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...
imunization 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 (≥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 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 \( \chi^2 \) test for trends and Poisson regression to obtain the relative risk (RR) per year. Proportions between groups were analysed by \( \chi^2 \).

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 an 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.
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%, \( P < 0.001 \)). 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; \( P < 0.001 \) (Poisson regression)] and from 51.4 to 95.1 [88.2% increase; RR 1.052, \( P < 0.001 \) (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.
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

<table>
<thead>
<tr>
<th>95–96</th>
<th>96–97</th>
<th>97–98</th>
<th>98–99</th>
<th>99–00</th>
<th>00–01</th>
<th>01–02</th>
<th>02–03</th>
<th>03–04</th>
<th>04–05</th>
<th>Overall difference (%)</th>
<th>P value†</th>
<th>RR (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2494</td>
<td>2033</td>
<td>2310</td>
<td>2104</td>
<td>2174</td>
<td>2161</td>
<td>2088</td>
<td>2183</td>
<td>2152</td>
<td>2341</td>
<td>−6.2</td>
<td>0.21</td>
<td>0.996 (0.990–1.002)</td>
</tr>
<tr>
<td>&lt;2 yr</td>
<td>19 174</td>
<td>20 075</td>
<td>21 962</td>
<td>21 725</td>
<td>21 157</td>
<td>19 931</td>
<td>18 665</td>
<td>20 185</td>
<td>20 192</td>
<td>21 824</td>
<td>13.8</td>
<td>0.35</td>
<td>1.005 (0.993–1.017)</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>18 969</td>
<td>14 445</td>
<td>16 443</td>
<td>15 090</td>
<td>14 818</td>
<td>14 412</td>
<td>13 516</td>
<td>13 069</td>
<td>12 968</td>
<td>13 319</td>
<td>−29.8</td>
<td>&lt;0.001</td>
<td>0.966 (0.955–0.977)</td>
</tr>
<tr>
<td>5–17 yr</td>
<td>4837</td>
<td>3463</td>
<td>4453</td>
<td>4069</td>
<td>3684</td>
<td>3876</td>
<td>3429</td>
<td>3288</td>
<td>3277</td>
<td>3784</td>
<td>−21.8</td>
<td>&lt;0.001</td>
<td>0.971 (0.960–0.982)</td>
</tr>
<tr>
<td>18–64 yr</td>
<td>919</td>
<td>786</td>
<td>851</td>
<td>824</td>
<td>922</td>
<td>880</td>
<td>857</td>
<td>949</td>
<td>881</td>
<td>949</td>
<td>3.3</td>
<td>0.08</td>
<td>1.010 (0.997–1.023)</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>705</td>
<td>597</td>
<td>606</td>
<td>641</td>
<td>555</td>
<td>542</td>
<td>648</td>
<td>784</td>
<td>616</td>
<td>691</td>
<td>−2.0</td>
<td>0.71</td>
<td>1.008 (0.966–1.050)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>462</td>
<td>285</td>
<td>113</td>
<td>279</td>
<td>248</td>
<td>274</td>
<td>463</td>
<td>329</td>
<td>479</td>
<td>278</td>
<td>−40.0</td>
<td>0.37</td>
<td>1.029 (0.966–1.092)</td>
</tr>
</tbody>
</table>

RR, Relative risk; CI, confidence interval.
* Otitis media (H71, H72, H74).
† χ² 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

