Empirical data on the varicella situation in Germany for vaccination decisions
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ABSTRACT
As epidemiological data concerning varicella in Germany were not available, a retrospective study was conducted to investigate the impact of the disease, focusing also on economic aspects. A representative German-wide sample of 1334 unvaccinated varicella cases was obtained in 1999 from randomly selected paediatric (P) and general, as well as internal, mainly adult (A), practices. Following representative weighting, the median age was 5 years, with 90% of cases aged < 12 years. The highest incidence was in children aged 5–6 years. Varicella-related complications occurred in 5.7% of patients, and accounted for 0.1 hospital days/case on average. Certificates of sick leave were issued for 1.3 sick days/case, with 0.6 days paid by health insurance funds to parents caring for their sick child, and 0.7 days paid by the employer. With an annual incidence of 760 000 diagnosed cases in Germany for the year 1999, this amounts to an annual cost of c.150 million Euro, with c. 50 million Euro paid by the statutory health insurance system. It was concluded that universal varicella vaccination in Germany would provide essential clinical improvements for patients and prevent hospital admissions. In addition, significant economic benefits can be expected, mainly because of the high level of indirect health costs in Germany.

Keywords  Chickenpox, costs, economic impact, healthcare costs, varicella

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INTRODUCTION
Varicella (chickenpox) is a highly communicable, vaccine-preventable disease that, in Germany, is non-notifiable. While a number of infectious diseases are controlled and repressed in industrialised countries, varicella incidence is nearly unchanged in Germany, with 760 000 new cases in a population of 82 million in 1999 [1]. Official recommendations for vaccination against varicella in Germany include only seronegative people at special risk, such as children with leukaemia, solid tumours or planned immunosuppression, as well as contacts of such children, medical staff, seronegative women who wish to become pregnant, and adolescents without a history of varicella [2]. In Germany, varicella is commonly considered to be a benign disease of young children with a mild course. However, a varicella vaccine is licensed for routine use in Japan and Korea, and general vaccination against varicella is recommended in the United States. The vaccine is well-tolerated and effective, with an estimated efficacy of > 90% [3,4].

The World Health Organisation [5] has raised the possible importance of varicella vaccination in industrialised countries from a health economic point of view. Because of the likelihood that nearly every person will contract varicella at some time, high indirect costs because of work loss may result, and economic analyses have already been carried out for some countries. Thus, a routine varicella vaccination programme for children in the USA was shown to be cost-effective [6] and, based on a cost–benefit analysis, possible improvements have also been described for France and Australia [7,8]. Similar results
justifying a universal vaccination programme for children aged 15 months have been published for Spain [9]. An epidemiological study in Italy [10] also suggested general vaccination of children aged > 18 months. Beutels et al. [11] attempted to analyse the benefits and costs of implementing a routine vaccination programme in Germany, but the lack of fundamental epidemiological data on varicella in Germany meant that estimates on prevalence and hospitalisation rates were adapted from USA studies to the German context, or were simply subject to expert opinion.

In order to supply the valid epidemiological data that is fundamental for economic evaluations of varicella vaccination strategies, the present study describes a retrospective, German-wide study. Data collection was focused on the age distribution, severity of disease course, complication rates and hospitalisations of diagnosed cases. Inability to work was assessed for diagnosed varicella cases, as well as for parents or guardians caring for an ill child. Certificates of sick leave are a cost factor in the German health care system, in particular for varicella. This is in accordance with other studies in industrialised countries [9,10,12] that stress the essential role of indirect costs in economic analyses of varicella. The present study aimed to provide an overview of the situation concerning varicella in Germany, as well as demographic information on sex distribution and health insurance status [13,14]. The data obtained should provide a basis for determining the direct and indirect costs of varicella infection in Germany.

MATERIALS AND METHODS

Results and conclusions were based on empirical data from a German-wide, epidemiological study of 1349 diagnosed varicella cases in 1999. Only unvaccinated cases were included in the analysis; therefore 15 cases were excluded (three were vaccinated and 12 had an unknown vaccination status).

Data were collected retrospectively from a random sample of 282 outpatient practices, comprising 231 paediatric (P) and 51 general, as well as internal, mainly adult (A) practices. Estimates obtained from data either in the (P) or (A) population are representative only within the stratum of paediatric varicella cases or diagnoses from general and internal practices, respectively. As the ratio of 231:51 may not reflect overall diagnosed varicella cases, the estimates were weighted between the (A) and (P) populations according to real prevalence rates in order to obtain representative results. This was done by using the German prescription index [1], yielding a ratio of 60:40 for (P):(A) for the year 1999. Thus, estimates from the (P) population were multiplied by a factor of 0.6, and those for the (A) population by 0.4. Adding the two products yields the overall representative estimates.

