AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Systematic Review of Factors Associated with Antibiotic Prescribing for Respiratory Tract Infections

Rachel McKay,[a] Allison Mah,[b] Michael R. Law,[c] Kimberlyn McGrail,[c] David M. Patrick[a,b]

School of Population and Public Health, University of British Columbia, Vancouver, Canada[a]; Division of Infectious Diseases, University of British Columbia, Vancouver, Canada[b]; Centre for Health Services and Policy Research, School of Population and Public Health, University of British Columbia, Vancouver, Canada[c]

Antibiotic use is a modifiable driver of antibiotic resistance. In many circumstances, antibiotic use is overly broad or unnecessary. We systematically assessed factors associated with antibiotic prescribing for respiratory tract infections (RTI). Studies were included if they used actual (not self-reported or intended) prescribing data, assessed factors associated with antibiotic prescribing for RTIs, and performed multivariable analysis of associations. We searched Medline, Embase, and International Pharmaceutical Abstracts using keyword and MeSH (medical subject headings) search terms. Two authors reviewed each abstract and independently appraised all included texts. Data on factors affecting antibiotic prescribing were extracted. Our searches retrieved a total of 2,848 abstracts, with 97 included in full-text review and 28 meeting full inclusion criteria. Compared to other factors, diagnosis of acute bronchitis was associated with increased antibiotic prescribing (range of adjusted odds ratios [aOR], 1.56 to 15.9). Features on physical exam, such as fever, purulent sputum, abnormal respiratory exam, and tonsillar exudate, were also associated with higher odds of antibiotic prescribing. Patient desire for an antibiotic was not associated or was modestly associated with prescription (range of aORs, 0.61 to 9.87), in contrast to physician perception of patient desire for antibiotics, which showed a stronger association (range of aORs, 2.11 to 23.3). Physician's perception of patient desire for antibiotics was strongly associated with antibiotic prescribing. Antimicrobial stewardship programs should continue to expand in the outpatient setting and should emphasize clear and direct communication between patients and physicians, as well as signs and symptoms that do and do not predict bacterial etiology of upper respiratory tract infections.

The rapid and ongoing spread of antimicrobial-resistant organisms threatens our ability to successfully treat a growing number of infectious diseases (1, 2). It is well established that antibiotic use is a significant, and modifiable, driver of antibiotic resistance (3–5), and that antibiotics are often misused (6). In settings where a prescription is required to access antibiotics, the prescriber-patient encounter is a logical target for improving appropriate use.

Despite the importance of the topic, there is no existing systematic review to identify drivers of antibiotic prescribing from real prescription data. A narrative review of factors influencing antibiotic prescribing highlighted the multiple sources of influence affecting a potential prescribing encounter, including factors related to the prescribing physician (e.g., fear of failure, diagnostic uncertainty, or inadequate training), the patient (e.g., a high-risk or vulnerable patient history), and the environment (e.g., regulation of pharmaceutical prescribing and dispensing and lack of resources for etiological diagnosis) (7). Another study systematically reviewed reasons for inappropriate antibiotic prescriptions, for any indication, from quantitative studies up to 2008; half of the studies in this review used data based on simulated case scenarios in which the physician was asked how he/she would respond clinically (8). The main focus of that review was attitudes of prescribers; it found that a desire to fulfill the expectations of the patient/parent and fear of possible complications in the patient were most consistently associated with inappropriate prescribing of antibiotics. The presence of one or more symptoms or signs (e.g., fever, pathological murmur, or productive cough) was associated with antibiotic prescription in most studies assessed. The review also explored characteristics of patients, prescribers, and health care organizations in relation to prescribing, but the included studies were either too small in number or too heterogeneous in approach to offer insights in these areas (8). The authors of this review discuss the limitations of simulated case scenarios in understanding prescribing behavior and call for further studies based on real prescription data.

Physician visits for respiratory tract infections (RTI) commonly result in an antibiotic prescription (9–12), despite the fact that most upper RTIs are viral in nature. In these cases, antibiotics provide no benefit; thus, guidelines limit their recommended use to certain situations where the etiology is likely bacterial (13–15). Given the common nature of both this condition and potentially inappropriate prescribing practices around it, we chose RTIs as the focus for this review. Factors associated with any antibiotic prescribing for RTI were assessed, with the understanding that a significant proportion of this prescribing is unnecessary and therefore would be considered inappropriate.

