B-ENT, 2012, **8**, 153-165

A pilot cost-of-illness study on long-term complications/sequelae of AOM

D. Strens[1], *G. Knerer*[2], *I. Van Vlaenderen*[1] *and I. J. M. Dhooge*[3]

[1]Deloitte, Life Sciences Industry Consulting, Diegem, Belgium; [2]GlaxoSmithKline Vaccines, Building W23 (D2-014), Wavre, Belgium; [3]UZ Ghent, Belgium Ghent University Hospital, Faculty of Medicine, ENT-department, Ghent, Belgium

Key-words. Cost of illness; pilot study; otitis media; complications; sequelae

Abstract. *A pilot cost-of-illness study on long-term complications/sequelae following AOM. Objectives*: Acute otitis media (AOM) commonly affects young children and occasionally results in serious complications/sequelae. This pilot cost-of-illness study aimed to assess the economic burden of long-term AOM complications/sequelae in Belgium, and to establish a thorough methodology for a larger study.
Methodology: We retrospectively reviewed charts of patients aged 10-20 years with long-term complications/sequelae considered to be AOM-related, and ≥ 8 years of follow-up. From a list of 215 eligible patients, we selected 25 patients representing each of seven categories of complications/sequelae.
Results: Included patients had a mean age of 12.9 years; nine had chronic suppurative otitis media with cholesteatoma; six sensorineural hearing loss; six chronic perforation of the tympanic membrane; and one each with conductive hearing loss, facial paralysis, neurological impairment after intracranial complications, and complications of surgery. During 8-15 years of follow-up, the most common complications were hearing loss, chronic otitis media (OM), and cholesteatoma. These generally occurred > 5 years after the first AOM event, although chronic OM occurred after a mean time of 3.3 years. Yearly public health care payer (PHCP) costs ranged from € 119 to € 7957 per patient, and were highest for patients with sensorineural hearing loss. Yearly costs to the patients ranged from € 7 to € 289 per patient, and were also highest for patients with sensorineural hearing loss.
Conclusions: Although complications/sequelae of AOM are rare, they can result in substantial costs. The applied methodology should be feasible for a larger study, with some minor adjustments.

Introduction

Acute otitis media (AOM) is very common during childhood, and can occasionally result in various complications and long-term sequelae. Fortunately, since the introduction of antibiotics, such events are now much less common.[1] A retrospective chart review from Finland estimated the annual incidence of serious AOM complications (e.g. mastoiditis, labyrinthitis, facial paralysis, meningitis, brain abscess, and hydrocephalus) to be 1.1/100,000 in children aged 0-14 years.[2] However, a study that included less serious complications, such as perforation of the tympanic membrane, reported that around 5% of AOM episodes are associated with complications. (See Giaquinto C, Silfverdal SA, Garcia-Sicilia J, Liese J, Larcombe J, García-Corbeira P, Pirçon J-Y, Rosenlund M. Complications and treatment of acute otitis media in children. Poster 011 presented at the 6th World Society for Pediatric Infectious Diseases, Buenos Aires, Argentina, 2009.)

Sequelae of otitis media (OM) include chronic suppurative otitis media (CSOM), atelectasis of the middle ear, adhesive OM, cholesterol granuloma, tympanosclerosis, ossicular discontinuity/fixation, and hearing loss. Hearing loss can also be considered to be a complication, and can be conductive, sensorineural, or mixed. Conductive hearing loss occurs if the transmission of sound to the inner ear is disrupted (e.g. by adhesive OM, tympanosclerosis, or atelectasis of the middle ear), whereas sensorineural hearing loss is caused by damage to the inner ear, the acoustic nerve, or both (e.g. caused by labyrinthitis).

AOM complications can be classified as intracranial or intratemporal (extracranial), with the latter being much more common.[2] The most frequent intratemporal complication is perforation of the

Funding: Funding for this study, as well as for writing and editorial support, was provided by GlaxoSmithKline Biologicals SA.

tympanic membrane, (See Giaquinto C, Silfverdal SA, Garcia-Sicilia J, Liese J, Larcombe J, García-Corbeira P, Pirçon J-Y, Rosenlund M. Complications and treatment of acute otitis media in children. Poster 011 presented at the 6th World Society for Pediatric Infectious Diseases, Buenos Aires, Argentina, 2009.) which causes conductive hearing loss. Small perforations generally heal spontaneously[3] and the associated hearing loss is usually temporary. CSOM, a "chronic inflammation of the middle ear and mastoid cavity, which presents with recurrent ear discharges or otorrhoea through a tympanic perforation,"[4] occurs in around 0.4% of children in Europe.[4] CSOM can also occur with cholesteatoma, a serious complication in which keratinizing stratified squamous epithelium accumulates in the middle ear and/or mastoid process. Infection of the mastoid process (mastoiditis) is another serious intratemporal complication and can lead to other intratemporal or intracranial complications. Intracranial complications, such as meningitis, brain abscess, and dural sinus thrombosis, are less common[2] but more serious than intratemporal complications. Patients can ultimately suffer neurological problems, such as development delay and motor, cognitive, speech, or visual impairment. Complications can also arise as a result of surgical interventions in patients with complicated AOM; for example, facial paralysis occurs in ~0.4% of patients who receive cochlear implants to treat hearing loss.[5] Facial paralysis can also occur in patients with chronic OM not treated with surgery.[6]

The complexity and associated sequelae of AOM complications can result in substantial medical costs over time; however, in the literature we found no cost data related to the management of long-term sequelae of AOM. Such data would provide valuable cost-benefit information for determining the potential cost-effectiveness of new methods aimed at reducing AOM incidence and/or complications/sequelae. Therefore, the objectives of the present study were to assess the economic burden associated with AOM leading to long-term (8-15 years after the first AOM event) complications/sequelae in Belgium. This was a pilot study designed to establish a thorough methodology for conducting a cost-of-illness study in a broader population, and to determine whether it is feasible to collect the data over a time period of 8-15 years after the occurrence of the first AOM event.

