# Epidemiology

# Burden of disease in children with respiratory tract infections in primary care: diary-based cohort study

# M J C Schot<sup>a,\*</sup>, A R J Dekker<sup>a</sup>, C H van Werkhoven<sup>a</sup>, A W van der Velden<sup>a</sup>, J W L Cals<sup>b</sup>, B D L Broekhuizen<sup>c</sup>, R M Hopstaken<sup>d</sup>, N J de Wit<sup>a</sup> and T J M Verheij<sup>a</sup>

<sup>a</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, <sup>b</sup>Department of Family Medicine, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands, <sup>c</sup>General Practice de Bongerd, Borculo, The Netherlands and <sup>d</sup>Star-shl diagnostic centers, Etten-Leur, The Netherlands.

\*Correspondence to: M J C Schot, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.136, PO Box 85500, 3508 GA Utrecht, The Netherlands; E-mail: m.j.c.schot-2@umcutrecht.nl

# Abstract

**Background**. Respiratory tract infections (RTIs) are a common reason for children to consult in general practice. Antibiotics are often prescribed, in part due to miscommunication between parents and GPs. The duration of specific respiratory symptoms has been widely studied. Less is known about illness-related symptoms and the impact of these symptoms on family life, including parental production loss. Better understanding of the natural course of illness-related symptoms in RTI in children and impact on family life may improve GP–parent communication during RTI consultations.

**Objective**. To describe the general impact of RTI on children and parents regarding illness-related symptoms, absenteeism from childcare, school and work, use of health care facilities, and the use of over-the-counter (OTC) medication.

**Methods**. Prospectively collected diary data from two randomized clinical trials in children with RTI in primary care (n = 149). Duration of symptoms was analysed using survival analysis.

**Results.** Disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities are very common during RTI episodes, with disturbed sleep lasting longest. Fifty-two percent of the children were absent for one or more days from childcare or school, and 28% of mothers and 20% of fathers reported absence from work the first week after GP consultation. Re-consultation occurred in 48% of the children. OTC medication was given frequently, particularly paracetamol and nasal sprays.

**Conclusion.** Appreciation of, and communication about the general burden of disease on children and their parents, may improve understanding between GPs and parents consulting with their child.

Key words: child, clinical study, primary health care, respiratory tract infections, signs and symptoms, respiratory

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## Key Messages

- Burden of childhood respiratory tract infections (RTIs) not only consists of respiratory symptoms.
- RTI affects sleep, eating, drinking and daily activities in children.
- Forty-eight percent of parents were absent from work in the first week after GP consultation.
- Awareness of the broader impact of RTI may facilitate GP-parent communication.

# Introduction

Respiratory tract infections (RTIs) are among the most common diagnoses in primary care, particularly in children (1,2). Although most RTIs are self-limiting, antibiotics are often prescribed (3,4). Even in a low-prescribing country such as the Netherlands, 48–63% of antibiotic prescriptions for RTI in children are considered to be noncompliant to guidelines (5,6). Overprescription of antibiotics is driven by diagnostic and prognostic uncertainty and by poor communication between GPs and parents (7–9). A systematic review reported that GPs often considered acute illness as a purely medical problem. This contrasted with parents voicing concerns of, for example, missing school. This mismatch led GPs to interpret these concerns as resistance to diagnosis or treatment decisions and as an implicit request for antibiotics. This might influence prescribing decisions (7). It has been suggested that a more bio-psycho-social approach may avoid some of the miscommunication (7).

Duration of respiratory symptoms in children, such as cough and nasal congestion, has been studied previously (10-12). After 1 week, symptoms in 75% of children have improved, but half may still be coughing. Cough recovers in 90% of the children by day 25. Recently, a large cohort study examined patterns in recovery from cough and found 66% of children was recovered by day 7, while 16% of children had persistent symptoms after 15 days (13). GPs tended to underestimate duration of symptoms (10). However, besides causing respiratory symptoms, RTI influences a child's daily functioning in general, for example, impacting sleeping, eating and school attendance. This can have a considerable impact on family life. Disturbed sleep was reported by 72% of parents with children with acute cough, for example (14). Furthermore, missed days at childcare or school may induce work absenteeism for parents, also adding to the burden of this common illness (15,16). A previous study reported reduced quality of life in parents of children with influenza-like illness, with total time spent caring for a child and severity of illness as factors independently associated with quality of life (17).

