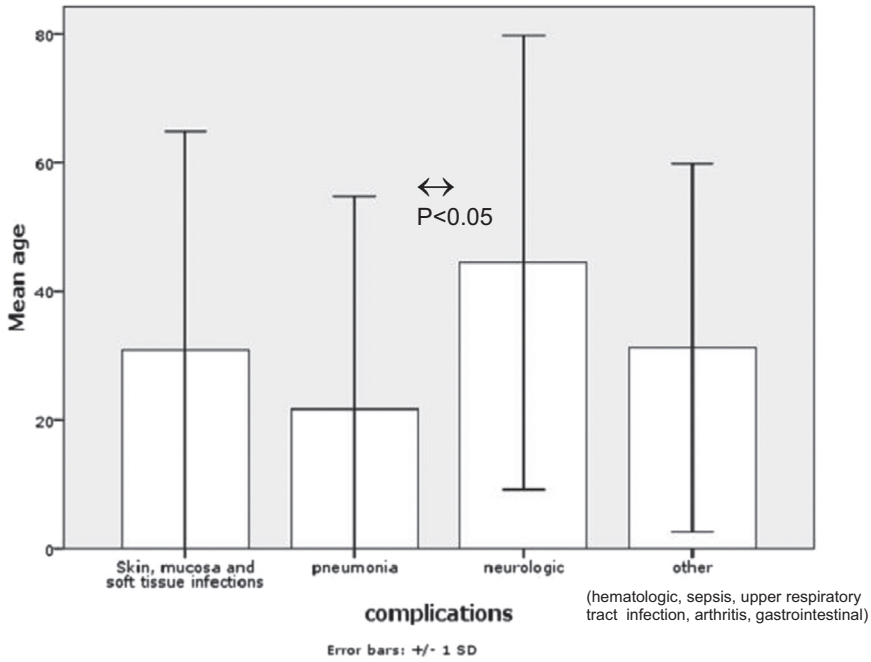

Fig. 2 – Distribution of complications according to age of the patients.

our study. Bozzola et al. [30] reported that although neurological complications did not usually result in permanent sequelae, they could lead to prolonged hospital stays and other indirect costs.

The indirect costs from absenteeism and loss of associated productivity are more important than the direct health care costs [31]. The proportion of indirect costs in the total cost of varicella was reported to range from 42% to 98% in different sudies [32]. The highest percentage reported by Lieu et al. [33] was explained by the inclusion of the cost of death or prolonged disability resulting from the disease. Only direct costs were evaluated in our study.

The costs of varicella-related hospitalizations may vary according to the epidemiologic features, management strategies of the disease, and the type of complications. Zhou et al. [17] estimated that in 2006, the direct per case medical cost of hospitalization for uncomplicated varicella, varicella pneumonia, and varicella encephalitis was US $3,317, US $4,213, and US $12,064, respectively. In Australia, the cost of hospitalization for children with varicella was reported to be US $3,272 per case in 2004 [2]. In Spain, hospitalization cost per case was US $5,113, with the total associated national cost excluding symptomatic treatment at US $516,531 [34]. We estimated the direct national cost of varicella-related hospitalizations as US $396,200 in Turkey. Differences in health service fees such as hospital and physician costs may explain why hospital care in Turkey costs less than in the United States, Australia, and Spain. For Brazil, a country with a socioeconomic background similar to that of Turkey, Valentim et al. [14] reported that the hospital cost for a case of varicella was US $439. In China, inpatient care cost was US $640 per case [35]. In previous studies, the costs of hospitalizations for varicella were significantly higher in children who had underlying diseases [15,23]. Only otherwise healthy children were included in our study.

Decisions on vaccine funding are often based on a number of variables, such as immunogenicity of the vaccine and the cost-effectiveness of the immunization program. The varicella vaccine prevents the disease in 85% of immunized children but offers a 97% protection against its most severe forms [36]. Moreover, the universal two-dose immunization has been shown to be cost-effective in Western temperate countries [37]. In Brazil, the cost-effectiveness of a universal vaccination program against varicella was dependent on the vaccine price and the required number of doses [14].