Materials and methods

Type of Study

In this pilot cost-of-illness study, a retrospective patient chart review was performed to assess the patterns of medical resource consumption and the direct costs related to the management of patients who developed complications/sequelae considered to be related to AOM.

Study population

Eligible patients were aged 10-20 years and had experienced at least one of the following complications/sequelae of AOM: (1) conductive hearing loss (air-bone gap ≥ 15 dB); (2) sensorineural hearing loss (> 20 dB at 6 and 8 kHz); (3) treated chronic perforation of the tympanic membrane; (4) persistent facial paralysis; (5) treated CSOM with cholesteatoma; (6) residual neurological impairment as a consequence of an intracranial complication (meningitis, extradural abscess, subdural/epidural empyema/abscess, brain abscess, sigmoid/dural sinus thrombosis, or otitic hydrocephalus); and (7) complications associated with surgical interventions for complicated AOM (facial nerve injury, hearing loss, vertigo, meningitis, cerebrospinal fluid leak, brain herniation, or altered taste sensation).

Patients were considered to have a sequela if their condition did not return to normal following a complication. Patients were also required to have had ≥ 10 years of follow-up since the first occurrence of AOM; however, a follow-up of < 10 years was allowed in some cases (minimum: 8.4 years) to achieve patient recruitment in all patient groups.

Patients were excluded if they had participated in a clinical trial related to AOM treatment during the study period, died during the first 10 years after the initial AOM event, or suffered from an otological or neurological problem or complication not related to AOM.

As this was a pilot study, the target sample size was 10-30 patients. A list of eligible patients was prepared at the University Hospital of Ghent, Belgium. The original intention had been to randomly select five patients from each of the above-listed seven groups of complications/sequelae; if less than five patients were available for a group, then all patients were to be selected. The ethics committee of the study centre approved the protocol, and informed consent was obtained from all participants.

Study period

The start date of the study period was the date of the first AOM event; medical resource use data were collected over a period of 8-15 years from this date. The end date of the study period was either the date at which the patient was selected by the investigator (if the selection date was ≤ 15 years after the start date) or the start date + 15 years (if the selection date was > 15 years after the start date).

Data collection, management, and analysis

The following data were collected by the study centre using a case report form: demographic data (date of birth, gender), AOM-specific information (age at first AOM event, age at first visit to an ear, nose, and throat (ENT) specialist at the study centre, and number of AOM events), data related to AOM complications (type, number, date(s), and outcome) and sequelae (type), and medical resource use data associated with AOM and its complications/sequelae (drugs, non-drug interventions, healthcare professional visits, laboratory tests, imaging, audiometric tests, hospitalizations, outpatient procedures, and hearing aids). Data collection, data analysis, follow-up, and reporting were performed by Deloitte, in collaboration with J. M. Dhooge.

Main outcome measure

The main outcome measure was the medical resource use directly related to AOM and to the management of complications and sequelae considered to be related to AOM. These data were used to calculate yearly costs.

Cost analysis

For the overall study period, we calculated the mean ± standard deviation (SD) and median (range) of the yearly costs per patient by patient group. Costs for each year of the study were also calculated, as well as the costs both from the public health care payer (PHCP) perspective and the patient perspective, according to the guidelines of the Belgian Health Care Knowledge Centre (KCE): "Richtlijnen voor farmaco-economische evaluaties in België".[7] Based on the medical consumption data, costs were calculated by multiplying each item of medical resource use by its respective unit cost from the PHCP perspective (RijksInstituut voor Ziekte-en Invaliditeitsverzekering/Institut National d'Assurance Maladie-Invalidité [RIZIV/INAMI]; http://www.inami.fgov.be/) and from the patient's perspective (reference year April 2010). Cost details are shown in Appendix Tables 1 and 2.

Results

Patient characteristics

A total of 215 patients were eligible for inclusion in the study: eight in Group 1, 13 in Group 2, 82 in Group 3, one in Group 4, 105 in Group 5, five in Group 6 and one in Group 7. Between September 2009 and May 2010, 25 of these patients were enrolled in this retrospective chart review, including one with conductive hearing loss (Group 1), six with sensorineural hearing loss (Group 2), six with chronic perforation of the tympanic membrane (Group 3), one with facial paralysis (Group 4), nine with CSOM with cholesteatoma (Group 5), one with neurological impairment after intracranial complications (Group 6), and one with complications of surgery (Group 7). Although more patients were available for some groups, they could not all be selected because no informed consent was obtained or insufficient data were available about the management before being treated in the participating centre. Characteristics of these 25 patients are shown in Table 1.

AOM complications and sequelae

Table 2 gives an overview of the observed complications in the whole study population; most commonly hearing loss, chronic OM, and cholesteatoma. Most complications occurred > 5 years after the first AOM event, with the exception of chronic OM, which occurred after a mean time of 3.3 years. Intracranial complications were only seen in one patient, who had meningitis and an epidural abscess following acute mastoiditis. Table 2 also shows how many patients with each complication suffered from long-term sequelae, e.g. of the 14 patients with hearing loss, eight suffered long-term hearing loss.

