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Trends in primary-care consultations, comorbidities, and antibiotic prescriptions for respiratory infections in The Netherlands before implementation of pneumococcal vaccines for infants

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SUMMARY

The burden of respiratory infections is mainly seen in primary healthcare. To evaluate the potential impact of new preventive strategies against respiratory infections, such as the implementation of pneumococcal conjugate vaccines for infants in 2006 in The Netherlands, we conducted a baseline retrospective cohort study of electronic primary-care patient records to assess consultation rates, comorbidities and antibiotic prescription rates for respiratory infections in primary care. We found that between 1995 and 2005, overall registered consultation rates for lower respiratory tract infections had increased by 42·4%, upper respiratory infections declined by 4·9%, and otitis media remained unchanged. Concomitantly, there was a steady rise in overall comorbidity (75·7%) and antibiotic prescription rates (67·7%). Since Dutch primary-care rates for respiratory infections changed considerably between 1995 and 2005, these changes must be taken into account to properly evaluate the effect of population-based preventive strategies on primary-care utilization.

Key words: Age-specific rates, antibiotic prescribing, epidemiology, general practice, respiratory tract infection.

INTRODUCTION

Respiratory tract infections (RTIs) are one of the most abundant reasons why people visit their primary-care physician [1, 2] and the most frequent indication for antibiotic prescriptions [3]. As such, respiratory infections account for one of the highest annual healthcare costs. For example, in the USA otitis media (OM) was responsible for at least US$ 3–5 billion costs in 1996 [4]. Therefore, prevention of RTIs via vaccinations against, for instance seasonal influenza viruses and pneumococci has a high priority in reducing disease burden in the community and costs of medical care. As most of the burden of these RTIs is only seen in primary healthcare, it is essential to evaluate primary healthcare utilization over the years when evaluating the effect of population-based preventive strategies, e.g. seasonal influenza or pneumococcal conjugate vaccination in the national

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immunization programme. To enable this evaluation, it must be known how trends in both consultation rates and antibiotic prescribing behaviour have developed over a longer period of at least a decade prior to the intervention, in order to avoid both over- and underestimation of the true effect. For example, the incidence of OM was already decreasing in the USA prior to the introduction of the 7-valent pneumococcal conjugate vaccination Prevenar™ (PCV-7) for infants and children [5]. Furthermore, pneumonia outside the target group of children for pneumococcal conjugate vaccination might also decrease due to herd effects after infant vaccinations [6].

In addition, differences and changes in primary healthcare systems, guidelines, surveillance strategies, and demography such as ageing and increases in comorbidities, need to be taken into account. Unfortunately, these factors may differ greatly between countries. Dutch healthcare is organized such that primary-care physicians function as a general first line of patient management and when necessary as a point of entry for both secondary and tertiary care. Medical drugs such as antibiotics can only be obtained with a prescription by a medical doctor and antibiotic prescription rates and antibiotic resistance are relatively low compared to many other industrialized countries [7]. Moreover, at least 70% of Dutch elderly ($\geqslant$65 years) annually receive seasonal influenza vaccination [8] and only a small number of very high-risk patients are recommended to receive the 23-valent polysaccharide pneumococcal vaccine [9]. Hence, in The Netherlands the effect of population-based strategies on primary-care consultations and antibiotic prescription rates can be evaluated within a well-structured primary-care system, in a population with low antibiotic resistance rates.

We aimed to assess age-related trends in rates of primary-care consultations, comorbidities and antibiotic prescriptions for acute RTIs in The Netherlands. This will provide a full overview of the impact of RTI on the overall primary healthcare utilization over the years, and allow for the evaluation of population-based strategies (such as PCV-7 implementation for infants) in the future.

METHODS

Data were retrospectively collected from the anonymous computerized medical database of the University Medical Centre Utrecht Primary Care Research Network. Main characteristics of this patient population are similar to the Dutch population as a whole and the source population is therefore representative of The Netherlands [10]. All registered patients between 1995 and 2005 were selected for this cohort study.

From 1995 onwards, medical data of all patients enlisted in the six participating primary-care centres have been recorded in the primary-care information system ELIAS® (ISoft, The Netherlands) using a uniform, structured, contact registration format. Patient demographics (date of birth, gender), date of entry, date of retraction, drug prescriptions and all diagnoses were recorded. The 35 participating primary-care physicians received continued medical education regarding the correct coding of diagnostic information according to the International Classification of Primary Care (ICPC) coding system, commonly used in Australia and Europe [11]. Drug prescriptions were recorded using the Anatomical Therapeutic Chemical (ATC) classification system code, as well as the drug name.

The primary outcomes were annual consultation rates of upper respiratory tract infections (URTIs), otitis media (OM), and lower respiratory tract infections (LRTIs). A URTI was defined as a consultation for acute upper respiratory tract infection (R74), sinusitis (R75), tonsillitis/peritonsillar abscess (R76), and/or laryngitis/tracheitis (R77). OM was defined as any registration of OM (H71, H72, H74). A LRTI was defined as pneumonia (R81), acute bronchitis/bronchiolitis (R78), and/or influenza (R80). To evaluate possible shifts between diagnostic and symptomatic recording, related symptomatic codes from each disease category were gathered [URTI symptoms: sneezing/nasal congestion (R07), sinus symptom/complaint (R09), throat symptom/complaint (R21), and/or tonsil symptom/complaint (R22); OM symptoms: ear pain/earache (H01), ear discharge (H04), bleeding ear (H05), and/or plugged feeling in ear (H13); LRTI symptoms: pain attributed to respiratory system (R01), shortness of breath/dyspnoea (R02), wheezing (R03), and/or cough (R05)].