Awareness of the type and extent of the broader impact of RTI on families may contribute to a better understanding between GPs and parents, better-informed management decisions and improved counselling of parents. We therefore studied the impact of RTI on children and their parents, with respect to duration of illness-related symptoms, absenteeism from childcare, school and work, use of health care facilities and the use of over-the-counter (OTC) medication in a cohort of children with RTI.

# Methods

# Study design

This observational diary-based study used data from two Dutch randomized clinical trials in children with RTI in primary care (see Supplementary Material for further details on the trials). Both trials aimed at reducing antibiotic prescriptions for children with RTI, the first through an online training for GPs and an information booklet for parents (18), and the second by introducing point-of-care C-reactive protein measurement in children with RTI (19). In both trials, parents were asked to fill out similar daily diaries. To avoid the impact of the trial interventions on the results of this cohort study, we only studied children in the control group of both trials. This ensured that children studied received usual care for RTI in general practice.

#### Study population

We included children aged between 3 months and 12 years old who were diagnosed with an acute RTI. Detailed eligibility criteria for the two randomized clinical trials are listed in Supplementary Material. For the purpose of this study, we grouped children based on the diagnosis as registered by the treating GP. International Classification of Primary Care (ICPC)-based diagnoses were dichotomized into upper RTI (URTI) and lower RTI (LRTI) (Supplementary Material).

# Data collection

Patient characteristics: sex, age, diagnosis by ICPC-code, and if applicable prescription of antibiotics were noted by the GP on the day of inclusion.

Parents kept a 14-day diary. At baseline, these included general questions on child characteristics and previous use of OTC medication. Second, the diary assessed symptoms through a list of symptoms to be rated daily on a 5-point-Likert scale ranging from 0 (no symptoms present) to 4 (very major problem). Illness-related symptoms rated were disturbed sleep, decreased intake of food and/ or fluid, feeling ill and disturbance at play or other daily activities. Respiratory symptoms similarly ranked were cough, phlegm, dyspnoea, wheezing and nasal congestion. Finally, diaries contained weekly questions concerning the use of OTC medication, the use of health care facilities and the absence from childcare, school and parents' work related to the child's illness.

# Outcomes

We defined three major outcomes:

- Duration of illness-related symptoms: disturbed sleep, decreased intake of food and/or fluid, feeling ill and disturbance at play or other daily activities.
- 2. Impact on family life, defined as the number of days children were absent from school or childcare, the number of hours parents were absent from work and the use of the health care system.
- 3. Use of OTC medication.

#### Duration of illness-related symptoms

The scores for four illness-related symptoms were summed to create a daily score of illness-related symptoms, with a maximum of 16 points. This score on day 1 was used as a proxy for severity of illness-related symptoms on the day of consultation. We regarded a child to be recovered on the first day none of these symptoms was ranked as a 2 (moderate problem) or higher, irrespective of subsequent values. We applied the same strategy to the respiratory symptoms, with a maximum score of 20 points.

#### Impact on family life

The number of days a child was absent from childcare or school was evaluated weekly. Time off work by parents is presented as hours missed per week. Use of healthcare facilities was analysed in four predefined categories: contact with GP, contact with out-of-hour service (OOH service), contact with pharmacy and contact with hospital (either emergency room or specialist).

### Use of OTC medication

Use of OTC medication was scored weekly, in four predefined categories: paracetamol, non-steroid anti-inflammatory drug (NSAID), cough medication and nasal sprays.

#### Analysis

Missing values for the baseline characteristics gender (n = 1), duration of symptoms before consultation (n = 6) and score for severity of symptoms (n = 16) were imputed using multiple imputation (20).

For patients with missing daily symptom scores, if the last entered value was scored as a 2 or higher, this was considered as a real missing value. Data were censored from that day on for the survival analysis. When no use of healthcare facilities, absence from daycare, school or parents' work was noted, it was assumed absent. When no medication was listed in the diary, it was assumed no medication was given.

All analyses were performed for the total group of children and separately for the two diagnostic categories: URTI and LRTI. As LRTI is generally regarded as a more severe illness, we hypothesized that outcomes might differ between these groups.

