

Varicella and its complications as cause of hospitalization

Varicella e sue complicanze come causa di ospedalizzazione

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INTRODUCTION

Varicella is an acute contagious disease that most commonly occurs in childhood. It is one of the most widespread viral infectious diseases and typically shows an endemic and epidemic trend.

Varicella is characterized by a generalized exanthema consisting of vesicles that develop in successive crops and that rapidly evolve to pustules, crusts and scabs. Varicella normally has a benign clinical course, but can occasionally develop into a more serious illness. Moreover, the infection can lead to serious complications, such as *Staphylococcus aureus* infections, otitis media, endocarditis, pneumonia, and rare central nervous system (CNS) events like cerebellar ataxia and encephalitis.

Varicella is more severe in adults, immunodeficient children, pregnant women, and newborn babies, and the risk of complications has been shown to be higher in adults than in children [1, 2]. Lethal outcome is very rare, with a mortality rate fluctuating between 0.29 and 0.46 deaths per 1 million [3]. Therefore, varicella runs a self-limited course in most cases, but may at times require hospitalization for severity or for complications. This study was conducted to analyze the hospitalization rate due to varicella or its complications in a tertiary care hospital in Italy, where varicella vaccination has not yet been implemented.

METHODS

A review was conducted of children with varicella admitted to the Giannina Gaslini Children's Research Hospital of Genoa, Italy. The number of patients hospitalized for varicella was retrospectively monitored from January 1st,

1995 to December 31st, 2004. Cases were identified by the ICD9 and ICD9-CM diagnostic codes: 052 (chickenpox); 0529 (chickenpox without complications); 0528 (chickenpox with not detailed complications); 0527 (chickenpox with other detailed complications); 0520 (chickenpox with cerebrovascular diseases) [4]. The type of complication(s) and the number of hospitalization days were analyzed for every admission. For each case reporting complications, the clinical report form was extracted and the events recorded.

RESULTS

During the 10-year study period, ICD9 or ICD9-CM codes for varicella were recorded in 346 (0.16%) out of 212,647 total hospital discharges. Varicella and correlated diseases were identified for a total of 3,010 days of hospitalization, mean 13 (CI 95% 4.81-21.19), for each patient (mean age 4.75 years).

Admissions for chickenpox (code 052) and chickenpox without complications (code 0529) totaled 276 (79.76%) for 2,183 days of hospitalization; 14 (4.4%) children were admitted with diagnosis of chickenpox without detailed complications (code 0528) for 99 days of hospitalization. Finally, chickenpox with detailed complications (0527) and cerebrovascular diseases (0520) accounted for 56 discharges (12.14%), for a total of 728 days. Fifteen patients needed more than one hospitalization (28 discharges) because of severe sequelae as result of CNS involvement (Table 1).

Table 2 presents the most common serious complications, such as bacterial skin infections, cerebellar ataxia, encephalitis or cerebral vasculitis, respiratory complications, thrombocytopenia, and conjunctival hyperemia. In the

other episodes, clinical report forms described other symptoms like severe cephalalgia, abdominal pain, dehydration, high fever, without specific organ involvement. During the 10-year observation period, no case of Reye syndrome was seen, and no fatal cases as a consequence of varicella infection were reported.

Among the observed events, two categories of varicella infection consequences were worthy of special attention: invasive bacterial infections and cerebrovascular complications.

In immunocompetent children, one of the most frequent complications of varicella is superinfection of the skin due to *Staphylococcus aureus* and increasingly Group A *Streptococcus* (GAS). We reported three particular cases of invasive infections:

1) A 3-year-old male worsened four days after onset of chickenpox. He presented high fever, septic aspect, hemorrhagic vesicles, diffuse pain, dehydration and shortly thereafter abdominal pain, diffuse edema and oliguria, and serious arthritis and cellulitis in the right leg. Laboratory examination showed an increase of total white blood cell count (13000/ mm³) and C-reactive protein (18 mg/dl), anemia (Hb 9,5 g/dl), reduction

of platelet count (95000/mm³), hypoalbuminemia, moderate hyper-transaminasemia; blood cultures were negative. Treatment with acyclovir and sulbactam-ampicillin and support therapy was started. The clinical course progressively improved. After 15 days, serum titer of antistreptolysin O rose remarkably (from 172 to 1990 IU/l).