Resource use

Table 3 shows the mean ± SD and median (range) of the yearly resource use over the entire study period. All patients visited an ENT specialist, with 0.61-2.73 visits per year. The patient with a surgical complication (Group 7) was the only patient in this study to require physiotherapy; these visits were for facial nerve paralysis treatment and they occurred ~60 times each year for 3 years, equating to 20.8 visits/year over 8.7 years of follow-up. The most

Table 1
Patient characteristics

	Patients (n = 25)
Males, *n* (%)	13 (52)
Age at recruitment, years	
Mean ± SD	12.9 ± 2.7
Median (range)	13 (8-20)
Age at first AOM event, years	
Mean ± SD	2.4 ± 2.2
Median (range)	2 (0-8)
Age at first ENT specialist visit at study centre, years*	
Mean ± SD	5.6 ± 3.7
Median (range)	6 (0-17)
Number of AOM events during the study period	
Mean ± SD	6.9 ± 3.0
Median (range)	7 (3-15)
Follow-up time after first AOM event, years	
Mean	10.9 ± 2.3
Median (range)	10.2 (8.4-15.0)
Patient groups, *n* (%)	
1. Conductive hearing loss	1 (4)
2. Sensorineural hearing loss	6 (24)
3. Treated chronic perforation of the tympanic membrane	6 (24)
4. Persistent facial paralysis	1 (4)
5. Treated CSOM with cholesteatoma	9 (36)
6. Residual neurological impairment as a consequence of intracranial complications	1 (4)
7. Complications associated with surgical interventions for complicated AOM	1 (4)

AOM: acute otitis media; CSOM: chronic suppurative otitis media; ENT: ear, nose, and throat; GP: general practitioner; SD: standard deviation.
*Data for the years prior to this visit were collected from GPs, paediatricians, or other ENT specialists.

Table 2
AOM complications and sequelae considered to be related to AOM

Complication	Patients, *n* (%)	Duration between first AOM and occurrence of complication, years		Complications resulting in long-term sequelae*, *n* (%)
		Mean	Median	
Intratemporal	24 (96)			
Hearing loss	14 (56)	5.3	5	8 (32)
Chronic OM	14 (56)	3.3	3	5 (20)
Cholesteatoma	9 (36)	7.1	8	3 (12)
Facial paralysis	2 (8)	5.0	5	1 (4)
Intracranial†	1 (4)			
Meningitis	1 (4)	7.0	7	1 (4)
Epidural abscess	1 (4)	7.0	7	0

AOM, acute otitis media; OM, otitis media.
*Patients whose condition did not returned to normal after the occurrence of a complication.
†One patient experienced both meningitis and epidural abscess following acute mastoiditis.

commonly performed outpatient test was audiometry, which occurred 0.13-1.85 times each year. The most common surgical procedure was the insertion of ventilation tubes, which occurred 0-1.03 times/year and was mainly performed in an outpatient setting within 5 years of the initial AOM event. Hospitalizations were infrequent, but occurred in all patient groups except for Group 1 (conductive hearing loss). Hospitalizations were mainly for surgical procedures, although the patient

Table 3

Medical resource use (units/year) per patient during the study period*

Resource	Group 1 (n = 1)	Group 2 (n = 6)		Group 3 (n = 6)		Group 4 (n = 1)	Group 5 (n = 9)		Group 6 (n = 1)	Group 7 (n = 1)
		Mean ± SD	Median (range)	Mean ± SD	Median (range)		Mean ± SD	Median (range)		
ENT specialist visit	1.02	2.05 ± 0.50	2.00 (1.45-2.63)	1.77 ± 0.51	1.63 (1.35-2.73)	1.22	1.32 ± 0.57	1.09 (0.61-2.54)	1.55	2.54
Physiotherapy visits	0	0	0	0	0	0	0	0	0	20.80
Audiometry	0.48	0.97 ± 0.51	0.93 (0.41-1.85)	0.38 ± 0.21	0.34 (0.19-0.71)	0.75	0.51 ± 0.30	0.47 (0.13-1.04)	0.31	1.39
Ventilation tubes†	0.20	0.30 ± 0.35	0.20 (0-0.97)	0.25 ± 0.14	0.23 (0.10-0.47)	0	0.26 ± 0.30	0.17 (0-1.03)	0	0.12
Hospitalization	0	0.09 ± 0.11	0.04 (0-0.23)	0.12 ± 0.08	0.12 (0-0.23)	0.09	0.21 ± 0.08	0.22 (0.07-0.35)	0.31	0.23
Brain CT	0.20	0.09 ± 0.08	0.10 (0-0.22)	0.09 ± 0.11	0.06 (0-0.29)	0.38	0.16 ± 0.06	0.15 (0.08-0.24)	0.21	0
Laboratory test	0	0.11 ± 0.18	0 (0-0.43)	0.05 ± 0.09	0 (0-0.20)	0	0.09 ± 0.09	0.09 (0-0.27)	0.10	0
Hearing aid	0.14	0.24 ± 0.24	0.24 (0-0.65)	0	0	0	0	0	0	0
Anaesthesia for CT or MRI‡	0	0.02 ± 0.04	0 (0-0.10)	0.03 ± 0.08	0 (0-0.19)	0.09	0.02 ± 0.05	0 (0-0.13)	0	0

CT: computed tomography; ENT: ear, nose, and throat; MRI: magnetic resonance imaging; SD: standard deviation. Group 1 = conductive hearing loss; Group 2 = sensorineural hearing loss; Group 3 = treated chronic perforation of the tympanic membrane; Group 4 = persistent facial paralysis; Group 5 = treated CSOM with cholesteatoma; Group 6 = residual neurological impairment as a consequence of intracranial complications; Group 7 = complications associated with surgical interventions for complicated AOM.
*Calculated by summing up the number of specific resources per patient per year and dividing by the numbers of years of the study period.
†Bilateral insertion of ventilation tubes on the same day was considered as one procedure.
‡Including day clinic.

with neurological impairment (Group 6) was hospitalized twice for intracranial complications, and the patient in Group 7 was hospitalized for a complication (facial paralysis) after a surgical procedure.