Recovery rates were analysed using survival analysis with Kaplan-Meier plots. Log-rank tests were used to test differences in recovery rates between children with URTI and LRTI. Secondary analysis was conducted using multivariable Cox regression to determine which of the baseline characteristics were associated with time to recovery of symptoms, and hazard ratios (HRs) were calculated. An HR < 1 indicates a longer time to recovery of symptoms. Given the two diagnostic categories, this resulted in four models. Model fit was checked for each of the four models, testing for collinearity between variables by calculating variance inflation factors, proportional hazards and linearity of continuous predictors. The proportional hazards assumption was not met for the baseline variable of illness-related symptoms and respiratory symptoms in children with URTI and for illness-related symptoms in children with LRTI. Therefore, we used time transformation of this variable in the analysis. Finally, we evaluated duration of each of the four illness-related symptoms separately.

We tested statistical significance of categorical variables using chi-square test or Fisher's exact test, as appropriate. All descriptive analyses were performed using SPSS statistics version 24. Multiple imputation, survival analysis and Cox regression analysis were performed using R version 3.5.1.

# Results

A total of 149 diaries (41% of total number of children in control groups of both trials) were available for analysis (67 URTI and 82 LRTI). Mean age in both groups was 3 years [SD 2.9 (URTI)/2.6 (LRTI)]. Mean duration of illness before consultation was 4.7 and 7.0 days for URTI and LRTI, respectively. During the first consultation, children with LRTI were prescribed antibiotics more often compared with children with URTI (52% versus 42%). The summed

score of illness-related symptoms was higher in children with LRTI. Baseline characteristics are listed in Table 1.

# Duration of illness-related symptoms

On the day of consultation, 90% of parents of children diagnosed with URTI and 94.2% of children diagnosed with LRTI reported disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities as more than a moderate problem (score  $\geq$  2). On day 7, this was 13.8% in the URTI group versus 27.8% in LRTI group, and this declined to 4.5% and 13.9% on day 14, respectively. Overall, the median time from the first consultation to the reported recovery of illness-related symptoms in children with URTI was 4 days versus 5 days in children with LRTI (*P* = 0.004, Fig. 1a).

Duration of the separate illness-related symptoms is shown in Table 2. Sleep disturbance persisted most, with a mean duration of 3.1 and 4.3 days for URTI and LRTI, respectively.

A higher baseline score for illness-related symptoms was associated with longer duration of symptoms in children with URTI [HR = 0.63 on day 1,95% confidence interval (CI) = 0.51-0.79]. For children with LRTI, three factors were associated with duration of symptoms: baseline score for illness-related symptoms (HR = 0.50 on day 1,95% CI = 0.36-0.69), age (HR = 1.17,95% CI = 1.46-1.32) and prescription of antibiotics (HR = 2.46,95% CI = 1.46-4.13) (see Supplementary Material for all HRs).

Respiratory symptoms were reported by parents to be moderate to severe for 87.1% of children with URTI and for 100% of children with LRTI on the day of consultation. Respiratory symptoms decreased during follow-up, with parents reporting symptoms still more than a moderate problem on day 14 in 7.5% of children with URTI and in 25.4% of children with LRTI. Overall, the median time to reported recovery of respiratory symptoms in children with URTI was 6 days versus 8 days in children with LRTI (P = 0.003, Fig. 1b).

# Impact on family life

More than half of the children were absent from childcare or school during the first week after consultation, for a median of 2 days. Twenty-eight percent of mothers and 20% of fathers took time off work for a median of 8 hours during the first week. Nearly a quarter of parents reported to have made extra arrangements for childcare during that week (LRTI 15% versus URTI 32%, difference 17%, P = 0.02) (Table 3). Absenteeism decreased during the second week after consultation with 13% of children being absent at childcare or school, and 5% of mothers and 4% of fathers being absent at work.

