Chickenpox complications, incidence and financial burden in previously healthy children and those with an underlying disease in Ankara in the pre-vaccination period

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SUMMARY: Özdemir H, Çandır MO, Karbuz A, Belet N, Tapısız A, Çiftçi E, İnce E. Chickenpox complications, incidence and financial burden in previously healthy children and those with an underlying disease in Ankara in the pre-vaccination period. Turk J Pediatr 2011; 53: 614-625.

The aim of this study was to determine the complications, financial burden and mortality caused by chickenpox using the data of Ankara, Turkey in the pre-vaccination period. The study was conducted as a retrospective sectional study. Of the 65 patients admitted to our hospital, 34 (52.3%) had been previously healthy, 10 (15.4%) had previous chronic disease and 21 (32.3%) were immunocompromised. The most common complications of chickenpox in those patient groups were skin and soft tissue infections (41.2%), hematological complications (50%) and gastrointestinal complications (38.1%), respectively. We found 10.6/100,000 and 8.7/100,000 rates of hospitalization due to chickenpox in Ankara for all children and for previously healthy children, respectively. The chickenpox-related mortality rate for the 0-17 age group was 3.03/1,000,000 in Ankara. In conclusion, we feel that a national vaccination program for chickenpox will lead to a significant decrease in the overall cost to our country.

Key words: chickenpox, children, complication, financial burden, varicella-zoster virus.

Chickenpox, caused by the varicella-zoster virus, is usually a childhood disease with fever and a rash. It is usually a self-limited disease. The disease course can rarely be more severe than expected and disseminate to cause involvement of various organs and complications. It can rarely be fatal[1]. The chickenpox vaccine that is currently used but not included in the national vaccination calendar in our country decreases the risk of severe disease or death due to chickenpox by 95%[2-4]. The risk of a severe course of disease and dissemination is higher in untreated children with an underlying chronic disease or those receiving immunosuppressive treatment that leads to an immune deficiency. It is therefore important from the prognostic point of view to hospitalize immunocompromised patients at an early stage and start intravenous acyclovir treatment[1]. Vaccination of the patients to decrease the risk of severe disease and dissemination and to prevent, thanks to preventive medicine, the financial cost, morbidity and mortality caused by chickenpox is important for community health.

Chickenpox vaccination is used in many countries to eliminate the unwanted effects of chickenpox. These countries have decided that chickenpox vaccination should be included in the routine vaccination program following disease burden calculations[5]. However, there are only a few studies on the disease burden caused by chickenpox in our country. Data from our country on the subject is therefore limited. We aimed to determine the complications, financial burden and mortality caused by chickenpox using the data of the region we serve (Ankara) in the period before the start of routine vaccination. We collected 2008 data from 11 centers providing inpatient services for children in Ankara and investigated the hospitalization rate in healthy children due to chickenpox by scaling the results

to the 2008 Ankara pediatric population. We calculated the chickenpox incidence in immunocompromised children using these data obtained from centers in Ankara. The cost per patient was calculated for healthy children and immunocompromised children. Our aim was to project the Ankara data to the pediatric population of our country to obtain preliminary information on the disease burden and financial cost in the pre-vaccination period. We tried to obtain epidemiological results by scaling the data obtained from the Ankara centers to the pediatric population for the whole country using the stratification method.

Material and Methods

The study was conducted as a retrospective sectional study at the Ankara University Medical School, Department of Pediatric Infectious Diseases. Patients hospitalized with a diagnosis of chickenpox between January 2000 and September 2009 were included in the study.

The chickenpox diagnosis was made based on the clinical findings and history. Serological tests were performed in atypical cases and those that were fatal. We went through the charts of patients hospitalized with chickenpox and collected information on the distribution of complications in this study. Data from the patients were collected separately for previously healthy children and immunocompromised children. We collected data on demographic features, concurrent disease, type of complication, inpatient days, last disease status, whether surgery was needed, and disease cost for healthy children. We similarly tried to access the demographic data, presence of complications, type of complication, inpatient days, and disease cost for immunocompromised patients. Patients with congenital immunodeficiencies were not included in the study.

