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Observed costs and health care use of children in a prospective cohort study on community-acquired pneumonia in Geneva, Switzerland

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Summary

QUESTIONS UNDER STUDY: Despite various efforts to estimate cost-effectiveness of pneumococcal conjugate vaccines, only scarce information on the cost burden of paediatric community acquired pneumonia (CAP) exists. The objective of this study was to prospectively calculate direct and indirect costs associated with treatment of CAP from a society perspective in children between 2 months and 16 years of age seeking care at a tertiary hospital in Geneva, Switzerland between December 2008 and May 2010.

METHODS: This cost of illness study population comprised children aged from 2 months to 16 years of age seeking care for CAP at the University Children's Hospital Geneva from January 2008 through May 2010 (a subset of patients taken from a larger multicentre prospective cohort). Hospital-associated costs for episodes of pneumonia were computed according to the REKOLE® system. Non-hospital costs were estimated by parental interviews at baseline and follow-up on day 14.

RESULTS: The overall cost for one episode of CAP was 11'258 CHF; 23'872 CHF for inpatient treatment and 1009 CHF for outpatient treatment. Severe pneumonia cases per World Health Organisation (WHO) definition used significantly more hospital resources than non-severe cases: 21'842 CHF versus 3479 CHF (p <0.0001).

CONCLUSION: Childhood CAP results in a significant medical cost burden that may have been underestimated in previous cost-effectiveness analyses of pneumococcal vaccine strategies.

Key words: *pneumonia; community-acquired pneumonia; costs; pneumococcal vaccines*

Introduction

With an estimated 156 million new clinical cases per year, childhood community acquired pneumonia (CAP) remains a leading aetiology of child morbidity and mortality worldwide and creates a significant cost burden [1]. Incidence rates in western countries, based on prospective population-based studies from the 1970s-1980s, are assumed to be around 20–40/1000 in children below 10 years of age [2]. The hospitalisation rate has been reported to be between 0.15% and 20.6% of all-cause pneumonia depending on case definition and region [2–4]. *Streptococcus pneumoniae* is the most important causative agent of paediatric pneumonia in children and is thought to account for around 40% of cases [5–8]. Routine infant immunisation with 7-valent pneumococcal conjugate vaccine (PCV 7) has decreased rates of pneumonia admissions in young children both in the US and Europe [5–7]. However, the effect has been partially offset by serotype replacement [9]. To expand on the success of vaccine intervention, new vaccines such as a 13-valent pneumococcal conjugate vaccine (PCV 13) have been developed. Increasingly, national recommendations about pneumococcal vaccines have included assessments of cost effectiveness, And Immunisation strategies with PCV 7 have been studied in a large number of countries. Interestingly, especially in Europe, very few reports on the cost burden of childhood pneumonia exist [10, 11]. Consequently the majority of cost-effectiveness analyses have been based merely on approximate cost estimation and expert panel reviews and hence are lacking in accuracy.

The objective of this study was to calculate direct and indirect costs associated with treatment of CAP in children between 2 months and 16 years of age seeking care at a tertiary hospital in Geneva, Switzerland.

Methods

Study population / study design

The study population comprised of children aged from 2 months to 16 years of age seeking care for CAP at the University Children's Hospital Geneva from January 2008 through to May 2010. This was a subset of patients taken from a larger multicentre prospective cohort study investigating aetiologies of CAP. The study was conducted at paediatric emergency departments of 3 major hospitals in Switzerland (Geneva, Lausanne and Sion). Cases from Geneva alone were considered for this analysis as hospital-

associated costs were only available for this subgroup. For pneumonia cases, inclusion criteria were: ≥2 months and ≤16 years of age, fever (>38 °C) and cough, and increased respiratory rate for age or respiratory distress, and radiographic pneumonia based on a paediatric radiologist's chest X-ray (CXR) read. Exclusion criteria were: chronic lung or heart diseases, immunodeficiency syndrome and hospital-acquired pneumonia. A child hospitalised more than once was counted as having a new case, provided that the child was symptom-free for at least 30 days between presentations. Written informed consent was obtained from the participants before enrolment. Ethical approval was obtained from the Research Ethics Committees of the Hospitals of Geneva, Lausanne and Sion. Case investigation included demographic data (age, sex, and vaccine status), clinical data, chest X-ray, and laboratory tests. At enrolment, parents were interviewed about direct and indirect expenditures caused by the child's illness before hospitalisation. Two weeks after initial enrolment (or after hospital discharge in case of prolonged hospitalisation) parents were again asked about expenditures and indirect costs accrued during the follow-up period. For cases in Geneva, about 17% of patients did not follow-up at 15 days. All hospital-associated costs were acquired for the entire hospitalisation period.