2) A 2-year-old female developed a superinfection of the skin one week after varicella onset. She presented widespread, secreting cellulitis similar to GAS infection on the back and extending to both glutei and sides. Cutaneous swab was positive for *Staphylococcus aureus* but not for GAS.

3) A 6-month-old male presented fever, few vesicles on the face and trunk, and meningeal syndrome. Blood tests showed initial DIC; blood culture detected a GAS. Brain CT scan showed a large left frontoparietotemporal hypodense area. After 24 hours, onset of apnea and right hemiparesis required ICU admission. MRI confirmed a diffuse area of altered signals in the region of the left middle cerebral artery, but MRA showed no vessel occlusions. After 72 hours the clinical picture improved. On the 11th

Table 1 - Number of admissions, total days of hospitalization and mean hospital stay (with 95% confidence interval) in patients with a diagnosis of varicella and absence or presence of not detailed or detailed complications.

Code	No. admission	Days of hospitalization	Mean days (CI 95%)
052/0529	276	2183	7.90 (6.4÷9.4)
0528	14	99	7.07 (4.07÷10.07)
0527/0520	56	728	13 (4.81÷21.19)
TOTAL	346	3010	9.32 (1.34÷17.30)

Table 2 - Complications among hospitalized children.

Type of complication	No. cases	Total days of hospitalization	Mean days	Mean age
Bacterial skin infections	7	53	7.6	3.1
Cerebellar ataxia	2	18	9	6.65
Encephalitis or cerebral vasculitis	13*	527	47.9	4.83
Respiratory complications	3	19	6.3	2.5
Conjunctival hyperaemia	2	10	5	6.9
Thrombocytopenia	1	4	4	4.68
Other	15	97	6.92	2.63
TOTAL	43*	728	13	3.84

*Discharges for complications after varicella infection were 56, but 13 children with CNS complications were admitted because of severe sequelae for a total of 26 hospitalizations

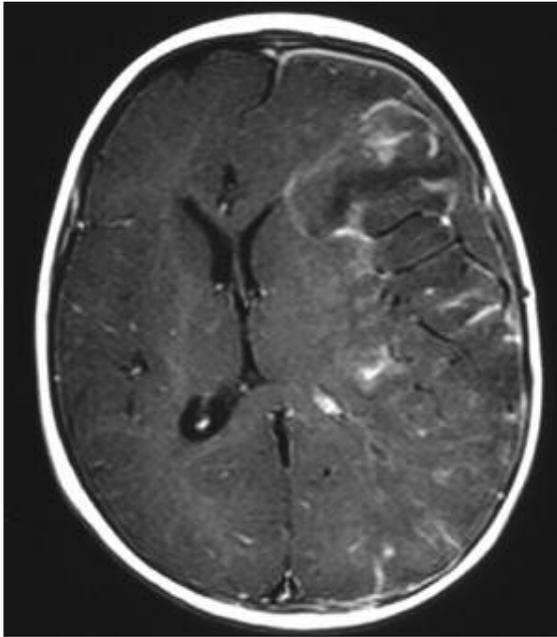


Figure 1 - Axial T1-weighted image shows marked swelling of the left cerebral hemisphere with loss of gray-white matter demarcation, contralateral midline shift, and scattered hyperintense areas consistent with hemorrhage.

day the child presented a worsened state of consciousness and severe pallor. CT scan showed extended bleeding in the lesion, interpreted as bleeding in the area of the middle cerebral artery. Thereafter the child slowly improved. Four years later, however, the child presented right hemiparesis and convulsant syndrome (Figure 1).

Apart from this last case of invasive infection due to GAS associated to vasculitis, which occurred in 2001, three children affected with cerebrovascular diseases following varicella were admitted to the Gaslini Hospital.

1) A 4-year-old male presented right hemiparesis persisting for an hour 7 days after onset of chickenpox. A similar episode lasting some minutes had been observed two days after onset of varicella. MRI showed ischemic-hemorrhagic lesions of left caudate and lenticular nuclei. MRA showed reduced flow in the middle cerebral artery area. Coagulation parameters were normal. After one week, right hemiparesis reappeared. MRI showed porencephaly at the sites of previously detected ischemic-hemorrhagic lesions, and MRA did not visualize the middle cerebral artery. After treatment clinical symptoms gradually improved. Anti-β2GP1 IgM anti-

bodies were positive and became negative after one month. At two year follow-up the child presented no further relapses.

