Original article

An inception cohort study assessing the role of pneumococcal and other bacterial pathogens in children with influenza and ILI and a clinical decision model for stringent antibiotic use

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Background: Influenza-like illness (ILI) is a common reason for paediatric consultations. Viral causes predominate, but antibiotics are used frequently. With regard to influenza, pneumococcal coinfections are considered major contributors to morbidity/mortality.

Methods: In the context of a perennial quality management (QM) programme at the Charité Departments of Paediatrics and Microbiology in collaboration with the Robert Koch Institute, children aged 0–18 years presenting with signs and symptoms of ILI were followed from the time of initial presentation until hospital discharge (Charité Influenza-Like Disease = ChILD Cohort). An independent QM team performed highly standardized clinical assessments using a disease severity score based on World Health Organization criteria for uncomplicated and complicated/progressive disease. Nasopharyngeal and pharyngeal samples were collected for viral reverse transcription polymerase chain reaction and bacterial culture/sensitivity and MaldiTOF analyses. The term 'detection' was used to denote any evidence of viral or bacterial pathogens in the (naso)pharyngeal cavity. With the ChILD Cohort data collected, a standard operating procedure (SOP) was created as a model system to reduce the inappropriate use of antibiotics in children with ILI. Monte Carlo simulations were performed to assess cost-effectiveness.

Results: Among 2,569 ChILD Cohort patients enrolled from 12/2010 to 04/2013 (55% male, mean age 3.2 years, range 0–18, 19% >5 years), 411 patients showed laboratory-confirmed influenza, with bacterial co-detection in 35%. Influenza and pneumococcus were detected simultaneously in 12/2,569 patients, with disease severity clearly below average. Pneumococcal vaccination rates were close to 90%. Nonetheless, every fifth patient was already on antibiotics upon presentation; new antibiotic prescriptions were issued in an additional 20%. Simulation of the model SOP in the same dataset revealed that the proposed decision model could have reduced the inappropriate use of antibiotics significantly ($P<0.01$) with an incremental cost-effectiveness ratio of -99.55€.

Conclusions: Physicians should be made aware that in times of pneumococcal vaccination the prevalence and severity of influenza infections complicated by pneumococci may decline. Microbiological testing in combination with standardized disease severity assessments and review of vaccination records could be cost-effective, as well as promoting stringent use of antibiotics and a personalized approach to managing children with ILI.

Introduction

Influenza-like illness (ILI) is a common diagnosis in the paediatric health-care setting [1]. On average, children <5 years experience five to six acute respiratory infections with and without fever per year [2]. Even though ILI is usually considered viral in origin, antibiotics are used frequently [3–5]. Analyses of health insurance data from 1.2 million children in Germany have shown that within 1 year, every third child has been treated with antibiotics at least once, regardless of the indication [6,7].

Coinfection with *Streptococcus pneumoniae* is considered a major contributor to morbidity and mortality in patients with influenza and ILI [8–10]. To further investigate the impact of viral–bacterial co-detection on disease severity in children with ILI, a prospective surveillance programme was established at the Charité Departments of Paediatrics and Microbiology in Berlin, Germany, in collaboration with the adjacent National Reference Centre for Influenza at the Robert Koch Institute. This prospective in-/outpatient cohort in one of Europe's largest academic medical centres encompasses the full spectrum of disease presentations, from mild forms of ILI to severe and fatal cases [11].

The aims of this analysis are as follows: to evaluate the prevalence of key viral and bacterial pathogens during perennial syndromic surveillance of paediatric patients presenting with ILI; to monitor disease severity according to standard criteria and to study the relationship between disease severity and detection of viral and bacterial pathogens in nasopharyngeal swab samples; to estimate the cost-effectiveness of standardized clinical assessments in conjunction with systematic microbiological testing to reduce the inappropriate use of antibiotics in children with ILI.

Methods

Cohort design and setting

The analysis was performed in the context of a quality management (QM) programme for the perennial surveillance of ILI at the Charité Departments of Paediatrics and Microbiology in collaboration with the National Reference Centre for Influenza at the Robert Koch Institute (RKI), Berlin, Germany (Charité Influenza-Like Disease = ChILD Cohort) [11–13]. The QM programme was approved by the institutional review board in December 2009 (IRB number EA4/008/10). Informed consent procedures were waived for the performance of enhanced infection control and diagnostic testing during routine clinical care. In this inception cohort (defined as a designated group of persons assembled early in the development of a specific clinical disorder) patients were monitored from the time of initial presentation (time of diagnosis) until hospital discharge.

Participants, data sources and variables

The QM programme 'Influenza-Like Illness' was established in December 2009 for the objective and standardized management of in- and outpatients with ILI at the Charité Department of Paediatrics. All patients presenting with ILI on screening days (that is, once-weekly in the emergency room (ER) in addition to all inpatients any day including holidays and weekends) became part of the QM programme as described previously [11–14]. ILI case criteria were defined as evidence of fever with a body temperature ≥38°C and ≥1 respiratory symptom (cough, rhinitis/coryza, red/sore throat, ear ache, dyspnea, tachypnea, laboured breathing, wheezing). For ethical reasons, patients could also be included in the QM programme if the treating physician suspected ILI and requested inclusion in the QM programme, regardless of the case definition.

All patients participating in the QM programme (ChILD inception cohort) underwent standardized clinical assessments by a specifically trained QM team. A complete physical examination was performed including naso/oropharyngeal exam, auscultation of the lungs, otoscopy and review of the current and past medical history including the vaccination status. To facilitate cross-cohort comparison of disease severity assessments, a composite clinical score (ViVI Disease Severity Score) was implemented, consisting of 22 weighed parameters based on WHO criteria for uncomplicated, complicated and progressive disease [15].