A comprehensive summary of relevant factors implicated in potentially unnecessary antibiotic use will encourage physicians to reflect critically on their own practice and will provide an evidence-based resource for intervention and policy design. Therefore, we conducted a systematic review of factors associated with outpatient antibiotic prescribing for acute respiratory tract infec-

Received 25 January 2016 **Returned for modification** 29 February 2016 **Accepted** 20 April 2016

Accepted manuscript posted online 2 May 2016

Citation McKay R, Mah A, Law MR, McGrail K, Patrick DM. 2016. Systematic review of factors associated with antibiotic prescribing for respiratory tract infections. Antimicrob Agents Chemother 60:4106–4118. doi:10.1128/AAC.00209-16.

Address correspondence to Rachel McKay, rachel.mckay@alumni.ubc.ca.

Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.00209-16.

tions from the quantitative literature. The purpose of this review was 2-fold: first, to identify characteristics of patients, physicians, and the environment that have been associated with antibiotic use, and second, to describe the strengths of associations reported.

MATERIALS AND METHODS

The protocol used for this review is registered with PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO (identifier CRD42014010097).

We restricted our formal review to quantitative studies, as we aimed to focus on the strengths of association reported in retrieved studies. This report follows the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16).

Search strategy. Medline, Embase, and International Pharmaceutical Abstracts were searched. Search terms were determined by specifying the broader concepts we sought to assess ("antibiotic," "outpatient," "appropriateness," "prescribing," and "factors") and by identifying relevant terms within these concepts. Keywords and MeSH (medical subject headings) terms were compared from known, relevant studies as well as similar reviews. In addition, the author of a relevant article (17) provided a list of search terms used in that review, which served as an additional reference. Our list was then further refined through discussion with a librarian and consensus among the study authors (the final list of search terms is available in the supplemental material).

Study selection. Peer-reviewed studies conducted using data from the Organization for Economic Cooperation and Development (OECD) countries were eligible for consideration. This restriction was used to limit the review to factors that could operate in similar health care system contexts and patient populations. In addition, included studies were required to have (i) used actual (not self-reported or intended) prescribing, dispensing, or sales data; (ii) investigated the prescription of antibiotics by physicians, i.e., not over-the-counter purchasing; (iii) been observational or experimental in design; (iv) been written in the English language; (v) described factors at one or more of the levels of interest and assessed the association with the primary outcome of whether or not an antibiotic was prescribed at an individual encounter; and (vi) performed multivariable analysis of the associations. These criteria were refined from those presented in the published protocol based on the initial stages of the review. We omitted 11 studies that included patients with pneumonia, where results were not reported separately for the subgroup of patients without pneumonia.

After performing the full search, titles retrieved from each database were combined and duplicates were removed. Two authors (R.M. and A.M.) screened each record for potential relevance. The full texts of these studies were then assessed for inclusion eligibility independently by the same two authors. Reference lists of included articles were hand-searched for additional studies. The final search was conducted on 14 October 2015.

Data extraction and quality assessment. A customized data extraction form was developed for this study. All studies that met inclusion criteria were then assessed for quality using a form developed for this review, as there is no single recommended tool for assessing the quality of observational studies. Our tool was based on the SIGN 50 (Scottish Intercollegiate Guidelines Network) for cohort and case-control studies, as recommended by a review of quality assessment tools (18), as well as incorporating elements of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Institutes of Health's National Heart, Lung, and Blood Institute (19). Two authors (R.M. and A.M.) independently performed data abstraction and study appraisal. Abstractions and appraisals were compared for each study, and any discrepancies or disagreements were resolved by discussion and consensus. Both reviewers extracted all of the information from each study. There were no major discrepancies between reviewers.

The primary outcome of interest was an antibiotic prescription. Because antibiotic prescribing is a decision made at the level of the prescriber but recorded at the level of the patient, there is a natural clustering of patients with prescribers when multiple patients are included per prescriber. We noted whether and how analysts accounted for this clustering.

