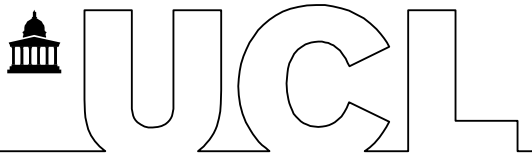

Lau, WC; Murray, M; El-Turki, A; Saxena, S; Ladhani, S; Long, P; Sharland, M; (2015) Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. Vaccine , 33 (39) pp. 5072-5079. 10.1016/j.vaccine.2015.08.022. Downloaded from UCL Discovery: http://discovery.ucl.ac.uk/1470580

ARTICLE

Title: Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom

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Abstract
Background: Studies have demonstrated a reduction for otitis media (OM) following the introduction of seven-valent pneumococcal conjugate vaccine (PCV7), but this has not been evaluated in the United Kingdom (UK). Moreover, there are limited data on any additional impact of PCV13 introduction in 2010.
Methods: We conducted an observational cohort study to investigate the trends in OM incidence and associated antibiotic prescriptions in children aged <10 year-olds during 2002-2012 using a national primary care database. Three time-periods were defined to estimate monthly incidence: pre-PCV7 (January 2002-August 2006), post-PCV7 (September 2007-March 2010), and post-PCV13 (April 2011-December 2012).
Results: Overall annual OM incidence declined by 51.3% from 135.8 episodes/1000 person-years in 2002 to 66.1 episodes/1000 person-years in 2012; antibiotic prescription rates for OM declined by 72.9% from 57.9 prescriptions/1000 person-years to 15.7

prescriptions/1000 person-years, respectively. PCV7 introduction was associated with significant decline in OM rates across all age-groups (21.8%; 95%CI, 20.2-23.4), including <2 year-olds (19.8%; 95%CI, 16.0%-23.5%); 2-4 year-olds (23.0%; 95%CI, 20.4%-25.4%) and 5-9 year-olds (20.2%; 95%CI, 17.6%-22.7%). There was an additional significant reduction in OM (18.5%; 95%CI, 16.7%-20.2%) and associated antibiotic prescribing (12.2%; 95%CI, 8.6%-15.6%) after the introduction of PCV13 across all age-groups. **Conclusion:** The introduction of PCV7 was associated with a 22% significant reductions in OM in children aged <10 year-olds with an additional 19% reductions after PCV13 introduction. These declines are equivalent to 592,000 and 15,700 fewer consultations and OM-related hospitalizations, respectively, in England and Wales every year. Although the continuing decline in OM rates in our study suggests that further reduction may continue to occur, it is important to monitor long-term trends in all pneumococcal diseases, including OM and pneumonia, because of increasing replacement of non-vaccine pneumococcal serotypes in carriage and disease.

Keywords: otitis media, pneumococcal conjugate vaccines, children, primary care, general practitioners

Introduction

Otitis media (OM) is one of the most common infections during childhood causing middle ear inflammation and is associated with fever, ear pain or effusion. Despite being an acute self-limiting condition that resolves spontaneously, it is among the leading causes for children to visit physician and is the most common reason for prescribing antibiotics to children with respiratory conditions [1]. The common bacterial pathogens to cause acute OM are *Streptococcus pneumoniae, Haemophilus influenzae* , and *Moraxella catarrhalis* either directly or as a complication of a viral upper respiratory tract infection [2]. Given the substantial economic and healthcare costs of pneumococcal disease and the emergence of penicillin- and multidrug-resistant pneumococcal strains [3,4], several countries have focused primarily on prevention rather than treatment by adding pneumococcal vaccination into their infant immunization schedules. In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) that protects against the seven most prevalent serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) was licensed in the United States (US) for use among infants and young children to prevent pneumococcal infections. In the United Kingdom (UK), PCV7 was introduced into the childhood immunization program in September 2006. Unlike other countries where the recommended 3-dose infant schedule, however, a 2-doses infant schedule at 2 and 4 months old with a booster after 12 months of age (2+1 schedule) was implemented, alongside a 12-month catch-up campaign for all children aged <2 years [5].

PCV7 introduction resulted in a rapid and sustained reduction in invasive pneumococcal disease (IPD) caused by the vaccine serotypes across all age-groups through direct and indirect (herd) protection [5]. Analysis of national Hospital Episode Statistics (HES) data also revealed 20% reduction in hospitalizations for pneumonia and empyema in England following PCV7 introduction [6]. The reduction in PCV7-type pneumococcal infections, however, was associated with an increase in non-vaccine serotypes in carriage and, consequently, in invasive disease, led to replacement of PCV7 in national immunization schedules with a 13-valent vaccine (PCV13) that provided protection against six additional serotypes (1, 3, 5, 6A, 7F and 19A) [7,8]. In the UK, PCV13 replaced PCV7 in April 2010 without a catch-up for older children. In other developed countries in Europe and North

America, the success of PCV7 in reducing community acquired-pneumonia and OM has been demonstrated in a number of clinical trials and observational studies [9-17].