<table>
<thead>
<tr>
<th>95–96</th>
<th>96–97</th>
<th>97–98</th>
<th>98–99</th>
<th>99–00</th>
<th>00–01</th>
<th>01–02</th>
<th>02–03</th>
<th>03–04</th>
<th>04–05</th>
<th>Overall difference (%)</th>
<th>P value†</th>
<th>RR (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2290</td>
<td>2403</td>
<td>2624</td>
<td>2857</td>
<td>2737</td>
<td>2642</td>
<td>2389</td>
<td>2477</td>
<td>2407</td>
<td>2341</td>
<td>−6.2</td>
<td>0.21</td>
<td>0.996 (0.990–1.002)</td>
</tr>
<tr>
<td>&lt;2 yr</td>
<td>6268</td>
<td>8045</td>
<td>9887</td>
<td>7618</td>
<td>8126</td>
<td>9097</td>
<td>9138</td>
<td>8311</td>
<td>8350</td>
<td>9392</td>
<td>49.8</td>
<td>0.04</td>
<td>1.020 (1.000–1.041)</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>5605</td>
<td>4651</td>
<td>4443</td>
<td>4069</td>
<td>3684</td>
<td>3876</td>
<td>3429</td>
<td>3288</td>
<td>3277</td>
<td>3784</td>
<td>−21.8</td>
<td>&lt;0.001</td>
<td>0.971 (0.960–0.982)</td>
</tr>
<tr>
<td>5–17 yr</td>
<td>1875</td>
<td>1700</td>
<td>1858</td>
<td>1909</td>
<td>1353</td>
<td>1847</td>
<td>1627</td>
<td>1443</td>
<td>1359</td>
<td>2275</td>
<td>21.4</td>
<td>0.57</td>
<td>0.995 (0.978–1.012)</td>
</tr>
<tr>
<td>18–64 yr</td>
<td>919</td>
<td>786</td>
<td>851</td>
<td>824</td>
<td>922</td>
<td>880</td>
<td>857</td>
<td>949</td>
<td>881</td>
<td>949</td>
<td>3.3</td>
<td>0.08</td>
<td>1.010 (0.997–1.023)</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>705</td>
<td>597</td>
<td>606</td>
<td>641</td>
<td>555</td>
<td>542</td>
<td>648</td>
<td>784</td>
<td>616</td>
<td>691</td>
<td>−2.0</td>
<td>0.71</td>
<td>1.008 (0.966–1.050)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>462</td>
<td>285</td>
<td>113</td>
<td>279</td>
<td>248</td>
<td>274</td>
<td>463</td>
<td>329</td>
<td>479</td>
<td>278</td>
<td>−40.0</td>
<td>0.37</td>
<td>1.029 (0.966–1.092)</td>
</tr>
</tbody>
</table>

RR, Relative risk; CI, confidence interval.
* Pneumonia (R81), acute bronchitis/bronchiolitis (R78), and influenza (R80).
† χ² 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

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>95–96</th>
<th>96–97</th>
<th>97–98</th>
<th>98–99</th>
<th>99–00</th>
<th>00–01</th>
<th>01–02</th>
<th>02–03</th>
<th>03–04</th>
<th>04–05</th>
<th>Overall difference (%)</th>
<th>P value†</th>
<th>RR (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.3</td>
<td>0.011</td>
<td>0.995 (0.990–1.001)</td>
<td>0.12</td>
</tr>
<tr>
<td>URTI</td>
<td>2139</td>
<td>2303</td>
<td>2528</td>
<td>2873</td>
<td>2630</td>
<td>2283</td>
<td>2253</td>
<td>2371</td>
<td>2279</td>
<td>2273</td>
<td>46.2</td>
<td>&lt;0.001</td>
<td>1.027 (1.016–1.038)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OM</td>
<td>539</td>
<td>569</td>
<td>687</td>
<td>769</td>
<td>771</td>
<td>677</td>
<td>727</td>
<td>640</td>
<td>742</td>
<td>788</td>
<td>46.2</td>
<td>&lt;0.001</td>
<td>1.018 (1.014–1.022)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LRTI</td>
<td>3808</td>
<td>4747</td>
<td>5163</td>
<td>6021</td>
<td>5527</td>
<td>5560</td>
<td>5261</td>
<td>5222</td>
<td>4573</td>
<td>5758</td>
<td>51.2</td>
<td>&lt;0.001</td>
<td>1.018 (1.014–1.022)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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).

