The health and economic burden of chickenpox and herpes zoster in Belgium

J. BILCKE[1]*†, B. OGUNJIMI[1,2]†, C. MARAIS[1], F. DE SMET[3,4], M. CALLENS[3],
K. CALLAERT[5], E. VAN KERSCHAVER[6], J. RAMET[2], P. VAN DAMME[1]
AND P. BEUTELS[1]

[1] *Center for Health Economic Research and Modeling Infectious Diseases* (*CHERMID*), *Vaccine and Infectious Disease Institute* (*Vaxinfectio*), *University of Antwerp, Wilrijk, Belgium*
[2] *Department of Paediatrics, Antwerp University Hospital, Edegem, Belgium*
[3] *National Alliance of Christian Sickness Funds, Brussels, Belgium*
[4] *Department of Occupational, Environmental and Insurance Medicine, Leuven, Belgium*
[5] *Interuniversity Institute for Biostatistics and statistical Bioinformatics* (*I-BioStat*), *Hasselt University, Diepenbeek, Belgium*
[6] *Child & Family, Brussels, Belgium*

SUMMARY

Varicella-zoster virus causes chickenpox (CP) and after reactivation herpes zoster (HZ). Vaccines are available against both diseases warranting an assessment of the pre-vaccination burden of disease. We collected data from relevant Belgian databases and performed five surveys of CP and HZ patients. The rates at which a general practitioner is visited at least once for CP and HZ are 346 and 378/100 000 person-years, respectively. The average CP and HZ hospitalization rates are 5·3 and 14·2/100 000 person-years respectively. The direct medical cost for HZ is about twice as large as the direct medical cost for CP. The quality-adjusted life years lost for ambulatory CP patients consulting a physician is more than double that of those not consulting a physician (0·010 *vs.* 0·004). In conclusion, both diseases cause a substantial burden in Belgium.

Key words: Ambulatory, cost, hospitalization, QALY, shingles, varicella.

INTRODUCTION

The varicella-zoster virus (VZV) is a member of the herpes family and is transmitted by close contact. It can cause the disease varicella [or chickenpox (CP)], most often in young children. After recovery from CP, the virus remains dormant within the body and may reactivate in later life causing the disease shingles [or herpes zoster (HZ)] [1, 2]. Vaccines have been shown to be efficacious in preventing CP and HZ. In order to evaluate the effectiveness and cost-effectiveness of the introduction of these vaccines in a specific population (both pre- and post-introduction), the health and economic burden of VZV disease in that population needs to be estimated. For Belgium, no such estimates are currently available. For instance almost all estimates of HZ burden used in a recent evaluation of the cost-effectiveness of HZ vaccination in Belgium, were simply taken from other countries [3].

To evaluate the net consequences of CP vaccination, estimates of the health and economic burden

* Author for correspondence: Dr J. Bilcke, Center for Health Economic Research and Modelling Infectious Diseases (CHERMID), Vaccine and Infectious Disease Institute (Vaxinfectio), University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium.
(Email: joke.bilcke@ua.ac.be)
† These authors contributed equally to this paper.

of both CP and HZ need to be made. This is because it was hypothesized by Hope-Simpson [2] that re-exposure to wild-type VZV would lower the probability of developing HZ. This so-called 'exogenous boosting' implies that a reduction in circulating wild-type VZV, as would be the case for universal vaccination programmes against CP, would lead to a – temporary – rise in HZ incidence. Although immunological evidence is scarce [4–6] current epidemiological evidence shows some support for the hypothesis [7–13] and cost-utility analyses examining the desirability of universal CP vaccination include the possibility of exogenous boosting [14–16].

This paper aims to estimate the health and economic burden of both CP and HZ in Belgium. Five surveys were specifically set up to obtain information that is not captured by any of the existing Belgian databases. One of these surveys measures for the first time the loss in quality of life separately for CP in children for whom medical care is sought, and for those where no medical care is sought. Moreover, estimates are obtained for the duration and severity of illness associated with HZ.

DATA SOURCES AND DATA ANALYSIS

All data were processed without patient-identifying information. All data extractions and associated analyses related to the National Christian Sickness Fund (NCSF) were performed at the Medical Management Department of the NCSF under the supervision of a medical advisor.

Rate of physician consultations

The Scientific Institute of Public Health (SIPH) has a sentinel system of 150 general practitioners (GPs) which reaches about 1·5% of the Belgian population (1·6% of the Flemish and Walloon population and 0·9% of the population in Brussels). The participating sentinel GPs are representative in terms of gender and age, with the exception of an overrepresentation in the 40–49 years age group [17]. The SIPH provided the age-specific number of people who visited a GP at least once for CP and HZ (for years 2006–2008), along with the sentinel catchment population estimates so that annual rates could be calculated. Information on the age and gender distribution of the sentinel population is lacking, therefore the same age and gender distribution as in the complete Belgian population is assumed when calculating the rates.

Note that in Belgium it is possible to consult a specialist directly (e.g. paediatrician or dermatologist), without consulting a GP first. The proportion of CP and HZ patients only consulting a specialist and not a GP will be estimated based on the NCSF surveys in ambulatory CP and HZ patients, and on the Child & Family survey (see later).

Rate of hospitalizations

The Minimal Clinical Data (MCD) is a mandatory registration of hospitalized patient information for every hospital in Belgium. From this database we obtained the birth year, gender, hospital admission and discharge date for hospitalized CP and HZ patients in the period 2000–2007. Patients were identified by ICD-9-CM codes '052' and '053' in primary or secondary diagnostic fields. Annual CP and HZ hospitalization rates are calculated by dividing the yearly number of CP and HZ hospitalizations from the MCD by the Belgian population from the same year.