1. Diagnosis of Complications

Diagnosis of skin and soft tissue infections: The diagnosis was made by inspecting the present chickenpox lesions of the patients and the results of cultures obtained from various areas together with antibiograms.

Diagnosis of pneumonia: The diagnosis was made by auscultation of respiratory sounds on physical examination, measurement of peripheral percutaneous oxygen saturation and evaluation of the chest X-ray.

Diagnosis of neurological complications: The diagnosis was made based on the clinical signs and symptoms (stiff neck, cerebellar ataxia, convulsion, and altered consciousness), lumbar puncture and cerebrospinal fluid microscopy and biochemistry, electroencephalography, and imaging results.

Diagnosis of gastrointestinal complications: The diagnosis was made based on the clinical signs and symptoms (such as abdominal pain, nausea and vomiting), feces examination, and an increase of liver enzymes to more than 200% of the normal standard range.

Diagnosis of hematological complications: The hemogram, peripheral smear and, when necessary, bone marrow investigations were used. The anemia diagnosis was made with hemoglobin levels that were lower than normal according to age, the thrombocytopenia diagnosis with a thrombocyte count under 150,000/mm^3, the leukopenia diagnosis with a leukocyte count under 4,000/mm^3, and a coagulation disorder diagnosis with a prolonged prothrombin time and activated partial thromboplastin time.

Diagnosis of other complications: The clinical picture and appropriate laboratory investigations were used.

Diagnosis of disseminated chickenpox: The clinical and laboratory findings reflecting multiple organ and system involvement were used.

2. Cost Calculation

The data obtained from healthy and immunocompromised children were analyzed. The cost calculation was made by finding the mean cost of a patient. For this purpose, we included the bed fees (normal ward and intensive care unit), the cost of laboratory and radiology investigations, the examination fees on first presentation to the outpatient department and on follow-up, the cost of antibiotics and acyclovir, other medications and disposables used, the fees of surgery and dressings, and the service and other costs. However, we did not calculate the costs for the loss of education of the patients and the loss

of work of the parents. The general financial burden was calculated separately for previously healthy children and immunocompromised children. The disease cost was calculated separately for healthy children and those with immunodeficiencies. The Turkish Lira (TL) was used for cost calculation (1 TL=0.7 $).

3. Societal Burden of Chickenpox Calculation

We calculated the rates of chickenpox-related complications and deaths in the community using the 2008 figures for the number of patients hospitalized because of chickenpox, whether the hospitalized patients were previously healthy or immunosuppressed, and the number of patients who died from the centers providing the data. All of the patients were living in Ankara. We also obtained information on the number of chickenpox cases admitted in 2008 from the 11 hospitals that provided inpatient treatment in Ankara city center to estimate the chickenpox complication and hospitalization rates and used these data to estimate the burden of chickenpox at the community level. We determined the incidence of chickenpox complications and hospitalization in our community using these data. We also estimated the inpatient and mortality rates using the number of children that were previously healthy. We calculated the societal burden of chickenpox complications using the mean treatment cost of the 65 patients admitted to our ward. The Turkish Statistical Institute 2008 population distribution data were used in the calculation of the societal burden. The age 0 to 17 general population group in Turkey consists of 17,693,476 persons according to the Turkish Statistical Institute 2008 census. The age 0-17 general Ankara population consisted of 1,234,246 persons. However, we believed we had not reached all cases and assumed that the data we obtained represented at least 80% of the Ankara population; thus, we made the calculations accepting a corrected population of 987,396 persons for Ankara by using 80% of these population numbers.

4. Statistical Methods

The demographic and clinical features of the patients, type and distribution of complications, treatments received, and complications secondary to the treatment were analyzed using percentages, chi-square test and, when necessary, the Mann-Whitney U test. We aimed to collect the data and scale them to Ankara and the whole of Turkey by using the stratification method to obtain epidemiological and financial information.

Results

1. Chickenpox Complications

Of the 65 patients admitted to the Ankara University Faculty of Medicine, Pediatric Infectious Diseases Department, 34 (52.3%) had been previously healthy and were hospitalized because of chickenpox complications. Ten patients (15.4%) had previous chronic disease and had usually been hospitalized to receive intravenous acyclovir treatment, while 21 patients (32.3%) were immunocompromised due to hematological/oncological disease and were hospitalized to receive intravenous acyclovir treatment. Table I presents the demographic and clinical features, mean inpatient duration and cost per patient for the 65 patients included in the study.