However, in the UK the impact of PCV7 to OM reduction and associated antibiotic prescription rates, where 2-dose infant schedule with a booster after 12 months of age was introduced, has not been assessed. Additionally, the additional benefit of PCV13 in further reducing the burden of OM and antibiotic use in children is uncertain. In this study, we used a national primary care database to assess trends in OM incidence and associated antibiotic prescriptions over an 11-year period encompassing the introduction of both PCV7 and PCV13 in the UK.

Methods

Study design

We conducted a retrospective cohort study to estimate incidence of OM and associated antibiotic prescribing from a primary care electronic healthcare database in children between January 2002 and December 2012.

Data source

The IMS Health (previously known as Intercotinental Medical Statistics), is an international healthcare information company, collecting anonymized health information within the UK and across the world. The IMS Disease Analyzer (IMS-DA) (formally known as Mediplus) is a longitudinal electronic healthcare database managed by IMS, containing medical records from nationally representative general practices in the UK (England, Wales, Scotland, and North Ireland). There are around 125 general practices and more than 500 general practitioners (GPs) have agreed to contribute their patients' medical data to IMS DA. GPs use the computer software to enter patient medical records in their daily clinical practice for patient management. Information held on the database includes patient demographics, diagnosis, clinical symptoms, and prescription details. The data are then electronically transmitted from GPs' computer systems to IMS DA. The quality of data recording has been monitored by the IMS Health over time [18]. The database contains approximately 2 million anonymous patient records and over 95 million prescriptions [19]. Diagnoses and clinical symptoms are coded using Read Clinical Terms, a hierarchical coding system [20,21]. The recorded Read codes are mapped to ICD-10 (International Statistical Classification Disease, 10th Revision) terminology by IMS Health. Prescribed drugs are coded based on the Anatomical Therapeutic Chemical (ATC) classification issued by the European Pharmaceutical Market Research Association (EPhMAP) [22]. The database has shown to be of high quality and is widely used in pediatric pharmaco-epidemiological studies [23,24].

Identification of otitis media episode and associated antibiotic prescribing

We included all children younger than 10 years, registered with a general practice for at least 6 months during the study period. Children temporarily registered with a general practice were excluded to ensure that there was no duplication of the same patients being permanently registered at another participating general practice. We identified children with one or more OM diagnoses between January 2002 and December 2012 by searching the IMS-DA using pre-defined diagnostic codes (Supplement Table1). Due to the acute nature of OM, some children may have had multiple OM episodes which could lead to close monitoring by GPs, resulting in multiple GP surgery visits. A 14-day screening period was set from the initial OM episode and any subsequent OM record during the screening period

was classified as a follow-up visit for the same episode; OM diagnosis after this period was counted as a new episode [24]. A major advantage of IMS-DA data over other UK healthcare databases is that prescriptions are directly linked by the GP to a clinical diagnosis at the time of consultation [25]. Antibiotic groups were defined based on the therapeutic level Anatomical Therapeutic Chemical (ATC)-J010.

Secular trends

We estimated annual incidence of OM and associated antibiotic prescribing rates between 2002 and 2012. Incidence was defined as the total number of OM episodes during the study period divided by the total person-years of the study population during the time period. We also calculated OM incidence with monthly time series data for the same period. The monthly incidence of OM was defined as total number of OM episodes during each month divided by the total person-months of the study population. The monthly incidence of antibiotic prescribing to OM treatment was also calculated for the study period. Age-specific incidence was calculated for the following age-groups: <2 year-olds, 2-4 year-olds, and 5-9 year-olds. The 95% confidence intervals (CIs) were estimated using Poisson distribution.

Interrupted time series analysis

We used a segmented linear regression model of an interrupted time series (ITS) to compare the change in OM incidence and associated antibiotic prescribing rates before and after the introduction of PCV7 and PCV13. Because it is generally recommended to have at least 12 time points before and any intervention in ITS analysis [26], we also compared incidence change at monthly intervals before and after the introduction of both PCVs. The ITS analysis was divided into pre- and post-intervention segments and the difference between the two segments allowed individual assessment of the impact of each intervention [27]. Three time-periods were defined to estimate monthly incidence: pre-PCV7 (January 2002-August 2006), post-PCV7 (September 2007-March 2010), and post-PCV13 (April 2011-December 2012). A 12-month transition period after the introduction of each vaccine (September 2006-August 2007 for PCV7; April 2010-March 2011 for PCV13) was included in the model to allow for increasing vaccine uptake in the target age-groups. In September 2006, the PCV7 was introduced into childhood immunization program. At the same time, a 12-month catch-up campaign was initiated. The national coverage of PCV7 after the 12-month transition period was 93.5% in children aged 12 month-old and 88.6% in children aged 24 month-old before the PCV13 replacement [28]. Similarly, the high vaccine uptake was reported after PCV13 introduction. The coverage after 12 months transition period of PCV13 introduction was 94.6% in children aged 12 month-old and 91.9% in children aged 24 month-old [29]. There are strong seasonal fluctuations for seasonal variation where OM rates are significantly higher in the winter months than in the summer; this variation was adjusted by adding an indicator for specific calendar months in the model. The models were accounted for first-order autocorrelation as error terms of consecutive observations were often correlated. Residual analyses of the final models showed no evidence of autocorrelations. Data management and analyses were performed using Stata SE software version 11.0 (Stata Corp., College Station, TX, USA) and Statistical Analysis System (SAS) v9.3 (SAS Inc., United States).