The ViVI Disease Severity Score was developed by the Vienna Vaccine Safety Initiative (ViVI) to enable the consistent and standardized documentation of key clinical findings at the point-of-care. The ViVI Score increases on a scale from 0 to 48 with an increasing number of pertinent clinical findings (data not shown).

According to the standardized operating procedure of the QM programme, nasopharyngeal swabs were obtained by the QM team and delivered directly to the National Reference Centre for Influenza (RKI) for PCR-testing/virology. Brushings of the posterior pharyngeal wall were collected for bacterial culture and matrix-assisted laser desorption/ionization and time-of-flight mass spectrometry (MaldiTOF) testing was carried out to reflect the presence of bacterial pathogens near the Eustachian tubes and in the upper airways [16–21]. The bacterial culture and sensitivity testing at the Charité Department of Microbiology was included in the QM programme after December 2010. The analysis is based on perennial QM data from December 2010 until April 2013. The Cohort was developed in compliance with the STROBE statement [22].

Virological analyses

Viral RNA extraction, cDNA synthesis and real-time (RT)-PCR for detection of influenza A or B virus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV) and adenovirus (AdV) were performed as recently described [23–26]. Primer sequences and probes for detection of human rhinovirus (HRV) can be provided upon request.

Microbiological analyses

Standard culture-based methods were applied for microbiological analyses of patient samples. Identification of bacteria was performed using commercial biochemical procedures (Vitek2 or Api; bioMérieux, Marcy l'Etoile, France) or MaldiTOF (microflexTM with biotyper software; Bruker Daltoniks, Bremen, Germany or VitekMS, bioMérieux). Sensitivity testing of antimicrobials was done using E-Test (bioMérieux) or Vitek2 (bioMérieux).

Terminology

Throughout the manuscript the term 'detection' was used to denote any evidence of viral or bacterial pathogens in the (naso)pharyngeal cavity.

Development of a model standard operating procedure

Based on ChILD Cohort data, a model standard operating procedure (SOP) was developed as a very simple and low-cost, time-saving procedure that could be applied easily in most routine care settings.

Patients were classified into four groups based on two key parameters: severity of illness at the time of initial presentation and review of the vaccination record.

The cutoff value for mild/moderate versus severe illness was based on the distribution of severity scores in the respective setting (that is, the mean ViVI Score in the respective cohort).

Patients were prioritized for microbiological culture if disease severity was assessed to be above average for the Cohort (that is, ViVI Score >15) or if patients were not fully vaccinated against major respiratory pathogens including pneumococcus and *Haemophilus influenzae*.

The model used the actual cost for pharyngeal swabs and bacterial culture and sensitivities (C&S) at the Charité Department of Microbiology and the current pricing of oral and intravenous antibiotics in Germany [27].

The SOP was specifically designed to introduce a 'wait and see' approach in line with common guidelines for prudent use of antibiotics [28]. In patients with mild disease who are not fully vaccinated, this can be achieved by delaying antibiotic prescription until bacterial culture results are available. In the absence of any detectable bacterial pathogen antibiotics may be avoided.

Cost-effectiveness analyses

The cost-effectiveness model design compares the costs of the SOP versus no-SOP strategy from the perspective of the German health authorities, with effectiveness expressed in clinical outcomes defined as 'rate of antibiotic therapy saved', which is equal to 1- rate of antibiotic prescription. To manage uncertainty, and as per best practice in economic modelling, 10,000 Monte Carlo simulations generated mean values and standard deviations (SD) of the three model outputs: costs, effectiveness and average cost-effectiveness. Monte Carlo simulations consist of a class of computational algorithms that rely on repeated random sampling to compute their results. This approach, also called the 'probabilistic sensitivity analysis', allows screening of all possible values of a given parameter according to a defined distribution shape and to recalculate the results. For the purpose of this study, it was possible to construct normal distribution shapes from mean and SD of resource utilization. Therefore, the model was able to construct distributions of results which are presented with their SD. Statistical tests (two groups mean tests with known variances deducted from cost-effectiveness SD) were performed to calculate potentially significant differences between cost-effectiveness ratios of treatment strategies.

Statistical methods

Categorical variables were compared using the χ^2 test. A *P*-value of less than 0.05 was considered statistically significant. To estimate the test power we calculated the minimum sample size needed for power of 0.7, 0.8 and 0.9 and varying effect sizes [29]. This test is able to detect very small effect sizes in the data with very good power (see also Additional file 1).

Numerical variables for comparing two groups (for example, age, in a group treated with antibiotics compared with a group without treatment) were evaluated using the Kullback–Leibler (KL) divergence [30], which has the advantage over other methods that it does not make any assumptions about the distribution of the dependent variable. By definition, the KL divergence cannot be negative and increases if two distributions become more different to each other.

Multivariate analysis was performed using a regression formalism with L_1 penalty, which is commonly known as Lasso [31]. The Lasso-specific parameter lambda determines how sparse the model will be, that is, the larger the value of lambda, the more variables will enter the model.

Disease severity scores (that is, ViVI Scores) were compared using the Mann–Whitney test for non-parametric variables.

Results

Baseline characteristics

From December 2010 to April 2013, a total number of 3,106 patients fulfilling ILI case criteria were automatically enrolled into the QM programme. Among these, a total of 2,569 patients (83%) had samples taken for virology (PCR) and bacterial C&S. In the remaining 17% of ChILD Cohort patients, samples were unavailable for administrative reasons (patient inaccessible or discharged prior to daily screening).

Leading respiratory symptoms at baseline were cough (77%), coryza (73%) and dyspnea (56%). Extra-pulmonary symptoms included malaise (47%), vomiting (32%) and diarrhoea (17%). At inclusion 66% of patients were hospitalized (15% intermediate care/intensive care unit [IMC/ICU], 51% non-ICU). Underlying conditions such as chronic pulmonary or cardiac diseases were reported at admission for 24% of patients.