To explore the age distribution of CP hospitalizations, the MCD cannot be used, as the number of CP cases recorded in the population aged <1 year in this database is underestimated. This is because the age at hospitalization in the MCD database is calculated as the difference between the year of hospitalization and the year of birth. Therefore the age distribution of CP hospitalizations in Belgium is explored using CP hospitalization data of members from the NCSF, which are recorded in the Carenet database. From the same database, monthly gender-specific CP hospitalization rates and age- and gender-specific HZ hospitalization rates were also derived to cross-validate trends in hospitalization rates observed in MCD. Carenet is designed for the exchange of information about hospital admissions, end of hospitalization and costs of hospitalizations between hospitals and health insurance companies through an electronic system. In July 2006 Carenet covered 88% of the Belgian hospital beds, in July 2009 this increased to 99%. NCSF is the largest health insurance company in Belgium, covering 42·2% of the Belgian population [(http://www.riziv.fgov.be/information/nl/statistics/people/2010/pdf/statisticspeople2010all.pdf), (in Dutch)]. We noted the existence of a slight bias in NCSF members compared to the Belgian population in favour of the older age groups and a minor underrepresentation of the unemployed (40·6% of the unemployed are NCSF members). From the Carenet database, we obtained

all records (1 May 2006–2009) on hospitalized patients who are members of the NCSF for which the diagnostic field included one of the following search strings 'wijnpokken', 'waterpokken', varicell', 'zona', 'zoster', 'gordelroos', ICD-9-CM code '053' or code '052'. A medical clinician searched the diagnostic fields of the retrieved records manually and removed all hospitalizations that were unlikely to be due to VZV, or for which this was unclear. Additionally, CP patients were categorized according to complication. Rates were obtained by dividing the number of NCSF hospitalizations in 2006–2009 by the age- and gender-specific Belgian population over the same years, the latter divided by 0·422 (since NCSF covers 42·2% of the Belgian population) and adjusted according to the number of Belgian hospital beds covered by Carenet.

Mortality rate

The Flemish Agency for Care and Health (FACH) provided all death certificates from 1998 to 2007 for residents of the Flemish region (representing 60% of the Belgian population) that contained ICD-10-CM codes 'B01' and 'B02' in any of the following fields for cause of death: the underlying cause of death [as defined by WHO (http://www.who.int/healthinfo/ statistics/mortdata/en/index.html)], the immediate cause (which is the final cause of death and follows on from the intermediate and/or underlying cause), the intermediate cause (those on the logical causal pathway from underlying cause to immediate cause of death) and the additional causes of death (that have played a role in the death of the person, but do not belong to the logical pathway from underlying cause to immediate cause of death; these causes are not related to those causing death directly) [http://www. zorg-en-gezondheid.be/uitleg.aspx#doodsoorzaak (in Dutch)]. These death certificates (i.e. for each of the causes of deaths for all ICD-10-CM codes recorded) were screened by expert clinicians, who indicated which of these deaths were likely avoidable through the avoidance of CP or HZ episodes. The death certificates related to CP in children were screened by two paediatricians, the death certificates related to CP in adults and to HZ were screened by five HZ experts.

Costs for ambulatory patients

Two surveys were set up through the NCSF to obtain the costs for ambulatory CP and HZ cases. The

NCSF launched an appeal on their website and in their monthly periodicals aimed at people who had experienced HZ over the last year (appeal October 2009) or CP over the last 6 months (appeal in January–February 2010), but were not hospitalized for these episodes. Interested people could provide their contact details. The contact details for the eligible NCSF members were distributed among 11 NCSF nurses who sent personalized letters to each of these members, together with a questionnaire which they were asked to complete. A few days later, a nurse contacted the eligible person by telephone, went through the questionnaire together, and recorded the answers.

The questionnaires sought information about all costs related to the CP or HZ period, including the direct medical costs [consultations with GPs and specialists, ambulatory technical investigations (e.g. laboratory tests), medication and care products], and the non-medical indirect and personal costs [non-reimbursed medication and care products, transportation, paid help (e.g. babysitter), and absence from work]. The questionnaires which were sent to CP and HZ patients were similar, except for some questions specifically related to either HZ or CP, e.g. the CP questionnaire enquired about the number of consultations to a paediatrician, whereas the HZ questionnaire enquired about the number of consultations to a specialist (e.g. a geriatrician).

The cost associated with work loss is calculated by multiplying the number of lost workdays by the average daily gross salary. In Belgium, the average daily gross salary of a blue-collar worker is €120.175, and that of a white-collar worker is €178.068 according to the National Social Security Office (NSSO) and the National Bank of Belgium [18]. No salary information is available for self-employed people and therefore a white-collar worker's salary was used as an estimate.

Costs for hospitalized patients

Two other surveys were set up through NCSF to obtain the costs for hospitalized CP and HZ cases. The method of contacting eligible persons was the same as described above for ambulatory patients; however, the way these people were selected differed. For the survey in hospitalized CP patients, 300 eligible hospitalized CP patients from NCSF were sampled from the most recent complete calendar years from the Carenet database. Complete years were considered as exploratory analyses and showed CP incidence to be

seasonal in Belgium. For the survey in hospitalized HZ patients, the most recent 900 NCSF HZ patients were selected from the Carenet database. The representativeness of both samples relative to the complete Carenet datasets was validated in terms of gender, age, length of hospital stay, and for CP only, season and complication group.

The questionnaires presented to the eligible persons contained the same questions about direct medical, non-medical indirect and personal costs as the questionnaires presented to ambulatory patients. However, these costs cover only the costs incurred before and/or after the stay in hospital. All direct medical costs incurred during the stay at the hospital were obtained from the Carenet database (e.g. per-day cost, costs of medical procedures, medication, care products). This database covers all costs to the national health system, and any co-payments by patients and their private insurance. The total cost of hospitalization for each patient was recalculated, by replacing the invoiced cost of stay (as reported in Carenet), by the hospital- and period-specific 100% cost per stay in that hospital multiplied by the number of days the patient remained in the hospital. This is because hospital per-day costs in Belgium are covered by two distinct systems of public health funding, and the invoiced per-day cost is only roughly about 20% of the total per-day opportunity cost [19].