Table II presents the demographic and clinical features, mean inpatient duration and cost per patient for the 34 patients who were previously healthy and were hospitalized for chickenpox complications. The skin and soft tissue infections in 14 of these patients consisted of 3 preseptal cellulitis cases, 3 lymphadenitis cases, 5 cellulitis cases, 2 invasive streptococcal infection cases, and 1 septic arthritis case. The cause of infection was Group A beta-hemolytic streptococcus in 2 cases and *Staphylococcus aureus* in 1 case. The pneumonia was part of a disseminated disease in 1 of the 8 patients with pneumonia. Neurological complications developed in 4 cases; 2 had cerebellar ataxia, 1 encephalitis and 1 febrile convulsion triggered by chickenpox. We found elevated liver test results in all 11 patients who developed gastrointestinal complications. The patient who developed disseminated chickenpox had pneumonia, thrombocytopenia, anemia, elevated liver function test results, and disseminated intravascular coagulation. The hematological complications of the 7 patients consisted of hemolytic anemia in 2, leukopenia in 1, thrombocytopenia in 1, coagulation disorder in 1, and venous thrombophlebitis in 2. Invasive

Table I. Demographic and Clinical Features and the Mean Inpatient Duration and Cost for the 65 Patients Hospitalized with a Diagnosis of Chickenpox

	n (%)
Total number of patients	65 (100)
Gender	
Male	43 (66.2)
Female	22 (33.8)
Mean age (months)	59±66
Previously healthy patients	34 (52.3)
Patients with an underlying disease	10 (15.4)
Immunocompromised patients	21 (32.3)
Complications	
Skin and soft tissue infections	14 (21.5)
Pneumonia	11 (16.9)
Neurological complications	4 (6.2)
Gastrointestinal complications	21 (32.3)
Hematological complications	11 (16.9)
Disseminated disease	2 (3.1)
Other	2 (3.1)
Mean inpatient duration (days)	6.2±5.9
Mean cost per patient (TL)	1052±1207

streptococcal infection was present in 2 patients who developed venous thrombophlebitis. We also found abnormal renal function test results in 2 patients. One of the patients with disturbed renal function had pneumonia, decreased oral intake and vomiting, while the other had renal

Table II. Demographic and Clinical Features and the Mean Inpatient Duration and Cost for the 34 Previously Healthy Patients Hospitalized for Chickenpox Complications

	n (%)
Total number of patients	34 (100)
Gender	
Male	21 (61.8)
Female	13 (38.2)
Mean age (months)	50.5±62.7
Mean inpatient duration (days)	6.85±6.73
Mean cost per patient (TL)	1260±1445
Complications	
Skin and soft tissue infections	14 (41.2)
Pneumonia	8 (23.5)
Neurological complications	4 (11.8)
Gastrointestinal complications	11 (32.4)
Hematological complications	7 (20.6)
Disseminated disease	1 (2.9)
Other	2 (5.9)
Comorbidity status	
Urinary tract infection	1 (2.9)
Urticaria	1 (2.9)
Gastroenteritis	1 (2.9)
Treatments	
Antibiotics only	17 (50)
Acyclovir only	4 (11.8)
Acyclovir and antibiotics	7 (20.6)
Acyclovir and steroids	1 (2.9)
Intravenous fluids only	4 (11.8)
Surgical treatment	2 (5.9)
Morbidity	3 (8.8)
Mortality	0 (0)

function disorder due to acyclovir. Surgical intervention and treatment were required as thoracentesis and chest tube placement in 1 patient who developed pneumonia and empyema and arthrocentesis in one patient who developed septic arthritis. Chickenpox caused no mortality but there was related morbidity in a total of 3 patients as scar-related sequelae secondary to invasive streptococcal infection in 2 patients and persistent thrombophlebitis in the pectoral region in 1 case.