Severe CAP episodes were identified per World Health Organisation (WHO) classification, that is, abnormal respiratory rate for age associated with the presence of ≥1 of the following: signs of respiratory distress (retractions, abdominal breathing, nasal flaring), moderate to severe dehydration, or oxygen requirement.

Cost estimation

This cost of illness analysis was directed from a societal perspective. As such it included both direct and indirect costs. Direct costs were defined as the cost of resources used for treating a CAP, whereas indirect costs were defined as the value of resources lost due to a CAP.

Direct medical costs, defined as the costs incurred for treating CAP, were calculated from hospital-associated costs as well as parental interviews. Provider costs, which meant patient-specific hospital-associated costs for both ambulatory treatment in the Paediatric Emergency Department as well as inpatient treatment, were computed according to the REKOLE® system [12]. REKOLE® is a comprehensive accounting algorithm used by Swiss hospitals to internally compute provider costs associated with outpatient and inpatient visits. Costs were attributed to categories as per REKOLE® guidelines. Categories included imaging, laboratory, medical and treatment services (including physician care and paramedical care; inpatient drugs; materials such as chest tubes; transport, overhead), nursing care, anaesthesia, intensive care unit, surgical procedures, as well as operating room. The parental report was used to estimate costs associated with medical visits outside of our institution, outpatient medications, childcare, as well loss of productivity. Loss of productivity was computed by multiplying the mean number of work absenteeism in hours by the average daily wage in Geneva in 2008 [13]. Outpatient medication prices were calculated using a 2010 Geneva drug price list (including VAT) provided by our pharmacy department. Outpatient medications were recorded in categories (e.g., beta-lactam antibiotic). The smallest package size of the most common prescribed drug from each category was used for calculation. One package was assumed for every child that took the same drugs before and after consultation. Prices of generic formulation were used when available. Patients lost to follow-up were completed as if no further expenses had occurred.

Data analysis

Data were managed and analysed using Excel (Microsoft, version 2007) as well as SAS (version 9.3). For inpatient provider costs, mean and median were calculated. As the distribution of cost data was heavily skewed, non-parametric testing as described by Hahn and Meeker was used to compute 95% confidence intervals for medians [14]. Wilcoxon rank test and Kruskal-Wallis test were used to assess for difference across two and three categories, respectively.

Results

From January 2008 to May 2010, 191 treatment episodes of CAP were enrolled into the study in Geneva. Only episodes (n = 176) for whom hospital-associated (outpatient and inpatient) cost data was available were included into the analysis. For all (n = 174) patients one treatment episode corresponded to one case except for one patient who was hospitalised twice and treated one time as an outpatient. For this patient only the first treatment episode was included. Baseline characteristics are displayed in table 1.

The admission rate among the study population was 47% (n = 78). The mean hospital stay was 7.9 days (range 1–30, median 5). A total of 12 children (15% of admissions) were admitted to the intensive care unit (ICU). When using a definition for severe pneumonia as per WHO (see method section), 70 (40%) cases could be classified as severe.

Hospital-associated costs

Cost estimates associated with inpatient and outpatient treatment at the Children's Hospital Geneva are displayed

Table 1: Baseline characteristics of study population and CAP-related outcomes.

Mean age in month (range)	57 (3,190)
Female (%)	81 (47)
Chronic conditions (%)	
None	159 (91)
– Asthma	8 (5)
– Sickle Cell	2 (1)
– Cardiac diseases	2 (1)
– Neurological	2 (1)
– Renal disease	1 (0.6)
3 doses of PCV7 given (%)	51 (31)
In school or day-care (%)	125 (72)
Hospital admission (%)	82 (47)
ICU admission (%)	12 (7)
Mean hospital stay in days (range)	7.9 (1–30)
Oxygen requirement (%)	48 (28)
Effusion/empyema (%)	38 (22)
Complications	
Bronchiectasis (%)	1 (0.6)
Necrotising pneumonia (%)	1 (0.6)

Table 2: Hospital costs associated with CAP.

