

Public beliefs on antibiotics and respiratory tract infections: an internet-based questionnaire study

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ABSTRACT

Background

Patient expectations are among the strongest predictors of clinicians' antibiotic prescribing decisions. Although public knowledge, beliefs, and experiences of antibiotics contribute to these expectations, little is known about these public views.

Aim

To gain insight into public knowledge, beliefs, and experiences of antibiotics and respiratory tract infections.

Design of study

Cross-sectional, internet-based questionnaire study.

Setting

Members of the general public aged 16 years and over in the Netherlands.

Methods

Public knowledge, beliefs, and experiences of antibiotics and respiratory tract infections, as well as predictors of accurate knowledge of antibiotic effectiveness, were measured using 20 questions with sub-items. The questionnaire was given to a Dutch community-based nationwide internet panel of 15 673 individuals. Of these, 1248 eligible responders were invited to participate; 935 responders (75%) completed the questionnaire.

Results

Of the participants, 44.6% accurately identified antibiotics as being effective against bacteria and not viruses. Acute bronchitis was considered to require treatment with antibiotics by nearly 60% of responders. The perceived need for antibiotics for respiratory tract infection-related symptoms ranged from 6.5% for cough with transparent phlegm, to 46.2% for a cough lasting for more than 2 weeks.

Conclusion

Public misconceptions on the effectiveness of, and indications for, antibiotics exist. Nearly half of all responders (47.8%) incorrectly identified antibiotics as being effective in treating viral infections. Doctors should be aware that unnecessary prescribing could facilitate misconceptions regarding antibiotics and respiratory tract infections. Expectations of receiving antibiotics were higher for the disease label 'acute bronchitis' than for any of the separate or combined symptoms prominently present in respiratory tract infection. Public beliefs and expectations should be taken into account when developing interventions targeting the public, patients, and physicians to reduce unnecessary prescribing of antibiotics for respiratory tract infections.

Keywords

antibiotics; community; public beliefs; respiratory tract infections; survey.

INTRODUCTION

In an era of increasing antimicrobial resistance, reducing over-prescribing of antibiotics for respiratory tract infections is considered a priority for general medical practice.¹ Respiratory tract infections comprise upper respiratory tract infections, such as the common cold, and lower respiratory tract infections, such as acute bronchitis and pneumonia. Most respiratory tract infections are viral in origin and self-limiting; therefore, antibiotics are seldom warranted. The probable exception is pneumonia which, regardless of aetiology, is usually treated with antibiotics.^{2,3} Important factors influencing over-prescription of antibiotics for respiratory tract infections are physicians' diagnostic uncertainty, patients' expectations of antibiotics, and physicians' assumptions regarding these expectations.⁴⁻⁷

Patient expectations are among the strongest predictors of clinicians' decisions regarding prescribing antibiotics; patients' knowledge, beliefs, and experiences of antibiotics are likely mediators of

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these expectations.⁸ For example, it has been recognised that a large proportion of people believe that antibiotics improve outcomes for bacterial as well as viral respiratory infections,⁹⁻¹² and previous studies have described patients' beliefs and expectations at the point of care for respiratory tract complaints.¹³⁻¹⁵ This study aimed to gain insight into the general public's knowledge, beliefs, and experiences of antibiotics and respiratory tract infections to determine predictors of accurate knowledge on antibiotic effectiveness.

METHOD

A cross-sectional survey among a sample of the general Dutch population was conducted during a 2-week period in October and November 2006, using an internet-based questionnaire. Approximately 800 responders were considered an adequate sample target to ensure generalisability of answers. Expecting a response rate of 60%, 1300 adult responders (aged ≥ 16 years) were invited to participate. These responders were randomly selected from a community-based nationwide internet panel of 15 673 individuals (Flycatcher Internet Research BV, Maastricht, the Netherlands) after stratification for sex, age, level of education (low/medium/high), and region of residence, based on national figures from Statistics Netherlands.

The questionnaire was developed by experts initially deciding which domains they considered most important. Questions to tap these domains were derived from previous international qualitative and quantitative scientific publications and further expert opinion.^{6,7,9-12} Two pilot studies were performed in general practice to check face validity, and the wording of some items was modified in light of this. Twenty questions with sub-items within the domains of the questions were included in the final instrument (for example, 'How often do you think the following complaints require antibiotic treatment ...' [question], '... if coughing up phlegm?' [sub-item]). Response options, including yes/no, agree/disagree, and Likert-type scale response items, were used as appropriate for each question.