The total direct medical cost of each hospitalized patient was thus calculated as the total direct medical cost of non-hospital care (obtained from the questionnaire) plus the total direct medical cost of the hospitalization itself (retrieved from the Carenet database and recalculated to represent the total per-day cost).

General information on CP and HZ disease

In addition to information on costs, the four NCSF surveys enquired about general characteristics of the CP and HZ episodes, as well as general background (an overview of the information requested is given in Table 1). Additionally, HZ patients were asked to give a score to the worst, least and average pain they experienced during their HZ episode.

Quality of life for CP patients

A survey was conducted through the Child & Family consultation offices. About 70% of children aged 0–3 years undergo regular check-ups at the Child &

Family consultation offices, located throughout Flanders. Questionnaires were distributed among Child & Family consultation offices, and completed in writing on a voluntary basis. Parents/carers completed the questionnaire within 6 months after their child experienced CP. The questionnaires were a shortened version of those used in the survey among ambulatory CP patients from NCSF (described above), and included additionally the EQ-5D-3L to estimate the loss in quality of life (http://www. euroqol.org/home.html). The survey started in mid-February 2010 and we received responses up to 7 July 2010. The quality-adjusted life days lost for each patient is calculated as 1 minus the EQ-5D-3L score multiplied by the number of days sick, and is calculated separately for patients consulting a physician (GPs as well as paediatricians), and patients not consulting a physician. As quality-adjusted life-days lost data are often highly skewed to the right (median much smaller than the mean), we fit a distribution to the data to estimate the average quality-adjusted life years (QALYs) lost due to a CP episode more accurately. Exploratory data analysis showed that the exponential distribution provided the best fit to the data. The expected value of an exponential distribution is 1/rate, and is modelled to depend on whether patients consult a physician ('consultPhys', 1 = yes, 0 = no):

$$1/\text{rate} = \beta_0 + \beta_1 \text{consultPhys}.$$

RESULTS

Rate of physician consultations

Chickenpox. The rate by which people visit a GP at least once for CP in Belgium is 346/100 000 person-years, and highest for children aged <10 years, with a peak at age 4 years (Fig. 1). The rates for boys and girls are similar and therefore not shown separately. The NSCF and Child & Family survey showed that 4% and 29%, respectively, of the people visiting a physician for CP only consulted a paediatrician and not a GP, and about 40% of the ambulatory CP patients do not consult a physician at all (Table 1).

Herpes zoster. The rate at which people visit a GP at least once for HZ in Belgium is 378/100 000 person-years, and increases with increasing age (Fig. 2). The NSCF survey showed that 99% of people with HZ consulted a GP at least once.

Table 1. *Characteristics of the hospitalized and ambulatory chickenpox (CP) and herpes zoster (HZ) patients obtained from respondents of five surveys*

Population covered	NCSF survey hospitalized CP (representative sample of NCSF members*)	NCSF survey ambulatory CP (NCSF members who responded to an open appeal)	Child & Family survey CP (children <3 years in Flanders, for whom parents/carers voluntary completed questionnaires presented at Child & Family consultation offices)	NCSF survey hospitalized HZ (representative sample of NCSF members†)	NCSF survey ambulatory HZ (NCSF members who responded to an open appeal)
Sample size	56	70	108	153	130
Survey completed by					
Person who had disease	10·5%	1·4%	0·0%	75·0%	94·0%
Parent	89·5%	97·2%	100·0%	0·0%	0·0%
Someone else (e.g. partner)	0·0%	1·4%	0·0%	25·0%	6·0%
Highest level of education within the family					
Higher	73·7%	91·4%	69·7%	24·2%	32·3%
General secondary	10·5%	4·3%	11·2%	13·7%	17·7%
Secondary technical	3·5%	4·3%	7·9%	11·8%	12·3%
Secondary vocational	12·3%	0·0%	10·1%	20·9%	17·7%
Primary school	0·0%	0·0%	0·0%	20·9%	15·4%
No diploma	0·0%	0·0%	0·0%	10·8%	3·8%
Duration of hospital stay (days)	4 (4·7) [2–13]	n.a.	n.a.	7 (10) [1–68]	NA
Duration of illness (days)	13 (13·7) [4–49]	6 (7)	7 (7)	60 (124) [3–892]c	34 (111) [0–2159]‡
First time HZ	n.a.	n.a.	n.a.	83%	78%
Suffer from other disease during HZ episode	n.a.	n.a.	n.a.	49%	40%
Post-herpetic neuralgia	n.a.	n.a.	n.a.	38·6%	25·8%
Scars from CP	71·9%	56%	n.a.	n.a.	n.a.
Medical care use					
Hospitalization	100·0%	0·0%	0·93% (1 person)	100·0%	0·0%
Emergency department without hospitalization	1·8%	0·0%	0·93% (1 person)	5·2%	5·3%
Specialist (e.g. paediatrician)	59·6%	7·1%	17·6%	53·6%	30·0%
General practitioner	50·9%	55·7%	48·1%	89·5%	98·5%
Ambulatory healthcare worker (e.g. nurse)	3·5%	0·0%	NA	20·9%	23·1%
No physician consultation	14·3%	42·9%	38·0%	3·9%	0·0%
Someone other than sick person interrupted working activities	71·4%	41·4%	42·6%	9·2%	0·8% (1 person)
Duration of interruption (days)	4 (6) [1–30]	2 (2) [0·5–8]	4 (4·7) [0·5–14]	2 (3) [0·5–10]	1
Sick person interrupted working activities	3·6% (2 persons)	0	n.a.	14·4%	19·2%
Duration of interruption (days)	10 and 30	n.a.	n.a.	15 (25) [4–128]	8 (10) [1–39]

NCSF, National Christian Sickness Fund; n.a., not available.

Results are shown either as a percentage of the number respondents that answered positively or as median (mean) [range].