Table III presents the demographic and clinical features, mean inpatient duration and cost per patient for the 21 immunosuppressed patients who were hospitalized for chickenpox complications. Liver function test results were elevated in all 8 patients who developed a gastrointestinal complication in this group, while morbidity or mortality due to chickenpox did not develop in any patient.

Table IV presents the demographic and clinical features and mean inpatient duration and cost per patient for the 10 patients who had an underlying chronic disease and were hospitalized for chickenpox complications. An increase in liver function test results was observed in 2 patients developing gastrointestinal complications in this group, while leukopenia was present in 1, thrombocytopenia in 3 and coagulation disorder in 1 of the 5 patients who developed a hematological complication. The patient who developed disseminated chickenpox had pneumonia, thrombocytopenia, elevated liver function test results, and disseminated intravascular coagulation. Morbidity was not observed in any patient, while a 6-year-old epilepsy patient died due to secondary multiple organ failure caused by disseminated chickenpox.

2. Societal Burden of Chickenpox

We found that a total of 105 patients had been treated for chickenpox as inpatients, while 3 had died in the 11 hospitals providing inpatient care for pediatric patients in Ankara in 2008. These 105 patients included 86 (81.9%) previously healthy children and 19 (18.1%) immunocompromised children. Projecting these data to the age 0-17 corrected general population data for Ankara, we found a 10.6/100,000 rate of hospitalization due to chickenpox in Ankara in 2008, and estimated that 1,875 subjects aged 0-17 would be hospitalized in Turkey for chickenpox in 2008. Evaluation of the hospitalization rate due to complications in previously healthy children

Table III. Demographic and Clinical Features and the Mean Inpatient Duration and Cost for the 21 Immunocompromised Patients Hospitalized for Chickenpox Complications

	n (%)
Total number of patients	21 (100)
Gender	
Male	16 (76.2)
Female	5 (23.8)
Mean age (months)	77.6±88.7
Mean inpatient duration (days)	5.95±2.0
Mean cost per patient (TL)	918±993
Conditions causing immunosuppression	
Solid tumor	15 (71.4)
Leukemia	3 (14.3)
Hematopoietic stem cell transplantation	3 (14.3)
Complications	
Gastrointestinal complications	8 (38.1)
Comorbidity status	
Pulmonary aspergillosis	1 (4.8)
Treatments	
Acyclovir only	17 (81)
Acyclovir and antibiotics	3 (14.3)
Acyclovir and intravenous immunoglobulin	1 (4.7)
Morbidity	0 (0)
Mortality	0 (0)

revealed a rate of 8.7/100,000 in Ankara in 2008 due to chickenpox, while 1,541 patients aged 0-17 would be expected to be hospitalized in Turkey. The chickenpox-related mortality rate for the 0-17 age group was 3.03/1,000,000 in Ankara, and 53 subjects aged 0-17 were expected to die from chickenpox in Turkey in 2008. We calculated the cost related to chickenpox complications for all patients and for previously healthy patients as 1052 TL and 1260 TL, respectively. Projecting this cost estimate to Ankara revealed a total cost of 110,460 TL and 108,360 TL, respectively, while projection for Turkey revealed these figures to be 1,972,500 TL and 1,941,660 TL, respectively (Table V).

Discussion

Chickenpox is usually a mild and self-limited disease. However, complications that may arise during the course of chickenpox may lead to a more severe course, hospitalization, and rarely, mortality. The distribution of chickenpox complications varies in different studies. Infection-related complications are more common in developing countries while neurological complications take center stage in developed countries. Chickenpox has a mild course but complications and the relevant medical care services that need to be used create a financial cost. It also frequently requires hospitalization in patients receiving immunosuppressive treatment or those with an underlying disease, as they are expected to suffer from a more severe course than usual. Chickenpox that arises during the course of malignant diseases usually causes significant problems with the treatment of the primary problem and can lead to an increased risk of its relapse. Many developed countries have now included chickenpox vaccination into the routine vaccine schedule after finding it cost-effective with financial burden calculations. We performed this study to determine the incidence of chickenpox complication distribution, the frequency of hospitalization due to chickenpox at the community level and the financial costs involved.