The prescription index [1] also allows an estimate of the incidence of diagnosed varicella cases for Germany, namely 760 000 cases for 1999. With a population of 82 million [15], an incidence rate was calculated of 9.5 new varicella cases in Germany/1000 inhabitants within a year.

**Study design**

The data from the sample of 1349 diagnosed varicella cases were collected cross-sectionally and retrospectively for the year 1999. Data were obtained anonymously from medical files via telephone interviews with a representative and German-wide sample of paediatric, general and internal practices. Physicians were chosen randomly from an electronic version of the classified directory (yellow pages) for Germany in two strata: one sample from listed paediatric practices, resulting in 231 compliant paediatricians; and a second sample from listed general and internal practices, resulting in 51 compliant general practitioners and internists acting as family doctors. For each of the compliant practices, a maximum of five diagnosed varicella cases was collected randomly. The sampling and evaluation effort took 12 months. It should be noted that hospitalisation events are commonly known to family doctors in Germany.

**Statistical analysis**

The age distribution of diagnosed varicella cases was displayed as a histogram with relative and cumulative frequencies, respectively. Mean age and ranges were calculated. Further results were presented as mean and probability estimates with respective 95% confidence intervals (CIs). If necessary, exact 95% CIs were computed for relative frequencies. Point sensitivity analysis with respect to the weighting of the (A) and (P) populations was also addressed. From sample size considerations, it was necessary to collect at least 1200 varicella cases (including 7% dropouts) in order to obtain 95% CIs enlarging ±1% for relative frequency estimates of 3%. The extension of ± 1% was considered to be sufficiently small.

**RESULTS**

Of 1349 collected varicella cases, 91 were immunocompromised, of which one was vaccinated. Excluding all the vaccinated cases and patients of unknown vaccination status, 1334 unvaccinated varicella cases were available for analysis. Of these, 50.1% were male, and 92.4% were members of a statutory health insurance scheme. The remaining patients, except two, were covered by private health insurance. The mean age at varicella diagnosis in the (P) population was 4.2 years (range 2 weeks – 34.9 years). The (A) population was older, with a mean age of 10.9 years (range 3 weeks – 54.4 years), which reflects the fact that general and internal practices take care mainly of adult patients. However, the (P) population
included a mother aged 34.9 years who was treated together with her daughter in a paediatric practice. Furthermore, some paediatricians have special consulting hours for teenagers. This yields a heavily right-skewed age distribution for the (P) population. The population seen in general and internal practices (A) is also right-skewed, with a slight but characteristic peak between 18 and 40 years. Half of the (A) cases were aged between 3 weeks and 6.1 years.

Representative weighting of the (A) and (P) populations yielded the overall age distribution of diagnosed varicella cases in Germany shown in Fig. 1. The mean age in the representative population was 7.4 years, with a median equal to the mode of 5 years. The cumulative frequency graph shows that 82.4% of the varicella patients were aged <8 years, confirming that varicella is mainly an infectious disease of children. However, the characteristic peak of the (A) population was still present, and 10% of diagnosed cases were aged >12 years.

Table 1 gives an overview of the observed varicella complications. In total, 92 complications were reported by physicians. Sixteen of these conditions were identified as coincident symptoms of other conditions unrelated to varicella disease, or varicella symptoms which were severe, but still normal during the course of the disease. Therefore these conditions were not included in the analysis of varicella complications. After correction, 76 complications were assessed as varicella-related in the raw data, corresponding to 5.9% of patients in the (P) population and 5.4% of patients in the (A) population, yielding a population-weighted varicella complication rate of \((0.6 \times 5.9\%) + (0.4 \times 5.4\%) = 5.7\%\).

As shown in Table 2, the most common complications for children aged <12 years were bacterial superinfection, otitis media, pneumonia and bronchitis. For the older age group, the most common complications were bacterial superinfection and lower respiratory tract infections, with many different diagnoses grouped together as ‘others’. No cases of otitis media or neurological disorders were confirmed in this age group. However, one case of fetal embryopathy associated with varicella infection in a pregnant woman was confirmed.