* The sample did not differ significantly from the total Carenet dataset with respect to the distribution of CP cases by age, gender, month, length of stay and complication group, although it did not include very old patients who were hospitalized, patients who stayed in the hospital for >14 days, and patients with a chronic comorbidity.

† The sample did not differ significantly from the Carenet dataset with respect to the distribution of hospitalized HZ patients by gender and age. The sample, however, includes proportionally fewer patients aged >80 years and patients who stayed for a long time (>50 days) in the hospital.

‡ There were 32% of patients still suffering from HZ when completing the questionnaire.
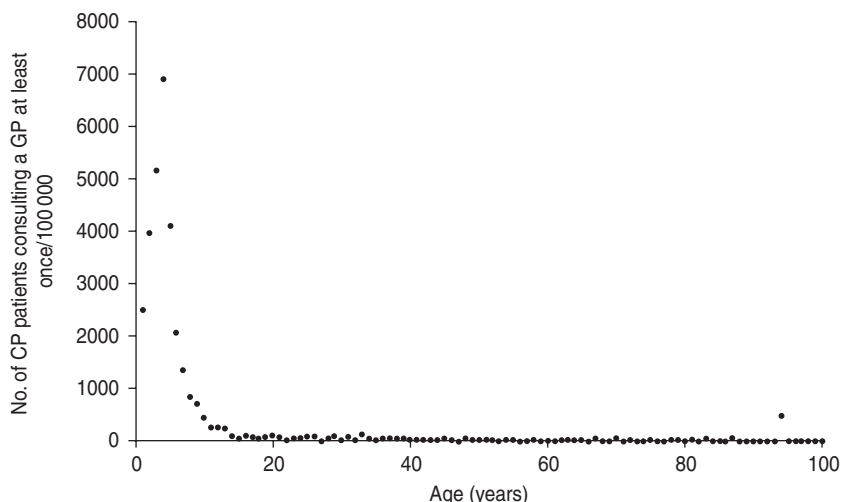
Fig. 1. Annual age-specific number of chickenpox (CP) patients that consult a general practitioner (GP) at least once, per 100 000 population (Scientific Institute of Public Health data, 2006–2008). As the observed rates for ages 102, 103 and 104 are very high (8402, 15 248 and 29 644/100 000, respectively), these points are not presented in this plot because it would make the plot less informative.
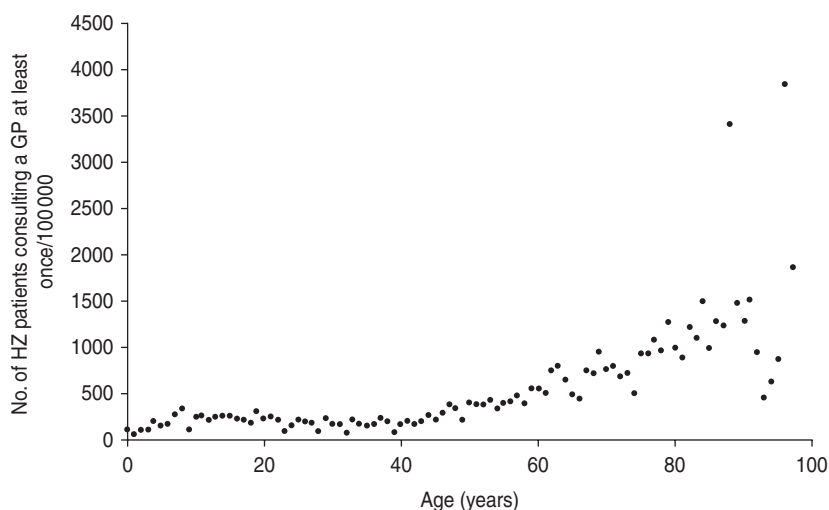

Fig. 2. Annual age-specific number of herpes zoster (HZ) patients with at least one general practitioner (GP) consultation per 100 000 (Scientific Institute of Public Health data, 2006–2008). As the observed rates for ages 102 and 103 are very high (8402 and 15 248/100 000, respectively), these points are not presented in this plot because it would make the plot less informative. Only patients for whom information on age and/or gender was available, are included (97·8%).

Rate of hospitalizations

Chickenpox. The hospitalization rate for primary cause CP in Belgium is on average 5·3/100 000 person-years, and peaks from April to June (monthly rates are shown in Fig. 3). The same peak in spring is observed from Carenet data (not shown). When including hospitalizations with CP coded in a secondary diagnostic field, the average annual rate is 8·9/100 000 person-years. Additionally, the CP hospitalization rate is highest for children aged <2 years and is

higher for boys compared to girls aged <4 years, and lower at age 4 years (Fig. 3). Of the hospitalized CP cases 40–45% had no complication, 10–15% had a mild skin infection and another 10–15% had an acute comorbidity which was possibly the primary reason for hospitalization.

Herpes zoster. The hospitalization rate for primary-cause HZ in Belgium is on average 14·2/100 000 person-years, and increases with increasing age (Fig. 4). As was the case for consultation rates, high
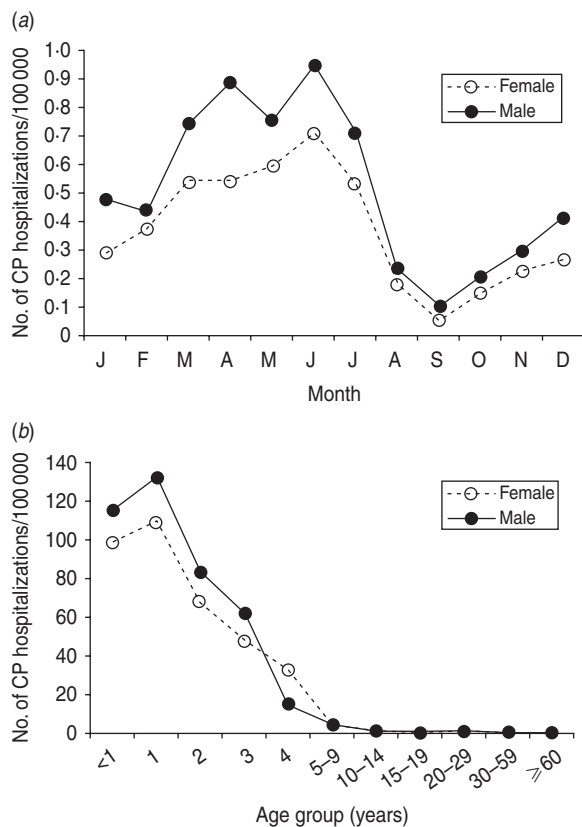
Fig. 3. (*a*) Average number of hospital admissions per month/100 000 population for primary-cause chickenpox (CP), by gender (Minimal Clinical Data database, 2000–2007). (*b*) Average annual number of hospital admissions/100 000 population for primary-cause CP, by age and by gender (Carenet database, 2007–2008).