Table IV. Demographic and Clinical Features and the Mean Inpatient Duration and Cost for the 10 Patients with an Underlying Chronic Disease Hospitalized for Chickenpox Complications

	n (%)
Total number of patients	10 (100)
Gender	
Male	7 (70)
Female	3 (30)
Mean age (months)	49.5±38.7
Mean inpatient duration (days)	4.6±2.2
Mean cost per patient (TL)	627±321
Underlying chronic diseases	
Juvenile rheumatoid arthritis	3 (30)
Crohn's disease	1 (10)
Chronic liver disease	1 (10)
Cerebral palsy	1 (10)
Congenital myopathy	1 (10)
Epilepsy	1 (10)
Down syndrome	1 (10)
Cystic fibrosis	1 (10)
Complications	
Pneumonia	3 (30)
Gastrointestinal complications	2 (20)
Hematological complications	5 (50)
Disseminated disease	1 (10)
Comorbidity status	0 (0)
Treatments	
Acyclovir only	3 (30)
Antibiotics only	1 (10)
Acyclovir and antibiotics	4 (40)
Morbidity	0 (0)
Mortality	1 (10)

Table V. Societal Burden in Ankara and Turkey for Chickenpox in 2008

Total number of patients hospitalized in Ankara (n)	105
Rate of chickenpox-related hospitalization in Ankara (/100,000)	10.6
Number of patients expected to be hospitalized in Turkey (n)	1875
Number of patients that were previously healthy hospitalized in Ankara (n)	86
Rate of patients that were previously healthy hospitalized in Ankara due to chickenpox (/100,000)	8.7
Expected number of patients that were previously healthy to be hospitalized in Turkey (n)	1541
Number of fatalities due to chickenpox in Ankara (n)	3
Mortality rate due to chickenpox in Ankara (/1,000,000)	3.03
Number of patients expected to die due to chickenpox in Turkey (n)	53
Total cost of all patients admitted to hospital in Ankara (TL)	110 460
Total cost of hospitalized patients that were previously healthy in Ankara (TL)	108 360
Expected costs of all hospitalized patients in Turkey (TL)	1 972 500
Total cost of hospitalized patients that were previously healthy in Turkey (TL)	1 941 660

The number of previously healthy patients in our study was 34, making up 52.3% of our study population. There were 13 female and 21 male patients. The mean age was 50.5±62.7 months and the inpatient duration 6.85±6.73 days. Skin and soft tissue infections were found in 14 (41.2%) of 34 patients. Pneumonia was found in 8 (23.5%) of our cases. A neurological complication was present in 4 (11.8%) patients. Liver function test results were elevated in 11 (32.4%) patients. Disseminated chickenpox developed in 1 patient. Hematological complications developed in 7 (20.6%) patients. The mean cost was 1260±1445 TL per patient. Ziebold et al. [6] (Germany) found a neurological complication rate of 61.3%, skin superinfection rate of 4.2%, infection-related complication rate of 37.6%, and pneumonia rate of 0.8% with a one-year follow-up in their study on 119 previously healthy chickenpox patients. In contrast to that study, our neurological complication rate in the previously healthy patient group was lower, at 11.8%. The infection-related complication rate was consistent with that study's results, at 40%. Our rate of pneumonia was higher than in Ziebold's[6] study, at 23.5%. Koturoğlu et al.[7] (Izmir, Turkey) reported a mean age of three years and the most common complication as infectious complications, seen in 79 patients (44%), in their study on 178 patients with previously normal immunity who were hospitalized for chickenpox between 1997 and 2001. Neurological complications were reported in 68 (38%) patients. We also found an infection-related complication rate of 41.2% in our previously healthy patient group, similar to this other study from our country, but our neurological complication rate was lower than found in this study.