In Turkey, one dose of varicella vaccine costs US $45 and the national birth cohort is 1.2 million. As a preventive measure, a universal vaccination program will require a large investment. In this study, however, we confirmed that hospitalization in varicella cases contributes to a significant cost burden even in previously healthy children. Our estimates of costs should contribute to future cost-effectiveness research in Turkey.

Table 3 – Total hospital costs (US dollar).

Variable	Cost				
	Mean	SD	Median	Min	Max
MED	206	469	108	0	4529
PHY	7	12	4	0	91
LAB	60	80	30	0	515
NC	28	30	20	0	185
HOS	106	73	88	0	696
Total	407	552	283	15	4886

MED, medications; PHY, physicians' fees for examinations and consultations; LAB, diagnostic tests and radiological examinations; NC, nurse care; HOS: bed stay; SD, standard deviation.

Conclusions

In Turkey, a significant number of otherwise healthy children have been hospitalized because of varicella and its complications. Data gathered about hospitalization expenses provide important

knowledge for future cost-effectiveness studies. This information will, therefore, assist policymakers in decisions about whether to include the varicella vaccine in childhood vaccination programs. Rates of complications may provide significant background knowledge for evaluating the impact of vaccinations against childhood varicella.

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REFERENCES

[1] Heininger U, Seward JF. Varicella. Lancet 2006;368:1365–76.
[2] Carapetis JR, Russell DM, Curtis N. The burden and cost of hospitalized varicella and zoster in Australian children. Vaccine 2004;23:755–61.
[3] Liese JG, Grote V, Rosenfeld E, et al. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. Pediatr Infect Dis J 2008;27:119–24.
[4] Dubos F, Grandbastien B, Hue V, et al. Epidemiology of hospital admissions for pediatric varicella infections: a one-year prospective survey in the pre-vaccine era. Epidemiol Infect 2007;135:131–8.
[5] Cameron JC, Allan G, Johnston F, et al. Severe complications of chickenpox in hospitalized children in the UK and Ireland. Arch Dis Child 2007;92:1062–6.
[6] Koturoglu G, Kurugol Z, Cetin N, et al. Complications of varicella in healthy children in Izmir, Turkey. Pediatr Int 2005;47:296–9.
[7] Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. Pediatrics 2004;114:786–92.
[8] Hambleton S, Phill D, Gershon AA. The impact of varicella vaccination in the United States. Semin Pediatr Infect Dis 2005;16:38–43.
[9] Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance–United States. 1995–2005. J Infect Dis 2008;197 (Suppl. 2):S71–5.
[10] Marin M, Watson TL, Chaves SS, et al. Varicella among adults: data from an active surveillance project, 1995–2005. J Infect Dis 2008;197 (Suppl. 2):S94–100.
[11] Quian J, Rüttimann R, Romero C, et al. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997–2005. Arch Dis Child 2008;93:845–50.
[12] Cenoz MG, Catalán JC, Zamarbide FI, et al. Impact of universal vaccination against chickenpox in Navarre, 2006–2010. An Sist Sanit Navar 2011;34:193–202.
[13] Pozza F, Piovesan C, Russo F, et al. Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. Vaccine 2011;29:9480–7.
[14] Valentim J, Sartori AM, de Soárez PC, et al. Cost-effectiveness analysis of universal childhood vaccination against varicella in Brazil. Vaccine 2008;26:6281–91.
[15] Azzari C, Massai C, Poggiolesi C, et al. Cost of varicella-related hospitalizations in an Italian pediatric hospital: comparison with possible vaccination expenses. Curr Med Res Opin 2007;23:2945–54.