variation in the hospitalization rates for very old ages is due to the very small number of persons of such age. Hospitalization rates showed no monthly trends (not shown).

Mortality rates

For the years 1998–2007 there were 193 deaths registered in the Flemish region with CP or HZ indicated as a cause of death.

Chickenpox. Seven deaths occurred in children, and were coded as potentially due to CP, and not to HZ. Two expert clinicians were in complete agreement and indicated that five of these seven children (age range 1.2–12.8 years) died because of CP, whereas they remained unsure about the remaining two children (aged 1.4 and 2.3 years, both girls). Considering only the five deaths for which both paediatric experts agreed were due to CP results in a CP mortality rate in the Flemish region of 0·050/100 000 person-years in

children aged < 15 years. Considering all seven deaths as due to CP results in a CP mortality rate of 0·070/ 100 000 person-years in children aged < 15 years. In adults, 14 potential deaths due to CP as a primary cause (age range 48–97 years) were evaluated by five expert clinicians. Considering all deaths for which at least four of the five clinical experts believed to be due to CP, results in a CP mortality rate in the Flemish region of 0·012/100 000 person-years in adults. Considering all 14 recorded deaths, but excluding those for which at least four of the five clinicians believed were not due to CP results in a CP mortality rate in the Flemish region of 0·018/100 000 person-years in adults.

Herpes zoster. No deaths due to HZ were recorded in children. From the 186 adult deaths recorded, only those for which HZ appeared as a primary cause of death were evaluated by the five expert clinicians (*n* = 59, age range 61–102 years). Considering all deaths for which at least four of the five experts believed were due to HZ (*n* = 10), results in a HZ mortality rate of 0·017/100 000 person-years. Considering all 59 recorded deaths, but excluding the 17 deaths for which at least four of the five clinicians believed were not due to HZ, results in a HZ mortality rate of 0·068/100 000 person-years.

Costs for ambulatory patients

Chickenpox. The median direct medical cost due to ambulatory-treated CP is €22 (40 % of respondents reported no costs, Table 2). The median direct medical cost for patients with comorbidity was €25 compared to €20 for patients without comorbidity. The costs for transport, non-reimbursed care products and non-reimbursed medication are presented in Table 3. Eight respondents had paid help at home, with associated costs ranging from €6 to €224. Forty-one per cent of the respondents reported work loss ranging from half a day up to 8 days, leading to a median cost of €0 based on the total sample (mean €153, maximum €1425) (Table 1).

Herpes zoster. The median direct cost due to ambulatory-treated HZ was €102 (Table 2). The direct costs for transport, non-reimbursed care products and non-reimbursed medication are presented in Table 3. Seven patients had paid help at home at a median cost of €14 (mean €81, maximum €415).

Table 2. *Summary total direct medical costs* (€) *for ambulatory chickenpox* (CP) *and herpes zoster* (HZ) *patients, and hospitalized CP and HZ patients* (*costs during hospital stay and costs outside the hospital setting*)

| | Ambulatory CP (n = 70) | Hospitalized CP (n = 56) | | Ambulatory HZ‡ (n = 131) | Hospitalized HZ‡ (n = 153) | |
		Costs during hospital stay†	Costs outside hospital		Costs during hospital stay†	Costs outside hospital
Minimum	0	1074	0	0	725	0
Median	22	2386	66	102	4136	215
Mean	21	2788	92	247	5438	456
Maximum	98	6058	531	2148	28 808	4765

* Total direct medical costs include costs of consultations, medical procedures, reimbursed medication and care products, and for hospitalized patients the costs of the hospitalization. Summary statistics based only on respondents who answered the cost-related questions.

† Includes 100 % per day cost (for details see the Methods section).

‡ There were 32 % still sick when completing the questionnaire, hence presented costs are an underestimation.
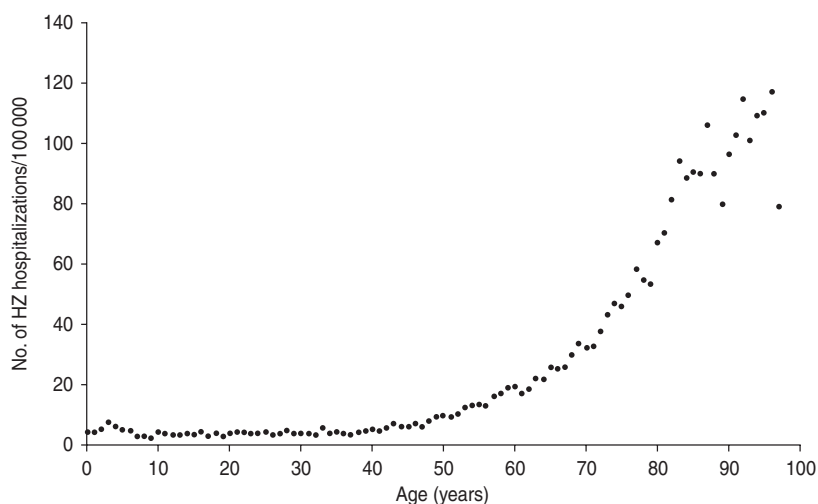

Fig. 4. Average annual number of hospital admissions/100 000 population for primary-cause herpes zoster (HZ), by age (Minimal Clinical Data database, 2000–2007).