Bacterial pathogens were detected in 35% of ILI patients and influenza infection was confirmed in 16%. Based on multivariate analysis, patients with normal flora compared to patients with bacterial pathogens are relatively similar with respect to baseline characteristics (Table 1). The most important features selected by multivariate analysis were 'age <1 year', 'influenza infection', 'antibiotic premedication' at lambda values of 0.11, 0.10 and 0.09, respectively.

Table 1. Characteristics, vaccination status, premedication and viral laboratory results in patients with influenza-like illness

	Bacterial pathogens[a] (*n*=911, 35.4%), *n* (%)	Normal flora (*n*=1,658, 64.6%), *n* (%)	*P*-values[b]
Age			
<1 year	365 (40.1)	441 (26.6)	<0.001
1–5 years	406 (44.6)	859 (51.8)	<0.001
>5 years	140 (15.4)	359 (21.6)	<0.001
Gender			
Male	525 (57.6)	887 (53.5)	0.042
Female	386 (42.4)	772 (46.5)	
Underlying condition			
Hepatorenal	105 (11.5)	168 (10.1)	0.015
Cardiac	79 (8.7)	112 (6.8)	0.271
Pulmonary	69 (7.6)	154 (9.3)	0.141
Vaccination			
H. Influenzae B[c]	766 (84.1)	1,452 (87.5)	0.389
S. pneumoniae[d]	742 (81.4)	1,403 (84.6)	0.042
Influenza[e]	45 (4.9)	93 (5.6)	0.474
Premedication[f]			
Antibiotic	227 (24.9)	593 (35.7)	<0.001
Neuraminidase inhibitor	1 (0.1)	0 (0.0)	–
Viral infection			
Influenza A/B	198 (21.7)	213 (12.8)	<0.001
RSV	149 (16.4)	277 (16.7)	0.824
HRV	178 (19.5)	312 (18.8)	0.651
AdV	66 (7.2)	142 (8.6)	0.242
HMPV	42 (4.6)	59 (3.6)	0.188

[a]The term pathogen was used to denote any positive bacterial culture result other than normal flora. [b]*P*-values were calculated using χ^2 test. [c]*Haemophilus influenzae B* vaccine was administered as part of the hexavalent vaccine (infanrix hexa®), which includes diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenza B* and hepatitis B vaccines. [d]*Streptococcus pneumoniae* vaccination included conjugate vaccines Prevenar7®, Synflorix® and Prevenar 13®. [e]Influenza vaccination during the current season. [f]Premedication was defined as any treatment within 7 days prior to swab. AdV, adenovirus; HMPV, human metapneumovirus; HRV, human rhinovirus; RSV, respiratory syncytial virus.

Antibiotic prescription rates in ILI patients

Information about antibiotic premedication was available in 2,552 cases (98%). Approximately 40% of all ILI patients received antibiotics (20% prior to presentation to the ER, 20% during hospitalization), 32% prior to specimen collection. Second-generation cephalosporins were the most commonly prescribed with 54%, followed by (amino)penicillins, and third generation cephalosporins with 13% and 7%, respectively.

In comparison, one ILI patient was pre-medicated with neuraminidase inhibitors (NAI), and 7% of patients with laboratory-confirmed influenza infection received NAI.

Vaccination coverage with pneumococcal vaccines

Vaccination histories were available in all patients. The majority of patients were up to date on immunizations against *Haemophilus influenzae B* (HiB, 86%) and *Streptococcus pneumoniae* (84%). Influenza immunization coverage rates were around 5%.

Prevalence of pneumococci

Bacterial pathogens were cultured in 35% of patient samples. *Haemophilus influenzae non-B* (15%) and *Staphylococcus aureus* (predominantly MSSA, 11%) were detected most commonly, as opposed to *Streptococcus pneumoniae* in 3% of samples. Multiple bacterial infections were observed in 9% of patients.

Virological analysis revealed HRV in 19% of cases, followed by RSV in 17% and influenza A/B in 16%. In comparison, AdV and HMPV were detected in 8% and 4% of patients, respectively. Multiple viral pathogens were present in 5% of cases; viral and bacterial pathogens were detected simultaneously in 22%. Viral infection without evidence of bacterial pathogens was determined in 36% of patients. In 13% of patients, bacterial pathogens were detected without evidence of viral infection as per PCR panel.

There was no significant difference in the detection rate with regards to pneumococci in patients with and without antibiotic pretreatment (2.1% compared to 3.3%). Slightly greater differences were seen with

regards to other bacterial pathogens, such as *H. influenzae* (11.0% compared to 17.5%) and *S. aureus* (7.2% compared to 13.2%) in patients with and without antibiotic pretreatment.

Prevalence of pneumococci in patients with influenza infection

The relative proportion of viral and bacterial pathogens in patients with viral–bacterial co-detection is displayed in Figure 1.

The combination of influenza and pneumococci was detected in 12/2,569 patients (0.5%). Three patients showed influenza, pneumococcus and no other bacterial or viral pathogen. In the remaining 9 cases, additional bacteriae were detected, namely *H. influenzae*, *S. aureus* and *enterobacteriaceae*.