		Treatment services			Laboratory			Imaging		
	n	Mean	Median (CI)	Range	Mean	Median (CI)	Range	Mean	Median (CI)	Range
Total	174	3877	456 (424, 2047)	176–36189	546	226 (209, 251)	0–11648	135	48 (48, 49)	0–1389

		Nursing Care			Anaesthesia			Operating Room Charges		
	n	Mean	Median (CI)	Range	Mean	Median (CI)	Range	Mean	Median (CI)	Range
Total	174	5812	0 (0, 1286)	0–74914	109	0 (0,0)	0–2440	187	0 (0,0)	0–4562

		Surgical Procedures			Total		
	n	Mean	Median (CI)	Range	Mean	Median (CI)	Range
Total	174	205	0 (0,0)	0–3879	10867	766 (766, 4500)	193–106449

		Treatment services			Laboratory			Imaging		
	n	Mean	Median (CI)	*p*	Mean	Median (CI)	*p*	Mean	Median (CI)	*p*
Outpatient treatment	96	383	365 (363, 364)		196	190 (184, 204)		39	37 (36, 48)	
Admission	78	8178	4127 (3539, 5673)	<0.0001	982	502 (389, 757)	<0.0001	252	75 (54, 150)	<0.0001
ICU										
Yes	12	10893	7798 (4077, 16942)	0.04	1790	530 (431, 1871)	0.2	403	228 (103, 823)	0.05
No	66	4076	3270 (2944, 3980)		833	502 (353, 757)		225	72 (55, 126)	
Surgical procedure										
Yes	23	17987	16720 (13888, 19315)	<0.0001	1715	1630 (1360, 1901)	<0.0001	595	576 (305, 823)	<0.0001
No	55	3641	2978 (2656, 3895)		689	366 (273, 498)		109	55 (52,73)	
Age group										
<1 year	12	3740	439 (369, 2620)	0.97	325	190 (125, 353)	0.2	147	48 (38, 120)	0.4
1 year – <5 years	106	4305	454 (424, 2545)		512	233 (204, 268)		148	48 (36, 48)	
≥5 years	56	3095	573 (364, 2743)		656	238 (214, 388)		107	48 (45, 55)	
Male	93	3118	455 (369, 1961)	0.07	427	210 (190, 236)	0.06	95	48 (36, 48)	0.03
Female	81	4748	1173 (442, 2944)		683	259 (217, 340)		180	48 (47, 54)	
Blood culture positive	8	13186	16831 (1173, 26576)	0.001	1267	930 (290, 3620)	0.003	413	255 (105, 1312)	0.0003
Blood culture negative	160	3502	454 (424, 1942)		526	224 (205, 250)		125	48 (48, 48)	
Non-severe	104	1635	372 (363, 424)	<0.0001	293	204 (190, 223)	<0.0001	62	48 (36, 48)	<0.0001
severe	70	7206	3661 (2743, 5145)		929	430 (268, 588)		242	55 (47, 105)	
<3 doses PCV7	103	3488	455 (424, 2188)	0.4	606	246 (217, 273)	0.5	140	48 (48, 50)	0.9
≥3 doses PCV7	61	4819	527 (393, 2978)		456	213 (190, 256)		138	48 (36, 50)	

in table 2. Mean costs for outpatient and inpatient treatment were 618 CHF and 23'481 CHF, respectively. Incurred costs were significantly higher during inpatient admissions requiring surgical procedures and ICU admission. Mean overall cost per CAP episode was 10'867 CHF. The greatest proportion of inpatient costs were made up of nursing care followed by the cost category comprising of physician care, overhead and drug costs. Severe pneumonia cases used significantly more hospital resources on average than non-severe cases: 21'842 CHF versus 3479 CHF ($p<0.0001$). No significant difference in mean hospital-associated costs was found between patients with completed PCV7 series versus patients with incomplete series, nor between different age groups. Patients with positive blood cultures had higher hospital costs compared to patients with negative blood culture (39'035 versus 9750 CHF, $p = 0.002$) though only 8 patients had positive blood cultures.