Biomedically accepted knowledge of antibiotic effectiveness (that is, knowing that antibiotics are effective against bacteria but not viruses) was assessed by combining true/false answers to two separate questions regarding bacteria and viruses: 'Antibiotics are effective in treating infections caused by bacteria/viruses'. Respiratory tract infection was defined by means of diagnoses (for example, sinusitis, tonsillitis, and acute bronchitis) and associated symptoms. Explanation boxes accompanied most questions. This proved helpful

How this fits in

Clinicians' decisions regarding prescribing antibiotics are often influenced and can be predicted by patient expectations. The knowledge that members of the public have of antibiotics, together with their beliefs and experiences of them, will shape these expectations. However, important misconceptions exist among the public about the effectiveness and the appropriate indications for antibiotics. Focusing on symptoms may be preferable to mentioning microbiological distinctions and disease labels when communicating with patients on antibiotics for respiratory tract infections.

when explaining commonly used medical terms, such as acute bronchitis.

The internet-based questionnaire software required responders to answer a question with sub-items before being able to continue to the next question; the automatic routing of questions prevented responders returning to and altering responses to questions already completed. Total time taken to complete the questionnaire was recorded and stored to detect possible errors (for example, responders who completed the questionnaire quickly and perhaps did not read everything properly).

All responders' answers were automatically entered into a data file which was checked for accuracy by two independent researchers. Data were analysed using SPSS (version 13.0). Frequencies and cross tables of pre-selected variables were calculated and χ^2 tests were performed to identify variables associated with the dependent variable 'accurate knowledge of antibiotic effectiveness' (that is, knowing that antibiotics are effective against bacteria but not viruses). Variables with $P \leq 0.10$ were selected for the multivariate logistic regression model for the dependent variable to examine independence of associations ($P \leq 0.05$). Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Sex, age, and level of education were eligible variables for the multivariate model.

RESULTS

Demographics

Of the 1300 adults invited to participate, 52 individuals could not be contacted as a result of undeliverable invitational e-mails. Of the 1248 eligible responders, 935 completed the online questionnaire (response rate 75%) within a set period of 2 weeks (19 responders did not fully complete the questionnaire). In total, 467 responders (49.9%) were male, and 372 (39.8%) and 249 (26.6%) had a medium and high level of

Table 1. Characteristics of the study population (n = 935) compared with national figures for the Netherlands.

Characteristic	Responders n (%)	the Netherlands ^a %
Males	467 (49.9)	49.0
Age, years		
16–29	164 (17.5)	20.8
30–44	283 (30.3)	28.6
45–59	303 (32.4)	26.5
≥60	185 (19.8)	24.1
Level of education		
Low	314 (33.6)	33.6
Medium	372 (39.8)	41.2
High	249 (26.6)	25.2
Experienced state of health		
Very good/good	708 (75.7)	79.9
Poor (less than good)	227 (24.3)	20.1
Parenthood		
Children 0–12 years old	234 (25.0)	n/a
Children 0–5 years old	122 (13.0)	n/a
Chronic pulmonary disease	105 (11.2)	n/a
Chronic disease in general	228 (24.4)	n/a

^aData derived from Statistics Netherlands 2006 (www.cbs.nl).

education respectively. Responders were representative of the general Dutch population with regard to sex, level of education, and experienced state of health, but older people (aged over 60 years) were under-represented. Other characteristics of the study population, including having a chronic disease and parenthood, are detailed in Table 1. There was no notable difference between characteristics of responders and non-responders.

Table 2. Responders' knowledge, beliefs, and experiences of antibiotics and respiratory tract infections (n = 935).

Knowledge	Agree, n (%)
Antibiotics are effective in treating bacterial but not viral infections	417 (44.6)
Antibiotics are effective in treating infections caused by bacteria	783 (83.7)
Antibiotics are effective in treating infections caused by viruses	447 (47.8)
Beliefs and experiences	Agree, n (%)
I usually know when I need antibiotics	349 (37.3)
Decisions regarding the prescription of antibiotics have to be taken by a doctor	869 (92.9)
I find being given a delayed prescription of antibiotics acceptable	371 (39.7)
Bacteria can become less susceptible (resistant) to antibiotics	859 (91.9)
If antibiotics have been prescribed before they will be required again for similar symptoms in the future	350 (37.4)
If antibiotics have cured me before they will be required again for similar symptoms in the future	233 (24.9)
Taking antibiotics helps patients feel better sooner if they have:	
Common cold	177 (18.9)
Acute bronchitis	635 (67.9)
Pneumonia	806 (86.2)