Costs

Yearly PHCP costs varied widely for different patients (Table 4). The highest yearly hospitalization cost was €1079 for the patient with neurological impairment (Group 6); hospitalization costs ranged from 0 to €727 in the other groups. Group 2 (sensorineural hearing loss) patients had the highest mean cost for outpatient procedures (€163), as well as the highest individual cost (€520); this group also had the highest yearly cost of hearing aids (mean: €1564), mainly due to four cochlear implants (each costing ~€20,000) in two patients. The yearly cost of hearing aids for the patient in Group 1 (conductive hearing loss) was €150; however, this patient also had the highest cost for hearing aids from the patient's perspective (Table 5), due to a bone-anchored hearing aid (BAHA), for which patients pay €1667 (compared to €150 towards cochlear implants) and the PHCP pays €1143 (Appendix Table 1). Total yearly costs varied from €119 to €7957, with both the lowest and highest costs in Group 2 (Table 4).

Yearly costs from the patient's perspective (Table 5) were generally low, apart from the high hearing aid cost for the BAHA in Group 1 (conductive hearing loss; €114). The main cost in Groups 2 and 7 was for health care professional visits (mainly ENT visits); while in Groups 4, 5, and 6, the highest cost was for hospitalizations (Table 5).

Figure 1A shows the mean PHCP annual costs during the pre-complication years, as well as during the year of the complication, and the post-complication years. During the year of the complication, the highest cost was €10,922 for the patient in Group 6 (neurological impairment); high costs were also incurred in Groups 2, 4, and 7. During the post-complication years, the highest mean yearly cost was in Group 2 (sensorineural hearing loss; €2928) due to expensive cochlear implants. Median cost results were generally quite similar to the means, except in Group 2, where the median costs during the complication and post-complication years were less than half the mean values (€2494 and €966, respectively), due to high hearing aid costs for one patient.

From the patient's perspective, the highest mean costs during the year of the complication were for the two patients in Group 6 (neurological impairment; €647) and Group 7 (surgical complication; €508), and the highest mean costs in the post-complication period were for the patient in Group 1 (due to the BAHA) (Figure 1B). Median cost results were generally similar to the means, although the complication and post-complication year costs for Group 2 were much lower than the means (€11 and €25, respectively), largely due to high visit costs for one patient.

Discussion

In this small pilot cost-of-illness study which included 25 patients with complications/sequelae considered to be related to AOM, the most common complications were hearing loss, chronic OM, and cholesteatoma. PHCP costs for complications/sequelae of AOM ranged from €119 to €7957 per patient per year, with the highest mean cost in Group 2 (sensorineural hearing loss), mainly due to cochlear implants. In Groups 3-7, the greatest cost was for hospitalizations; while in Group 1 (conductive hearing loss), outpatient procedures and hearing aids made up the majority of the PHCP costs. Although ENT specialist and physiotherapist visits occurred much more frequently than hospitalizations and hearing aids, the high cost of cochlear implants and hospitalization meant that these costs were predominant. To the best of our knowledge, this is the first study to report on costs of long-term complications/sequelae of AOM; therefore, it is not possible to compare these findings with those of other studies. Another healthcare cost study carried out in Belgium reported that the annual health management cost of children with attention-deficit hyperactivity disorder (ADHD) is €688 (calculated by subtracting the PHCP cost of the control group from that of the ADHD group and updating 2002 costs to 2010 costs),[8] which is lower than the mean cost of treating patients with AOM complications in Groups 2, 6, and 7 in the current study.

Although a relatively small proportion of AOM cases result in complications/sequelae, a substantial number of children are still affected, due to the high incidence of AOM. In just one hospital, 215 patients were eligible for inclusion in this study, and for the 25 patients included, the total cost amounted to over

Table 4

Yearly costs per patient from the PHCP perspective by patient group

Resource	Group 1 (n = 1)	Group 2 (n = 6)		Group 3 (n = 6)		Group 4 (n = 1)	Group 5 (n = 9)		Group 6 (n = 1)	Group 7 (n = 1)
		Mean ± SD	Median (range)	Mean ± SD	Median (range)		Mean ± SD	Median (range)		
Hospitalizations, €	0	216 ± 288	121 (0-727)	198 ± 146	173 (0-381)	288	343 ± 119	369 (110-466)	1079	527
Outpatient procedures, €	161	163 ± 184	84 (35-520)	141 ± 62	132 (59-240)	34	107 ± 74	89 (0-275)	0	59
Healthcare professional visits[1], €	21	246 ± 336	46 (29-816)	40 ± 10	39 (28-55)	24	26 ± 11	22 (12-51)	38	249
Hearing aids, €	150	1564 ± 2572	454 (0-6617)	0	0	0	0	0	0	0
Drugs, €	2	1 ± 1	1 (0-2)	19 ± 29	2 (0-70)	2	5 ± 8	1 (0-23)	7	6
Laboratory tests, €	0	3 ± 3	3 (0-9)	1 ± 2	0 (0-6)	0	3 ± 2	3 (0-7)	3	0
Other tests (imaging, audiometric), €	40	89 ± 76	65 (35-237)	30 ± 31	13 (10-88)	57	30 ± 8	32 (17-47)	34	31
Total, €	374	2283 ± 3002	1155 (119-7957)	429 ± 121	455 (237-551)	405	514 ± 167	556 (296-793)	1160	871

[1] Health care professional visits include mainly ENT visits.