Ethical approval

This study protocol was approved by the IMS Independent Scientific and Ethical Advisory Committee.

Results

The study population comprised 567,275 children aged <10 year-olds contributing 2,297,996 person-years between January 2002 and December 2012 from family practices contributing to the database. There were 240,419 OM episodes identified in 106,709 children and 41.1% (43,843/106,709) of children received an antibiotic for OM treatment over the 11-year period. The median age at 1st OM episode was 3.0 years (interquartile range [IQR]: 1-5 years) and approximately half of the episodes occurred in boys (52.2%; 55,672/106,709). There was approximately 46.6% (49,739/106,709) of children with more than one OM episode during study period.

Incidence of otitis media

During pre-PCV7 (2002-2005), the mean annual OM incidence was 133.3 episodes (95%CI, 131.8-134.8) in <10 year-olds, with the highest incidence in <2 year-olds (204.4 episodes/1000; 95% CI, 201.8-207.0), followed by 2-4 year-olds (180.6 episodes/1000; 95% CI, 179.1-182.2) and 5-9 year-olds (93.0 episodes/1000; 95% CI, 92.2-93.8). OM was strongly related to seasonality, with peak rates observed in winter months compared to the other months. The annual incidence of OM in <10 year-olds declined by 51.3% from 135.8 episodes/1000 person-years (95% CI, 134.4-137.3) in 2002 to 66.1 episodes/1000 person-years (95% CI, 64.9- 67.4) in 2012.

Following a transition period of 12 months after PCV7 introduction (September 2006 to August 2007), there was a 21.8% (95% CI, 20.2-23.4%) decline in the monthly incidence of OM in children aged <10 years (Figure 1A). This decline was significant in <2 year-olds (19.8%; 95% CI, 16.0-23.5%), 2-4 year-olds (23.0%; 95% CI, 20.4-25.4%) and 5-9 year-olds (20.2%; 95% CI, 17.6-22.7%) (Figure 2). After PCV13 introduction, there was an additional 18.5% (95% CI, 16.7-20.2%) decline in monthly OM incidence overall, with significant declines observed among <2 year-olds (6.6%; 95%CI, 1.9-11.0%), 2-4 year-olds (13.0%; 95% CI, 10.1-15.9%) and 5-9 year-olds (20.0%; 95% CI, 17.3-22.6%) (Figure 2).

Antibiotic prescription rates for otitis media treatment

The antibiotics prescribed for OM were consistent year-on-year over the whole study period (Supplement Figure1). Amoxicillin was the most commonly prescribed antibiotic, accounting for 78.1-82.3% of OM-associated prescriptions annually, followed by erythromycin (6.8-8.7%), co-amoxiclav (3.1-4.7%), penicillin V (1.5-2.3%), clarithromycin (0.5-2.2%) and others (3.0-6.8%). A seasonal variation was also observed for antibiotic prescription rates, with higher rates in winter months compared with other months (Figure 3). Overall, antibiotic prescription rates fell by 72.9%, from 57.9 prescriptions/1000 person-years (95% CI, 56.9-58.9) in 2002 to 15.7 prescriptions/1000 person-years (95% CI, 15.1-16.3) in 2012.

Antibiotic prescribing rates for OM were already declining before the introduction of pneumococcal conjugate vaccination (Figure 1B). After PCV7introduction, however, there was an additional 18.9% (95% CI, 16.0-21.7%) monthly reduction in antibiotic, prescription rates overall and for <2 year-olds (18.5%; 95%CI, 11.7-24.7%), 2-4 year-olds (17.5%; 95%CI, 12.9-21.9%), and 5-9 year-olds (21.8%; 95%CI, 17.2-26.2%) (Figure 3). Replacement of PCV7 with PCV13 was associated with a further 12.2% (95%CI, 8.6-15.6%) monthly reduction in antibiotic prescription rates overall, but this reduction was only significant for 5-9 year-olds (18.6%; 95%CI, 13.1-23.8%) (Figure 3).

Discussion

The introduction of pneumococcal conjugate vaccine into the UK childhood immunization program was associated with a significant decline in the incidence of OM and associated antibiotic prescribing in children younger than 10 years of age. As is typical of OM, children aged less than <2 years had the highest rates with a characteristic winter peak. Although PCV7 was targeted at younger children, the similar significant declines in OM incidence were observed across all age groups studied. Replacement of PCV7 with PCV13 in April 2010 was associated further declines in OM incidence and associated antibiotic prescription rates.

Older age children may benefit from the indirect impact of the program, as has been reported for invasive pneumococcal disease and hospitalizations for bacterial pneumonia and empyema in England and Wales.[5,6] Since conjugate vaccines also prevent carriage, targeting the initial PCV7 program to include age-group with the highest pneumococcal carriage rates (<2 year-olds) resulted in more rapid indirect (herd) protection through reduced transmission of pneumococcal vaccine serotypes to unvaccinated and older children and adults. Since indirect protection lags behind direct protection, the continuing decline in OM incidence among 2-4 and 5-9 year-olds even after PCV13 introduction is likely due to a combination of the vaccinated cohorts getting older and the indirect protection offered to the older, unvaccinated age groups.