Knowledge, beliefs, and experiences

The majority of responders (83.7%) endorsed the view that antibiotics are effective in treating infections caused by bacteria (Table 2). However, almost half of responders (47.8%) believed that antibiotics are effective in treating viral infections. The results for these two questions were combined to assess overall knowledge of antibiotic effectiveness and 44.6% of responders accurately identified antibiotics as effective against bacterial and not viral infections.

Of the responders, 93.1% correctly identified penicillin as an antibiotic. Most (n = 806, 86%) had used antibiotics at some point in the past: 236 (25.2%) during the past 12 months for any reason, and 92 (9.8%) in the past year for a respiratory tract infection. Almost a third (31.3%) had obtained information on antibiotics in the past 12 months, mostly from a doctor (53.6%). The perceived need for antibiotic treatment for respiratory tract infection-related symptoms ranged from 6.5% for a cough with transparent phlegm to 46.2% for a cough lasting more than 2 weeks. Similar frequencies to those for the perceived need for antibiotic treatment were found for the perceived need to consult a doctor with these symptoms (Table 3).

Predictors of accurate knowledge of antibiotic effectiveness

Acknowledgement of developing antimicrobial resistance (OR 3.18, 95% CI = 1.75 to 5.79) and high level of education (OR 3.03, 95% CI = 2.11 to 4.36) were the strongest predictors of accurate knowledge of antibiotic effectiveness (Table 4). Female sex was also significantly associated with accurate knowledge (OR 1.54, 95% CI = 1.17 to 2.04). No significant association was observed for having a chronic pulmonary disease ($\chi^2 = 1.16$, degrees of freedom [df] = 1, $P = 0.28$) or being a parent of at least one child aged ≤12 years ($\chi^2 = 1.72$, df = 1, $P = 0.19$).

DISCUSSION

Summary of main findings

These data reveal important misconceptions that members of the general public have about the effectiveness of, and the appropriate indications for using, antibiotics. Only 44.6% of responders accurately identified antibiotics as being effective against bacteria but not viruses. Expectations for antibiotics were higher for the disease label 'acute bronchitis' than for any of the separate or combined respiratory tract symptoms prominently present in respiratory tract infection.

Female sex, use of antibiotics at any time previously, and recent information on antibiotics

were independently associated with accurate knowledge of antibiotic effectiveness. One possible explanation is that women consult more frequently, often with their children, and therefore receive more accurate information on antibiotics; however, the finding that women had more accurate knowledge was independent of having children in the household.

GPs usually apply a low threshold to prescribe for lower respiratory tract infection in patients with chronic pulmonary disease based, for instance, on evidence of some beneficial effects of antibiotics for acute exacerbations in patients with severe chronic obstructive pulmonary disease or specific symptomatology.³ Yet, surprisingly, patients with chronic pulmonary disease did not have more accurate knowledge of antibiotics, despite that they generally are high consulters and receive frequent antibiotic treatment.

Strengths and limitations of the study

To date, this is one of the largest studies on public views of antibiotics and respiratory tract infections in Europe. This study was community-based, while most other research has studied patient populations.¹³⁻¹⁶ Performing this study among the general population allowed the researchers to gain more insight into views on antibiotics and respiratory tract infections before people become unwell and consult. A high response rate was achieved and the study sample was representative of the general Dutch population for most baseline characteristics; the only limitation in this regard was that older people were under-represented.

A limitation of any survey is the potential for recall and response bias. The internet-based questionnaire may have introduced selection bias, as only internet users were invited to participate in the study. The assumption that internet users were better educated did not hold in this regard, given that the level of education of the study sample was similar to that of the Dutch population. However, it may partly explain the under-representation of older people in the study.

Comparison with existing literature

Although many people correctly endorsed the view that antibiotics are generally effective against bacterial infections, nearly half of the responders also endorsed the view that antibiotics are effective in treating viruses. This was surprising, as the Netherlands has low prescribing figures for respiratory tract infections which are mostly viral and self-limiting in origin;¹⁷ therefore, it was expected that the Dutch public would have been better informed. A study investigating public views

Table 3. Responders' perceived need for antibiotic treatment and need to consult for respiratory tract symptoms and infections (n = 935).