Other outcomes were contact-based antibiotic prescription rates (ATC J01) and common comorbidities present at of the time of consultation for RTI. Since there is no direct link between the ICPC coding and antibiotic prescriptions, all antibiotics prescribed between the day of consultation and up to 7 days after the consultation were taken into account. Moreover, the total number of antibiotic prescriptions and the total number of antibiotics for RTIs was determined.

A comorbidity was considered present when at least one ICPC diagnosis, dated prior to the consultation date for the RTI, indicated an immunocompromising condition, other malignancy considered non-immunocompromising in previous 5 years, chronic pulmonary disease, diabetes mellitus, or cardiovascular disease. See Appendix (available online) for the corresponding ICPC codes.

Statistical analyses

Annual rates for primary-care consultations per 100 000 person-years were estimated by determining the total number of first RTI consultations in a specific year and dividing it by the total number of person-years registered at all participating primary-care physicians in the same year. Each subject contributed the amount of time he/she was registered with one of the participating primary-care centres and hence, persons could contribute less than 1 year. A year was defined as the period from 1 July to 30 June of the succeeding year, so all years include one respiratory season (on the northern hemisphere). Consultation rates were stratified by diagnosis and age group (<2, 2–4, 5–17, 18–64, 65–74, ⩾75 years).

Of all recorded consultations for RTI (including consultations for RTI symptoms), both the annual contact-based antibiotic prescription rate and common underlying comorbidity groups present at the time of consultation were determined per 100 consultations. A new consultation was recorded after a consultation-free period of at least 28 days.

The total number of antibiotic prescriptions and the total number of antibiotic prescriptions for RTIs were calculated per 1000 registered patients per year.

All time trends were analysed using the χ^2 test for trends and Poisson regression to obtain the relative risk (RR) per year. Proportions between groups were analysed by χ^2.

RESULTS

The study population consisted of 91 950 patients attributing to 609 820 person-years. Between 1 July 1995 and 30 June 2005, a total of 133 546 consultations for RTIs or symptomatic RTIs were recorded; 79 436 for RTIs and 54 020 for RTI symptoms. The sex distribution was relatively stable over the years with on average 47·9% (range 47·3–48·6%) males. The age distribution was comparable to the overall Dutch population with a mean age of 36·6 years (36·0 years in 1995–1996 and 37·4 years in 2004–2005; 5·9% aged <5 years, 12·6% aged ⩾65 years).

Consultation rates

Between 1 July 1995 and 30 June 2005, the overall consultation rates for any consultation regarding a RTI (diagnostic or symptomatic) increased 13·4% from 15 999 [95% confidence interval (CI) 15 714–16 284] in 1995–1996 to 18 136 (95% CI 17 821–18 451) in 2004–2005 [yearly RR 1·003, $P<0·01$ (Poisson regression)].

In total, 46 277 consultations concerning a URTI were made by 28 105 patients, of which 61·2% (95% CI 61·7–62·6) were acute upper respiratory infections, 23·6% (95% CI 23·2–24·0) sinusitis, 11·2% (95% CI 10·9–11·5) tonsillitis, and 3·0% (95% CI 2·9–3·2) laryngitis. Overall annual consultation rates for URTIs had declined by 4·9% from 7359 (95% CI 156–7562) consultations in 1995–1996 to 6997 (95% CI 6789–7205) consultations per 100 000 person-years in 2004–2005 with a yearly RR of 0·991 (Table 1, Fig. 1). Importantly, after a minimal decline, the overall consultation rate for URTIs showed an increasing trend from 2001–2002 onwards and consultations for URTIs remained stable in the elderly.

Overall, 15 759 consultations regarding OM were made by 9538 patients. During the study period, consultation rates for OM remained stable with an average of 2204 consultations per 100 000 person-years (Table 2; Fig. 1). A decline in consultations for OM was seen in the 2–17 years group (Table 2).

During the same period, participating primary-care physicians were consulted by 11 776 patients regarding a LRTI, adding up to 17 400 consultations. On average, 70·2% (95% CI 69·5–70·9) of consultations were due to bronchitis, 20·2% (95% CI 19·6–20·8) due to pneumonia, and 9·6% (95% CI 9·1–10·1) due to influenza. The overall primary-care consultation rate for LRTIs increased from 2290 (95% CI 2174–2406) in 1995–1996 to 3262 (95% CI 3117–3407) consultations per 100 000 person-years in 2004–2005, which is an overall increase of 42·4% with a yearly RR of 1·015 (Table 3, Fig. 1). Increases in consultation rates were seen in both bronchitis and pneumonia. A decrease was seen in consultations for influenza.

Consultations due to RTI symptoms were mainly due to symptoms of LRTIs (65·3%, 95% CI 64·9–65·7). Consultation rates of OM symptoms were low, on average 691 per 100 000 person-years.