Twenty-five respondents missed work for between one and 39 days, leading to a median cost of €0 for the complete sample (mean €234, maximum €4452) (Table 1). One respondent indicated that someone else could not go to work because of the respondent having HZ, and that this person missed work for 1 day (Table 1).

Costs for hospitalized patients

Chickenpox. NCSF questionnaire responses were obtained from 53 % of the persons receiving the questionnaire ('eligible persons'). The main reason why responses from eligible persons were not obtained was that 34 % of them could not be reached by telephone (no response to telephone calls or telephone number not available). Other reasons included: eligible persons did not want to participate in the survey (8 %), or were not members of NCSF (2 %). Based on the 57 completed questionnaires, the median direct medical cost due to CP that leads to hospitalization was €2386 (during hospitalization) and €66 (outside the hospital setting) (Table 2). The median direct medical cost for patients without any comorbidity was €2277, compared to €2867 for patients with a comorbidity (of which patients with a moderate bacterial infection of the skin, an infection of the joints or osteomyelitis reported the highest costs). There is a strong positive correlation between length of stay in the hospital and total direct medical costs, and a weaker, but still positive relationship between

Table 3. *Percentage of respondents that paid* $< €20$, *between* $€20$ *and* $€50$, *or* $> €50$ *for transport, non-reimbursed care products and non-reimbursed medication related to ambulatory chickenpox (CP) and herpes zoster (HZ) patients, and hospitalized CP and HZ patients*

	Ambulatory CP (*n* = 70)			Hospitalized CP (*n* = 56)		
	Transport	Care products	Medication	Transport	Care products	Medication
$< €20$	63%	84%	73%	32%	71%	57%
€20–50	0%	7%	4%	39%	9%	7%
$> €50$	0%	0%	0%	29%	11%	5%
No answer given	37%	9%	23%	0%	7%	25%
	Ambulatory HZ (*n* = 131)			Hospitalized HZ (*n* = 153)		
	Transport	Care products	Medication	Transport	Care products	Medication
$< €20$	69%	51%	22%	30%	48%	39%
€20–50	14%	14%	29%	29%	9%	19%
$> €50$	7%	13%	44%	38%	15%	20%
No answer given	11%	22%	5%	3%	31%	22%

total direct medical costs and the number of days sick (results not shown). The costs for transport, non-reimbursed care products and non-reimbursed medication are presented in Table 3. Three of the patients had paid help (e.g. a babysitter) of which the costs were €10, €50, and €100. Seventy-one per cent of the respondents interrupted their working activities because their child was hospitalized for CP, ranging from 1 to 30 days work loss, leading to a median cost of €447 (mean €562, maximum €2493) (Table 1). Four adults (>18 years) were hospitalized for CP, and two of them reported being unable to work for 10 and 30 days (giving an associated work loss cost of €1781 and €3605, respectively) (Table 1).

Herpes zoster. NCSF questionnaires were completed by 59% of the persons receiving the questionnaire ('eligible persons'). Similar to the CP questionnaires, 22% of the eligible persons could not be reached by telephone. Additionally, 10% of the eligible persons did not complete the questionnaire because of their overall poor health status at the time they were contacted, 3% because they did not want to participate in the survey, and 2% because the eligible person had died. Based on the 153 completed questionnaires, the median direct medical cost due to HZ leading to hospitalization is €4136 (during hospitalization) and €215 (outside the hospital setting) (Table 2). There is no clear relationship between total direct medical cost and the age of the patient, but there were extremely high costs for all patients aged >70 years (results not

shown). The costs for transport, non-reimbursed care products and non-reimbursed medication per HZ episode are presented in Table 3. Twelve patients had paid help at home at a median cost of €231 (range €1–2576). Fourteen per cent of the respondents missed work for between 4 and 128 days, leading to a median cost for the complete sample of €0 (mean €600, maximum €22 790) (Table 1). Fourteen respondents indicated that someone else could not go to work (for half a day up to 10 days) because of the respondent having HZ, leading to a median cost for the complete sample of €0 (mean €47, maximum €1781) (Table 1).

General information on CP and HZ disease obtained from the five surveys (Table 1)