[16] Tseng HF, Tan HF, Chang CK. Varicella epidemiology and cost-effectiveness analysis of universal varicella vaccination program in Taiwan. Southeast Asian J Trop Med Public Health 2005;36:1450–8.
[17] Zhou F, Ortega-Sanchez IR, Guris D, et al. An economic analysis of the universal varicella vaccination program in the United States. J Infect Dis 2008;197(Suppl 2):S156–64.
[18] Istanbul Health Directorate. Istanbul health statistics 2010. Available from: http://www.istanbulsaglik.gov.tr/w/anasayfalinkler/pano3.asp. [Accessed April 10, 2013].
[19] Istanbul Health Directorate. Kanuni Sultan Süleyman Educational and Treatment Hospital. Available from: http://www.istanbulsaglik.gov.tr/w/sb/tedk/bakirkoy.asp. [Accessed April 10, 2013].
[20] Turkish Statistical Institute. Address-based population registration system. Available from: www.tuik.gov.tr/VeriTabanlari.do?vt_id=9&ust_id=5. [Accessed April 10, 2013].
[21] Grimprel E, Levy C, de La Rocque F, et al. Pediatric varicella hospitalizations in France: a nationwide survey. Clin Microbiol Infect 2007;13:546–9.
[22] Lopez AS, Zhang J, Brown C, et al. Varicella-related hospitalizations in the United States, 2000–2006: the 1-dose varicella vaccination era. Pediatrics 2011;127:238–45.
[23] Dinleyici EC, Kurugol Z, Turel O, et al. The epidemiology and economic impact of varicella-related hospitalizations in Turkey from 2008 to 2010: a nationwide survey during the pre-vaccine era (VARICOMP study). Eur J Pediatr 2012;171:817–25.
[24] Alp H, Altinkaynak S, Ertekin V, et al. Seroepidemiology of varicella-zoster virus infection in a cosmopolitan city (Erzurum) in the eastern Turkey. Health Policy 2005;72:119–24.
[25] Savas S, Dallar Y, Arikan I, et al. Varicella-zoster virus seroprevalence in children between 0-15 years old. Mikrobiyol Bul 2004;38:69–75.
[26] Pinquier D, Lécuyer A, Levy C, et al. Inverse correlation between varicella severity and level of anti-varicella zoster virus maternal antibodies in infants below one year of age. Hum Vaccin 2011;7:534–8.
[27] Lécuyer A, Levy C, Gaudelus J, et al. Hospitalization of newborns and young infants for chickenpox in France. Eur J Pediatr 2010;169:1293–7.
[28] Lesko SM, O'Brien KL, Schwartz B, et al. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;107:1108–15.
[29] Peterson CL, Mascola L, Chao SM, et al. Children hospitalized for varicella: a prevaccine review. J Pediatr 1996;129:529–36.
[30] Bozzola E, Tozzi AE, Bozzola M, et al. Neurological complications of varicella in childhood: case series and a systematic review of the literature. Vaccine 2012;30:5785–90.
[31] Preblud SR. Varicella: complications and costs. Pediatrics 1986;78:728–35.
[32] Soárez PC, Novaes HM, Sartori AM. Impact of methodology on the results of economic evaluations of varicella vaccination programs: is it important for decision-making? Cad Saude Publica 2009;25(Suppl. 3): S401–14.
[33] Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. JAMA 1994;271:375–81.
[34] Piqueras Arenas AI, Otero Reigada MC, Pérez-Tamarit D, et al. Hospitalizations for varicella in the Hospital Infantil La Fe, Valencia, Spain, 2001–2004. An Pediatr (Barc) 63:120–4.
[35] Da YP, Luo LY, Song LZ. Economic burden of inpatient of varicella in Shandong, Gansu, and Hunan provinces, 2007. Zhongguo Yi Miao He Mian Yi 2009;15:438–42.
[36] Gershon AA, Takahashi M, Seward J. Varicella vaccine. In: Plotkin SA, Orenstein WA, eds., Vaccines (4th ed.). Philadelphia: WB Saunders, 2004.
[37] Flatt A, Breuer J. Varicella vaccines. Br Med Bull 2012;103:115–27.