PHCP: public health care payer. Group 1 = conductive hearing loss; Group 2 = sensorineural hearing loss; Group 3 = treated chronic perforation of the tympanic membrane; Group 4 = persistent facial paralysis; Group 5 = treated CSOM with cholesteatoma; Group 6 = residual neurological impairment as a consequence of intracranial complications; Group 7 = complications associated with surgical interventions for complicated AOM.

Table 5

Yearly costs per patient from the patient's perspective by patient group

Resource	Group 1 (n = 1)	Group 2 (n = 6)		Group 3 (n = 6)		Group 4 (n = 1)	Group 5 (n = 9)		Group 6 (n = 1)	Group 7 (n = 1)
		Mean ± SD	Median (range)	Mean ± SD	Median (range)		Mean ± SD	Median (range)		
Hospitalizations, €	0	10 ± 12	5 (0-27)	14 ± 10	12 (0-27)	20	26 ± 11	24 (8-46)	60	40
Outpatient procedures, €	0	0	0	0	0	0	0	0	0	0
Healthcare professional visits[1], €	3	74 ± 110	7 (4-261)	6 ± 2	5 (4-8)	3	3 ± 1	3 (2-7)	6	56
Hearing aids, €	114	11 ± 21	0 (0-52)	0	0	0	0	0	0	0
Drugs, €	1	0 ± 0	1 (0-1)	12 ± 18	2 (0-45)	1	2 ± 3	1 (0-8)	2	2
Laboratory tests, €	0	0	0	0	0	0	0 ± 0	0 (0-1)	0	0
Other tests (imaging, audiometric), €	2	4 ± 2	4 (2-7)	2 ± 1	2 (1-3)	4	2 ± 1	2 (1-4)	2	5
Total, €	120	99 ± 131	21 (7-289)	33 ± 13	31 (23-59)	28	34 ± 14	37 (12-57)	71	103

[2] Health care professional visits include mainly ENT visits

Group 1 = conductive hearing loss; Group 2 = sensorineural hearing loss; Group 3 = treated chronic perforation of the tympanic membrane; Group 4 = persistent facial paralysis; Group 5 = treated CSOM with cholesteatoma; Group 6 = residual neurological impairment as a consequence of intracranial complications; Group 7 = complications associated with surgical interventions for complicated AOM.