† x² 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

<table>
<thead>
<tr>
<th></th>
<th>95–96</th>
<th>96–97</th>
<th>97–98</th>
<th>98–99</th>
<th>99–00</th>
<th>00–01</th>
<th>01–02</th>
<th>02–03</th>
<th>03–04</th>
<th>04–05</th>
<th>Overall difference (%)</th>
<th>P value†</th>
<th>RR (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21.7</td>
<td>21.3</td>
<td>29.3</td>
<td>30.1</td>
<td>30.2</td>
<td>31.3</td>
<td>30.8</td>
<td>32.2</td>
<td>34.3</td>
<td>36.4</td>
<td>67.7</td>
<td>&lt;0.001</td>
<td>1.050 (1.046–1.054)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;2 yr</td>
<td>24.9</td>
<td>24.7</td>
<td>27.2</td>
<td>24.3</td>
<td>26.2</td>
<td>27.4</td>
<td>28.6</td>
<td>28.3</td>
<td>31.1</td>
<td>34.2</td>
<td>37.6</td>
<td>&lt;0.001</td>
<td>1.034 (1.023–1.045)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>27.4</td>
<td>25.2</td>
<td>25.3</td>
<td>30.2</td>
<td>28.5</td>
<td>28.8</td>
<td>28.9</td>
<td>31.1</td>
<td>32.0</td>
<td>35.2</td>
<td>38.6</td>
<td>&lt;0.001</td>
<td>1.030 (1.019–1.041)</td>
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</tr>
<tr>
<td>5–17 yr</td>
<td>26.4</td>
<td>21.5</td>
<td>27.0</td>
<td>25.6</td>
<td>25.7</td>
<td>27.2</td>
<td>26.9</td>
<td>27.8</td>
<td>30.7</td>
<td>31.6</td>
<td>19.8</td>
<td>&lt;0.001</td>
<td>1.026 (1.017–1.037)</td>
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</tr>
<tr>
<td>18–64 yr</td>
<td>18.9</td>
<td>20.0</td>
<td>30.9</td>
<td>32.3</td>
<td>32.1</td>
<td>33.8</td>
<td>33.0</td>
<td>34.0</td>
<td>36.4</td>
<td>38.2</td>
<td>102.5</td>
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<td>1.062 (1.057–1.067)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>18.5</td>
<td>20.9</td>
<td>31.6</td>
<td>31.6</td>
<td>33.3</td>
<td>32.8</td>
<td>31.8</td>
<td>36.4</td>
<td>35.7</td>
<td>37.6</td>
<td>103.6</td>
<td>&lt;0.001</td>
<td>1.060 (1.046–1.073)</td>
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</tr>
<tr>
<td>≥75 yr</td>
<td>23.1</td>
<td>20.8</td>
<td>28.8</td>
<td>27.2</td>
<td>27.8</td>
<td>29.0</td>
<td>28.7</td>
<td>30.4</td>
<td>32.4</td>
<td>35.7</td>
<td>54.2</td>
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<td>1.045 (1.031–1.060)</td>
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<tr>
<td>URTI</td>
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<td>23.2</td>
<td>35.8</td>
<td>36.4</td>
<td>36.9</td>
<td>34.6</td>
<td>34.8</td>
<td>36.8</td>
<td>40.0</td>
<td>41.0</td>
<td>86.1</td>
<td>&lt;0.001</td>
<td>1.054 (1.048–1.059)</td>
<td>&lt;0.001</td>
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<tr>
<td>OM</td>
<td>33.6</td>
<td>33.1</td>
<td>36.0</td>
<td>40.7</td>
<td>38.4</td>
<td>41.1</td>
<td>42.1</td>
<td>41.2</td>
<td>44.0</td>
<td>48.4</td>
<td>44.1</td>
<td>&lt;0.001</td>
<td>1.038 (1.030–1.046)</td>
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<tr>
<td>LRTI</td>
<td>41.5</td>
<td>41.1</td>
<td>53.9</td>
<td>56.1</td>
<td>55.2</td>
<td>65.8</td>
<td>64.9</td>
<td>66.1</td>
<td>68.7</td>
<td>70.4</td>
<td>69.6</td>
<td>&lt;0.001</td>
<td>1.058 (1.051–1.064)</td>
<td>&lt;0.001</td>
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<td>RTI symptoms</td>
<td>9.2</td>
<td>10.2</td>
<td>14.5</td>
<td>15.8</td>
<td>15.4</td>
<td>14.7</td>
<td>14.1</td>
<td>15.2</td>
<td>13.7</td>
<td>15.1</td>
<td>63.8</td>
<td>&lt;0.001</td>
<td>1.031 (1.025–1.036)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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.

† x² test for trends.

‡ Poisson regression.

A year was defined as the period from 1 July to 30 June of the succeeding year.
<table>
<thead>
<tr>
<th>Overall</th>
<th>Difference (%)</th>
<th>P value</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>&lt;0.001</td>
<td>1.057 (1.052–1.062)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;2 yr</td>
<td></td>
<td>&lt;0.001</td>
<td>0.936 (0.911–0.961)</td>
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<tr>
<td>2–4 yr</td>
<td></td>
<td>&lt;0.001</td>
<td>0.990 (0.973–1.007)</td>
<td>0.26</td>
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<tr>
<td>5–17 yr</td>
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<td>&lt;0.001</td>
<td>1.087 (1.072–1.101)</td>
<td>&lt;0.001</td>
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<tr>
<td>18–64 yr</td>
<td></td>
<td>&lt;0.001</td>
<td>1.076 (1.069–1.084)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65–74 yr</td>
<td></td>
<td>&lt;0.001</td>
<td>1.034 (1.023–1.045)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 yr</td>
<td></td>
<td>&lt;0.001</td>
<td>1.035 (1.024–1.040)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>8.3</td>
<td>9.7</td>
<td>11.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>5.1</td>
<td>6.5</td>
<td>7.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5</td>
<td>1.9</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0.7</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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.

† χ² 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 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 ±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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We thank all members and participating primary-care physicians of the University Medical Centre Utrecht Primary Care Research Network for creating the database used in the study.

DECLARATION OF INTEREST

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REFERENCES