Non-hospital costs

Estimated prescription medication costs are outlined in table 3. Only four patients were not prescribed antibiotics either before or after treatment at the Children's Hospital Geneva. Interestingly, 20% (35) of patients were prescribed cough syrup and/or nasal decongestants; treatments that were shown to be non-effective or even harmful in patients with respiratory symptoms [15]. A total of 15 fathers (8%) and 53 mothers (30%) reported leave of absence from work. The reported mean length of leave of absence was 12.5 hours (2–80) for fathers and 17.8 hours (2–42) for mothers and hence 4.4 per episode of CAP. Based on a mean hourly salary of 36.25 CHF in the Canton of Geneva we calculated leave of absence related costs to be 159 CHF per CAP episode. Only eight parents reported illness-related childcare expenditures. The mean expenditure was 106 CHF and thus 0.9 CHF per CAP episode. The average number of consultations with other medical providers including primary care paediatricians and physician urgent care home visits was one per CAP case (range 0–4). We assumed an average charge of 200 CHF per outpatient treatment by non-hospital providers (based on informal consultation of general paediatrician's with an office in the Canton of Geneva).

Taking all charges together the estimated mean overall cost for one episode of CAP in our study cohort was 11'258 CHF; 23872 CHF for inpatient and 1009 CHF for outpatient treatment. Assuming a population at risk of about 82000 (15) and an annual incidence rate of 4.0 cases/1000 for children aged two months to 16 years (based on previ-

		Nursing care			Anaesthesia			Operating Room Charges		
	n	**Mean**	**Median (CI)**	***p***	**Mean**	**Median (CI)**	***p***	**Mean**	**Median (CI)**	***p***
Outpatient treatment	96	NA	NA		NA	NA		NA	NA	
Admission	78	12965	6087 (4498, 7970)	NA	246	0 (0, 0)		419	0 (0,0)	NA
ICU										
yes	12	22802	12262 (6347, 43670)	0.02	288	0 (0, 146)	0.7	419	0 (0,0)	0.9
no	66	11177	5029 (4154, 7134)		238	0 (0,0)		420	0 (0,0)	
Surgical procedure										
yes	23	27341	23286 (17150,32480)	<0.0001	814	849 (101, 1596)	<0.0001	1467	1443 (100, 2327)	NA
No	55	6954	4414 (3563, 5693)		NA	NA		NA	NA	
Age group				0.8			0.6			0.6
<1 year	12	7832	0 (0, 4722)		48	0 (0,0)		72	0(0,0)	
1 year - <5 years	106	5883	0 (0, 2150)		144	0 (0,0)		232	0 (0,0)	
≥5 years	56	5244	0 (0, 3744)		56	0 (0,0)		120	0 (0,0)	
Male	93	4033	0 (0, 1033)	0.08	100	0 (0,0)	0.4	156	0 (0,0)	0.3
Female	81	7854	0 (0, 2502)		118	0 (0,0)		218	0 (0,0)	
Blood culture positive	8	21572	18760 (0, 61482)	0.003	368	0 (0,1717)	0.01	706	0 (0, 2933)	0.07
Blood culture negative	160	5186	0 (0, 1237)		99	0 (0,0)		166	0 (0,0)	
Non-severe	104	1351	0 (0, 0)	<0.0001	33	0 (0,0)	0.001	57	0 (0,0)	0.002
severe	70	12439	4885 (3563, 7471)		223	0 (0,0)		380	0 (0,0)	
<3 doses PCV7	103	5371	0 (0, 1286)	0.4	86	0 (0,0)	0.2	141	0 (0,0)	0.2
≥3 doses PCV7	61	7289	0 (0,3247)		161	0 (0,0)		173	0 (0,0)	