Disease severity

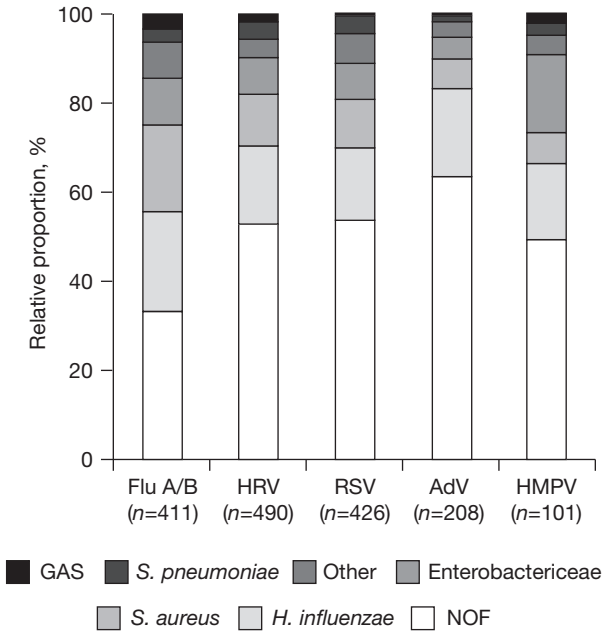
Disease severity scores were determined in all patients. ViVI Scores were normally distributed in this cohort, ranging from 0 to 33 with a median of 15 and a mean of 15.2 (SD 5.6; Figure 2).

The mean ViVI Score for patients without evidence of bacterial pathogens was 15.2 (95% CI 14.9, 15.5) compared to 15.5 (95% CI 15.1, 15.9; P=0.204) in patients with positive bacterial cultures.

The three patients with the combination of influenza and pneumococci (without additional pathogens) showed an average ViVI Score of 14.

Otitis media was clinically diagnosed in 19% of patients, pneumonia in 17% of all cases. Patterns of bacterial pathogens were similar in patients diagnosed with either otitis or pneumonia, compared to patients without complications or progressive disease.

Figure 1. Relative proportion of bacterial pathogens in patients with different viruses identified



Real-time PCR was used for viral detection, bacteriae were cultured. In order to compare bacterial co-detection rates, relative proportions were calculated for patients with different viral infections. The respective number of patients is provided in parentheses. AdV, adenovirus; GAS, Group A streptococci; *H. influenzae*, *Haemophilus influenzae non-B*; HMPV, human metapneumovirus; HRV, human rhinovirus; NOF, normal oropharyngeal flora; Other, other bacteriae, mainly streptococci (*Streptococcus pyogenes* and *Streptococcus agalactiae*), other gram-negative bacteriae (mainly *Pseudomonas species*, *Acinetobacter species*, *Moraxella catarrhalis* and *Neisseria meningitidis*) and other gram-positive bacteriae; RSV, respiratory syncytial virus; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

Antibiotic prescription is determined by disease severity

For an independent view of factors contributing to antibiotic prescription we performed KL divergence statistics. Among all factors studied, three parameters were most significant: first of all, an association with elevated ViVI Scores (KL=6.41) was observed. This means that in patients with more severe disease, antibiotics were prescribed more commonly. Figure 3 presents the relative ViVI Score distribution in patients with and without antibiotic prescription in the ER. The second most important factor associated with antibiotic prescription was elevated C-reactive protein (CRP) (KL=3.35) followed by hospitalization (KL=1.26). Evidence of pneumococcal vaccination (KL=0.008) or bacterial detection (KL=0.001) did not seem to influence antibiotic prescription.

The mean ViVI Score for patients receiving antibiotic prescription was 17.6 (median 18, range 0–33, SD 5.7, 95% CI 17.2, 18.0) compared to a mean ViVI Score of 14.3 (median 14, range 0–31, SD 5.7, 95% CI 14.0, 14.6) in patients without antibiotic treatment (P<0.001).

Blood samples for CRP analysis were obtained as part of routine care in 76% of patients receiving antibiotic treatment and in 50% of patients not receiving antibiotics. The mean CRP values were at 57.4 mg/l (median 30.8, range 0.2–440, SD 75, 95% CI 57.0, 57.8) for patients with antibiotic treatment, compared with 23 mg/l (median 8.6, range 0.2–328, SD 41.4, 95% CI 17.1, 28.9) in patients without (P<0.001).