Data synthesis. Adjusted odds ratios (aOR) were extracted for each factor-antibiotic prescription association. Meta-analysis was not pursued, as significant heterogeneity among studies was expected. All factors identified were extracted. Selected forest plots are presented in Fig. 2. An alpha of 0.05 was used in all studies for constructing confidence intervals (CIs) and was the basis of our interpretation of statistically significant and nonsignificant findings.

RESULTS

Description of included studies. Our initial search identified 3,435 records, of which 2,848 nonduplicate titles were screened for inclusion (Fig. 1). Our initial search included non-English articles; however, of the few non-English abstracts retrieved and reviewed, none met the criteria for inclusion. Forty-four articles were considered relevant. Of these, 16 were determined to be of insufficient quality or to have insufficient details to allow further inclusion. The 28 included articles were considered to be of good or high quality (11, 20–46) (Table 1). Two studies reported results as risk ratios (34, 37), which precluded us from directly comparing them to the odds ratios reported in the other studies, given that antibiotic prescription is a relatively common occurrence. Consequently, results from these studies are included in the tables but not in the forest plots.

Just over half of the included studies were from the United States ($n = 15$) (11, 20, 21, 24, 26, 28, 30, 31, 33, 38–40, 45–47), with the remainder from Canada ($n = 3$) (34, 37, 43), The Netherlands ($n = 2$) (29, 35), Germany ($n = 2$) (23, 42), Italy ($n = 1$) (27), the United Kingdom ($n = 1$) (25), Belgium ($n = 1$) (22), and a network of 13 European countries ($n = 3$) (36, 41, 44). Eight of the U.S. studies used the NAMCS (National Ambulatory Medical Care Survey) or NHAMCS (National Hospital Ambulatory Medical Care Survey) data sets for their analyses (11, 28, 31, 33, 38–40, 46). Analyses included pediatric populations only in 5 studies (20, 27, 28, 38, 43) and adult populations only in 10 studies (11, 23–25, 39–42, 46, 47), while the rest either included all ages or did not specifically describe the patient population.

One study explored prescribing of both physicians and nurse practitioners (33). We only report the results from the physicians to allow comparison with the other studies.

Methodological quality of studies. The reasons for a study to receive an overall quality rating of poor were the lack of appropriate control (or description of control) for confounders ($n = 5$), inadequate presentation of results (lack of confidence intervals [$n = 2$] or lack of clear presentation of results in tables [$n = 1$]), using nationally representative survey data but failing to provide the study sample size (i.e., reporting only the extrapolated population estimates; $n = 4$), and using potentially biased study samples or methods ($n = 4$).

Despite most studies discussing both patient-level and physician-level factors, many of these did not adequately account for the clustering of patients with physicians or did not adequately describe the methods for doing so. Failing to account for this clustering tends to underestimate the variation in a statistical model (48), thus underestimating the width of the confidence interval and giving a false impression of precision.

Appropriateness of prescribing. While all studies focused on acute respiratory tract infections, they differed with regard to which diagnoses were specifically included and excluded. All stud-