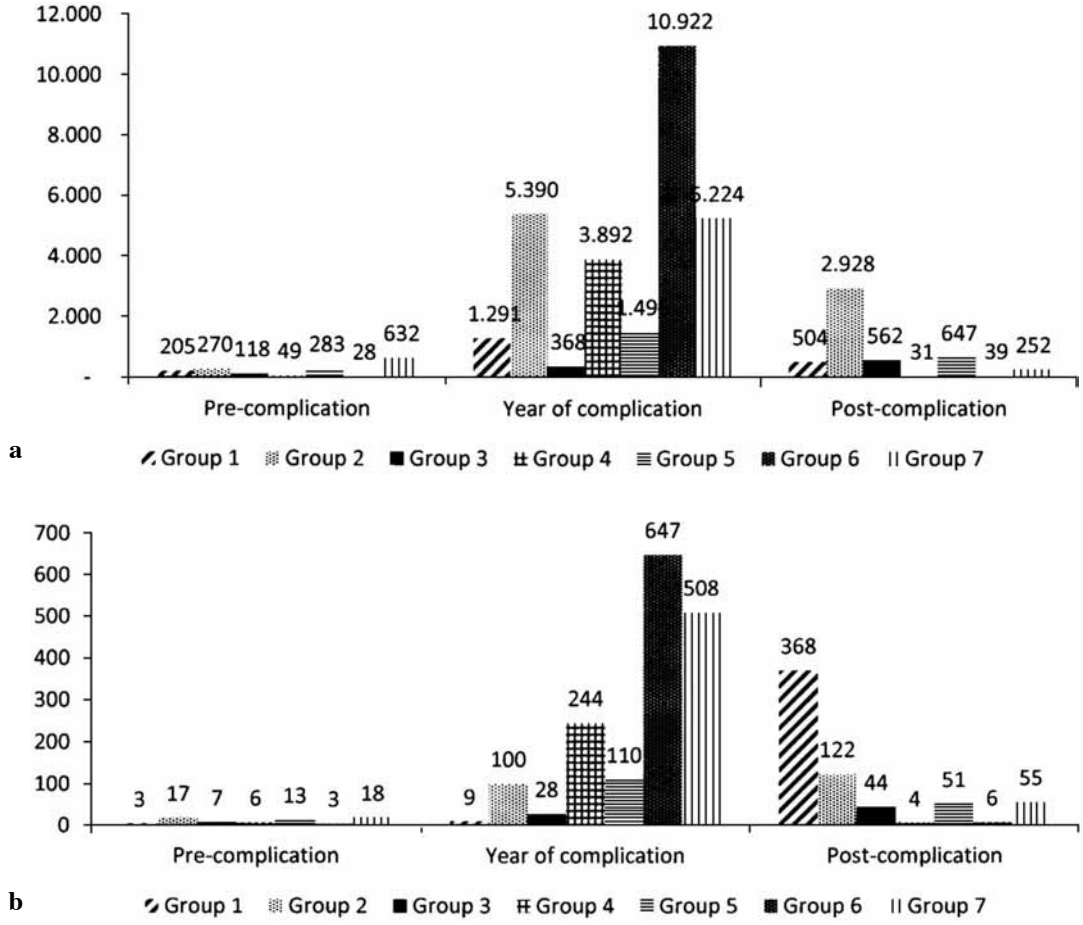

Figure 1

Mean yearly cost from the (a) PHCP and (b) patients' perspective during the following time periods: pre-complication, year of the complication, and post-complication. PHCP, public health care payer. Group 1 = conductive hearing loss; Group 2 = sensorineural hearing loss; Group 3 = treated chronic perforation of the tympanic membrane; Group 4 = persistent facial paralysis; Group 5 = treated CSOM with cholesteatoma; Group 6 = residual neurological impairment as a consequence of intracranial complications; Group 7 = complications associated with surgical interventions for complicated AOM.

€ 250,000 (PHCP plus patient perspective costs) for the duration of the study. It is therefore clear that complications/sequelae of AOM result in a considerable economic burden. Complications/ sequelae can also affect the quality of life of those affected. For example, CSOM can cause deafness, delayed intellectual development, limited employability, and a disturbed social life.[4]

As already mentioned, the incidence of AOM complications has decreased since the introduction of antibiotics.[1,9,10] Furthermore, the incidence of mastoiditis is reportedly higher in countries where antibiotic use for AOM is discouraged, compared to countries where antibiotic use for AOM is very common (3.8 vs. 1.2-2.0 per 100,000 person-years among children aged 0-14 years).[11] However, it has been postulated that AOM complications could become more common as antibiotic resistance increases.[12] Indeed, various studies have reported an increasing incidence of suppurative complications,[10] particularly mastoiditis,[13-17] although other studies have not found such an increase.[18,19] While it is not yet clear whether increasing antibiotic resistance is affecting the incidence of complications such as mastoiditis, high levels (ranging from 29%[17] to 88%[14] in the US (where there is a very high rate of antibiotic prescriptions for AOM[11])) of penicillin-resistant *Streptococcus pneumoniae* strains have been found in patients with mastoiditis. These values are much higher than the 4% penicillin resistance found among children with AOM (without mastoiditis) due to *S. pneumo-*

niae in Denmark, where antibiotic use for AOM is low.[20]

Vaccination against pathogens such as *S. pneumoniae* and non-typeable *Haemophilus influenzae*, which tend to result in more severe OM and complications than other pathogens, has the potential to reduce the disease burden of AOM and its complications/sequelae.[21,22] This practice should have the added advantage of reducing antibiotic consumption and hence antibiotic resistance. For example, a study in France found that introduction of the pneumococcal conjugate vaccine, coupled with a plan to reduce antibiotic use for AOM, resulted in less antibiotic usage, less pneumococcal nasal carriage, and reduced rates of highly penicillin-resistant strains.[23] The results of the present study underscore the importance of considering the financial burden of the complications of OM in justifying the cost of vaccination.

In the current study, the original intention had been to recruit five patients from each of the seven patient groups, but this was not feasible. Conductive hearing loss (Group 1) is a prevalent sequela of AOM, but only one patient could be selected for this group because conductive hearing loss is generally due to chronic perforation of the tympanic membrane, and patients with this complication were allocated to Group 3 ($n = 6$). It was also only possible to recruit one patient in each of the facial paralysis, intracranial complications, and surgical complications groups (Groups 4, 6, and 7). This is mainly because these are rarer complications, and it was not possible to obtain informed consent for further patients, or data on management before treatment in the participating centre was not provided. This was compounded by the fact that some patient groups were retrieved by means of the hospital IT system, which changed during the course of the study period. If the complication occurred before the system change, patients could not be retrieved. This issue mainly affected the data of patients with intracranial complications. Ultimately, most patients were recruited in the CSOM + cholesteatoma ($n = 9$), sensorineural hearing loss ($n = 6$), and perforated tympanic membrane ($n = 6$) groups. This was in contrast to the original plan; however, as these are the most prevalent complications of AOM, this probably provides a more representative sample of patients than including five from each group.

Regarding follow-up time, the original objective had been to follow patients for 10-15 years from the first AOM event. However, in order to be able to recruit at least one patient in each of the seven groups, six patients had a shorter follow-up time (minimum: 8.4 years). Data for the full 15 years were only available for four patients.

One limitation of this study was that prior to the first visit to the study centre (at a mean age of 5.6 years), the only available data were from general practitioners (GPs), paediatricians, and other ENT specialists; these data were less detailed than those collected in the study centre. This might explain the rather high mean age at the time of first AOM event (2.4 years). Furthermore, some of the early information on resource use was incomplete; thus, the costs for the pre-complication period could be underestimated, and these results should be evaluated with caution. We also acknowledge that the relationship between otological diseases and AOM is very complex, and while it is likely that the complications and sequelae included in this study were caused by AOM, such a link cannot be proven. Other weaknesses are the restricted number of patients and the fact that they were all recruited from one study centre. However, this was a pilot study; thus, its results should be taken as indicative rather than factual, and should be interpreted with these drawbacks in mind.