Table 1. *Primary-care consultation rates for upper respiratory tract infections* per 100 000 person-years*

	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95 % CI)	*P* value‡
Overall	7359	6807	6740	7119	6749	6711	6209	6332	6566	6997	−4·93	<0·001	0·991	(0·988–0·994)	<0·001
<2 yr	26 106	29 774	26 717	28 305	29 795	28 264	27 090	30 871	32 854	30 946	18·54	<0·001	1·017	(1·006–1·028)	<0·01
2–4 yr	14 753	15 072	14 961	15 847	15 448	13 627	13 564	12 528	14 286	12 936	−12·32	<0·01	0·982	(0·971–0·994)	<0·01
5–17 yr	6785	6200	6962	6557	5464	5973	6161	5500	5256	5868	−13·52	<0·001	0·977	(0·968–0·986)	<0·001
18–64 yr	7018	6205	6162	6558	6313	6128	5475	5704	5806	6296	−10·30	<0·001	0·985	(0·981–0·989)	<0·001
65–74 yr	4914	4985	4357	4865	4392	5344	4412	4097	4460	5271	7·28	0·70	0·997	(0·982–1·013)	0·70
⩾75 yr	4162	3929	3445	4715	3972	4139	3323	3486	4387	5162	24·04	0·16	1·012	(0·995–1·031)	0·17

RR, Relative risk; CI, confidence interval.
* Acute upper respiratory tract infection (R74), sinusitis (R75), tonsillitis/peritonsillar abscess (R76), and laryngitis/tracheitis (R77).
† χ^2 test for trends.
‡ Poisson regression.
A year was defined as the period from 1 July to 30 June of the succeeding year.

During the study period, consultation rates for both OM symptoms and LRTI symptoms also increased over the years (Table 4, Fig. 1). In contrast, annual consultation rates for URTI symptoms remained stable.

Antibiotic prescription rates

In 28·9% (95% CI 28·7–29·2) of all 133 546 consultations for RTIs, patients received an antibiotic prescription. Antibiotics for RTIs were more frequently described to adults and the elderly (Table 4), and to patients with comorbidities (31·7% compared to 28·2%, $P<0{\cdot}001$). Overall contact-based antibiotic rates rose over the years from 21·7% (95% CI 21·0–22·4) in 1995–1996 to 36·4% prescriptions (95% CI 35·6–37·2) in 2004–2005 (67·7% increase, RR 1·050) (Table 5). This increase was seen in all different disease categories. Increases were most prominent in adults and the elderly (Table 5).

The total number of antibiotic prescriptions and the total number of antibiotic prescriptions for RTIs (diagnostic or symptomatic) also increased over the years, 113·5–206·7 [82·1% increase; RR 1·060; $P<0{\cdot}001$ (Poisson regression)] and from 51·4 to 95·1 [88·2% increase; RR 1·052, $P<0{\cdot}001$ (Poisson regression)] prescriptions per 1000 registered patients, respectively. Increases were seen in all disease categories (data not shown).

Comorbidity rates

In 20·9% (95% CI 20·7–21·1) of all consultations for RTIs at least one comorbidity was present, of which chronic pulmonary disease and cardiovascular disease were most common: 12·3% (95% CI 12·1–12·5) and 8·4% (95% CI 8·2–8·5), respectively. Comorbidities were more frequent with rising age (Table 6). The overall presence of comorbidities in patients with recorded contacts for a RTI increased over the years from 14·0 (95% CI 13·4–14·7) in 1995–1996 to 24·7 (95% CI 23·9–25·4) per 100 consultations in 2004–2005 (75·5% increase, RR 1·057). The presence of cardiovascular disease and diabetes rose most prominently (Table 6).

DISCUSSION

This large representative primary-care cohort study is unique in providing age-related trends in primary-care consultations for RTIs over a 10-year period

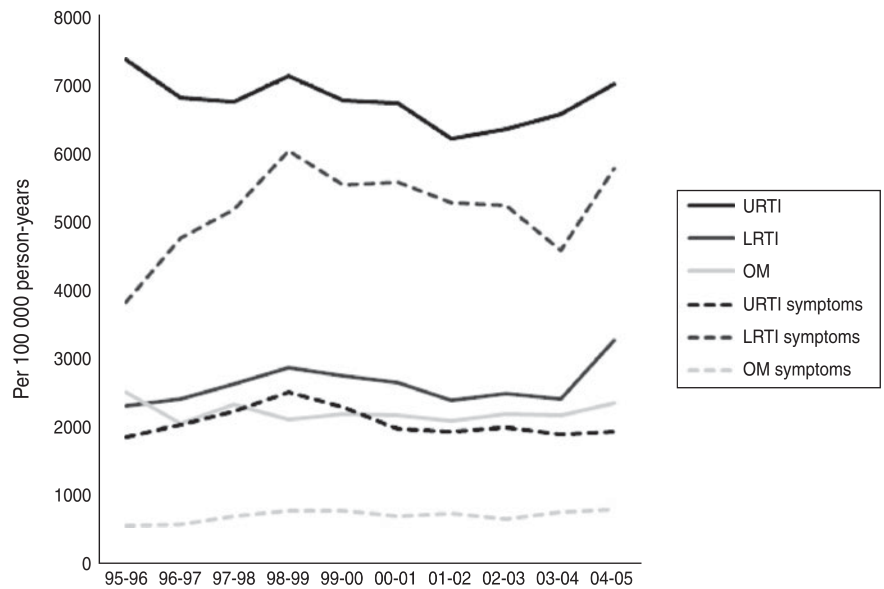

Fig. 1. Primary-care consultation rates for respiratory tract infections. URTI, Upper respiratory tract infection; LRTI, lower respiratory tract infection.