On average, patients recover faster from CP than from HZ and stay in the hospital for a shorter period. About half of CP patients consult a GP, and 17% see a specialist (paediatrician), whereas almost all HZ patients consult a GP at least once during their HZ episode, and a large part also visit a specialist. More than half of the CP patients reported having scars from CP. A significant proportion of HZ patients reported having had a prior HZ episode (17–22%). Almost half of HZ patients suffered from another disease during their HZ episode, and 56% of the hospitalized and 38% of the ambulatory HZ patients were immunocompromised or had other conditions that would exclude them according to the exclusion
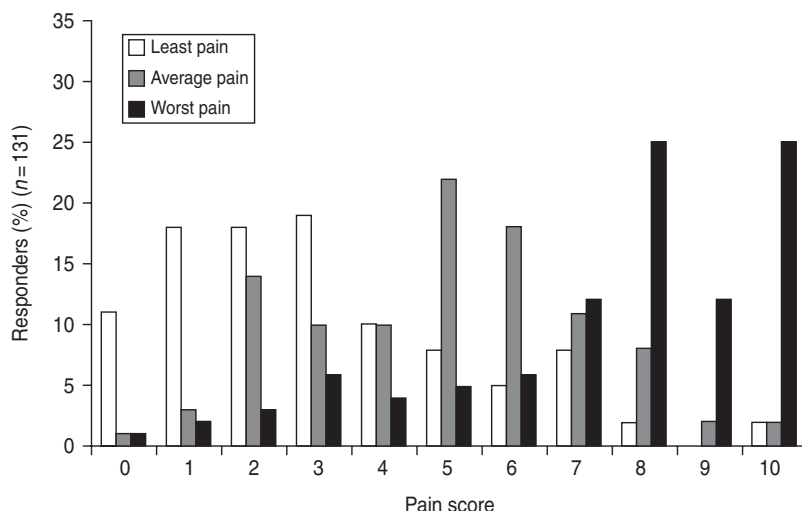
Fig. 5. Worst, least and average pain during the entire herpes zoster (HZ) episode of ambulatory HZ patients, on a scale from 1 (no pain) to 10 (worst pain imaginable). Pain scores were recorded retrospectively, from patients who had experienced HZ over the past year (average age 63 years, median 65 years).
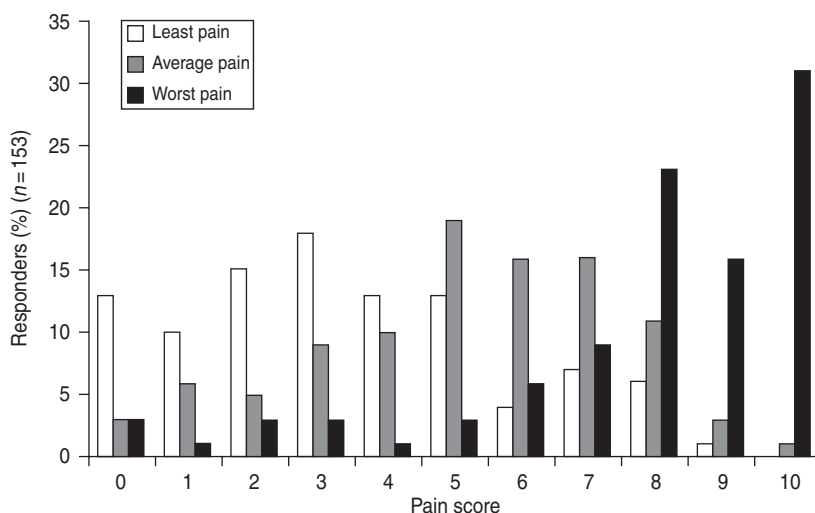

Fig. 6. Worst, least and average pain during the entire herpes zoster (HZ) episode of hospitalized HZ patients, on a scale from 1 (no pain) to 10 (worst pain imaginable). Pain scores were recorded retrospectively, from patients who had experienced HZ over the past year (average age 68 years, median 72 years).

criteria used in the Shingles Prevention Study [20]. The pain associated with HZ is presented in Figures 5 and 6. The proportion of hospitalized and ambulatory HZ patients with post-herpetic neuralgia (PHN) (defined as having a pain score of $\geqslant 3$ on the 'worst pain' question from the Zoster Brief Pain Inventory [21], and being sick for >90 days) is 39% and 26%, respectively. The proportion of respondents reporting that someone interrupted their working activities is much larger for persons caring for children with CP than for (partners of) persons having HZ.

Quality of life for CP patients

Twenty-eight (26%) of the 108 respondents of the Child & Family survey did not complete one or more of the EQ-5D-3L questions, probably because these questions were believed to be irrelevant for young children (e.g. one of the questions enquires if the child had problems caring for him/herself). Therefore unanswered questions were treated as if the child had no impairment on his/her quality of life unless there were any written comments indicating otherwise. This was the case for one respondent, who indicated that

his/her child had fever and low energy levels. The fitted parameters ($\beta_0 = 0.22$ and $\beta_1 = 0.33$) from the model $1/\text{rate} = \beta_0 + \beta_1 \text{consultPhys}$ are almost the same when including or excluding the one hospitalized CP patient. On average, a child with CP has 0.010 QALYs lost when consulting a physician (minimum 0, maximum 0.020), and 0.004 QALYs when no physician is consulted (minimum 0, maximum 0.053). These estimates are age-independent (within the relatively narrow age group we surveyed).

DISCUSSION

In order to estimate the health and economic burden of VZV-related diseases in Belgium we examined the hospitalization and physician consultation rates, the costs and the quality of life related to CP and shingles.

VZV-related physician consultations and hospitalizations

Based on the MCD and SIPH databases, the population-averaged rates at which a GP is visited at least once for CP and HZ are 346 and 378/100 000, respectively, and the CP and HZ hospitalization rates are 5·3 and 14·2/100 000 person-years, respectively, in Belgium. We believe that the rates presented are unlikely to suffer from underreporting: registering of each hospitalization is mandatory in Belgium (MCD), and the rate at which GPs are consulted at least once is based on data from sentinel GPs recording all HZ cases and CP cases (SIPH). It is, however, unclear how accurate the diagnosis and reporting of CP and HZ cases is in these two databases. Differences in the accuracy with which cases are reported, diagnosed and/or recorded may explain the variation in rates reported by different countries. For example, Brisson & Edmunds [22] estimated CP and HZ hospitalization rates of 4·5 and 4·4/100 000 person-years, respectively, and a CP GP consultation rate of 522/100 000 person-years, whereas Coplan et al. [23] estimated CP and HZ hospitalization rates of 2·6 and 2·1/100 000 person-years, respectively. These differences may of course also be caused by differences in the accessibility and/or organization of healthcare systems.

To estimate the total incidence of CP and HZ cases in Belgium, data are needed on the proportion of CP and HZ cases not consulting a physician, or consulting a physician other than a GP. The NCSF and the Child & Family survey both show that about 40% of the ambulatory CP patients do not consult a physician at all. However, the proportion of CP cases consulting a paediatrician and not a GP differs substantially between these two databases: 4% (NCSF survey) compared to 29% (Child & Family survey). Sample sizes of both surveys are relatively small and it is unclear which of the two surveys is most reliable. Unlike the NCSF survey, the Child & Family survey only covers children aged <3 years, for whom parents may be more likely to consult a paediatrician directly. The NCSF survey in ambulatory HZ patients shows that almost all patients (99%) consult a GP at least once during their HZ episode.