Symptom	Perceived need for antibiotic treatment (always/often), n (%)	Perceived need to consult (always/often), n (%)
Sore throat	65 (7.0)	19 (2.0)
Cough with transparent phlegm	61 (6.5)	57 (6.1)
Cough with yellow/green phlegm	264 (28.2)	264 (28.2)
Cough with fever	243 (26.0)	145 (15.5)
Cough lasting more than 2 weeks	432 (46.2)	438 (46.8)
Respiratory tract infection		
Common cold	11 (1.2)	
Acute bronchitis	557 (59.6)	
Pneumonia	850 (90.9)	

on antibiotics in the US exposed a similar percentage of responders as the current study, who incorrectly identified antibiotics as being effective against viral infections.¹¹

Public misconceptions on antibiotic effectiveness are most likely facilitated by unnecessary antibiotic prescriptions for self-limiting respiratory illnesses. Other research has shown that previous antibiotic treatment was the strongest predictor for patients expecting antibiotics in the future.¹⁸⁻¹⁹ Given this, it is not unusual that a general population might lack some knowledge of antibiotic efficacy.

Implications for clinical practice and future research

The most important step in enhancing public knowledge on antibiotics is to restrict unnecessary prescriptions of them, thereby establishing evidence-based expectations about antibiotic treatment. More effective education about appropriate antibiotic use, focusing on the treatment of cough and acute bronchitis, could help in this regard. Dutch prescription rates for

Table 4. Factors independently associated with accurate knowledge of antibiotic effectiveness.

Factor	Odds ratio (95% confidence interval)
Female	1.54 (1.17 to 2.04)
Level of education	
Low	1.00 (reference)
Medium	1.79 (1.30 to 2.47)
High	3.03 (2.11 to 4.36)
Acknowledgement of developing bacterial resistance	3.18 (1.75 to 5.79)
Use of antibiotics at any time	2.12 (1.38 to 3.25)
Received or searched for information on antibiotics during the past 12 months ^a	1.50 (1.12 to 2.01)

^aInformation obtained from doctor, pharmacist, pharmacy, patient leaflet, the internet, or the media.

acute bronchitis are comparable to the US and the UK, where approximately 80% of patients consulting with this diagnosis are prescribed antibiotics.²⁰⁻²¹

The majority of this study's responders considered antibiotic treatment necessary for acute bronchitis. This misconception was independent of age, sex, or level of education. The proportion of responders who endorsed the view that antibiotics helped the symptoms of acute bronchitis resolve more quickly than recovery without antibiotics was much higher than for any of the separate respiratory tract symptoms (Table 3). In other words, expectations for antibiotics were highest when mentioning the disease label 'acute bronchitis' (Table 3), compared with when mentioning separate or combined symptoms commonly used in the definition of acute bronchitis (prominent cough with phlegm occurring for any duration).

Although antibiotics do not meaningfully alter the course of uncomplicated acute bronchitis for most people,³ up to 50% of the public expect a prescription for antibiotics when consulting with an ongoing cough. This expectation exists regardless of country or continent, as found by Pechere in an intercontinental study.¹⁶ GPs are often in time-pressured consultations with limited options for dealing with these expectations. Steering clear of disease labels and microbiological distinctions, and focusing on symptoms may help GPs to restrict their prescribing of antibiotics while providing patients with accurate information on the necessity of antibiotics for specific symptoms.

Several interventions that involve giving patients accurate information can improve the appropriateness of prescribing antibiotics. That some 40% of the study population considered a delayed prescription acceptable, despite the rarity of this prescribing strategy in the Netherlands, merits further research. Even when using this strategy of delayed prescription, setting realistic goals about the likely clinical course — and its long duration in particular, both with and without treatment with antibiotics — is crucial to changing incorrect assumptions about treatment using antibiotics. Training physicians in communication skills could be an additional means to achieving this,^{22,23} as could educational interventions aimed at informing doctors and patients. Multifaceted educational interventions have proven to be most effective in this regard.²⁴⁻²⁷

Possible future interventions involving information on antibiotics and respiratory tract infections aimed at the general public should consider focusing on educating younger

generations. They will be the ones consulting with respiratory tract infections for many years to come, especially when consulting with their children. For many people suffering from a non-resolving severe cough, treatment using antibiotics appears to be the obvious solution. Such inappropriate expectations persist irrespective of national prescribing figures or international borders. Hence working towards a more appropriate management of respiratory tract infections using antibiotics requires an international effort. Acknowledging the public's views on antibiotics and respiratory tract infections remains crucial to this endeavour for both researchers and physicians.