Most serious complications led to hospitalisation, with an average of 0.1 inpatient days/diagnosed varicella case. Table 3 stratifies hospitalisation rates according to the type of complication and age group. For children, the average number of inpatient treatment days was 2.6 on the intensive care unit and 1.3 on a regular ward because of neurological varicella disorders, as well as 0.7 intensive care days and 11.6 regular ward days for varicella-induced pneumonia or bronchitis. Observed hospitalisation in the adult group was 9.1 days on average because of pneumonia. No intensive care cases were observed in the adult population resulting from any complication. Only a few children were hospitalised

### Table 1. Complications associated with varicella infection

<table>
<thead>
<tr>
<th>Complication</th>
<th>Absolute number of cases in raw data</th>
<th>Average number of days in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial superinfection (skin &amp; scars)</td>
<td>35</td>
<td>0.7</td>
</tr>
<tr>
<td>Acute neurological disorder (suspected or confirmed)</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>Pneumonia or bronchitis</td>
<td>12</td>
<td>3.5</td>
</tr>
<tr>
<td>Otitis media</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7</td>
<td>0.1</td>
</tr>
<tr>
<td>Embryopathy</td>
<td>1</td>
<td>fetal malformation</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Superinfected angina lacunaris</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

The following conditions were documented, but not assessed, as complications of varicella: mild eye signs, stomatitis, vulvitis, abdominal pain, ear complaints, fever, intertrigo, balanitis, diaper dermatitis, atopic eczema, viral infection, enanthema of vagina and mouth, lymphadenitis, angina, febrile convulsion for other conditions, herpes labialis, dysuria, suspected meningitis (not confirmed).

### Table 2. Age-related complications associated with varicella infection

<table>
<thead>
<tr>
<th>Percentage frequency of varicella complications (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged ≤ 12 years</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Bacterial superinfection of skin, soft tissue and scars</td>
</tr>
<tr>
<td>Acute neurological disorder (suspected or confirmed)</td>
</tr>
<tr>
<td>Pneumonia or bronchitis</td>
</tr>
<tr>
<td>Otitis media</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

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Fig. 1. Age distribution of varicella cases in Germany.
because of superinfections of the skin. The average inpatient period was 5.3 days on a regular ward. No cases of hospitalisation with otitis media were recorded.

Point sensitivity analysis of hospitalisation rates with respect to the weighting ratio of 60 : 40 from 50 : 50 to 70 : 30 for the (P) and (A) populations, respectively, resulted in a maximum variation of ± 6% for neurological disorders. This was smaller than half the range of the respective 95% CIs for any of the displayed complication rates.

Table 4 summarises the main items accounting for direct and indirect costs of varicella infection. Of the diagnosed varicella cases, 16.3% were considered to take a severe course by the treating physician, while complications occurred in 5.7% of the cases. Most of the indirect costs were associated with certificates of sick leave. In 12% of all cases, certificates of sick leave for parents caring for their ill child were issued, with an average length of 5.9 days. For a further 10% of cases, an average of 7.3 days of work loss was documented. For the diagnosed varicella cases that obtained certificates of sick leave (22%), the mean work absenteeism was 6.6 days. After weighting for the real prevalence rates of the (A) and (P) populations, this results in 1.3 days of inability to work/diagnosed varicella case. Of these 1.3 days, 0.6 days are paid by health insurance funds to parents caring for their sick child, while 0.7 days/diagnosed varicella case are paid by employers to an employee unable to work because of varicella disease. A more detailed compilation of work losses according to diagnosed complications, stratified to children and adults, is given in Table 5.

Applying the human capital approach, the indirect costs of varicella were assessed for Germany. With an annual incidence of 760 000 diagnosed cases in 1999 [1,16], and assumed costs of 150.3 Euro/sick day, the indirect costs amount to 150 million Euro/year. In the context of health insurance, 70% of net wages are directly reimbursed in Germany to parents caring for their child, amounting to c.50 million Euro/year related to varicella.

**DISCUSSION**

The present study provides estimates based on diagnosed varicella cases. Data were collected from across Germany, and the sampling was representative of both rural and urban areas. Taking into account the adjustment for the (A) and (P) populations, representative estimates were obtained for the age distribution, complications, sick benefits and demographic features of diagnosed varicella cases. According to the sample size considerations, computed 95% confidence intervals and point sensitivity ranges were sufficiently small for rates down to 3% based on the whole study population. This indicates satisfying accuracy for epidemiological conclusions and further cost analyses.