including both comorbidities and antibiotic prescription rates per age group. It shows the great impact of RTIs on overall primary healthcare over the years and can be used as a basis to evaluate the introduction of population-based strategies such as the implementation of PCV-7 for infants.

Our study showed a >40% rise in the overall consultation rate for LRTIs, in contrast to stable consultation rates for OM, and a 5% decline in overall consultations for URTIs in The Netherlands between 1995 and 2005; whereas the age distribution remained stable. Concomitantly, there was a steady rise in both the overall comorbidity- and contact-based antibiotic prescription rates of 75·7% and 67·7%, respectively.

Consultation rates

Trends in consultation rates for RTIs in literature vary greatly. The observed declines in URTIs and OM in children are in accord with other European [12–14] and Dutch literature [15, 16]. A rise in consultations for LRTIs was also seen by Van Gageldonk-Lafeber *et al.* [17] who described a 75% increase in primary-care consultations and hospitalizations for pneumonia in The Netherlands between 2001 and 2007. On the other hand, in Sweden and the UK the overall consultation rates for acute bronchitis and pneumonia remained unchanged [12–14].

Moreover, during the study period, there were no changes in healthcare access, available healthcare services or guidelines that can explain this increase in LRTIs. It therefore remains unclear whether the overall increase in the consultation rate of LRTIs reflects a true increase in illness, changes in registration by primary-care physicians or a changing consultation pattern of patients with respiratory complaints. A true increase in illness could be driven by a rise in predisposing comorbidities, although primary-care physicians might have more accurately reported LRTI episodes due to education. However, a switch from symptomatic to diagnostic coding does not appear to have taken place, since consultations for LRTI symptoms also show a significant increase within this cohort (Table 4). Moreover, when adding the related symptomatic codes to the disease categories, trends over time remained the same (data not shown).

Changes in consultation patterns might have been influenced by the rise in antibiotic prescriptions. Such rises have been described to lower the consultation threshold leading to more consultations [18, 19]. Furthermore, there is a natural occurrence of varying incidences in infectious diseases that could partly explain the results. It could, for instance, explain the sudden increase of bronchitis and pneumonia from 2003–2004 to 2004–2005, possibly driven by the strong influenza season of 2004–2005 (Table 3) [20]. This variation, however, does not explain the

Table 2. *Primary-care consultation rates for otitis media* per 100 000 person-years*

	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95 % CI)	*P* value‡
Overall	2494	2033	2310	2104	2174	2161	2088	2183	2152	2341	−6·2	0·21	0·996	(0·990–1·002)	0·21
<2 yr	19 174	20 075	21 962	17 625	21 157	19 931	18 665	20 185	20 192	21 824	13·8	0·35	1·005	(0·993–1·017)	0·41
2–4 yr	18 969	14 445	16 443	15 090	14 818	14 412	13 516	13 069	12 968	13 319	−29·8	<0·001	0·966	(0·955–0·977)	<0·001
5–17 yr	4837	3463	4453	4069	3684	3876	3429	3288	3277	3784	−21·8	<0·001	0·971	(0·960–0·982)	<0·001
18–64 yr	919	786	851	824	922	880	857	949	881	949	3·3	0·08	1·010	(0·997–1·023)	0·08
65–74 yr	705	597	606	641	555	542	648	784	615	691	−2·0	0·71	1·008	(0·966–1·050)	0·71
⩾75 yr	462	285	113	279	248	274	463	329	497	278	−40·0	0·37	1·029	(0·966–1·092)	0·37

RR, Relative risk; CI, confidence interval.
* Otitis media (H71, H72, H74).
† χ^2 test for trends.
‡ Poisson regression.
A year was defined as the period from 1 July to 30 June of the succeeding year.

Table 3. *Primary-care consultation rates for lower respiratory tract infections* per 100 000 person-years*

	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95 % CI)	*P* value‡
Overall	2290	2403	2624	2857	2737	2642	2389	2477	2407	3262	42·4	<0·001	1·015	(1·010–1·021)	<0·001
<2 yr	6268	8045	9887	7618	8126	9097	9138	8311	8350	9392	49·8	0·04	1·020	(1·000–1·041)	0·05
2–4 yr	5605	4651	4447	5014	4988	5735	4810	4777	4507	5447	−2·8	0·93	0·999	(0·979–1·020)	0·94
5–17 yr	1875	1700	1858	1909	1358	1847	1627	1443	1359	2275	21·4	0·57	0·995	(0·978–1·012)	0·57
18–64 yr	1617	1798	1888	2266	2227	1921	1739	1822	1761	2465	52·5	<0·001	1·016	(1·008–1·024)	<0·001
65–74 yr	4117	4824	5499	5173	4657	4753	3963	4755	4230	5655	37·3	0·68	1·003	(0·988–1·019)	0·69
⩾75 yr	5723	5068	6100	6417	6483	5976	5312	5655	6015	7410	29·5	0·03	1·016	(1·001–1·031)	0·04
Bronchitis	1513	1690	1919	1914	1825	1988	1682	1848	1719	2230	47·4	<0·001	1·019	(1·013–1·026)	<0·001
Pneumonia	481	419	436	532	542	534	597	489	534	717	49·1	<0·001	1·040	(1·027–1·052)	<0·001
Influenza	297	295	269	411	370	120	110	140	154	316	6·4	<0·001	0·937	(0·921–0·954)	<0·001