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Competing interests

The authors have stated that there are none

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REFERENCES

1. Nordberg P, Monnet DL, Cars O. *Antibacterial drug resistance: options for concerted action*. Geneva: World Health Organization, 2005.
2. Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev* 2005; **3**: CD000247.
3. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; **26**(6): 1138-1180.
4. Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations — a questionnaire study. *BMJ* 1997; **315**(7107): 520-523.
5. Coenen S, Michiels B, Renard D, et al. Antibiotic prescribing for acute cough: the effect of perceived patient demand. *Br J Gen Pract* 2006; **56**(524): 183-190.
6. Davey P, Pagliari C, Hayes A. The patient's role in the spread and control of bacterial resistance to antibiotics. *Clin Microbiol Infect* 2002; **8**(Suppl 2): 43-68.
7. Butler CC, Rollnick S, Pill R, et al. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998; **317**(7159): 637-642.
8. Butler CC, Rollnick S, Kinnersley P, et al. Reducing antibiotics for respiratory tract symptoms in primary care: consolidating 'why' and considering 'how'. *Br J Gen Pract* 1998; **48**(437): 1865-1870.
9. Emslie MJ, Bond CM. Public knowledge, attitudes and behaviour regarding antibiotics: a survey of patients in general practice. *Eur J Gen Pract* 2003; **9**(3): 84-90.
10. Belongia EA, Naimi TS, Gale CM, Besser RE. Antibiotic use and upper respiratory infections: a survey of knowledge, attitudes, and experience in Wisconsin and Minnesota. *Prev Med* 2002; **34**(3): 346-352.

11. Wilson AA, Crane LA, Barrett PH, Gonzales R. Public beliefs and use of antibiotics for acute respiratory illness. *J Gen Intern Med* 1999; **14**(11): 658–662.
12. Corbett KK, Gonzales R, Leeman-Castillo BA, *et al.* Appropriate antibiotic use: variation in knowledge and awareness by Hispanic ethnicity and language. *Prev Med* 2005; **40**(2): 162–169.
13. Little P, Dorward M, Warner G, *et al.* Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. *BMJ* 2004; **328**(7437): 444.
14. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ* 1997; **315**(7117): 1211–1214.
15. Welschen I, Kuyvenhoven M, Hoes A, Verheij T. Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. *Fam Pract* 2004; **21**(3): 234–237.
16. Pechere JC. Patients' interviews and misuse of antibiotics. *Clin Infect Dis* 2001; **33**(Suppl 3): S170–173.
17. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**(9459): 579–587.
18. Gonzales R, Corbett K. The culture of antibiotics. *Am J Med* 1999; **107**(5): 525–526.
19. Hong JS, Philbrick JT, Schorling JB. Treatment of upper respiratory infections: do patients really want antibiotics? *Am J Med* 1999; **107**(5): 511–515.
20. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997; **278**(11): 901–904.
21. Kuyvenhoven MM, Verheij TJ, de Melker RA, van der Velden J. Antimicrobial agents in lower respiratory tract infections in Dutch general practice. *Br J Gen Pract* 2000; **50**(451): 133–134.
22. Briel M, Langewitz W, Tschudi P, *et al.* Communication training and antibiotic use in acute respiratory tract infections. A cluster randomised controlled trial in general practice. *Swiss Med Wkly* 2006; **136**(15–16): 241–247.
23. Altiner A, Brockmann S, Sielk M, *et al.* Reducing antibiotic prescriptions for acute cough by motivating GPs to change their attitudes to communication and empowering patients: a cluster-randomized intervention study. *J Antimicrob Chemother* 2007; **60**(3): 638–644.
24. Little P, Rumsby K, Kelly J, *et al.* Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *JAMA* 2005; **293**(24): 3029–3035.
25. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005; **4**: CD003539.
26. Gonzales R, Steiner JF, Lum A, Barrett PH Jr. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. *JAMA* 1999; **281**(16): 1512–1519.
27. Welschen I, Kuyvenhoven MM, Hoes AW, Verheij TJ. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. *BMJ* 2004; **329**(7463): 431.