Theodoridou et al.[8] (Greece) reported rates of 21.3% for skin complications, 17.5% for respiratory complications and 16.5% for neurological complications in their study on 573 patients (consisting of chronic patients, immunocompromised patients and previously healthy subjects) with chickenpox in the pre-vaccination period. Our complication rates are similar to those in their study, but we had a lower rate of neurological complications. Tseng et al.[9] (Taiwan) reported a mean age of 4.7 years and a male-female ratio of 1.7:1 from their study on 136 patients (consisting of immunocompromised children, those with an underlying or chronic disease and previously healthy subjects) hospitalized for chickenpox. The mean inpatient duration was 5.5 days, and the most common complications were soft tissue and secondary bacterial complications, at 44%, followed by nervous system involvement at 23%, pneumonia at 18%, thrombocytopenia at 12%, and liver function disorder at 10%. An agent was isolated in 27% of patients with bacterial skin involvement (*S. aureus* in 12, *Streptococcus pyogenes* in 4). We similarly found a higher rate (66.2%) for male children. The mean age at 59 months and the high rate of infection-related complications, at 36.8%, were similar to our study. *S. aureus* was isolated in 3 patients from the localized skin infection

and Group A beta hemolytic streptococcus in 2 patients from the localized soft tissue infection in our study. Marchetto et al.[10] (Italy) reported a mean inpatient duration of 5 days for 349 patients (previously healthy or with an underlying serious disease) hospitalized because of chickenpox complications. A total of 261 cases were diagnosed with complicated chickenpox, and neurological complications were the most common, with 38.3%. Their study reported an incidence of 24.1% of skin and soft tissue infections, 21.8% for lower respiratory tract infections and 9.2% for hematological disorders. In contrast, we found a low rate of neurological complications and high rates of skin and soft tissue infections, pneumonia and hematological involvement. Our mean inpatient duration of 6 days is consistent with their study. Cameron et al.[11] (England and Ireland) reported a mean age of three years for the 188 patients aged 0-14 who were hospitalized due to severe chickenpox complications. The bacterial infection rate was 46%. The mean age was lower in their study than in ours, while non-infectious complications were more common, as in our study. Neurological complications were reported as the most common by Liese et al.[12] (Germany) in their study on 918 patients (immunosuppressed, previously healthy or with an underlying chronic disease) with a mean age of 3.3 years and by Jaeggi et al.[13] (Switzerland) in their study on 113 children who were previously healthy or had an underlying disease. Bonhoeffer et al.[14] (Switzerland) reported a higher rate of infection-related complications in their study on 335 previously healthy and immunocompromised children, similar to our study. Almuneef et al.[15] (Saudi Arabia) found skin and soft tissue infections to be the most common complications, at a rate of 34%, in 3,802 chickenpox cases. They found a rate of 28% for pneumonia, 10% for bacteriemia, 7% for encephalitis and cerebellitis, and 7% for myositis and necrotizing fasciitis. Our rates of infection and neurological complications were consistent with this study.

Infection-related complications are more common in developing countries, while neurological complications take center stage in developed countries. This may be one reason for the higher rate of infection-related complications and lower rate of neurological complications in our study. It is also possible that some patients with a neurological complication and especially cerebellar ataxia were admitted to the Neurology Ward and therefore not included in our study, as our study was on patients hospitalized with a diagnosis of chickenpox. Our neurological complication rate may also have been low, as it only included hospitalized patients, while cerebellar ataxia is a benign complication, and the patients are usually followed in the outpatient department. The rates for complications other than infectious and neurological complications were similar to studies from our country and other countries.

Two previously healthy children hospitalized for chickenpox complications in our study had scar development, while 1 had superficial venous thrombosis of the pectoral region following invasive infection, for a total of 3 (4.6%) patients out of 65 with sequelae. Liese et al.[12] (Germany) found the rate of chronic sequelae in 918 patients hospitalized for complications as 1.7%. Theodoridou et al.[8] (Greece) found two chronic sequelae consisting of necrotizing fasciitis and deep vein thrombosis secondary to infection in 573 patients hospitalized for chickenpox. We found a higher sequelae rate in the previously healthy group, and in fact, all were in this group. The high rate of sequelae in our patient group may be due to our high infection-related complication rate. Marchetto et al.[10] (Italy) found chronic sequelae at the six-month follow-up in 3 children with a diagnosis of encephalitis and cerebellitis out of 349 children hospitalized for chickenpox complications. We did not find any neurological sequelae in our study. Cameron et al.[11] (England and Ireland) found sequelae on discharge in 41 (21.8%) of the 188 patients hospitalized for severe chickenpox complications. Ataxia and scarring sequelae of the skin were the most common. Our sequelae rate was lower than found in their study. We believe the high sequelae rate in their study is due to the higher risk of the patients included, as they had suffered severe complications. Bonhoeffer et al.[14] (Switzerland) reported a sequelae rate of 4% in their study on previously healthy and immunocompromised children, similar to our study.