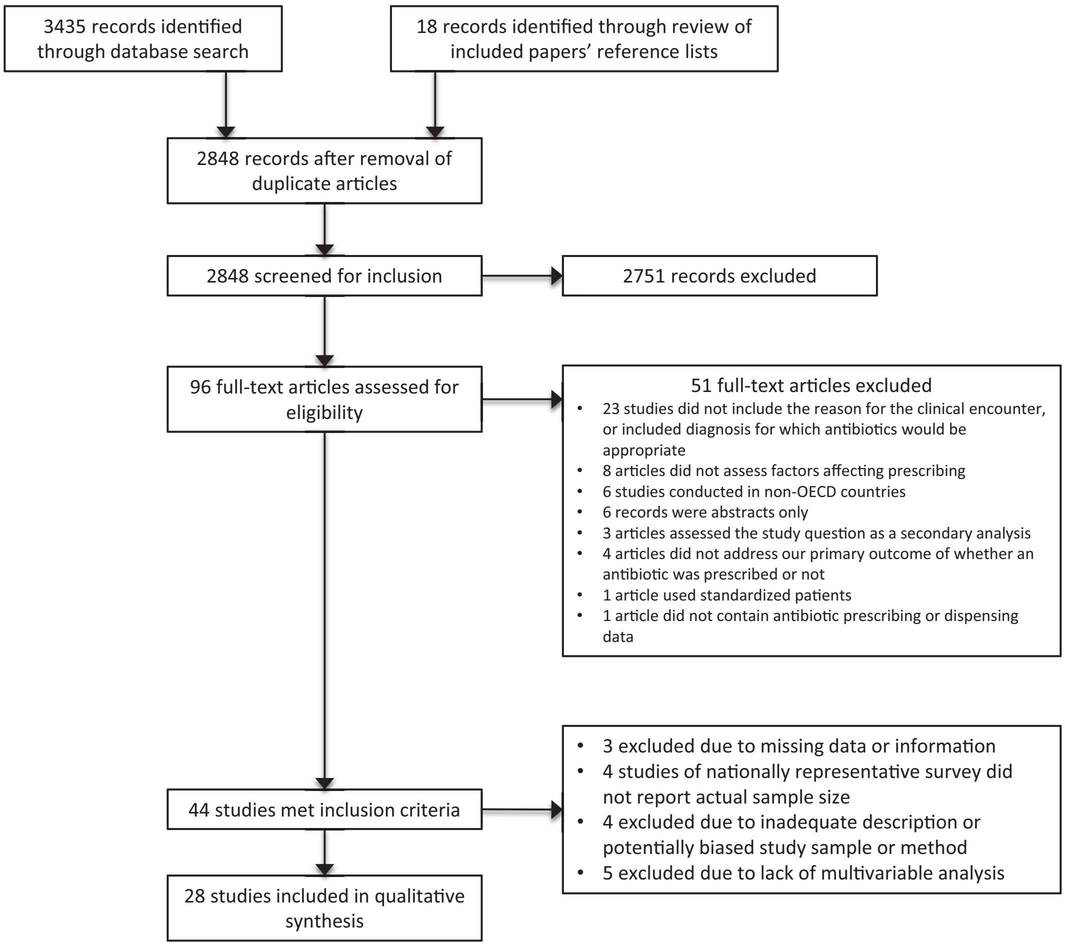

FIG 1 Flow chart of literature search and study inclusion criteria.

ies were focused on overprescription of antibiotics (the use of antibiotics in cases where they are never or rarely indicated). Some additionally reported underprescription (lack of prescription in cases where guidelines suggest they should be used) or other aspects of appropriate antibiotic use, such as selection of the optimal drug in cases where antibiotic use is considered necessary. Where these aspects of appropriateness were differentiated, we only extracted information on overprescribing.

Factors associated with inappropriate antibiotic prescription for RTI. Eighty factors were discussed in one or more studies, while 29 were addressed in three or more studies (Table 2; a table of all factors identified is included in the supplemental material). Results presented here focus on those factors addressed in at least three or more studies. We are not able to address every factor, so we selected some to be discussed in more depth. The presentation of factors here is grouped into those at the patient level (e.g., diagnosis of acute bronchitis, patient expectation of antibiotics, and factors associated with illness presentation, including the presence of fever, purulent sputum or nasal discharge, tonsillar exudate, and abnormal tympanic membrane) and those at the physician level (e.g., specialty of the physician and whether the physician perceives that the patient expects an antibiotic prescription).

Patient-level factors. Patient age and sex were the most commonly studied factors. Of the 10 studies that explored sex (11, 20, 25, 28, 30, 33, 37, 38, 40, 43), just one found a statistically significant association between male sex and higher odds of antibiotic prescription (43). Nineteen studies explored age as a factor (11, 20–22, 25, 27–30, 33, 35, 37–43, 46); of all of the comparisons made, 18 aORs were nonsignificant, 10 suggested that older people had higher odds/risk of a prescription than younger people, and 3 suggested that younger people had higher odds. However, the age groupings and reference categories differed across all studies. Nine studies assessed medical comorbidities as a factor associated with prescribing (20–22, 24, 26, 27, 37, 41, 46); in seven of those, no association was found, while in two studies the presence of comorbidities was associated with prescribing. The types of comorbidities, and the ways they were captured, varied by study.