- 2) A 6-year-old male presented left hemiparesis 12 days after onset of varicella. MRI showed focal signal alteration at the right basal ganglia. MRA showed rarefaction in blood circulation on the sides of the lesions. After therapy, the clinical course progressively improved. The study of prothrombotic plasma factors revealed slightly increased activity of PAI-1 (plasminogen activator inhibitor). Anti β2GP1 IgM antibodies were positive and became negative after one month. No relapse was observed at 18-month follow-up (Figures 2 and 3).
- 3) A 6-year-old male, one month after varicella onset, presented hyposthenia and gait impairment that regressed spontaneously. After some days, he presented a second episode and left facial paralysis. MRI showed focal signal alteration in the right nucleo-capsular region. MRA revealed no vessel occlusions or parietal alterations. Immunologic investigations and coagulation tests were negative. The child received therapy and symptoms regressed without sequelae after some days. At 1 year from onset, the child still receives antiplatelet therapy and showed no further neurological sequelae.

DISCUSSION AND CONCLUSIONS

This study provides an epidemiological analysis of the incidence of chickenpox and its complications in hospitalized children in a tertiary care children's hospital in Genoa, Italy.

Varicella identification codes were recorded in 346 (0,16%) discharges, and complications were observed in 12.14% of hospitalized varicella cases, findings that reflect other authors' observations [5-7]. Most studies used hospital admission as the sole criterion defining severity of the complications and inclusion in their studies; less serious complications, such as respiratory or gastrointestinal complications, most commonly ranked second or third [8]. In other works complications were more frequently documented in preschool children, who have the highest age-specific incidence rates because of the "favorable" conditions for transmission and absent herd immunity [9-10].

In the present data analysis the mean age of hospitalization was 4.75 years, but the mean age of complications was 3.84 years.

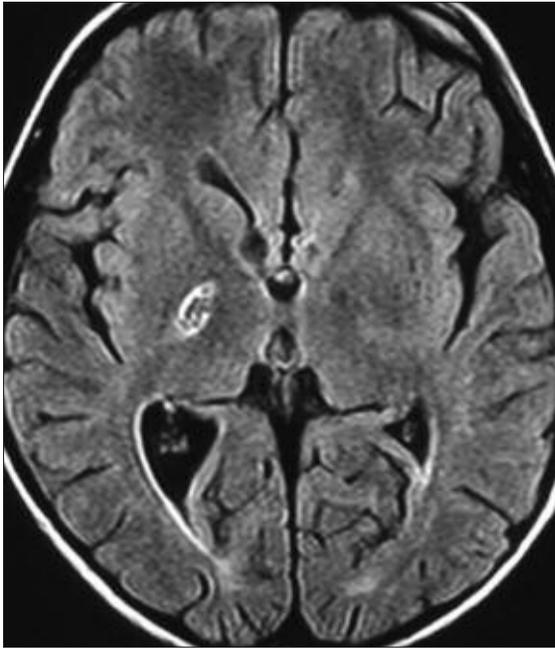


Figure 2 - Axial FLAIR image shows hyperintense lesion involving the right globus pallidus and internal capsule.

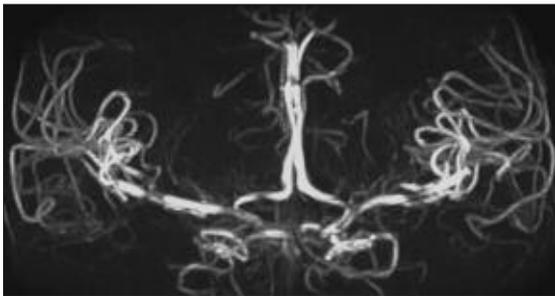


Figure 3 - Coronal MIP from TOF3D MR angiography shows reduced flow at level of the right lenticulostriate arteries (compare with unaffected left side).