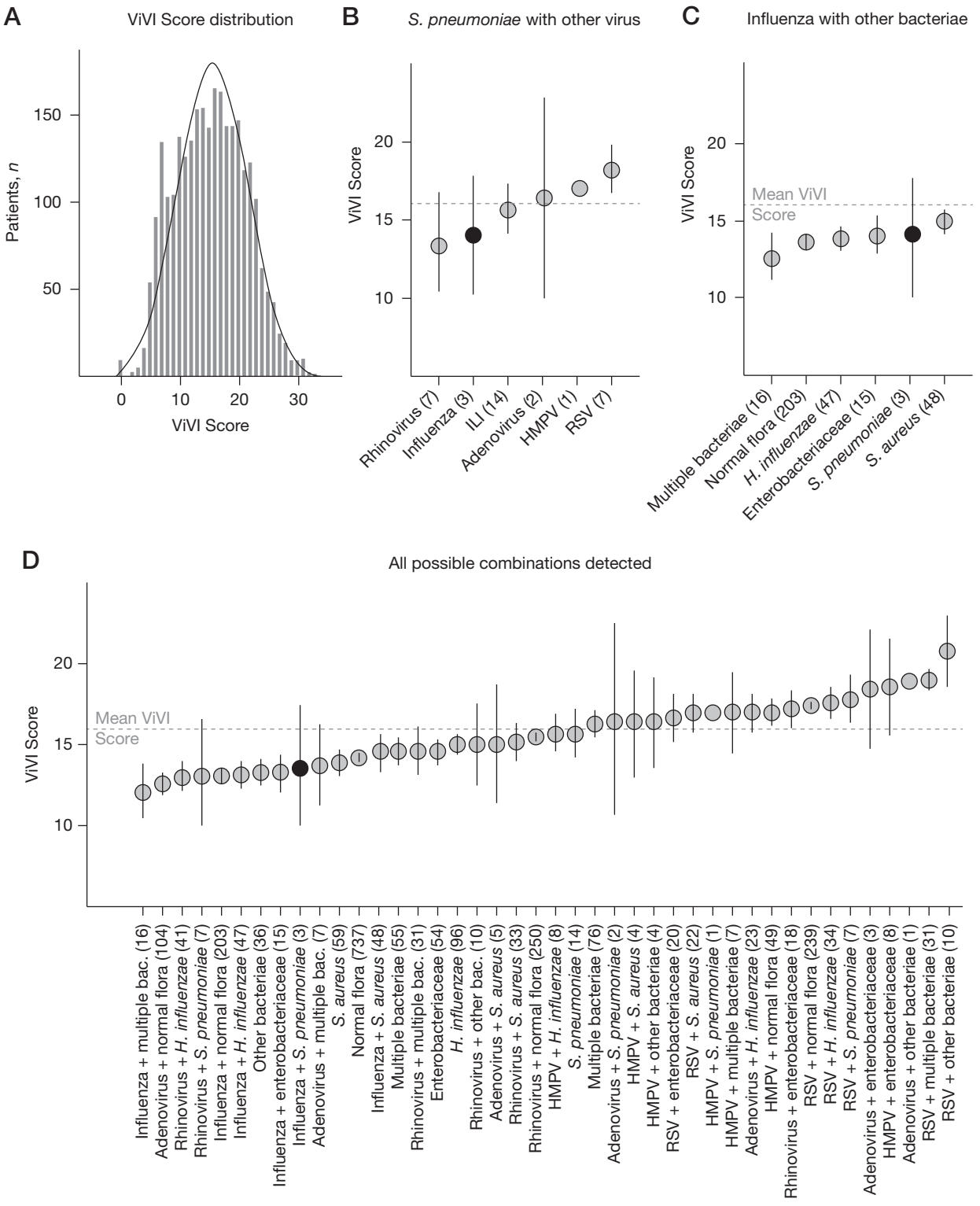
Outpatients showed significantly lower ViVI Scores (mean 10.3; SD 4.2, 95% CI 10.0, 10.6) compared with patients admitted to the regular wards (mean 17.2; SD 4.8, 95% CI 16.9, 17.5; P<0.001) versus ICU (mean 20.3; SD 4.7, 95% CI 19.8, 20.8; P<0.001).

A simple model SOP for the reduction of antibiotic use

The model SOP was based on the following assumptions (Figure 4):

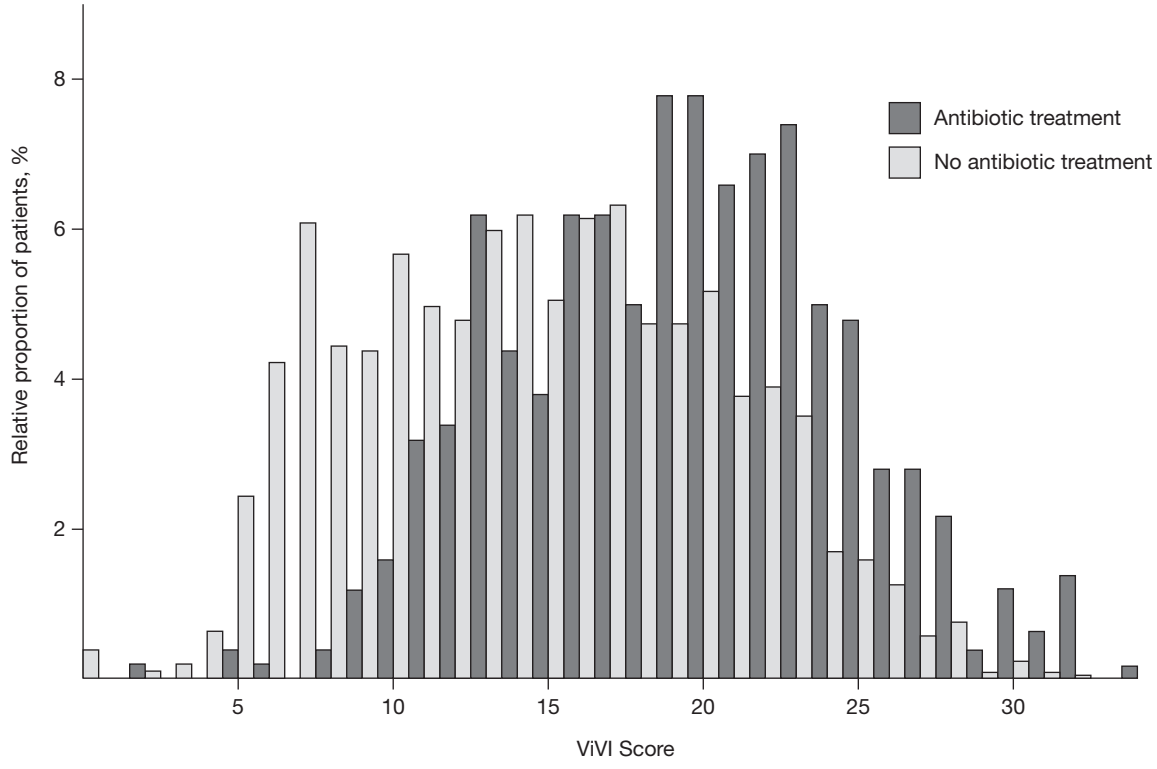
A 'wait-and-see' approach with respect to antibiotic treatment would be undertaken in patients with

Figure 2. Distribution of ViVI Scores



(A) Overall distribution of ViVI Scores and **(B)** average ViVI Scores among patients with pneumococci and other respiratory viruses, with **(C)** influenza and other bacteriae, and **(D)** among patients with any possible combinations detected. (A) ViVI Score distribution among all patients. A normal distribution curve (Gauss curve) was added for comparison. (B, C&D) For each combination mean ViVI Scores and the standard deviations (SD) are displayed. *H. influenzae*, *Haemophilus influenzae non-B*; HMPV, human metapneumovirus; ILI, other reason for influenza-like illness (ILI) except for the five viruses examined; Multiple bacteriae, more than one bacterial pathogen detected; Other bacteriae, mainly streptococci, other gram-negative bacteriae (mainly *Pseudomonas species*, *Acinetobacter species*, *Moraxella catarrhalis* and *Neisseria meningitidis*) and other gram-positive bacteriae; RSV, respiratory syncytial virus; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