At a population level, the 21.8% decline in OM incidence among <10 year-olds after PCV7 introduction is equivalent to 356,000 fewer GP consultations and 9,400 fewer hospitalizations annually in England and Wales [30]. Replacement with PCV13 resulted in a further 18.5% decline in OM incidence in this age group, equivalent to 236,000 fewer GP consultations and 6,300 hospitalizations annually [30], resulting in large cost savings to the National Health Service in addition to the benefits achieved through prevention of IPD, bacterial pneumonia and empyema.

A major consequence of the decline in the incidence of OM is the associated reduction in antibiotic prescription rates for OM. The antibiotics prescribed for children with otitis media are in accordance with treatment recommendations in the British National Formulary for Children (BNFC), with amoxicillin being the predominant antibiotic of choice [31]. The decline in antibiotic prescription rates for OM prior to PCV introduction is likely to have been driven by national campaigns to reduce antibiotic prescriptions for self-limiting, viral infections in children [32]. On the background of this decline, however, we observed further reductions in antibiotic prescription rates for OM following the introduction of PCV7 initially but also after replacement with PCV13. This is an important finding, given the global concerns regarding inappropriate antibiotic use and increasing antibiotic resistance rates.

Findings in relation to previous studies

The reduction of OM incidence in our study is similar to clinical trials and observational studies in other countries evaluating the effect of PCV7 in preventing childhood OM. A recent systematic review reported the efficacy of PCV7 against all-cause acute OM episodes to be 0-9% in randomized controlled trials but 17-23% in non-randomized observational studies, consistent with our findings [33]. We have additionally identified a further decline of a similar magnitude within two years of PCV13 introduction. This is consistent with a recent US study using a health insurance claims database, there was a significant reduction in

primary care visits for OM and recurrent OM following PCV13 introduction, mainly in <2 year-olds [34]. In the US, PCV7 introduction was associated with a 41% reduction in antibiotic prescriptions for OM in children aged <2 year-olds [17]. In France and the Netherlands, too, antibiotics prescriptions for OM fell significantly among 6-month to 2 year-olds and 1-9 year-olds, respectively, after PCV7 introduction [35,36]. This is the first study to demonstrate further reductions in antibiotic prescription rates for OM after PCV13 introduction.

Strength & limitations

Pneumococcal surveillance in England and Wales is restricted to laboratory-confirmed, invasive cases. This is the first UK study to investigate the impact of both PCV7 and PCV13 on OM incidence and antibiotic use in a community setting. The strength of our study is its size, generalizability and representative coverage of patients attending GP surgeries across the UK (England, Scotland, Wales, and Northern Ireland). An important limitation of our study, however, is that we do not have pneumococcal serotype data and culture results for OM cases. The routine microbiology cultures are rarely taken from patients presenting to primary care with otitis media. This is a general limitation in UK primary care database. As the laboratory data and culture results are not available in the IMS DA, we were unable to investigate whether the frequency of *Streptococcus pneumonia* isolation changed in our study. In addition, since tympanocentesis is not performed for OM diagnosis GP clinical practice in the UK, there are no data available to assess the contribution of *Streptococcus pneumonia* to OM in different age groups or changes in serotype distribution following PCV introduction. OM is, therefore, invariably diagnosed clinically and is, therefore, subjective to the attending clinician. While this may have an effect on overall diagnosis rates for OM, it is unlikely to affect trends over time. Secondly, this is an ecological study to evaluate the impact of PCV on OM rates and we cannot directly attribute the observed reductions to PCV introduction. However, there were two statistical significant reductions on OM incidence when ITS was performed after the PCV interventions. In addition, we did not identify any systematic changes in diagnostic or administrative practices that might otherwise explain the reduction in OM incidence or associated antibiotic prescription rates following PCV7 introduction or replacement with PCV13. Thirdly, the patients' vaccination histories are not completely recorded in primary care database. In UK, the vaccination status is recorded in any of following medical records: 1) patient-held record or Personal Child Health Record for children (e.g. the Red Book); 2) patient's GP record or other patient record; 3) Child Health Information System; 4) practice computer system [37]. The National Institute for Health and Care Excellence (NICE) guidance stated that vaccination status of children and young people should be checked at every appropriate opportunity [38]. As we cannot access to individual child's health records in all aforementioned medical records, we were unable to accurately to ascertain immunization status in our study subjects. Fourthly, several predisposing risk factors to otitis media have been reported such as age, socioeconomic index, breastfeeding, smokers in the household, attending day care [39,40]. However, most of this information is not captured in the IMS DA so we cannot investigate whether some children have risk factors predisposing to otitis media in our study. Fifthly, otitis media is a self-limiting acute condition and it sometimes spontaneously resolves without the need for antibiotic treatment. We were unable to obtain data on those children who have OM but didn't visit GP for antibiotic treatment in the community. Finally, as with all studies analyzing large administrative databases, there is potential for misclassification bias when using diagnostic codes to define OM. Clinicians may also prefer certain diagnostic codes over

others to support their clinical decision to prescribe or not prescribe antibiotics to individual patients. Although we did not conduct a validation study to verify diagnostic codes for OM, the codes that we used are similar to previous studies using the Read code system [41]. However, although code choice for analysis could potentially influence absolute counts and, possibly, age distribution of cases, such biases are unlikely to affect trends over time and therefore, the reduction in OM cases and antibiotic prescription rates are most likely to be attributable to PCV introduction.