RR, Relative risk; CI, confidence interval.
* Pneumonia (R81), acute bronchitis/bronchiolitis (R78), and influenza (R80).
† χ^2 test for trends.
‡ Poisson regression.
A year was defined as the period from 1 July to 30 June of the succeeding year.

Table 4. *Primary-care consultation rates for symptoms related to respiratory tract infections* per 100 000 person-years*

Symptoms	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95% CI)	*P* value‡
URTI	2139	2303	2528	2873	2630	2283	2253	2371	2279	2273	6·3	0·11	0·995	(0·990–1·001)	0·12
OM	539	569	687	769	771	677	727	640	742	788	46·2	<0·001	1·027	(1·016–1·038)	<0·001
LRTI	3808	4747	5163	6021	5527	5560	5261	5222	4573	5758	51·2	<0·001	1·018	(1·014–1·022)	<0·001

RR, Relative risk; CI, confidence interval; URTI, upper respiratory tract infection; OM, otitis media; LRTI, lower respiratory tract infection.

* Symptoms URTI: sneezing/nasal congestion, sinus symptom/complaint (R09), throat symptom/complaint (R21), and/or tonsil symptom/complaint (R22). Symptoms OM: ear pain/earache (H01), ear discharge (H04), bleeding ear (H05), and/or plugged feeling ear (H13). symptoms LRTI: pain related to respiratory system (R01), shortness of breath/dyspnoea (R02), wheezing (R03), and/or cough (R05).

† χ^2 test for trends.

‡ Poisson regression.

A year was defined as the period from 1 July to 30 June of the succeeding year.

Table 5. *Contact-based antibiotic prescription* rates by primary-care physicians per 100 consultations of respiratory infections*

	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95% CI)	*P* value‡
Overall	21·7	21·3	29·3	30·1	30·2	31·3	30·8	32·2	34·3	36·4	67·7	<0·001	1·050	(1·046–1·054)	<0·001
<2 yr	24·9	24·7	27·2	24·3	26·2	27·4	28·6	28·3	31·1	34·2	37·6	<0·001	1·034	(1·023–1·045)	<0·001
2–4 yr	27·4	25·2	25·3	30·2	28·5	28·8	28·9	31·1	32·0	35·2	28·6	<0·001	1·030	(1·019–1·041)	<0·001
5–17 yr	26·4	21·5	27·0	25·6	25·7	27·2	26·9	27·8	30·7	31·6	19·8	<0·001	1·026	(1·017–1·037)	<0·001
18–64 yr	18·9	20·0	30·9	32·3	32·1	33·8	33·0	34·0	36·4	38·2	102·5	<0·001	1·062	(1·057–1·067)	<0·001
65–74 yr	18·5	20·9	31·6	31·6	33·3	32·8	31·8	36·4	35·7	37·6	103·6	<0·001	1·060	(1·046–1·073)	<0·001
⩾75 yr	23·1	20·8	28·8	27·2	27·8	29·0	28·7	30·4	32·4	35·7	54·2	<0·001	1·045	(1·031–1·060)	<0·001
URTI	22·0	23·2	35·8	36·4	36·9	34·6	34·8	36·8	40·0	41·0	86·1	<0·001	1·054	(1·048–1·059)	<0·001
OM	33·6	33·1	36·0	40·7	38·4	41·1	42·1	41·2	44·0	48·4	44·1	<0·001	1·038	(1·030–1·046)	<0·001
LRTI	41·5	41·1	53·9	56·1	55·2	65·8	64·9	66·1	68·7	70·4	69·6	<0·001	1·058	(1·051–1·064)	<0·001
RTI symptoms	9·2	10·2	14·5	15·8	15·4	14·7	14·1	15·2	13·7	15·1	63·8	<0·001	1·031	(1·025–1·036)	<0·001

RR, Relative risk; CI, confidence interval; URTI, upper respiratory tract infection; OM, otitis media; LRTI, lower respiratory tract infection; RTI, respiratory tract infection.

* All ATC (J01) registrations up to seven days after the consultation date.

† χ^2 test for trends.

‡ Poisson regression.

A year was defined as the period from 1 July to 30 June of the succeeding year.