Figure 3. Relative distribution of ViVI Scores in patients with and without antibiotic prescription in the emergency room



The mean ViVI Score for patients receiving antibiotic prescription was 17.2 (95% CI 16.8, 17.6) compared with a mean score of 14.2 (95% CI 13.9, 14.5) in patients without antibiotic treatment (P<0.001).

below-average disease severity (ViVI Score ≤15) compared with the rest of the cohort, and documented vaccination status against pneumococcus and HiB.

In patients with mild–moderate disease and *without* evidence of vaccination against pneumococci and HiB, bacterial cultures would be obtained for targeted antibiotic therapy to be initiated according to C&S results. The same procedure would apply to patients with above average ILI disease severity (moderate/severe disease, ViVI Score >15) and *positive* evidence of pneumococcal and HiB vaccination: if possible, antibiotic treatment would be delayed until bacterial C&S are available for targeted therapy in cases with evidence of bacterial pathogens.

Unvaccinated patients with moderate/severe disease (ViVI Score >15) would be treated empirically without delay and with subsequent adjustment after C&S results have become available. In all instances, bacterial C&S would be used as soon as possible to guide targeted, individualized antibiotic therapy.

Cost-effectiveness

The SOP strategy appeared significantly (P<0.01) more efficacious (73% of antibiotic prescriptions saved) when compared to the no-SOP strategy with 61% of antibiotic prescriptions saved. In the German health-care system, antibiotics require medical prescription. If prescribed by a physician, the cost for antibiotic treatment is usually reimbursed through the health insurance system (either statutory or private health insurance). Total costs per patient were estimated at 16.71€ (SD 23.6) for the SOP strategy and at 28.96€ (SD 42.2) for the no-SOP strategy. Hence, corresponding mean cost-effectiveness ratios showed significantly lower costs (P<0.01) per antibiotic prescription saved for the SOP strategy (22.82€, SD 32.23), as compared with the no-SOP strategy (47.7€, SD 69.5; Additional file 2).

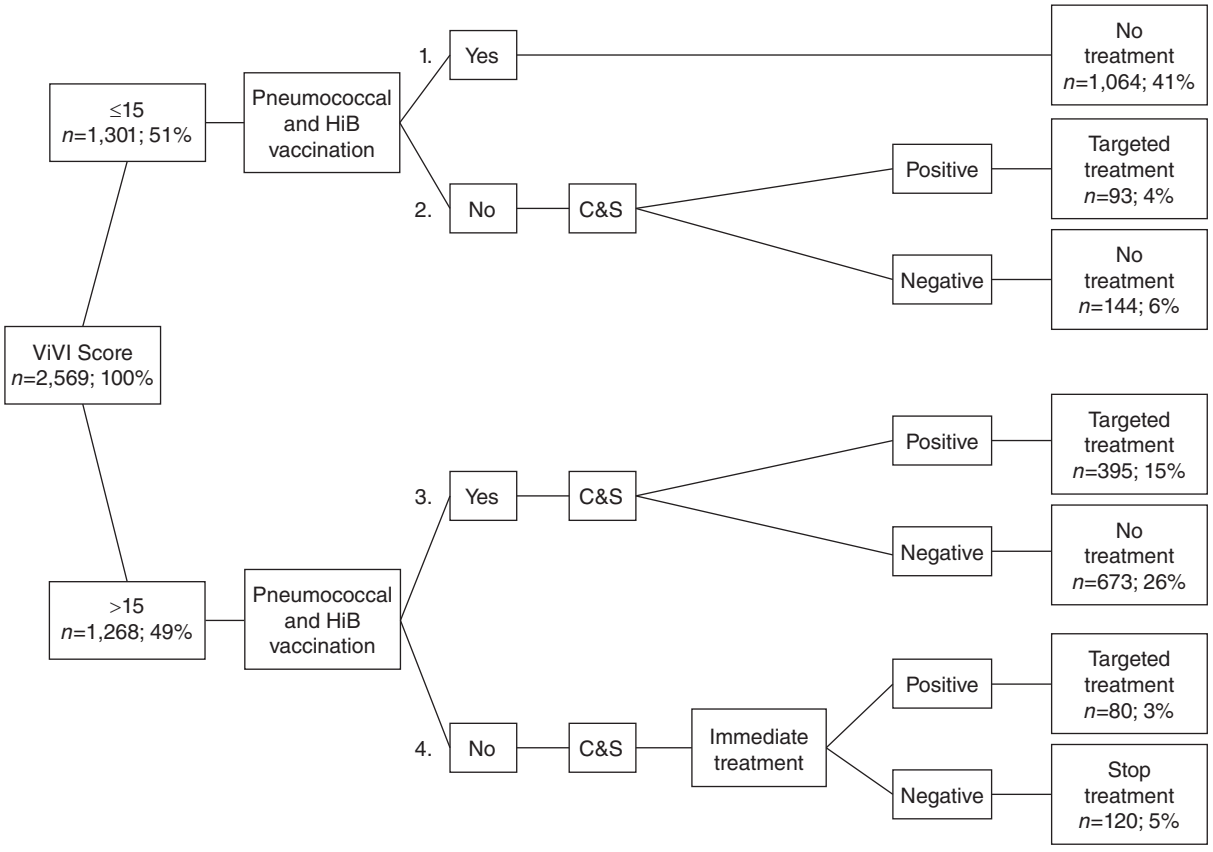
Incremental cost-effectiveness ratio was -99.55€, with a negative sign confirming that the strategy SOP is 'dominant' over the strategy no-SOP (lower costs and better effectiveness).