Conclusion

The introduction of PCV7 was associated with a significant reduction in primary care consultations for OM and antibiotic prescribing rates, with a similar additional decline within two years of PCV7 replacement with PCV13. These reductions were observed not only in vaccine-eligible children but also among older children because of indirect protection and it is likely that older age groups not included in our study will also have benefitted from this indirect protection. Although the continuing decline in OM rates during 2012 suggests that further reductions may continue to occur, it will be important to monitor long-term trends in all clinical manifestations of pneumococcal disease, including OM and pneumonia, because of increasing replacement of non-vaccine pneumococcal serotypes in carriage and disease [5,42]

Acknowledgement

We thank all general practitioners that have contributed to the IMS DA database. We also thank Dr Antonio Gasparrini from London School of Hygiene and Tropical Medicine provided advice on interrupted time series analysis.

Author Contributions: Mike Sharland, Ian Wong, Sonia Saxena, Paul Long, and Shamez Ladhani conceptualized and designed the study. Macey Murray and Aisha El-Turki carried out the initial data extraction and data cleaning. Yingfen Hsia and Wallis Lau carried out the final data analyses, drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted. All authors critically reviewed the manuscript and approved the final manuscript as submitted.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study is funded by a Pfizer unrestricted educational grant. Dr Sonia Saxena is funded by a National Institute for Health Research Career Development Fellowship (NIHR CDF-2011-04-048). This article presents independent research commissioned by the National Institute for Health Research (NIHR) under the Collaborations for Leadership in Applied Health Research and Care (CLAHRC) programme for North West London. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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Figure 1A Interrupted time series analysis of monthly incidence of otitis media in children <10 year-olds, 2002-2012

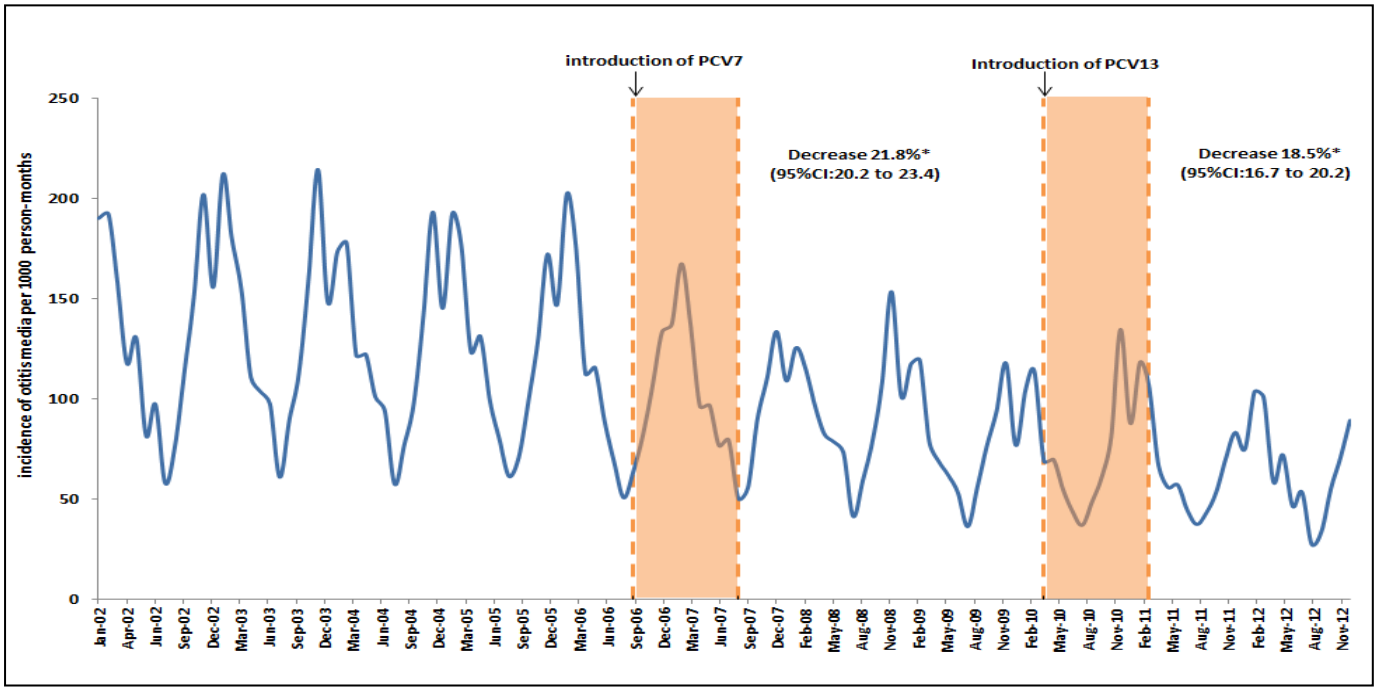


Figure 1B Interrupted time series analysis of monthly antibiotic prescribing rates for otitis media treatment in children <10 year-olds, 2002-2012