Table 6. *Comorbidity* rates in primary-care patients per 100 consultations of respiratory infections*

	95–96	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	Overall difference (%)	*P* value†	RR	(95% CI)	*P* value‡
Overall	14·0	16·7	18·6	19·7	21·7	22·5	22·5	24·4	25·0	24·7	75·7	<0·001	1·057	(1·052–1·062)	<0·001
<2 yr	8·6	6·0	7·5	5·5	4·9	6·2	6·2	5·9	4·5	3·1	−63·7	<0·001	0·936	(0·911–0·961)	<0·001
2–4 yr	12·0	14·2	15·8	16·6	16·9	12·9	13·7	12·0	13·7	13·1	9·0	0·23	0·990	(0·973–1·007)	0·26
5–17 yr	8·6	10·7	13·2	14·3	19·2	18·7	18·9	21·0	20·1	19·6	126·4	<0·001	1·087	(1·072–1·101)	<0·001
18–64 yr	10·4	13·0	14·4	15·5	17·3	18·8	19·0	21·3	21·9	21·7	108·7	<0·001	1·076	(1·069–1·084)	<0·001
65–74 yr	37·3	44·0	47·8	48·1	51·0	52·9	53·8	55·4	54·4	53·9	44·5	<0·001	1·034	(1·023–1·045)	<0·001
⩾75 yr	49·1	54·5	57·8	60·9	62·0	63·5	64·5	67·9	71·7	68·7	39·8	<0·001	1·035	(1·024–1·040)	<0·001
Chronic pulmonary disease	8·3	9·7	11·1	11·5	12·8	13·4	13·7	14·4	14·3	14·0	69·1	<0·001	1·054	(1·048–1·060)	<0·001
Cardiovascular disease	5·1	6·5	7·0	7·6	8·5	9·1	8·9	10·2	10·5	10·7	111·8	<0·001	1·075	(1·067–1·082)	<0·001
Diabetes	1·5	1·9	2·2	2·8	3·2	3·0	3·2	3·6	4·4	4·5	194·8	<0·001	1·113	(1·100–1·126)	<0·001
Malignancies	0·7	1·0	1·0	0·9	1·0	1·0	0·9	0·9	1·1	0·9	15·7	0·33	1·011	(0·990–1·032)	0·31
Immunocompromised	0·3	0·5	0·5	0·6	0·6	0·7	0·6	0·7	0·7	0·6	74·7	<0·001	1·046	(1·019–1·031)	<0·001

RR, Relative risk; CI, confidence interval.

* At least one International Classification of Primary Care (ICPC) diagnosis, dated prior to the consultation date for respiratory tract infection, indicating an immunocompromising condition, other malignancy (in previous 5 years), chronic pulmonary disease, diabetes mellitus, or cardiovascular disease.

† χ^2 test for trends.

‡ Poisson regression.

A year was defined as the period from 1 July to 30 June of the succeeding year.

steady rise in LRTIs over 10 years. Hence, future research is required to explore possible changes in consultation patterns in Dutch primary-care patients with LRTI.

Antibiotic prescription rates

The observed rise in contact-based antibiotic prescription rates has been previously reported in Dutch primary healthcare, especially in OM [15, 16, 21]. In contrast, international data [12, 13, 22, 23] show more stable trends for prescription rates in OM and URTIs. Kuyvenhoven *et al*. [15] also described stable prescribing rates for sinusitis and tonsillitis in The Netherlands when comparing 1987 and 2001. To our knowledge, our study is the first Dutch study to report on population-wide trends of antibiotic prescription rates for LRTIs. Previously, Venmans *et al*. [24] described an increasing trend in Dutch diabetic patients.

This study also shows an increasing trend in the total volume of prescribed antibiotics and the total volume of prescribed antibiotics for RTIs in primary care. Surprisingly, the total volume of ambulatory dispensed antibiotics in The Netherlands has remained stable [25, 26]. The same applies for primary-care prescription rates for children when comparing 1987 and 2001 [21]. Moreover, studies from the USA, UK and Sweden have either described decreasing [13, 22, 23, 27] or unchanged [12, 14] trends in dispensed antibiotic prescriptions for RTIs. It is unclear what drives this observed rise in antibiotic prescriptions. As the incidence of URTIs and OM has changed little over the years, an increase based on changes in consultation threshold seems unlikely. The observed increase in comorbidities, on the other hand, could have led to an increase in disease severity and complications lowering the prescribing threshold of primary-care physicians. Moreover, a similar trend has been reported in Dutch diabetic patients with LRTIs [24].

However, also here, a more accurate registration of antibiotic prescriptions over the years, could have underestimated the results of the previous years. Moreover, there are clear differences in the absolute number of prescriptions between primary-care research networks and between primary-care research networks and ambulatory dispensed prescription rates [3], making it difficult to compare antibiotic prescription rates from primary care between databases and to national reimbursement data.

These differences in rates need to be studied further in order to properly evaluate the effect of an intervention on antibiotic prescription rates, and herewith possibly prevent antimicrobial resistance, rising costs and patients experiencing unnecessary side-effects from antibiotics. Overall, the average prescription rate per RTI consultation in The Netherlands is still much lower than in the UK [13] and the USA [22, 23] (both $\pm 60\%$).

Comorbidity rates

Many common comorbidities (i.e. diabetes, chronic lung disease, malignancies) are known to affect the immune system and thus predispose patients to RTIs. Hak *et al*. have previously described the presence of comorbidity groups in Dutch primary-care patients with RTIs, showing that patients with chronic medical conditions, and especially those with chronic lung disease, have a greater than twofold increased risk for LRTIs [1].