Eight of our patients with immunodeficiency had increased liver function test results as a complication. We did not have any patients with dissemination or sequelae, and none of our patients died. Intravenous acyclovir was administered to all our patients in this group. Vural et al.[16] (Istanbul, Turkey) did not find dissemination or any complication in any of the 30 pediatric oncology cases with chickenpox infection. This may be due to the earlier initiation of intravenous acyclovir treatment. We similarly did not find disseminated disease or death in any patient. The low rate of complication and absence of death may be associated with excluding the patients with congenital immunodeficiencies. Çelik et al.[17] (Adana, Turkey) reported that 72 children with malignancy who developed zona zoster and chickenpox were discharged without development of any severe disease following acyclovir treatment. This result was consistent with our study. We found that early acyclovir treatment is very useful in preventing dissemination in high-risk patients with chickenpox. Bonhoeffer et al.[14] (Switzerland) reported a secondary bacterial infection in 5 (26%) cases, neurological complications in 3 (16%) cases and pneumonia in 1 (5%) case among immunosuppressed patients. No hepatitis was found. The acyclovir usage rate for this group of patients was reported as 97%. No complications developed in the immunocompromised patients in our study other than disseminated disease and hepatitis.

A five-year-old male patient being followed with epilepsy died of multiple organ failure following chickenpox infection dissemination in the group having an underlying chronic disease. We had no patients who developed sequelae in this patient group. Jaeggi et al.[13] (Switzerland) found that complications were observed at older ages, while the hospitalization period was shorter in patients with a previous chronic disease. We also found the mean inpatient duration of the group with an underlying chronic disease to be shorter than for the other groups and, in contrast to this study's results, that the mean age of patients with a chronic disease was younger than the other groups. Marchetto et al.[10] (Italy) reported chronic sequelae in 3 children diagnosed with encephalitis and cerebellitis out of 349 children hospitalized for chickenpox complications. It has been stated that 38.5% of the cases with an underlying disease become complicated. We found that patients with an underlying disease constituted 15.4% of the patient population. We also found that 70% of the patients in this group had received acyclovir treatment. We had a lower rate of acyclovir usage for children with an underlying disease compared to this study. However, we found no disseminated disease in this group. The lower complication rate in this group compared to the healthy group could be related to the early parenteral acyclovir treatment due to the risk of disseminated disease.

Our chickenpox-related hospitalization rates for previously healthy children and all children were 8.7/100,000 and 10.6/100,000, respectively. The hospitalization rate due to chickenpox in previously healthy subjects has been reported as 12/100,000 by Bonsignori et al.[18] (Italy) and 4.1/100,000 by Lin et al.[19] (United States [U.S.]). Comparison of our hospitalization rate for chickenpox with data from other countries revealed a similar rate to a Swiss study, while our rate was lower than studies from Canada, Germany and Greece (29.2/100,000, 14.1/100,000 and 15.3/100,000, respectively), but higher than rates from the U.S. and a previous study from our country (5/100,000 and 6.3/100,000, respectively)[5,7,8,12,13,20].

Our chickenpox-related mortality rates for all children and previously healthy children were 3/1,000,000 and 1/1,000,000, respectively. Studies from Germany and the U.S. have reported much lower rates of chickenpox-related mortality than our study (0.4/1,000,000 and 0.67/1,000,000), while a study from Switzerland reported a rate closer to ours (1/1,000,000) [12,14,21].

Davis et al.[5], in their national study covering the 1993-2001 period in the U.S., found a hospitalization rate of 5/100,000 due to chickenpox between 1993 and 1995, which had decreased to 2.6/100,000 in 1999 and 1.3/100,000 in 2001 after chickenpox vaccine entered the routine vaccination calendar in 1995. Hospital costs related to chickenpox decreased from 161.1 million $ to 50.9 million $ in 2001. Staat et al.[22] (U.S.) reported a decrease in chickenpox-related hospitalization

from 15.7/100,000 to 5.5/100,000 following vaccination, while emergency service usage decreased from 178.2/100,000 to 61.2/100,000.