Infectious complications are known to occur mostly in infants and toddlers, infections of the skin being the most commonplace varicella-associated event reported in most published works [5, 11-19]. Bacterial superinfection of skin lesions with either *Staphylococcus aureus* or GAS is frequent in otherwise healthy children and can lead to disfiguring scars. Most often hospitalization is not needed; in the event of severe infection, however, it can lead to cellulitis, abscesses or systemic infection. In fact, in our study we found seven (2%) discharges for bacterial skin infections, and while this number is low, we believe it is important to place focus on the mainly invasive complications associated to chickenpox that we observed [8]. In infants, the skin with vari-

cella lesions was most likely the portal of entry for GAS [20]. And, indeed, infants represent a vulnerable risk group for developing invasive GAS complications, particularly during the first two weeks of disease [21-22].

In accordance with the study of Ziebold et al., in our study encephalitis and cerebral vasculitis were the most frequent complications (2.9%), and accumulated 295 days of hospitalization (9.8%) [8]. During the period under study, four cases of cerebrovascular disease (stroke) after varicella infection were observed. Stroke is a rare pathology in children, and indeed our Institute treated only 50 cases of cerebrovascular diseases due to different causes from 2001 to 2004 (A.C. Molinari, personal observation).

The role of VZV infection in pediatric stroke is reported with increasing frequency. Stroke following primary VZV infection in children occurs from a few days to some months after the exanthema [23-24]. Its frequency was initially suggested to be approximately one out of every 6,500 cases of varicella in 1990, while a more recent evaluation estimated an absolute risk in one out of every 15,000 children [25, 26]. However, the frequency could be even higher than thought: due to diagnostic difficulties, in fact, many cases become manifest several months after the acute infectious episode [24].

Recently, a review of U.S. national records on deaths for which varicella was listed as the underlying cause revealed a doubling in the rate of cases that had at least one varicella-associated complication, rising from 38% in 1990-1994 (200/525 deaths) to 79% in 1999 to 2001 (93/118 deaths) [3]. In our study from 1995 through 2004 there were no deaths attributable to chickenpox, even if important and severe sequelae were registered.

Apart from vaccination, no countermeasures are likely to effectively control the dissemination of varicella or the frequency of zoster in a susceptible community. Varicella vaccines based on the attenuated Oka-strain of VZV have been marketed since 1974, and the positive results of extensive safety, efficacy and cost-effectiveness analyses have warranted the introduction of these vaccines into the childhood immunization programs of several industrialized countries. The recent publication by Seward et al. demonstrates that varicella cases have decreased dramatically in three investigated US populations only 5 years after implementation of universal childhood vaccination. With coverage rates reaching levels of between

74 and 84%, the number of cases declined by 71-84%, respectively [27]. An even more recent study reports a dramatic decline in varicella-related mortality for all ages, races, and ethnic groups after the increased use of vaccine [3]. Studies in Australia, Spain and Italy confirm the finding that direct medical costs are only a small portion of the total costs of varicella infection (28-30). Wagenpfeil et al. estimated the indirect costs of varicella in Germany at 150 million Euros/year, taking into account an annual incidence of 760,000 diagnosed cases in 1999 [29, 31-33]. Varicella causes enormous costs, particularly in terms of lost earnings generated by parents' forced absence from work to care for their sick children. Health economics studies point out the cost-effectiveness (from a

third-party payer perspective) and the cost savings to society that vaccination programs can achieve. Our retrospective data regarding a single tertiary case pediatric hospital shows that hospitalization due to varicella or its sequelae may present an important medical and indirect economic problem. In Italy, varicella vaccination was only recently formally introduced into the Childhood Vaccination Calendar and the National Vaccine Schedule [34]. A good understanding of the epidemiology of VZV infections and a keen awareness of the potential of clinical signs and sequelae for complications and deaths can further underpin this program.

Keys words: varicella, complications, hospitalization

SUMMARY

Varicella is an acute contagious disease that most commonly occurs in childhood. Although normally benign, varicella can occasionally develop into a more serious illness. Moreover, the infection can lead to serious complications, such as *Staphylococcus aureus* infections, otitis media, endocarditis, pneumonia, and rare central nervous system (CNS) events like cerebellar ataxia and encephalitis.