However, this is the first study to describe comorbidities of primary-care patients with RTIs over time. The observed rise in comorbidities is consistent with the reported rise of comorbidities in elderly patients hospitalized for pneumonia [28].

It is unclear whether the overall increase of registered chronic disease reflects a true increase in illness, changes in registration by primary-care physicians or a changing consultation pattern. Over the years, Dutch primary healthcare has not only become more aware of comorbidities, but chronic medical conditions are also more frequently monitored. This could simultaneously have led to better registration. Furthermore, when patients use primary healthcare more frequently, they are more likely to be diagnosed with a RTI. Moreover, our data shows that patients with comorbidities are also more likely to receive antibiotics possibly lowering their consultation threshold.

Measuring the effect of population-based strategies

Trends in consultation rates and antibiotic prescription rates vary greatly between countries. This is caused by many factors such as differences in primary-care systems, coding, guidelines, consultation behaviour, demography, influenza and pneumococcal vaccine coverage, etc. Moreover, several countries do not report on these trends at all. In addition, some efficacy articles compare time-points before and after implementation, without describing what happened in between, risking both over- and underestimation of the true effect. Knowing this, results from international literature cannot easily be extrapolated to other countries and regions. Hence, to evaluate the impact of population-based strategies placebo-controlled efficacy studies or cheaper trend analyses need to be performed, taking all these trends into account. The University Medical Centre Utrecht Primary Care Research Network is ongoing and will soon be used to evaluate the implementation of PCV-7 for all infants born after 31 March 2006 on primary healthcare utilization in The Netherlands. Furthermore, in upcoming years, the ongoing randomized controlled CAPITA trial (Community Acquired Pneumonia Immunization Trial in Adults) will establish the effect of a 13-valent pneumococcal conjugate vaccine in the elderly (⩾65 years) on LRTIs [29].

Strengths and limitations

This is the first study to show recent trends in primary-care consultation rates, comorbidities and antibiotic prescription rates in The Netherlands. The medical database of the University Medical Centre Utrecht Primary Care Research Network is a well-implemented and long-running network covering almost 60 000 enlisted patients that are representative of the whole Dutch population. This large cohort was examined for over 10 years. Furthermore, as antibiotics in The Netherlands are not available over-the-counter, these data provide a reliable insight in non-hospital antibiotic use for respiratory infections. These data are therefore sufficient for evaluation of population-based strategies against respiratory infections such as the implementation of PCV-7.

Some potential limitations of this study need to be taken into account. First, this study is based on patients visiting a primary-care physician, which is a well-known underestimation of the true incidence rate in the community. All severe cases, however, are unlikely to have gone unregistered. Second, misclassifications between years and physicians because of differences in classifications or changing guidelines cannot be ruled out. Participating physicians received continuous training that started before the start of our study and most guidelines regarding RTIs have not undergone substantial changes in coding and antibiotic policies [30–36]. However, as mentioned before, primary-care physicians might have registered diagnoses and antibiotic prescriptions more accurately over the years due to a general awareness of the importance of recording and monitoring chronic diseases. This might have led to an overestimation of the rises in consultations, antibiotic prescription rates, and comorbidity rates. Importantly, these limitations are one of the reasons trends should receive surveillance.

CONCLUSIONS

Within the well-structured primary healthcare of The Netherlands, primary-care rates in consultations, comorbidities, and antibiotic prescriptions for respiratory infections have changed considerably between 1995 and 2005. As the burden of many diseases is primarily seen in primary care, these trends in primary healthcare should be carefully followed. To properly evaluate the effect of a population-based strategy effecting primary healthcare utilization, these changes in primary-care consultation rates must be taken into account.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

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REFERENCES

1. **Hak E, *et al.*** Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National