Discussion

The results of this inception cohort study are surprising in several respects.

First of all, the combination of influenza and pneumococci was uncommon with 0.5%. This is in contrast

Figure 4. A simple model for the reduction of antibiotic use in patients with mild versus moderate to severe ILI



Mild influenza-like illness (ILI) was defined as a composite clinical score (ViVI Score) ≤15, moderate to severe disease as a ViVI Score >15. HiB, *Haemophilus influenzae B*; C&S, microbacterial culture and sensitivity.

to previous studies focusing on patients with severe pneumonia in ICU-settings, where influenza-pneumococcal co-detection rates of 14% up to 62% were reported [9,10,32]. The low prevalence of pneumococci observed in the ChILD Cohort may be attributed to an 84% pneumococcal vaccination rate and to the prospective and consecutive enrolment of patients with ILI, including patients with very mild to very severe disease. Antibiotic pretreatment had no significant effect on the detection of pneumococci in pharyngeal swabs. Despite the large number of subjects in this cohort with positive bacterial cultures, only few showed evidence of pneumococci with insufficient power for extensive statistical analysis. Therefore, sub-analyses addressing different pneumococcal serotypes were not feasible in this comparatively healthy cohort, contrary to international pneumococcal surveillance efforts focusing on invasive and lower airway disease [33–35].

Observer effects were largely eliminated through the consistent application of pre-defined ILI and QM criteria. The often subjective decision whether or not to swab a patient or to send samples for virological and/or microbiological testing was replaced by the SOPs of a perennial QM programme.

Secondly, disease severity was not significantly increased in patients with pneumococci or other bacterial pathogens compared to those with normal flora. However, RSV infection seemed to increase disease severity in this cohort. This finding was reflected when assessing disease severity using the ViVI Score, but also when standard parameters (for example, admission to the ICU versus non-ICU) were applied. The ICU-admission rate among patients with detection of pneumococci was below average (14% compared with 17%), whereas patients with RSV showed an ICU admission rate of 20%. This result was expected, as detection of bacteria may also represent bacterial colonization. Additional tests will be required in the future to distinguish invasive bacterial infection from colonization, and viral infections from bacterial infections or combinations thereof.

These findings may again be very different in a cohort focusing on ICU patients with underlying conditions and progressive disease, and when contributing pathogens

are assessed retrospectively [8–10,36–39]. The ChILD inception cohort, however, included any type of ILI including very mild to severe disease presentations in a setting where immunization rates with pneumococcal conjugate vaccines approached 90%.

Our findings are in line with recent studies, demonstrating a marked effect of pneumococcal vaccination on bacterial colonization and invasive pneumococcal disease [33–35,40,41]. Physicians may not be fully aware of this new situation and continue prescribing antibiotics even without any laboratory evidence of bacterial colonization or coinfection. This success of pneumococcal immunization programmes should be communicated more clearly: vaccines are an effective means of decreasing pneumococcal complications, as opposed to 'pre-emptive' antibiotic use, which would further increase the risk of pneumococcal drug resistance.

The 10% prevalence of antibiotic resistance suggests that even brief periods of antibiotic pre-exposure may begin to influence bacterial culture results. Higher rates of antibiotic resistance have been reported in France, Italy and Spain whereas antibiotic use may be more restrictive in Scandinavia and some Benelux countries [42–44]. The virological analyses in the ChILD Cohort are performed by the National Reference Centre for Influenza at the RKI, and are thus in line with the national and European surveillance systems for influenza and other respiratory viruses.

Even though influenza vaccines are licensed and available for all age groups above 6 months of age in Germany, influenza vaccination rates were very low in this Cohort (5%). The likely reason is the absence of a universal recommendation for influenza vaccination in Germany. Seasonal influenza vaccination is advised for individuals aged >65 years as well as in specific risk groups including pregnant women, health-care professionals and patients with underlying conditions or immunodeficiency [42–44]. Even in at-risk groups however, vaccination coverage rates remain as low as 10% [45–47].

Interestingly, NAIs were hardly ever prescribed in this setting, even in patients with laboratory-confirmed influenza. This indicates that paediatricians in Germany may be feeling less familiar with the concept of antiviral therapy as opposed to antibiotics [48–50]. Future SOPs may include additional guidance for the prevention of influenza infections through vaccination, as well as for timely antiviral therapy in laboratory-confirmed cases according to evidence-based guidelines [51]. The rate of antibiotic pretreatment was alarmingly high in this ILI cohort (32%), raising the need for new and effective measures to promote a more stringent and targeted use of antibiotics in paediatric ILI patients.

Based on the real-life cohort data, a hypothetical model SOP was developed using standardized clinical assessments of disease severity (VVI Disease Severity Score), active solicitation of vaccination histories, and bacterial cultures and sensitivity. The model SOP was designed to be simple and cost-effective, allowing adjustments to different levels of disease severity in diverse populations, including in resource-restrained settings. The Charité Department of Paediatrics represents one of the largest paediatric medical centres in Europe including two ERs covering multi-ethnic (Central European and international migrant) populations in both inner city Berlin and suburban settings. Whilst the findings in this cohort may be generalized to some extent, the prevalence of bacterial pathogens may vary in different parts of Europe and beyond.

The unavailability of a universally accepted clinical disease severity score for children with ILI is a clear weakness. We therefore used The ViVI Disease Severity Score for the purpose of cross-cohort comparison based on WHO criteria [11,52]. Clinical signs and symptoms of upper and lower respiratory disease (including pneumonia and otitis) were all captured as part of the disease severity score.