Diagnosis of bronchitis. Six studies assessed the association of a diagnosis of bronchitis with an antibiotic prescription (20, 21, 30, 33, 37, 38); all found statistically significant positive associations (aORs ranging from 2.9 to 15.9), although only two reported the number of unique physicians in the sample and accounted for clustering (Fig. 2a).

Factors related to physical exam findings. The results of physical exam findings (fever, purulent sputum or nasal discharge, abnormal respiratory exam, physical exam findings of tonsillar exudate, and physical exam findings of abnormal tympanic membrane) were heterogenous but tended toward higher odds of pre-

TABLE 1 Description of included studies

Study author and reference	Study description	No. and age of participants	Factor(s) examined[a]	Authors' conclusions and summary of key findings[b]
Ahmed et al. (20)	Retrospective cross-sectional study of pediatric patients presenting to primary care providers' offices, convenient care clinics, and emergency departments for upper RTI, pharyngitis, or bronchitis	904 children aged 0–18 yr	dx, sp, age, sex, ins, st, fv, cmb, co, cng	Emergency department physicians and family practice physicians were more likely to prescribe antibiotics for acute respiratory illnesses than pediatricians
Akkerman et al. (29)	Prospective cross-sectional study of factors associated with antibiotic prescribing for acute otitis media	458 patients aged 0–87 yr with a median age of 4 yr	age, sv, pppe	Patients who should not have been prescribed an antibiotic according to guidelines were younger than 24 mo and more severely ill according to GP, and their GP assumed their parents expected an antibiotic
Akkerman et al. (35)	Prospective cross-sectional study of patients with sinusitis, tonsillitis, or bronchitis assessing patients' expectations of antibiotics for their illness and factors affecting inappropriate prescribing	1,490 patients aged 0–98 yr	ins, co, sv, pppe, inflam, whz, age	Patients who received an antibiotic prescription that was not in accordance with the Dutch national guidelines had more inflammation signs, such as fever, were more severely ill according to their GP, and their GP more frequently assumed that they expected an antibiotic than those who did not receive an antibiotic prescription
Altiner et al. (42)	Prospective cross-sectional study of patients presenting with acute cough, examining factors associated with antibiotic prescription	2,745 patients aged 16–96 yr	sv, fv, sm, dos, age, n pt fv, sv pt pr	The more severely ill a patient was rated by their physician, the more likely they were to receive antibiotics, especially if the rest of the patients in that physician's practice were relatively healthy
Aspinall et al. (21)	Prospective cross-sectional study of patients presenting with acute respiratory illness to Veterans Affairs emergency departments	667 patients with a mean age of 55 yr	cmb, fv, spm, sob, abs, dx, age, sp	Antibiotic use was high and varied substantially for URIs and acute bronchitis; specific signs and symptoms, a diagnosis of acute bronchitis, and provider age and specialty were associated with antibiotic prescribing
Brown et al. (30)	Retrospective cross-sectional database review to assess factors related to antibiotic prescription for acute upper respiratory tract infections	2,413 patients aged 18–64 yr	dx, age, sex, race, urb	63% of people received antibiotics for a nonbacterial respiratory tract infection
Butler et al. (36)	Data obtained from a prospective cohort of primary care networks from 13 European countries, looking at antibiotic prescription for acute cough as well as patient symptom resolution over time	2,419 patients aged 35–60 yr	spm	Adults presenting in primary care with an acute cough and who produced discolored sputum were more likely to be prescribed antibiotics
Cadieux et al. (34)	Retrospective cross-sectional data obtained from a historical cohort and administrative databases, assessing factors associated with inappropriate antibiotic prescriptions for acute respiratory illness	104,230 patient encounters over 9 yr	mcq, img, yr in p, vol	Physicians who had been in practice longer, who were international medical graduates, and who had high-vol practices were more likely to prescribe antibiotics inappropriately
Cadieux et al. (37)	Retrospective cross-sectional data from historical cohort and administrative database assessing physician clinical skills on licensing exams in relation to inappropriate antibiotic prescribing	129,592 patient encounters over 15 yr	loc, dx, sex, age, urb, pt edu, pt inc, cmb, p clin sc, vol, img, sp	Better clinical and communication skills on licensing exams reduced the risk of antibiotic prescription for viral respiratory infections among female physicians but not male physicians; younger, more well-educated patients were less likely to be prescribed an antibiotic; patients with more comorbidities were more likely to receive antibiotics
Coenen et al. (22)	Prospective cross-sectional data collection to assess factors affecting antibiotic prescription for acute cough	1,448 patients presenting to GP office with acute cough	age, cmb, sm, sv, pppe, dos, spm, fv, ha, mya, whz, sob, cp, ano, fat, hr, abs, pd, re, fu, gpt, fee, geo, spiro, p age, p load, hm v	Physician-perceived patient demand for antibiotics is associated with prescription of antibiotics