Survey of General Practice. *Family Practice* 2006; **23**: 291–294.
2. **Fleming DM, *et al.*** Impact of infections on primary care – greater than expected. *Communicable Disease and Public Health* 2002; **5**: 7–12.
3. **Akkerman AE, *et al.*** Antibiotics in Dutch general practice: nationwide electronic GP database and national reimbursement rates. *Pharmacoepidemiology and Drug Safety* 2008; **17**: 378–383.
4. **Gates GA.** Cost-effectiveness considerations in otitis media treatment. *Otolaryngology-Head and Neck Surgery* 1996; **114**: 525–530.
5. **Sox CM, *et al.*** Trends in otitis media treatment failure and relapse. *Pediatrics* 2008; **121**: 674–679.
6. **Grijalva GC, *et al.*** Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* 2007; **369**: 1179–1186.
7. **Goossens H, *et al.*** Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579–587.
8. **CBS Statline.** Seasonal influenza vaccination per age, gender and risk group [in Dutch]. (http://statline.cbs.nl/StatWeb/publication/?VW = T&DM = SLNL&PA = 37471&D1 = a&D2 = (l-4)-l&HD = 110307-1940&HDR = G1&STB = T). Accessed 7 March 2011.
9. **Health Council of the Netherlands.** *Pneumococcal Vaccine in Elderly Adults and Risk Groups*. The Hague: Health Council of the Netherlands, 2003.
10. **Akkerman AE, *et al.*** Interactive medical information of the Utrecht Primary Care Research Network and the Almere Care Group. Validity and generalizability of information on GP-infonet [in Dutch]. *Huisarts en Wetenschap* 2008; **51**: 90–95.
11. **Lamberts H, Woods M (eds).** *ICPC, International Classification of Primary Care*. New York: Oxford University Press, 1987.
12. **Ashworth M, *et al.*** Age-related changes in consultations and antibiotic prescribing for acute respiratory infections, 1995–2000. Data from the UK General Practice Research Database. *Journal of Clinical Pharmacy and Therapeutics* 2006; **31**: 461–467.
13. **Gulliford M, *et al.*** Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *Journal of Public Health* (*Oxford, England*) 2009; **31**: 512–520.
14. **Neumark T, *et al.*** Trends in number of consultations and antibiotic prescriptions for respiratory tract infections between 1999 and 2005 in primary healthcare in Kalmar County, Southern Sweden. *Scandinavian Journal of Primary Health Care* 2009; **27**: 18–24.
15. **Kuyvenhoven M, *et al.*** Management of upper respiratory tract infections in Dutch general practice; antibiotic prescribing rates and incidences in 1987 and 2001. *Family Practice* 2006; **23**: 175–179.
16. **Plasschaert AI, *et al.*** Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995–2003. *Pediatrics* 2006; **117**: 1879–1886.
17. **van Gageldonk-Lafeber AB, *et al.*** Time trends in primary-care morbidity, hospitalization and mortality due to pneumonia. *Epidemiology and Infection* 2009; **137**: 1472–1478.
18. **Moore M, *et al.*** Effect of antibiotic prescribing strategies and an information leaflet on longer-term reconsultation for acute lower respiratory tract infection. *British Journal of General Practice* 2009; **59**: 728–734.
19. **Little P, *et al.*** Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *British Medical Journal* 1997; **315**: 350–352.
20. **The WHO European Influenza Network.** Seasonal flu in The Netherlands: seasons 1996–2009 [in Dutch]. (http://www.euroflu.eu/cgi-files/grapher_cs_v1.cgi?region = Netherlands&lang = nl). Accessed 1 August 2010.
21. **Otters HB, *et al.*** Trends in prescribing antibiotics for children in Dutch general practice. *The Journal of Antimicrobial Chemotherapy* 2004; **53**: 361–366.
22. **Roumie CL, *et al.*** Trends in antibiotic prescribing for adults in the United States – 1995 to 2002. *Journal of General Internal Medicine* 2005; **20**: 697–702.
23. **Steinman MA, *et al.*** Changing use of antibiotics in community-based outpatient practice, 1991–1999. *Annals of Internal Medicine* 2003; **138**: 525–533.
24. **Venmans LM, *et al.*** Incidence and antibiotic prescription rates for common infections in patients with diabetes in primary care over the years 1995 to 2003. *International Journal of Infectious Diseases* 2009; **13**: e344–e351.
25. **European Surveillance of Antimicrobial Consumption.** Esac interactive database (http://app.esac.ua.ac.be/esac_idb/consumption/rates.htm). Accessed 30 August 2010.
26. **Kuyvenhoven MM, van Balen FA, Verheij TJ.** Outpatient antibiotic prescriptions from 1992 to 2001 in the Netherlands. *The Journal of Antimicrobial Chemotherapy* 2003; **52**: 675–678.
27. **Fleming DM *et al.*** The reducing incidence of respiratory tract infection and its relation to antibiotic prescribing. *British Journal of General Practice* 2003; **53**: 778–783
28. **Fry AM, *et al.*** Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *Journal of the American Medical Association* 2005; **294**: 2712–2719.
29. **Hak E, *et al.*** Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Netherlands Journal of Medicine* 2008; **66**: 378–383
30. **Appelman CLM, *et al.*** Dutch College of General Practitioners' practice guideline on acute otis media [in Dutch]. *Huisarts en Wetenschap* 1990; **33**: 242–245.
31. **Appelman CLM, *et al.*** Dutch College of General Practitioners' practice guideline on acute otis media (first revision) [in Dutch]. *Huisarts en Wetenschap* 1999; **42**: 362–366.
32. **Balder FA, *et al.*** Dutch College of General Practitioners' practice guideline on acute sore throat [in Dutch]. *Huisarts en Wetenschap* 1990; **33**: 323–326.

33. **Dagnelie CF, *et al.*** Dutch College of General Practitioners' practice guideline on acute sore throat (first revision) [in Dutch]. *Huisarts en Wetenschap* 2010; **42**: 271–278.
34. **de Bock GH, *et al.*** Dutch College of General Practitioners' practice guideline on sinusitis [in Dutch]. *Huisarts en Wetenschap* 1993; **36**: 255–257.
35. **van de Lisdonk EH, *et al.*** Dutch College of General Practitioners' practice guideline on otis media with effusion in children (first revision) [in Dutch]. *Huisarts en Wetenschap* 2000; **43**: 171–177.
36. **Verheij ThJM, *et al.*** Dutch College of General Practitioners' practice guideline on acute cough [in Dutch]. *Huisarts en Wetenschap* 2003; **46**: 496–506.