This study was conducted to analyze the hospitalization rate due to varicella or its complications in a tertiary care hospital in Italy, where varicella vaccination has not yet been implemented. The review was carried out on cases of children with varicella identified by ICD9 and ICD9-CM diagnostic codes and admitted to the Giannina Gaslini Children's Research Hospital of Genoa, Italy,

from January 1st, 1995 to December 31st, 2004. For each case reporting complications, the clinical report form was extracted and the events recorded. Varicella was recorded in 346 (0,16%) out of 212,647 total hospital discharges. Chickenpox with detailed complications and cerebrovascular diseases accounted for 56 discharges (12.14%), for a total of 728 days. Fifteen patients needed more than one hospitalization because of severe sequelae as result of CNS involvement. We reported three particular cases of invasive infections and four children affected with cerebrovascular diseases following varicella. Our retrospective data regarding a single tertiary care pediatric hospital shows that hospitalization due to varicella or its sequelae may present an important medical and indirect economic problem.

RIASSUNTO

La varicella rappresenta una delle malattie infettive contagiose di più frequente osservazione nell'infanzia. Nonostante che il suo andamento clinico sia abitualmente benigno, essa può occasionalmente dar luogo a forme cliniche gravi. Inoltre, la varicella può determinare serie complicanze quali le infezioni da Staphylococcus aureus, l'otite media, l'endocardite, la polmonite e, raramente, manifestazioni a carico del Sistema Nervoso Centrale, quali l'atassia cerebellare e l'encefalite. Scopo del presente studio è stato quello di analizzare il tasso di ospedalizzazione per varicella e sue complicanze in un ospedale italiano nel quale la vaccinazione anti-varicella non è stata ancora implementata.

Questa rassegna si riferisce quindi alla casistica di bambini affetti da varicella identificati con i codici di dimissione corrispondenti a ICD9 e ICD9-CM e ricoverati presso l'ospedale Giannina Gaslini di Genova,

Italia, nel periodo compreso tra Gennaio 1995 e Dicembre 2004. La diagnosi di varicella è stata registrata in 346 (0.16%) dei 212.647 bambini ricoverati. Il numero totale di bambini che presentavano complicanze correlate alla varicella e complicanze cerebro-vascolari è risultato pari a 56 dimissioni (12.14%) per un totale di 728 giorni di ospedalizzazione. Quindici dei bambini affetti da varicella hanno avuto la necessità di più di un ricovero a causa di gravi sequele a seguito di coinvolgimento e di complicanze a carico del SNC. Nel presente studio riportiamo anche la descrizione di tre casi di infezione invasiva e di quattro bambini affetti da complicanze cerebro-vascolari.

Il nostro studio retrospettivo dimostra che l'ospedalizzazione per varicella e/o per le sue complicanze può rappresentare un importante problema sanitario ed indirettamente un importante problema economico.