Coudeville et al.[23] (France and Germany) postulated three different types of disease distribution by creating an analytical model for the financial burden of the vaccination in their study on the financial costs of chickenpox vaccination. The vaccination rate was calculated as 90% in the first phase, 70% in the second and 45% in the third, and 90% vaccination led to a cost decrease of 61% in Germany and 60% in France. The cost per case in France was 144.5 € for children under 18 and 1043.4 € for those over 18. The calculations for Germany were 162.5 € for children under 12 and 865.3 € for those aged 12 and over. The chickenpox-related annual social security costs in France are 148 million €, while the insurance costs are 30 million €. These values were 144 million and 93 million €, respectively, for Germany. Banz et al.[24] (Germany) studied the financial results of vaccination by creating an analytical model for a 30-year period to calculate the profit and loss amounts by age for chickenpox vaccination. Vaccination was evaluated separately for three patient groups in this model. They assumed that all children aged about 15 months were vaccinated in the first group, adolescents aged 11-12 years who had not had the disease in the past were vaccinated in the second group, and a combined approach was used in the third group. They started the study assuming a vaccination figure of 85% and vaccine efficacy of 86% by evaluating the seroprevalence and inpatients. It was postulated that 611,000 chickenpox cases and 4,700 major complications could be prevented with such an activity. The annual profit was 51.3 million € and the risk/benefit ratio 4.12. The risk/benefit ratio for adolescent vaccination was 8.44. Vaccination of children gave results similar to combined vaccination, and routine vaccination could significantly decrease costs. Seward et al.[25] (U.S.) found a decrease of 71%, 84% and 79% for the number of chickenpox cases and hospitalized patients in three separate regions after 1995, the year vaccination was started, in their study encompassing the period 1995- 2000. Lenne et al.[26] (Spain) reported that there are 400,000 chickenpox cases, 1,500 hospitalizations and 15 deaths due to chickenpox in Spain every year. The study calculated the profit and loss rates associated with two separate types of vaccination, one vaccinating at 1-2 years of age and the other a 2-11 years capture program. It was reported that the vaccine would decrease morbidity and the number of cases by 89%, prevent 1,230 hospital admissions, and provide a cost savings of 3982 € per year. Wutzler et al.[27] (Germany) reported in their age-dependent analytic model study that 85% coverage by vaccination would decrease chickenpox cases by 82.7% and prevent 4,700 severe cases annually. This model indicates that chickenpox could be eradicated within 18 years. Scuffham et al.[28] (Australia) evaluated the risk/benefit ratio for four vaccination strategies in their study. The first group had no vaccination, the second group had all the infants vaccinated, the third group had adolescents with no history of chickenpox vaccinated, and the fourth group had all infants and all children up to 11 years of age who had not had chickenpox vaccinated, and the mean cost of each chickenpox case prevented in the 2nd, 3rd and 4th groups was estimated as 64 $, 530 $ and 418 $, respectively. The infant program was found to have the best risk/benefit ratio. They report that this program could prevent 4,400,000 chickenpox cases, 13,500 hospitalizations and 30 chickenpox-related deaths in 30 years. Vaccine administration was found to definitely cost less that no administration.

In conclusion, our chickenpox complication rate of 10.6/100,000 was higher than the 5/100,000 rate found in the U.S. in the period before vaccination and the 6.3/100,000 rate in a previous study from our country. There has been a significant decrease in the number of hospital presentations and hospitalizations due to chickenpox in countries where a vaccination program was started. It was also found that patient presentations, follow-up observation, examination and treatment cost, and hospitalization costs decreased markedly following the start of vaccination. We believe that once routine chickenpox vaccination begins, there will also be a marked decrease in the number of children with severe disease, who are hospitalized, who suffer sequelae due to complications, or who die due to chickenpox. Taking into account all hospital presentations, patient care, treatment, and rehabilitation costs that may be necessary during the follow-up and

the loss of work of the parents simultaneously, we feel that a national vaccination program will lead to a significant decrease in the overall cost to the country, as observed in other countries with such a program.

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