 Table 1. Baseline characteristics of 149 children consulting the GP with respiratory tract infection

	URTI ( <i>n</i> = 67)	LRTI ( <i>n</i> = 82)
Male sex, $n$ (%)	31 (47)	37 (45)
Mean age, years (SD)	2.8 (2.9)	2.9 (2.6)
Siblings, <i>n</i> (%) yes	39 (58)	59 (72)
Child care or school attendance, $n$ (%)	56 (83.6)	68 (82.9)
Mean pre-consultation illness duration,	4.7 (3.1)	7.0 (5.5)
days (SD)		
Mean general symptom severity score (SD)	8.3 (4.3)	9.1 (4.1)
Mean respiratory symptom severity score (SD)	6.9 (4.6)	10.7 (4.1)
Antibiotics prescribed, <i>n</i> (%)	28 (42)	43 (52)

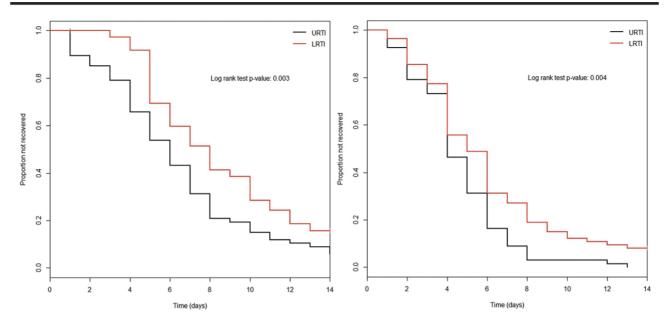


Figure 1. Recovery from illness-related symptoms and respiratory symptoms in days for children with URTI and LRTI. Panel 1: Recovery from illness-related symptoms. Panel 2: Recovery from respiratory symptoms.

Table 2. Mean duration of illness-related symptoms (days and 95%)
confidence interval), the result of Kaplan–Meier analysis

	URTI	LRTI
Disturbed sleep	3.1 (2.6–3.7)	4.3 (3.5-5.1)
Decreased intake of food and/or fluid	2.9 (2.2-3.5)	3.2 (2.6-3.8)
Feeling ill	2.3 (1.8-2.9)	3.7 (3.1-4.4)
Disturbance at play or other daily activities	2.4 (1.9–3.0)	3.3 (2.6–4.0)

In the first week after consultation, 48% of children re-consulted the GP, and 7% of children visited an OOH service. The pharmacy was visited by 36% of parents in the first week, compared with 4% in the second week (Table 3).

# Use of OTC medication

OTC medication was given to the majority of children and was highest in the week before the consultation (86.6%). Paracetamol was given most frequently throughout the entire follow-up period, followed by nasal spray and cough syrup (Table 4).

# Discussion

# Summary of main findings

RTI in children have a profound effect on the general well-being of children consulting in general practice. On the day of consultation, >90% of children experience disturbed sleep, decreased intake of food and/or fluid, feeling ill and/or disturbance at play or other daily activities. Disturbed sleep persisted longest. Overall, respiratory symptoms persist longer than illness-related symptoms. The severity of symptoms on the day of consultation was related to the duration of symptoms throughout the follow-up period. Approximately half of the children were absent for one or more days from childcare or school. The absence from work was reported by 28% of mothers and 20% of fathers, for 8 hours on average. Re-consultation occurred in almost half of the children. OTC medication was given frequently to children with RTI, particularly paracetamol and nasal sprays. As LRTI is generally regarded as a more serious illness, we decided to analyse the duration of symptoms separately for the two groups. Although we found statistical differences in the duration of symptoms, the absolute differences were minimal. Children with URTI and LRTI did not differ significantly in the absence from childcare or school and re-consultation with a GP.

# Strengths and limitations

Unique to our study is the detailed description of illness-related symptoms associated with the well-being of a child with RTI. Diary data in both studies were collected longitudinally in daily diaries. The daily collection of symptom scores minimized the probability of recall bias. The use of data collected in two different trials provided a larger group of children with URTI and LRTI.

A possible limitation of our study was the representativeness of the sample. Forty-one percent of all parents in both trials returned the diaries. However, children with and without returned diaries did not differ significantly at baseline in the trials (data not shown). Whether the duration of symptoms or severity of symptoms influenced the return rate of the diaries is unknown. It is possible that this affects the generalizability of the results. Furthermore, our results regard families consulting for RTI and may not necessarily apply to (the majority of) children who do not visit a GP (16). The reported diary-recorded duration of symptoms is the duration of symptoms after the first GP consultation. This was a mean of 4.7 and 7 days after the URTI and LRTI onset, respectively. The presented data, therefore, probably underestimate the impact of a complete disease episode. However, our aim was to inform GPs about the impact of an RTI on a child and its parents at the moment of consultation; therefore, this selected group does provide useful information. Finally, although we found certain factors significantly related to the recovery of symptoms in this cohort, our study was not designed to determine causal effects. The identified determinants need further exploration to determine whether they are causally related to illness duration.