		Surgical Procedures			Total		
	n	**Mean**	**Median (CI)**	***p***	**Mean**	**Median (CI)**	***p***
Outpatient treatment	96	NA	NA	NA	618	603 (591, 631)	<0.0001
Admission	78	457	0 (0,0)	NA	23481	11570 (8313, 16478)	
ICU							
yes	12	662	0 (0, 1551)	0.5	37260	20721 (10890, 68676)	0.03
no	66	420	0 (0,0)		20975	9255 (8000, 14802)	
Surgical procedure				NA			<0.0001
yes	23	1551	1474 (1039, 1939)		51333	44669 (36599, 68676)	
No	55	NA	NA		11833	8227 (7229, 10890)	
Age group							
<1 year	12	151	0 (0,0)	0.5	12316	652 (569, 7632)	0.6
1 year – <5 years	106	270	0 (0,0)		11492	759 (682, 5297)	
≥5 years	56	93	0 (0,0)		9372	846 (664, 7500)	
Male	93	127	0 (0,0)	0.13	8058	695 (637, 3325)	0.04
Female	81	295	0 (0,0)		14091	1568 (720, 7500)	
Blood culture positive	8	1520	1513 (0,3879)	<0.0001	39035	43238 (1568, 96871)	0.002
Blood culture negative	160	147	0 (0,0)		9750	746 (681, 3535)	
Non-severe	104	44	0 (0,0)	<0.0001	3479	665 (621, 717)	<0.0001
severe	70	443	0 (0,0)		21842	8665 (7229, 12909)	
<3 doses PCV7	103	212	0 (0,0)	0.4	10033	772 (706, 4552)	0.8
≥3 doses PCV7	61	216	0 (0,0)		13291	825 (662, 7312)	

ously reported annual incidence rates of 6.6/ 1000 for patients less than two years and 5.0/1000 for children less than 5 years in Switzerland [17]), one would expect 328 CAP cases per year in children aged 2 month to 16 years living in the canton of Geneva. In 2009, 74 cases were included into our study. The remaining pneumonia cases were either treated by primary care providers or not enrolled into the study (provider failed to enrol patient or parents refused participation). Estimating that around 70% of all cases presenting to the Paediatric Emergency Department were included in the study, one could assume that around 106 cases presented to the Paediatric Emergency Department. Consequently, 222 (67.7%) would have been treated at a general paediatrician's office. Setting the cost for a routine consultation at a general paediatrician's office at 250 CHF (including prescribed medications), and based on the results from our study, yearly paediatric CAP-associated inpatient and outpatient treatment costs in Canton of Geneva would be 1'113'390 CHF and 115'394 CHF, respectively.

Discussion

To our knowledge this study is the first detailed report on the cost burden of childhood CAP in Europe. This study is limited by the fact that it is a single-centre study as well as inherent issues of the REKOLE® system: the system assigns costs based on hospital criteria that may vary across care-centres. Though overall, when comparing our cost data with assumptions used for cost-effectiveness calculations related to introduction of PCV-7 in Switzerland, it appears that costs were probably underestimated. In the cost-effectiveness study, cost data was calculated on the basis of resource utilisation by a subset of 114 patients treated at the University Hospital in Geneva between 1991 and 2000 (the patient population is hence very similar to our study). Data was then completed by expert panel consultation [17]. Cost assumptions for uncomplicated and complicated pneumococcal pneumonia were 1950 CHF and 7200 CHF, respectively which is below our estimates. One could argue that cost assumptions for pneumococcal pneumonia should be set even higher given that the latter are associated with higher complication rates compared to all causes of pneumonia. Yet, the Swiss cost-effectiveness model by Ess and al. was quite robust to health care cost variations but more sensitive to variations in incidence and case fatality rate [17]. The calculated costs in our study were also higher than reports from other western regions. For example, Black et al. allocated USD 1464 (1997 value, 1380 CHF) to one pneumonia episode with radiographic consolidation treated at Kaiser Permanente in California, USA [18]. The analyses included medical and non-medical costs. In Germany, outpatient, office-based treatment for pneumonia was estimated at € 77 (in 2000 values); costs of hospital admission for pneumonia at € 2424 based on an average length of stay of 7.9 days [19]. Our analysis may overestimate costs for outpatient treatment for pneumonia as it was conducted in a tertiary referral centre which is certainly a limitation of our study. This is why the admission rate was 42% which is significantly higher than that in previous reports (2–4). Based on our incidence estimates around 63% of cases of uncomplicated pneumonia would have been treated at outpatient paediatric offices- a population that was not included in our study. Based on the design, our cohort only included cases with radiographic consolidation whereas most outpatient pneumonias may be diagnosed by clinical evaluation alone. Furthermore, one could argue that there is a tendency to ordering a greater number of diagnostic tests at a tertiary level university hospital. On the other hand our study excluded children with chronic medical conditions who are at great risk for developing complicated pneumonia. In a study in Germany, Kalies et al. reported that up to 21% cases of invasive pneumococcal disease occurred in patients with chronic medical conditions [20]. In the present study we also estimated indirect costs and family expenditure both of which have hardly been reported for childhood CAP. The majority of costs were reflected by direct medical costs. Given the small contribution of indirect medical costs we assume that treating patients lost to follow-up at 15 days as if no further costs occurred introduced no significant bias in our analysis. Only 37% of patients reported leave of absence from work which may appear an underestimation. However, in 2009, one partner was working 49% part-time or less among around 62.3% of couples. Loss of parental income may indeed only be present in around 40% of cases [21]. This may be much higher on other countries. In the initial US cost-benefit analyses by Lieu et al, more than half of the projected savings were from reduced work-loss by parents who care for ill children or averted productivity loss due to disability or death caused by pneumococcal disease [22]. The overwhelming majority of direct medical costs were determined by hospitalisation. This expected difference in resource utilisation underscores the necessity of reducing admission rates and length of stay whenever possible. Clearly, not all patients with pneumonia require referral to secondary care as evidenced by a recent study from Norway that reported a secondary care consultation of 147 / 100'000 per year for children with CAP [4]. Indications for inpatient treatment, besides complications such as hypoxemia and dehydration, have traditionally included parental antibiotic treatment. Several studies, including two in the developed world, have compared parenteral and enteral antibiotics. There is good evidence that oral and parenteral antibiotic treatment may be equivalent in uncomplicated CAP [23–25]. The picture may increasingly be complicated by the observation that whilst studies show reduction in overall incidence of pneumonia after introduction of PCV-7, rates of severe pneumonia may be rising [26]. Complicated, and hence more expensive, pneumonia cases have been attributed to serotype 1, 3, and 19A, among others [27, 28]. Serotype 1, 3, and 19A are not included in PCV7 but in PCV13. Consequently, there may