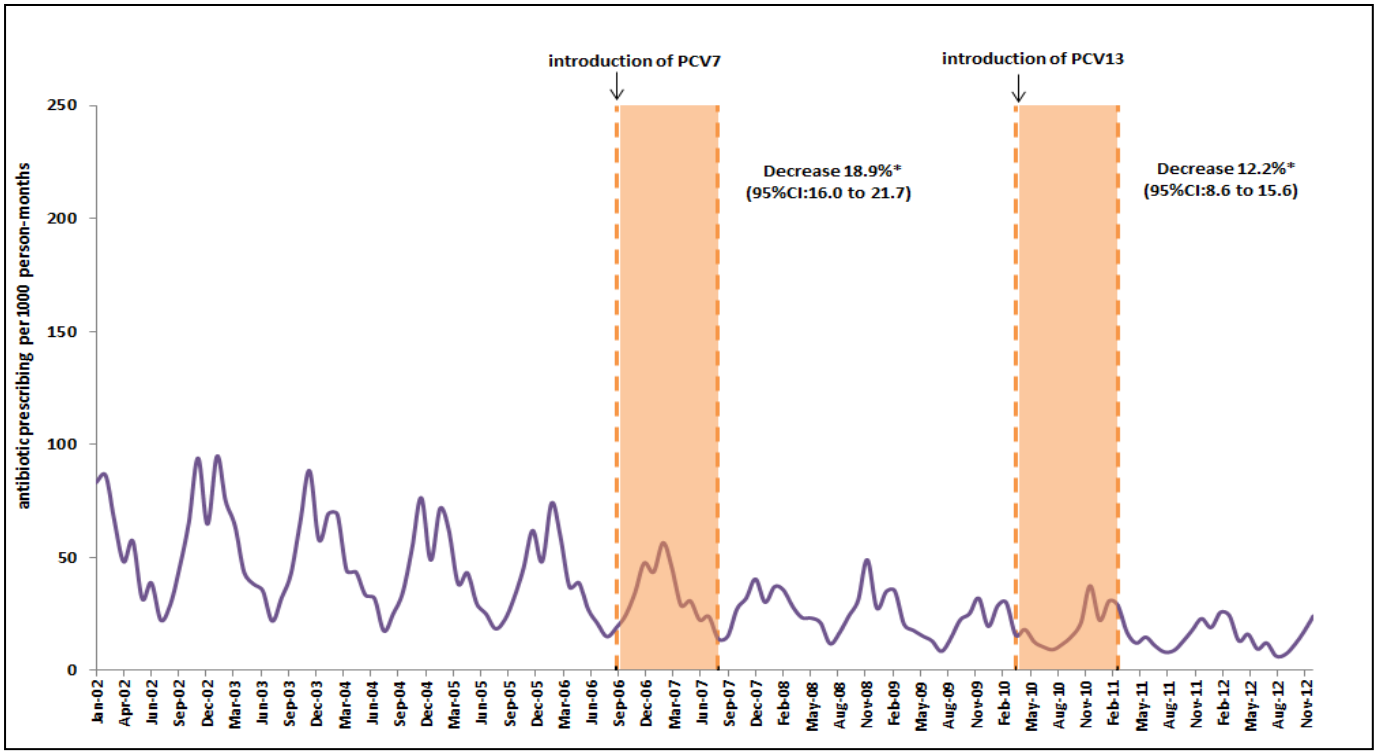
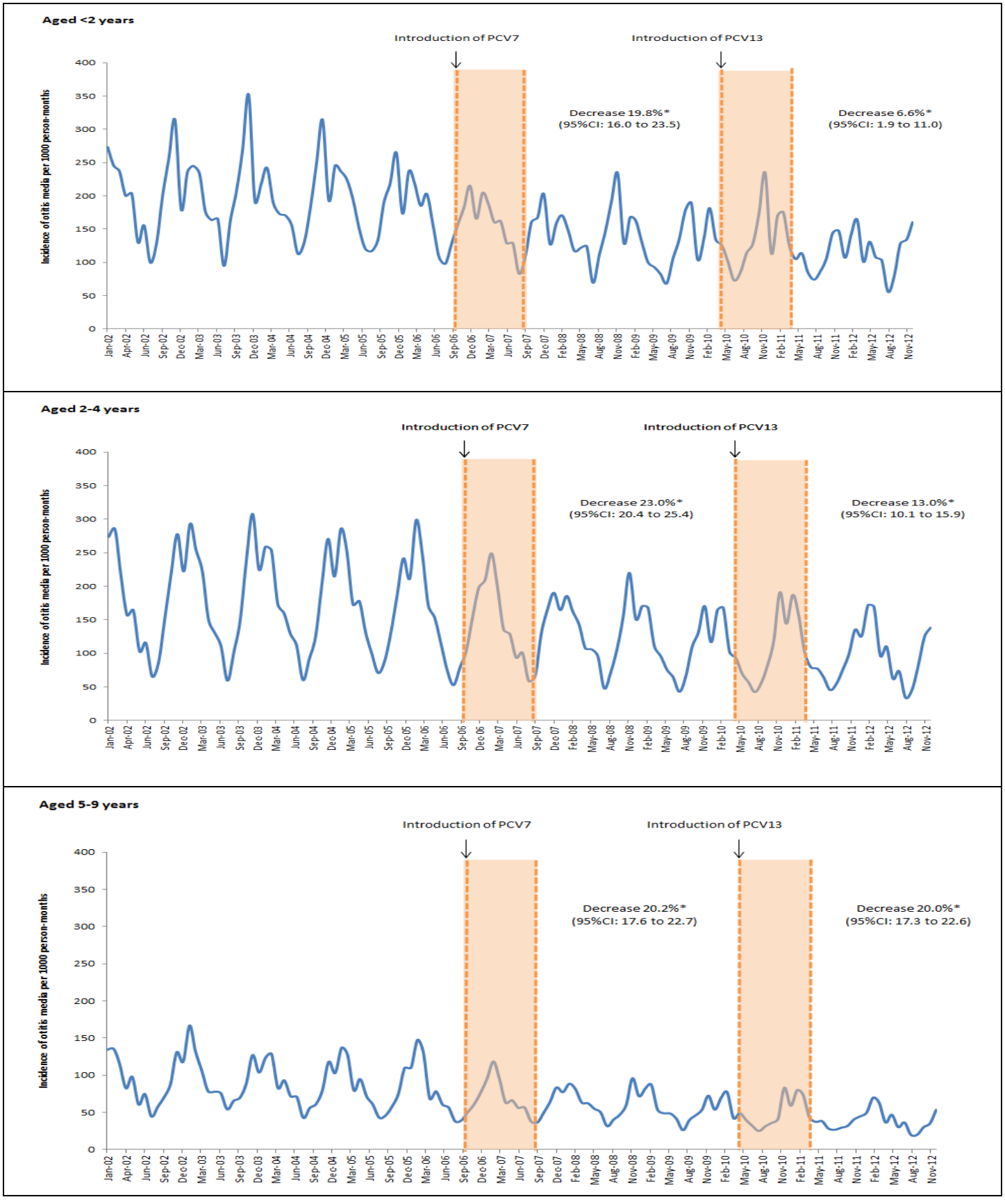