## Comparison with existing literature

Recovery rates for respiratory symptoms in our cohort were similar to rates found in other studies (10,11,21,22). A recent study found

Table 3. Diary-reported absenteeism and use of the health care system after visiting a general practitioner
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	Week 1				Week 2			
	URTI ( <i>n</i> = 67) <i>n</i> (%)	$\frac{\text{LRTI}}{n \ (\%)}$	Total ( <i>n</i> = 149)		URTI ( <i>n</i> = 67)	LRTI ( <i>n</i> = 82)	Total ( <i>n</i> = 149)	
			n (%)	Median (range)	<i>n</i> (%)	n (%)	n (%)	Median (range)
Absent from childcare or school	32 (48)	45 (55)	77 (52)	2 days (1-5)	5 (7)	14 (17)	19 (13)	1 day (1–5)
Mother absent from work	13 (19)	28 (34)	41 (28)	8 hours (1-16)	1 (2)	6 (7)	7 (5)	8 hours (1-8)
Father absent from work	9 (13)	21 (26)	30 (20)	8 hours (1-25)	0*	6 (7)*	6 (4)	8 hours (1-24)
Need for extra childcare	10 (15)*	26 (32)*	36 (24)		0	3 (4)	3 (2)	
Contact with GP office, phone	3 (4.5)*	16 (20)*	19 (13)		0	2 (2)	2(1)	
Contact with GP in practice	26 (39)	45 (57)	71 (48)		1 (2)	5 (6)	6 (4)	
Contact with OOH service	3 (5)	7 (14)	10(7)		0	2 (2)	2(1)	
Contact with hospital	1 (2)	3 (4)	4 (3)		0	5 (6)	0	
Contact with pharmacy	22 (33)	31 (39)	53 (36)		1 (2)	0 (0)	6 (4)	

\*Statistically significant difference between children with URTI and LRTI with P < 0.05.

Table 4. Diary-reported use of over-the-counter medication

	Week before consultation		Week 1			Week 2			
	URTI ( <i>n</i> = 67)	LRTI ( <i>n</i> = 82)	Total ( <i>n</i> = 149)	URTI ( <i>n</i> = 67)	LRTI ( <i>n</i> = 82)	Total ( <i>n</i> = 149)	URTI ( <i>n</i> = 67)	LRTI ( <i>n</i> = 82)	Total ( <i>n</i> = 149)
Use of OTC (total)	60 (90%)	69 (84%)	129 (86.6%)	48 (72%)	53 (65%)	101 (67.8%)	9 (13%)	17 (21%)	26 (17.4%)
Use of paracetamol	50 (75%)	56 (68%)	106 (71.1%)	37 (55%)	38 (46%)	75 (50.3%)	5 (8%)	10 (12%)	15 (10.1%)
Use of NSAID	1 (2%)	1 (1%)	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Use of cough syrup	22 (30%)	28 (34%)	48 (32.2%)	11 (16%)	20 (24%)	31 (20.8%)	2 (3%)	5 (6%)	7 (4.7%)
Use of nasal spray	27 (40%)	27 (45%)	54 (43%)	20 (30%)	32 (39%)	52 (34.9%)	5 (8%)	9 (11%)	14 (4.9%)

absenteeism in 28% of parents when their child had an infectious episode, with a median of 2 days. This is lower than the nearly 50% we found, possibly because these children were probably less ill, as only a minority of these children visited a GP (16). Previous studies have shown that this absenteeism affects quality of life in parents and is also a main driver of total societal costs of RTI (15,17,23,24).