Although vaccination for immunocompromised patients is recommended in Germany, only
one vaccinated patient was identified among 91 patients in this category. Other data (male:female ratio and membership of private and statutory health insurance schemes) were in accordance with the birth cohort and the demographic situation of the whole German population [15]. The relatively high number of children in the (A) population (50% were aged between 3 weeks and 6.1 years) can be explained by the fact that the rural population commonly consults a general practitioner as family doctor, while paediatric practices are concentrated in cities and urban areas.

When the age distribution of diagnosed varicella cases in the epidemiological study (Fig. 1) was compared to the age distribution according to seroprevalence data from a German seroepidemiological survey [16,17], only slight differences were observed in the age group of 2–15 years, while almost no differences were found in the other age groups. In the age group of 2–15 years, the percentage of varicella cases in the seroprevalence study was slightly higher (2.5% – 9.8%) than in the present study of diagnosed cases, perhaps because of undiagnosed disease in some patients. Beutels et al. [11] estimated the rate of non-diagnosed varicella cases in Germany as 10%, based on a representative survey [18]. Estimates based on seroprevalences may be influenced by these slight differences. The present study focused only on diagnosed cases, since it was only for such cases that complication rates, number of physician visits and hospitalisation data were available. Taking into account the lower incidence rate of diagnosed vs. seroprevalence cases, both approaches are mathematically equivalent.

Comparing the age distribution of diagnosed cases in Germany with the situation in the UK [19], it was observed that the shape of the distribution functions coincided. Furthermore, the characteristic peak was also present in both countries, although the cases in Germany were much younger (mean 7.4 years; median, mode 5 years) than in the UK (mean 14.2 years; median, mode 9 years). This has to be seen in the light of a possible previous age-shift in the UK [16]. The mean age in an Italian paediatric population with cases aged 0–14 years was comparable to the (P) population in the present study, namely 4.5 ± 2 years in Italy [10] and 4.2 years in Germany. The specified complication rate (3.5%) in Italy was lower than the German rates (5.4% in the (A) and 5.9% in the (P) population), probably because bacterial superinfection of skin, soft tissue and scars was not considered as a varicella complication in Italy. The difference of 2.4% between the Italian rate and the (P) population rate in the present study fits very well with the observed complication rate associated with bacterial superinfections for children (aged ≤12 years) in Table 2. In this way the Italian data validate and reinforce the overall complication rate estimated in the present study.

The results of the study demonstrate that it is a misconception to believe that varicella is uniformly a mild disease. The study also confirmed findings from a study in the USA [20] that the probability of severe complications, such as lower respiratory tract infections, are increased in the adult population, as indicated by the presence of pneumonia and bronchitis in Table 2. These types of severe complications, together with the neurological disorders seen in the child population, require hospitalisation in most cases (Table 3). Most of the direct costs associated with varicella arise from complications and hospitalisations generally paid by statutory health insurance funds in Germany. Studies in Australia, Spain and Italy [9,10,12] confirm the finding that direct medical costs are only a small part of the total costs of varicella infection.

The present study is the first to collect data directly on work loss caused by varicella infection in Germany. There is a special situation in Germany, since 48% of the indirect costs of varicella caused by loss of working days (i.e., 0.6 of 1.3 days in Table 4) are paid by the statutory health insurance scheme. Considering only these indirect costs, and taking into account the fact that c.90% of varicella cases are diagnosed [18], it seems that there are significant economic arguments in favour of a universal vaccination policy, from both the health budget and social perspectives. However, more sophisticated approaches are necessary to account for coverage rates and potential age-shifts. An initial economic analysis, based on the population model of Halloran et al. [21], showed that universal varicella vaccination could provide significant clinical and economic benefits to German society [22]. A detailed economic analysis [23] demonstrated that a routine immunisation programme that succeeded in vaccinating all healthy children aged 1–1.5 years...
would be cost-effective from the viewpoint of society, as well as third-party payers.

A limitation resulting from the size of the study population is the accuracy of estimating events such as rare complications and hospitalisations that occur at a frequency of < 3%. However, according to sensitivity analyses [23], these rare events do not contribute significantly to varicella costs on a population level. For reasons of completeness, the structured complication and hospitalisation rates observed are shown in Tables 2 and 3.

In conclusion, according to the efficacy results [3,4] and epidemiological findings, the introduction of universal varicella vaccination in Germany would provide significant clinical improvements for patients and reduce hospital admissions. In addition, significant economic benefits can be expected for society as a whole, as well as health insurance funds, because of the high impact of indirect costs in Germany.

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