Interestingly, the ViVI Score accurately reflected the physician's perception of disease severity as evident from antibiotic prescribing practices by doctors who had no prior knowledge of the scores. The scoring was done by an independent QM team at the time of initial presentation. As evident from independent bioinformatics analyses, the ViVI Score also reflected the physician's decision to admit patients to the hospital. Patients in need of ICU admission showed the highest ViVI Scores. This information may be useful to improve health service research in the future. To further validate the ViVI Score, future studies should establish the distribution of disease severity in different populations, age groups and ethnicities. The ViVI Score was designed to measure disease severity based on clinical signs and symptoms, regardless of the trigger. The score should therefore be used in combination with enhanced diagnostics.

Moreover, the newly developed model SOP should be evaluated prospectively, including in both high- and low-resource settings where cost-effectiveness and modalities of routine care may differ, as do antibiotic and antiviral prescription practices.

Since doctors like to base their decisions on test results, this SOP can teach physicians that the vast majority of patients indeed do *not* harbour any bacterial pathogen that would need to be treated with an antibiotic, and that high fevers and ILI symptoms are likely to be viral in origin. It might be helpful to share negative culture results also with the parents, who are often requesting antibiotic treatment for their children [50].

In this inception cohort brushings of the posterior pharyngeal wall were used to detect upper airway pathogens. The method was chosen due to its routine use

in paediatrics with availability in all patients with mild as well as severe disease. A potential weakness is the underrepresentation of nasal MSSA/MRSA colonization as MRSA screenings are usually performed from superficial nasal swabs.

Older records also indicate that pharyngeal samples taken via the nasal (versus oral) route may be beneficial for the detection of pneumococci, but more recently, simple throat swabs have been established as the most commonly used method for the surveillance of pneumococcal colonization and vaccine effectiveness studies [15]. This is not surprising as brushings of the posterior pharyngeal wall, if performed accurately, will reflect the bacteria present in the sensitive area where the nasal and oral cavities meet, and where most infections of the middle ear (via the Eustachian tubes) and the lower airways (if descending from the upper airways) are expected to originate [53–55].

The aim of the QM programme was to screen for a number of key respiratory and bacterial pathogens in children with ILI, that is, across the entire spectrum of mild disease to severe acute respiratory illness. The ChILD Cohort uses a simplified version of the new WHO ILI definition as the basis for syndromic surveillance [16–21]. It is currently subject to active debate at the WHO level (informal consultation with the Global Influenza Surveillance and Response System on 25–27 March 2015), as well as at the ECDC (expert consultation on 23–24 November 2015), regarding which case definition might be most suitable for a combined surveillance of influenza, RSV and other key respiratory pathogens [56–58]. The fact that physicians were allowed to ask for inclusion of their patient into the QM programme based on their clinical ILI diagnosis (independent of the case definition), allowed for some flexibility representing an additional strength of the ChILD Cohort design. Future analyses will explore the sensitivity of different case definitions for different viral and bacterial pathogens [57,58].

The detection of bacteria in the pharynx alone cannot be used to predict the subsequent clinical course. On the contrary, our data indicate that at least at the time of initial presentation, disease severity seems to be driven mostly by the viral pathogens detected. Future studies should establish reliable, ideally non-invasive biomarkers to help distinguish bacterial colonization from invasive disease. The SOP can then be adopted accordingly to reduce the inappropriate use of antibiotics even further.

The inability to distinguish colonization from coinfection in the pharyngeal space would represent a weakness in any surveillance system restricted to non-invasive sampling methods. Bronchoalveolar lavages are rarely performed in children with mild disease, and serology or blood cultures have been shown to be notoriously insensitive for infectious processes located in the middle ear or the lungs [58–60]. It is promising to see that biomarker research is underway that may help to distinguish bacterial colonization from (super)infection [61,62].

An evidence-based approach to antimicrobial therapy will help to establish the actual disease burden associated with different respiratory pathogens, some of which are soon to be treatable and/or preventable [63]. Targeted point-of-care diagnostics could be applied to facilitate timely decision-making. Clinical management strategies could be improved further towards individualized therapy in children with ILI. Second-generation sequencing technologies, systems biology and microbiome analyses may shed additional light on the complex interactions between respiratory pathogens and disease outcomes in infants and children [64].

In conclusion, among more than 2,500 ILI patients, the prevalence of pneumococci was surprisingly low (3%), the combination of influenza and pneumococci was found in only 3 patients; in an additional 9 patients, influenza and pneumococci were detected along with other bacterial pathogens. Patients with the combination of influenza and pneumococci detected in the upper respiratory tract showed below average disease severity compared to the remaining group of ILI patients with other viruses and/or bacteriae. No significant increase in disease severity could be found in patients with positive bacterial culture compared to those with normal flora.

Even though pneumococcal vaccination rates in the ChILD Cohort were relatively high with 84%, almost half (40%) of the children presenting with predominantly viral ILI were treated with antibiotics.

Based on real-life ChILD Cohort data, a simple clinical decision model was developed for a cost-effective approach for stringent antibiotic use showing that medication cost and inappropriate antibiotic use could be reduced significantly ($P<0.01$).

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the manuscript. AB performed cost effectiveness analyses and contributed to the manuscript. TA led and supervised the bacteriology work and provided important intellectual input to all aspects of the study. BS led and supervised the virology work and provided important intellectual input to all aspects of the study. BR conceptualized and designed the QM programme, led the study and supervised the writing of the manuscript.

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There is no additional data available.

Disclosure statement

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Additional files

Additional file 1: Sample size calculations can be found at http://www.intmedpress.com/uploads/documents/3602_Tief_Addfile1.pdf

Additional file 2: Cost-effectiveness simulations can be found at http://www.intmedpress.com/uploads/documents/3602_Tief_Addfile2.pdf

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