A previous study in adults reported comparable rates of selfmedication in patients with RTI (25), most often paracetamol. Paracetamol is useful for treating pain and fever, but evidence on its effect on well-being is lacking. However, it is likely that treating fever and pain would lead to improvement of well-being (26,27). There is no evidence for effectiveness of other OTC medication for the treatment of RTI symptoms in children (28,29). These medications are however still recommended by physicians (30,31). A qualitative study found that GPs usually did not recommend OTC medication for cough and cold, but parental anxiety and the need to 'do something' sometimes influenced their recommendations (31).

Re-consultation rates differ in various studies (11,21,32), but are generally lower than the 48% we found. We hypothesize that this may be due to an easily accessible primary health care system in the Netherlands.

# Implications for practice and further research

As the reason for encounter in consultations for RTI is determined not only by respiratory symptoms but also by their consequences, it is important that a GP is aware of the impact RTI has on a child and its family (7). When consulting with their child with RTI, trust in the clinician, openness in communication and continuity of care are important to parents. This influences their acceptance of the final treatment decision of the GP and enhances compliance with the chosen treatment (33). Exploring parents' concerns and perceptions and reassuring parents about the general symptoms of RTI, and appreciating the impact of disturbed sleep or diminished appetite will increase the mutual understanding between parents and GP. In turn, this is beneficial in the process of shared decision-making, a process that has been shown to reduce the prescription of antibiotics, also in children (7,34,35).

Disease impact should be incorporated alongside information on respiratory symptoms in patient information in leaflets and websites.

Knowledge about the frequency of OTC medication use and its drivers may further facilitate shared decision-making between parents and GPs. GPs have a task in informing parents, and the use of OTC medication must be balanced against costs and possible side effects. Robust evidence of effectiveness is not available for most of the medications used (27–29). However, well-being may be improved by the use of paracetamol or NSAIDs.

We noticed that children often re-consulted their GP. Further research might focus on reasons for this healthcare-seeking behaviour and may help identify strategies to reduce unnecessary re-consultations and enhance self-management.

# Conclusion

RTI impacts not only a child's general well-being but also family life as nearly half of the children stay home from childcare or school during the first week after consultation, and nearly half of the parents are absent from work. OTC medication is given to the majority of children, 1 week before and 1 week after consulting their GP. Communication about this general impact of RTI can improve understanding between GPs and parents and enhance shared decision-making.

# Supplementary material

Supplementary data are available at Family Practice online.

# Declaration

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Ethical approval: the Ethics Committee of University Medical Centre Utrecht, the Netherlands, approved both trials from which data for this study was used. The RAAK trial (Rational Antibiotic use Kids) was registered at the Dutch Trial Register, trial identifier: NTR4240. The PRICE trial (Point-of-caRe C-reactive protein to assist In primary care management of Children with lower rEspiratory tract infection) was registered at the Dutch Trial Register, trial identifier NTR4399.

Conflict of interest: none.

# References

- Van der Linden M, van Suijlekom-Smit L, Schellevis F, van der Wouden J. Tweede Nationale Studie Naar Ziekten En Verrichtingen in de Huisartspraktijk. Het Kind in de Huisartspraktijk [Second National Survey of Morbidity and Interventions in General Practice: The Child in General Practice]. Utrecht, The Netherlands: NIVEL,2005.
- Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Fam Pract* 2005; 22: 367–74.
- Dekker ARJ, Verheij TJM, van der Velden AW. Antibiotic management of children with infectious diseases in Dutch Primary Care. *Fam Pract* 2017; 34: 169–74.
- Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* 2011; 128: 1053–61.
- Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract* 2015; 32:401–7.
- Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. J Antimicrob Chemother 2005; 56: 930–6.
- Cabral C, Horwood J, Hay AD, Lucas PJ. How communication affects prescription decisions in consultations for acute illness in children: a systematic review and meta-ethnography. *BMC Fam Pract* 2014; 15: 63.
- Lucas PJ, Cabral C, Hay AD, Horwood J. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care* 2015; 33: 11–20.
- Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. *Soc Sci Med* 2015; 136–7: 156–64.
- Hay AD, Wilson A, Fahey T, Peters TJ. The duration of acute cough in pre-school children presenting to primary care: a prospective cohort study. *Fam Pract* 2003; 20: 696–705.

- Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. *Br J Gen Pract* 2002; 52: 401–9.
- Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD; TARGET Programme Team. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ* 2013; 347: f7027.
- Wensaas K-A, Heron J, Redmond N, *et al.* Post-consultation illness trajectories in children with acute cough and respiratory tract infection: prospective cohort study. *Fam Pract* 2018; 35: 676–683.
- 14. De Blasio F, Dicpinigaitis PV, Rubin BK, De Danieli G, Lanata L, Zanasi A. An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome. *Cough* 2012; 8: 1.
- Lambert SB, Allen KM, Carter RC, Nolan TM. The cost of communitymanaged viral respiratory illnesses in a cohort of healthy preschool-aged children. *Respir Res* 2008; 9: 11.
- Peetoom K, Crutzen R, Dinant G-J, Cals J. Most preschool children with fever and common infection symptoms do not consult the family physician. *Fam Pract* 2019; 36: 371–373.
- Chow MY, Yin JK, Heron L et al. The impact of influenza-like illness in young children on their parents: a quality of life survey. Qual Life Res 2014; 23: 1651–60.
- Dekker ARJ, Verheij TJM, Broekhuizen BDL *et al.* Effectiveness of general practitioner online training and an information booklet for parents on antibiotic prescribing for children with respiratory tract infection in primary care: a cluster randomized controlled trial. *J Antimicrob Chemother* 2018; 73: 1416–22.
- 19. Schot MJ, Van den Bruel A, Broekhuizen BD *et al.* Point-of-care C-reactive protein to assist in primary care management of children with suspected non-serious lower respiratory tract infection: a randomised controlled trial. *BJGP Open* 2018; 2: bjgpopen18X101600.
- 20. Rubin DB. Inference and missing data. Biometrika 1976; 63: 581-92.
- Harnden A, Perera R, Brueggemann AB *et al.* Respiratory infections for which general practitioners consider prescribing an antibiotic: a prospective study. *Arch Dis Child* 2007; 92: 594–7.
- Mitra A, Hannay D, Kapur A, Baxter G. The natural history of acute upper respiratory tract infections in children. *Prim Health Care Res Dev* 2011; 12: 329–34.
- Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. *BMC Fam Pract* 2008; 9: 10.
- 24. Ehlken B, Ihorst G, Lippert B et al.; PRIDE Study Group. Economic impact of community-acquired and nosocomial lower respiratory tract infections in young children in Germany. Eur J Pediatr 2005; 164: 607–15.
- 25. Hamoen M, Broekhuizen BD, Little P *et al.*; GRACE clinical study group. Medication use in European primary care patients with lower respiratory tract infection: an observational study. *Br J Gen Pract* 2014; 64: e81–91.
- de Bont EG, Brand PL, Dinant GJ, van Well GT, Cals J. Risks and benefits of paracetamol in children with fever. *Ned Tijdschr Geneeskd* 2014; 158: A6636.
- 27. Sjoukes A, Venekamp RP, van de Pol AC *et al.* Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst Rev* 2016; 12: CD011534.
- Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev* 2014; 11: CD001831.
- Deckx L, De Sutter AI, Guo L, Mir NA, van Driel ML. Nasal decongestants in monotherapy for the common cold. *Cochrane Database Syst Rev* 2016; 10: CD009612.
- 30. Cohen-Kerem R, Ratnapalan S, Djulus J, Duan X, Chandra RV, Ito S. The attitude of physicians toward cold remedies for upper respiratory infection in infants and children: a questionnaire survey. *Clin Pediatr (Phila)* 2006; 45: 828–34.
- Biezen R, Brijnath B, Grando D, Mazza D. Management of respiratory tract infections in young children – a qualitative study of primary care providers' perspectives. NPJ Prim Care Respir Med 2017; 27: 15.

- 32. Little P, Stuart B, Francis N et al.; GRACE consortium. Effects of internetbased training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; 382: 1175–82.
- 33. Brookes-Howell L, Wood F, Verheij T, *et al.* Trust, openness and continuity of care as key ingredients for acceptance of antibiotic prescribing decisions for children with RTIs: a four-country, primary care qualitative study. *Fam Pract* 2014; 31: 103–110.
- 34. Francis NA, Butler CC, Hood K, Simpson S, Wood F, Nuttall J. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009; 339: b2885.
- 35. Coxeter P, Del Mar CB, McGregor L, Beller EM, Hoffmann TC. Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2015; 11: CD010907.