Table 3: Prescribed medications.

Medication	Number of units	Commercial name	Unit price (CHF)	Total (CHF)
Beta-lactam	*156*	Amoxi-Mepha™ (200 mg / 4 ml), Mepha Pharm	8	*1248*
Macrolide	28	Klaciped™ (250 mg / 5 ml), Abbott	44.85	1255.80
Beta-lactam with clavulanic acid	6	Augmentin Duo™, GlaxoSmithKline	28.90	173.40
Beta-paracetamol	114	Dafalgan sirop™, Bristol Myers Squibb	6.65	758.1
NSAID	84	Algifor sirop™, Vifor	9.80	823.20
Bronchodilators	19	Ventolin spray™, GlaxoSmithKline	9.75	185.25
Inhaled steroids	10	Axotide 125 spray™, GlaxoSmithKline	55.30	553
Antihistamine	7	Claritine™ sirop, Essex	15.90	111.30
Cough syrup	21	Calmerphan-L™, Doetsch Grether	9.65	202.65
Nasal decongestant	17	Nasivine™ gtt 0.01%, Iromedica	6.50	110.50
				5421.20 **= 31.16 / CAP episode**

be a cost-benefit in replacing PCV7 by PCV13. Resistant strains of bacteria, new serotypes of pneumococcus, the increase in empyema and necrotising pneumonia, the interaction between viruses and bacteria, and highly virulent PVL-pos *S. aureus* have proven to be increasingly challenging (9, 28).

Conclusion

Childhood CAP continues to be a significant cause of morbidity and results in significant medical cost burden. Cost analysis should play a significant role in evaluation of preventive immunisation strategies and case management. To our knowledge this study is the first detailed report on the cost burden of childhood CAP in Europe and suggests that CAP-associated costs may have been underestimated in previous cost-effectiveness analyses of pneumococcal vaccine strategies. More effort should be made to treat uncomplicated pneumonia on an outpatient basis as this may lead to substantial savings. As a matter of course treatment decisions should mainly be taken on clinical and not on cost considerations, especially in an era challenged by the changing epidemiology of CAP after the introduction of PCV.

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References

Annexe 1
Formulaire d'information aux parents concernant l'étude sur la recherche des causes de pneumonie chez l'enfant.

Annexe 2
Formulaire de consentement parental concernant l'étude sur la recherche des causes de pneumonie chez l'enfant.

Annexe 3
Formulaire d'information aux parents concernant l'étude sur la recherche des causes de pneumonies chez l'enfant.

Annexe 4
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