Although data collection by the study centre was complicated, we think that with some minor changes the applied methodology would be feasible in a larger population. Proposed changes include defining the study period from the time of AOM complication (rather than first AOM event) to recruitment, having no time constraints on the length of follow-up (rather than only 8-15 years), including patients of any age (rather than only 10-20 years), and including patients based on the prevalence of complications (rather than a certain number per group) in order to have a representative sample. Removing the restrictions on age and length of follow-up would increase the number of eligible patients. Another advantage of including patients of any age is that patients with conductive hearing loss due to tympanosclerosis — which usually occurs after the age of 20 years — could be included. Having no requirement for pre-complication data (other than age at first AOM) would also increase the number of eligible patients; however, an alternative approach would need to be used if it was considered important to collect accurate data regarding the

resource use consumption during the period between occurrence of first AOM and occurrence of a complication.

Conclusions

The most common complications/sequelae of AOM in this group of patients were hearing loss, chronic OM, and cholesteatoma. Complications/ sequelae generally occurred around 5-7 years after the first AOM event and resulted in considerable long-term PHCP costs. PHCP costs amounted to € 119 to € 7957 per year per patient with complications, mainly driven by hearing aids and hospitalizations. In general, the applied methodology used in this pilot cost-of-illness retrospective patient chart review is considered to be feasible for a larger study, with some minor adjustments.

Acknowledgements

The authors acknowledge Gudrun Serraes for data collection and Abdelilah Ibrahimi (XPE Pharma and Science c/o GlaxoSmithKline Vaccines) for editorial assistance and manuscript coordination. Writing and editorial assistance during the preparation of this manuscript was provided by Jenny Lloyd and funded by GlaxoSmithKline Biologicals SA.

Conflict of Interest

At the time that this study was conducted, D. Strens and I. Van Vlaenderen were employees of Deloitte, and G. Knerer was an employee of GlaxoSmithKline group of companies. I. Dhooge's institution has received funding from GlaxoSmithKline Biologicals SA.

References

1. Leskinen K. Complications of acute otitis media in children. *Curr Allergy Asthma Rep*. 2005;5(4):308-312.
2. Leskinen K, Jero J. Complications of acute otitis media in children in southern Finland. *Int J Pediatr Otorhinolaryngol*. 2004;68(3):317-324.
3. Davidson BJ, Morris MS. The perforated tympanic membrane. *Am Fam Physician*. 1992;45(4):1777-1782.
4. World Health Organization. *Chronic suppurative otitis media: Burden of Illness and Management Options*. Geneva, Switzerland, 2004. Available at: http://www.who.int/pbd/deafness/activities/hearing_care/otitis_media.pdf. Accessed January 17, 2012.
5. Roland JT. Complications of cochlear implant surgery. In: Waltzman SB, Cohen NL, Eds. *Cochlear implants*. Thieme Medical Publishers, New York, 2000:171-175.
6. Ozbek C, Somuk T, Ciftçi O, Ozdem C. Management of facial nerve paralysis in noncholesteatomatous chronic otitis media. *B-ENT*. 2009;5(2):73-77.
7. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. *Richtlijnen voor farmaco-economische evaluaties in België. KCE reports 78A*. Federaal Kenniscentrum voor de Gezondheidszorg, Brussel, 2008.
8. De Ridder A, De Graeve D. Healthcare use, social burden and costs of children with and without ADHD in Flanders, Belgium. *Clin Drug Investig*. 2006;26(2):75-90.
9. House HP. Otitis media; a comparative study of the results obtained in therapy before and after the introduction of the sulfonamide compounds. *Arch Otolaryngol*. 1946;43:371-378.
10. Zapalac JS, Billings KR, Schwade ND, Roland PS. Suppurative complications of acute otitis media in the era of antibiotic resistance. *Arch Otolaryngol Head Neck Surg*. 2002; 128(6):660-663.
11. Van Zuijlen DA, Schilder AG, Van Balen FA, Hoes AW. National differences in incidence of acute mastoiditis: relationship to prescribing patterns of antibiotics for acute otitis media? *Pediatr Infect Dis J*. 2001; 20(2):140-144.
12. Poole MD. Otitis media complications and treatment failures: implications of pneumococcal resistance. *Pediatr Infect Dis J*. 1995;14(4 Suppl): S23-S26.
13. Benito MB, Gorricho BP. Acute mastoiditis: increase in the incidence and complications. *Int J Pediatr Otorhinolaryngol*. 2007;71(7):1007-1011.
14. Antonelli PJ, Dhanani N, Giannoni CM, Kubilis PS. Impact of resistant pneumococcus on rates of acute mastoiditis. *Otolaryngol Head Neck Surg*. 1999;121(3):190-194.
15. Navazo-Eguía AI, Conejo-Moreno D, De-La-Mata-Franco G, Clemente-García A. Acute mastoiditis in the pneumococcal vaccine era [in Spanish]. *Acta Otorrinolaringol Esp*. 2011; 62(1):45-50.
16. Bahadori RS, Schwartz RH, Ziai M. Acute mastoiditis in children: an increase in frequency in Northern Virginia. *Pediatr Infect Dis J*. 2000; 19(3):212-215.
17. Katz A, Leibovitz E, Greenberg D, Raiz S, Greenwald-Maimon M, Leiberman A, Dagan R. Acute mastoiditis in Southern Israel: a twelve year retrospective study (1990 through 2001). *Pediatr Infect Dis J*. 2003; 22(10):878-882.
18. Kværner KJ, Bentdal Y, Karevold G. Acute mastoiditis in Norway: no evidence for an increase. *Int J Pediatr Otorhinolaryngol*. 2007;71(10):1579-1583.
19. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. *Pediatrics*. 2009;123(2): 424-430.
20. Nielsen HU, Konradsen HB, Lous J, Frimodt-Møller N. Nasopharyngeal pathogens in children with acute otitis media in a low-antibiotic use country. *Int J Pediatr Otorhinolaryngol*. 2004; 68(9):1149-1155.
21. Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, Dhooge I, Hoberman A, Liese J, Marchisio P, Palmu AA, Ray GT, Sanders EA, Simões EA, Uhari M, van Eldere J, Pelton SI. Otitis media and its consequences: beyond the earache. *Lancet Infect Dis*. 2010;10(3):195-203.
22. Haggard M. Poor adherence to antibiotic prescribing guidelines in acute otitis media – obstacles, implications,