REFERENCES

- [1] Guess H.A., Broughton D.D., Melton L.J., Kurland L.T. Population-based studies of varicella complications. *Pediatrics* 78, 723-727, 1986.
- [2] Preblud S.R. Age-specific risks of varicella complications. *Pediatrics* 68, 14-17, 1981.
- [3] Huong Q., Nguyen M.P.H., Aisha O. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N. Engl. J. Med.* 352, 450-458, 2005.
- [4] World Health Organization. Manual of the international statistical classification of diseases, injuries and causes of death: based on the recommendations of the Ninth Revision Conference, 1975, and adopted by the Twenty-ninth World Health Assembly. WHO, Geneva, 1977.
- [5] Choo P.W., Donahue J.G., Manson J.E., Platt R. The epidemiology of varicella and its complications. *J. Infect. Dis.* 172, 706-712, 1995.
- [6] Dunkle L., Arvin A., Whiley R. et al. A controlled trial of aciclovir for chickenpox in normal children. *N. Engl. J. Med.* 325, 1539-1544, 1991.
- [7] Bullowa J.G.M., Wishik S.M. Complications of varicella. *Am. J. Dis. Child.* 49, 923-926, 1935.
- [8] Ziebold C., von Kries R., Lang R., Weigl J., Schmitt H.J. Severe complications of varicella in previously healthy children in Germany: a 1-year survey. *Pediatrics* 108, e79, 2001, <http://www.pediatrics.org/cgi/content/full/108/5/e79>.
- [9] Yawn B.P., Yawn R.A., Lydick E. Community impact of childhood varicella infections. *J. Pediatr.* 130, 759-765, 1997.
- [10] Fairley C.K., Miller E. Varicella-zoster virus epidemiology—a changing scene? *J. Infect. Dis.* 174, S314-S319, 1996.
- [11] Jaeggi A., Zurbrugg R.P., Aebi C. Complications of varicella in a defined central European population. *Arch. Dis. Child.* 79, 472-477, 1998.
- [12] Peterson C.L., Mascola L., Chao S.M. Children hospitalized for varicella: a prevaccine review. *J. Pediatr.* 129, 529-536, 1996.
- [13] Paul E., Thiel T. Zur Epidemiologie der Varizella-Zoster-Infektion. Ergebnisse einer prospektiven Erhebung im Landkreis Ansbach. *Hautarzt.* 47, 604-609, 1996.
- [14] Aebi C., Ahmed A., Ramilo O. Bacterial complications of primary varicella in children. *Clin. Infect. Dis.* 23, 698-705, 1996.
- [15] Preblud S.R. Varicella: complications and costs. *Pediatrics* 78, 728-735, 1986.
- [16] Maharshak N., Somekh E. Hospitalization for varicella in central Israel. *Acta Paediatr.* 88, 1279-1283, 1999.
- [17] Peterson C.L., Mascola L., Chao S.M. Children hospitalized for varicella: a pre-vaccine review. *J. Pediatr.* 129, 529-536, 1996.
- [18] Jackson M.A., Burry V.F., Olson L.C. Complications of varicella requiring hospitalization in previously healthy children. *Pediatr. Infect. Dis. J.* 11, 441-445, 1992.
- [19] Rianza Gomez M., de la Torre Espi M., Mencia Bartolome S., et al. Complications of varicella in children. *An. Esp. Pediatr.* 50, 259-262, 1999.
- [20] Ulloa-Gutierrez R., Dobson S., Forbes J. Group A Streptococcal Subdural Empyema as a Complication of Varicella. *Pediatrics* 115, 112-114, 2005.
- [21] Laupland K.B., Davies D., Low D.E. et al. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. *Pediatrics* 105, e60, 2000, <http://pediatrics.aappublications.org/cgi/content/full/105/5/e60>.
- [22] Law B., MacDonald N., Halperin S. et al. The Immunization Monitoring Program Active (IMPACT) prospective five year study of Canadian children hospitalized for chickenpox or an associated complication. *Pediatr. Infect. Dis. J.* 19, 1053-1059, 2000.
- [23] Askalan R. et al. Chickenpox and stroke in childhood: a study of frequency and causation. *Stroke* 32, 1257-1262, 2001.
- [24] Sebire G., Meyer L., Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. *Ann. Neurol.* 45, 679-680, 1999.
- [25] Ichiyama T., Houdou S., Kisa T., Ohno K., Takeshita K. Varicella with delayed hemiplegia. *Pediatr. Neurol.* 6, 279-281, 1990.
- [26] Ganesan V., Kirkham F.J. Mechanisms of ischaemic stroke after chickenpox. *Arch. Dis. Child.* 76, 522-525, 1997.
- [27] Seward J.F., Watson B.M., Peterson C.J., Mascola L., Pelosi J.W. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. *JAMA* 287, 606-611, 2002.
- [28] Diez-Domingo J., Ridao M., Latour J., Ballester A., Morant A. A cost benefit analysis of routine varicella vaccination in Spain. *Vaccine* 17, 1306-1311, 1999.
- [29] Fornando P., Gandini F., Marin M. et al. Epidemiology and cost analysis of varicella in Italy: results of a sentinel study in a pediatric practice. *Pediatr. Infect. Dis. J.* 18, 414-419, 1999.
- [30] Ferson M.J., Shen W.L., Stark A. Direct and indirect cost of chickenpox in young children. *J. Paediatr. Child. Health.* 34, 18-21, 1998.
- [31] Wagenpfeil S., Neiss A., Banz K., Wutzler P. Empirical data on the varicella situation in Germany for vaccination decisions. *Clin. Microbiol. Infect.* 10, 425-430, 2004.
- [32] Verschreibungsindex für Pharmazeutika (VIP). Requests: IMS HEALTH GmbH OHG, Hahnstr 60528, 30-32, Frankfurt am Main [<http://www.imshealth.de>], 2000.
- [33] Wutzler P., Färber I., Wagenpfeil S., Bisanz H., Tischer A. Seroprevalence of varicella-zoster virus in the German population. *Vaccine* 20, 121-124, 2001.
- [34] Nuovo piano nazionale vaccini 2005-2007. GU n. 86 del 14-04-2005.