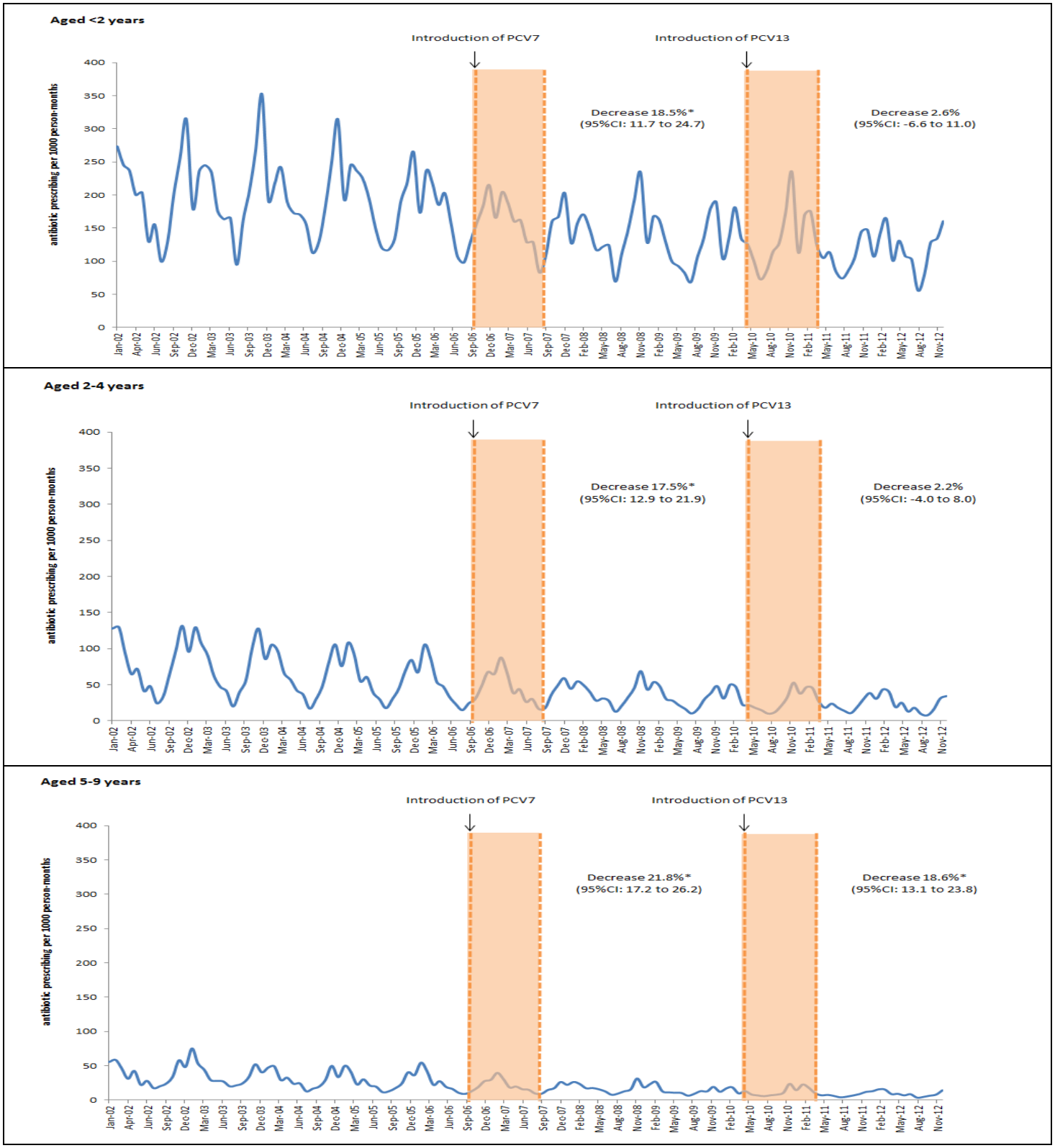