and possible solutions. *Eur J Pediatr*. 2011;170(3):323-332.
23. Cohen R, Levy C, de La Rocque F, Gelbert N, Wollner A, Fritzell B, Bonnet E, Tetelboum R, Varon E. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use on nasopharyngeal carriage of nonsusceptible pneumococci in children with acute otitis media. *Pediatr Infect Dis J*. 2006;25(11): 1001-1007.

Ingeborg J. M. Dhooge
UZ Ghent
Belgium Ghent University Hospital
Faculty of Medicine
ENT-department
De Pintelaan 185
B-9000 Ghent, Belgium
Tel.: 0032 9 332 23 32
E-mail: ingeborg.dhooge@ugent.be

Appendix

Table 1

PHCP and patient costs for hospitalizations, outpatient procedures, health care professional visits, and hearing aids (April 2010)

Resource	Unit cost (PHCP)	Nomenclature code or source*	Patient co-payment	Nomenclature or source
Hospitalizations				
Hotel cost, €/day†	355.07	https://www.riziv.fgov.be	D1: 41.41 D2-90: 14.14 D91 +: 5.02	766065 766264 799621
Medical supervision ICU + ER, €/day	47.64	590181/590203	0	NA
Supervision: D1-D5, €/day	8.81	598124	4.96	598146
Supervision: D6-D12, €/day	3.91	598021	1.93	598021
Supervision: D13-M6, €/day	1.95	598043	0.96	598043
Laboratory lump sum, €/stay	21.46	591603	7.44	591603
Lump sum imaging, €/stay	8.53	460821	6.20	460821
Other technical procedures, €/stay	NA	NA	16.40	700000
Pharmaceutical costs, €/day	NA	NA	0.62	NA
Outpatient procedures, €‡				
Day clinic	360.03	Hotel cost + supervision	0	NA
Ventilation tubes	147.10	257482/201110	0	NA
Myringoplasty	479.22	257876/200196	0	NA
Mastoid surgery	479.22	255371/200196	0	NA
Transtympanal drainage	147.10	257471/201110	0	NA
Surgery for BAHA	479.22	258506/200200	0	NA
Surgery for cochlear implant	1581.40	258263/200060	0	NA
Health care professional visits, €				
ENT specialist	20.05	102535	2.62	NA
Physiotherapist	9.52	564255	2.37	NA
Hearing aids, €				NA
Cochlear implant	19,087.96	Information brochure on cochlear implants provided by http://www.kids.be/	150.44	NA
BAHA	1143.00	“Hoorcentrum Gent”	1667.00	NA
Classic	1059.73	679151	0	NA

BAHA: bone-anchored hearing aid; D: day; ENT: ear, nose, and throat; ER: emergency room; ICU: intensive care unit; M: month; NA: not applicable; PHCP: public health care payer.
*https://www.riziv.fgov.be.
†The hotel cost is a fixed cost which includes all costs for the hospital stay, including nursing costs, consumables, and overheads.
‡Surgery and anaesthesia costs.

Table 2

PHCP and patient costs for laboratory and other tests for inpatients and outpatients

	Inpatient			Outpatient		
	Unit cost (PHCP), €	Nomenclature (https://www.riziv.fgov.be) or source	Patient co-payment, €	Unit cost (PHCP), €	Nomenclature or source	Patient co-payment, €
Laboratory tests						
Routine test	9.60	Routine test	*	27.76	Routine test including lump sum	8.70
RAST	11.64	6 × IgE test (6 × 556286)	*	28.33	6 × IgE + lump sum (6 × 556275 + 592852)	0
Glucose spinal fluid (including lumbar puncture)	44.76	544084/474106	*	37.74	544073/474095	7.02
Other tests						
Audiometry	26.02	255021	0	22.12	255010	3.90
Skin reaction test	61.99	532582	0	53.31	532571	8.68
CT brain	88.45	257622	0	85.97	257611	2.48
MRI brain	88.45	459406	0	85.97	459395	2.48
EEG	66.32	477142	0	57.64	477131	8.68
ECG	16.94	475086	0	14.40	475075	2.54
Ultrasound	26.63	460165	0	24.15	460154	2.48
BERA	497.75	257806	0	497.75	257795 (including day hospital and anaesthesia)	0

BERA: brainstem-evoked response audiometry; CT: computed tomography; ECG: electrocardiogram; EEG: electroencephalogram; IgE: immunoglobulin E; MRI: magnetic resonance imaging; PHCP: public health care payer; RAST: radioallergosorbent test.
*Covered by fixed cost/stay.