Annual and age-specific trends in rates are consistent with other studies (e.g. [22, 23]): the CP hospitalization rate shows a seasonal pattern with a peak from April to June [24] and is highest in children aged <5 years, the HZ hospitalization rate increases with increasing age, and CP-related deaths occur mostly in adults.

VZV-related costs

The direct medical cost for HZ is about twice as much as the direct medical cost for CP, possibly because patients with HZ are sick on average for a longer time. However, CP causes substantially more work loss, which results in higher indirect (work loss associated) costs. These results should be interpreted with care since there are a number of limitations with respect to the data on which these results are based. First, 32% of the respondents of the NCSF surveys in HZ patients were still suffering from HZ when they completed the questionnaire; hence costs related to HZ are likely to be underestimated. On the other hand, the survey in ambulatory HZ patients was voluntary, which may have led to a bias to respondents with more severe disease and therefore a possible overestimation of costs. Second, the majority of respondents for the survey in ambulatory CP patients were highly educated. This may have overestimated the average personal costs (not-reimbursed) associated with a CP episode. However, the major part of the costs associated with ambulatory CP episodes were found to be related to physician consultations, and we cannot infer whether bias in education level of the respondents would result in a biased picture of healthcare use for CP. Moreover, 10% of eligible persons for the NCSF survey in hospitalized HZ patients did not complete the questionnaire because

of their poor health status at the time of the survey. Consequently, the survey may be biased towards generally more healthy persons. Last, the presented indirect costs (associated with work loss) are based on relatively small numbers, and are calculated indirectly by multiplying the number of workdays lost with the average daily gross salary in Belgium (i.e. a human capital based approach, which is common in economics).

CP quality of life

The QALYs lost for ambulatory CP patients consulting a physician, is more than double that for those not consulting a physician (0·010 *vs.* 0·004). This is slightly higher than the average of 0·004 QALYs lost estimate based on a study in England & Wales [16]. Unfortunately, our study did not cover older children (>3 years) and children hospitalized for CP. Another limitation is that QALYs lost were measured retrospectively, whereas the EQ-5D-3L should ideally be completed during the illness. We know of no study that measured QALY loss due to CP in adults directly. Some studies derived it indirectly: Smith & Roberts [25] derived quality of life due to CP from a study of utility values for other medical conditions [26]. Merrett *et al.* [27] estimated QALY loss for newly arrived immigrants and refugees in Canada, to be 0·006, 0·009 or 0·012 for a CP case without complication, hospitalized for supportive care, and hospitalized for complications, respectively (based on Brisson & Edmunds [16] and Smith & Roberts [25]). The latter QALY loss estimates for adults are low compared to our estimates for children with CP.

Duration and severity of HZ

Hospitalized HZ patients spend a median of 7 days in the hospital and remain sick for a median of 60 days, whereas ambulatory HZ patients are on average sick for 34 days which is in accord with other published work (e.g. [28]), but not with others reporting 2 weeks median duration of pain (e.g. [29]). Note that on the one hand our estimates are possibly underestimated, as 32% of the patients were still sick at the time they completed the questionnaires, but on the other hand the duration of illness may be overestimated as the ambulatory HZ sample is possibly biased towards more severe cases. The proportion hospitalized HZ patients with PHN, defined as having a pain score of ⩾3 (on the 'worst pain' question) appearing or persisting 90 days after start of the disease, ranged from 30% in patients aged <60 years up to 53% in patients aged >80 years. As expected, these results for hospitalized HZ patients are greater than the PHN rates ranging from 7·7% to 24·1% described for the overall HZ population [20, 29–31]. Notably, 17% of the hospitalized and 22% of the ambulatory HZ patients reported that it was not the first time they had suffered from HZ. This percentage is rather high compared to the literature reporting proportions up to 5% [32]. A reason for this may be that the percentage is based on the answers of the patients and not on the judgement of a medical doctor. Possibly, patients erroneously consider two more severe periods of HZ with a milder period in between as two distinct HZ episodes. Moreover, 49% of the hospitalized and 40% of the ambulatory patients reported a co-morbidity, which is in accord with studies reporting that immunocompromised people have a higher risk for getting HZ [33]. Using the Shingles Prevention Study exclusion criteria [20] we noted a maximum exclusion rate for children hospitalized for HZ of 19%, in accord with Brisson & Edmunds [22], but largely discrepant with one Canadian study reporting 89% immunocompromised children [34]; however, the Canadian study focused on tertiary centres.

Particular challenges for estimating burden of (HZ) disease in elderly

The probability of developing HZ increases with increasing age, which causes the following difficulties for estimating the disease burden:

- Estimating how the HZ burden changes by age becomes increasingly more difficult for older ages, because the number of surviving elderly decreases rapidly with further increasing age.
- Older people are more likely to have comorbidities, which makes it more difficult to assess which deaths, costs and QALYs are related to HZ (and can be prevented by HZ vaccination). We assessed the HZ-related costs by conducting a survey, specifically enquiring about all costs related to HZ. However, respondents did not always find it easy to distinguish between costs related to HZ or another disease. Alternatively, a matched case-control study could be conducted, assessing the incremental costs due to HZ indirectly when comparing a population with HZ with a similar population without HZ [35, 36]. One of the major difficulties of such an

approach is, however, the choice of an appropriate control group and potential confounding of HZ patients and other chronic illnesses in immunologically weaker patients.

- Furthermore, as HZ can persist for a long time, short studies cannot capture all of the burden associated with HZ. For instance, 32% of the respondents of our surveys where still ill from HZ when they completed the questionnaire, implying that the costs estimated from these surveys are likely underestimated.

CONCLUSION

VZV causes a substantial health and economic burden in Belgium. The higher cost and morbidity related to HZ and the possibility of an increase in HZ incidence necessitate cost-utility analyses on strategies that substantially reduce the circulation of VZV, to calculate their impact against the two infectious diseases simultaneously.

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DECLARATION OF INTEREST

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