Figure 2 Interrupted time series analysis of monthly incidence of otitis media by age groups, 2002-2012



*Indicates significant reduction (P<0.05). The orange shades represents the transition period for PCV7 (September 2006-August 2007) and PCV13 (April 2010-March 2011).

Figure 3 Interrupted time series analysis of monthly antibiotic prescription rate for otitis media by age groups, 2002-2012



*Indicates significant reduction (P<0.05). The orange shades represents the transition period for PCV7 (September 2006-August 2007) and PCV13 (April 2010-March 2011).

SUPPLEMENT

TABLE1 Otitis Media diagnostic codes in IMS Disease Analyze, 2002-2012
FIGURE 1The most commonly prescribed antibiotics for otitis media treatment in children < 10 year-olds

SUPPLEMENT TABLE1 Otitis Media diagnostic codes in IMS Disease Analyze, 2002-2012

Read code	Description	Total episodes	Percentage (%)
F51..	Nonsupp otitis media + eustach	71,594	29.79
F510.	Acute non supp otitis media	49,897	20.75
F52..	Suppurative otitis media	48,041	19.98
F520.	Acute suppurative otitis media	17,377	7.22
F52z.	Otitis media NOS	14,557	6.05
F512.	Chron ot med with eff-mucoid	11,458	4.77
.F621	Acute nonsupp. otitis media	6,010	2.49
F527.	Acute right otitis media	3,938	1.64
F526.	Acute left otitis media	3,255	1.35
.F62.	Nonsuppurative otitis media	3,061	1.27
F528.	Acute bilateral otitis media	2,009	0.84
.F625	Otitis media NOS	1,861	0.77
.F631	Acute suppurative otitis media	1,07	0.50
.F63.	Suppurative otitis media	927	0.39
F511.	Chron ot media with eff-serous	752	0.31
F523.	Chronic supp.otitis media NOS	565	0.24
F524.	Purulent otitis media NOS	503	0.21
.F623	Chronic mucoid otitis media	432	0.18
F510z	Acute nonsup.otitis media NOS	425	0.18
F5100	Acute otit media with effusion	387	0.16
F518.	Chron ot med with eff-unspec	334	0.14
F514.	Nonsupp. otitis media unspec.	211	0.09
F5101	Acute serous otitis media	210	0.09
F5200	Acute supp.otit.media-drum OK	192	0.08
F5201	Acute supp.otit.med.+drum rupt	162	0.07
F5141	Serous otitis media NOS	147	0.06
F5102	Acute mucoid otitis media	122	0.05
F521.	Chron supp ot med-tubotympanic	107	0.04
F5142	Catarrhal otitis media NOS	96	0.04
F513.	Chron ot med with eff-other	87	0.04
F512z	Chronic mucoid otitis med. NOS	85	0.04
F520z	Acute supp. otitis media NOS	77	0.03
A552.	Postmeasles otitis media	72	0.03
.F633	Chronic purulent otitis media	55	0.02
F5240	Bilateral supp otitis media	48	0.02

.F622	Chronic serous otitis media	46	0.02
.F63Z	Purulent otitis media NOS	33	0.01
F5112	Bilateral chron serous otitis	24	0.01
F511z	Chronic serous otit.media NOS	14	0.006
F514z	Nonsuppurat. otitis media NOS	13	0.005
F522.	Chron supp ot med-atticoantral	13	0.005
F5143	Mucoid otitis media NOS	7	0.003
F5131	Chron ot med with eff-purulent	4	0.002
F5103	Acute sanguinous otitis media	2	0.001
F5105	Acute allerg.mucoid otit.media	1	0.0004
F5121	Mucosanguinous chr.otit.media	1	0.0004

SUPPLEMENT FIGURE 1The most commonly prescribed antibiotics for otitis media treatment in children < 10 year-olds