Coenen et al. (44)	Cross-sectional data from a prospective cohort from 13 European countries assessing the association of patient expectations with physician prescribing practices	2,690 patients with a median age of 48 yr	pt exp, pt hp, pt ask, pppe	Patient expectations, hopes, or asking for antibiotics were not associated with symptom severity at presentation or symptom resolution during the subsequent 28 days regardless of whether an antibiotic was prescribed; patient expectations and physician perception of patient views were strongly associated with antibiotic prescribing
Dosh et al. (45)	Cross-sectional study of factors associated with prescription of antibiotics for acute respiratory infections in outpatient family practice	482 patients over the age of 4 yr	rhin, pnd, pur ND, abs, sin tn	Presence of rales, rhonchi, sinus tenderness, postnasal drainage, purulent nasal discharge, and clinician's perceptions of clinical course of the illness affected the likelihood of antibiotic prescription
Fischer et al. (23)	Prospective cross-sectional study using medical student observation to assess factors associated with antibiotic prescription for respiratory tract infections	273 patients aged 14–88 yr	ab ph, tm abn, la, abs, sin tn, fat, whz, fv, spm	Antibiotic prescribing was associated with specific patient symptoms and physical exam results
Gaur et al. (38)	Retrospective cross-sectional examination of NHAMCS data to determine factors associated with antibiotic prescription for viral respiratory tract infections	1,952 patients aged 0–18 yr	age, sex, race, geo, ins, dx, hous st, nontch, bf gl	Staff physicians are more likely to prescribe antibiotics for viral respiratory tract illness than trainees, and staff at non-teaching hospitals are more likely to prescribe antibiotics than staff at teaching hospitals
Gonzales et al. (11)	Retrospective cross-sectional database review to assess factors related to antibiotic prescription for acute upper respiratory tract infections	548 patients aged greater than 18 yr old	age, sex, race, geo, ins, sp	Only rural practice was an independent risk for antibiotic therapy for URIs
Gonzales et al. (24)	Retrospective cross-sectional data from an insurance database was used to assess factors associated with antibiotic prescription in acute upper respiratory tract infection	322 patients above the age of 18 yr	sm, pur ND, spm, ab ph, tm abn, sin tn, la, fv, cmb, mis wk	33% of patients with URI were prescribed antibiotics, often in the setting of purulent manifestations, with purulent nasal discharge, green phlegm production, tonsillar exudate, and current tobacco use predicting antibiotic prescription for URIs
Holmes et al. (25)	Cross-sectional survey of physicians assessing factors associated with antibiotic prescribing for acute respiratory illness	391 patients above the age of 16 yr	sex, age, spm, abs	Although the minority of patients had abnormal signs on physical exam, when present, discolored sputum and abnormal chest findings increased the chances of antibiotic prescription
Kozyrskyj et al. (43)	Retrospective cross-sectional study of population-based database to assess factors associated with antibiotic prescription	4,870 patients with a mean age of 85 yr	p age, img, sp, year, sea, age, sex, pt inc	Almost half of physician visits for viral RTIs resulted in an antibiotic prescription, and second-line antibiotics were prescribed in 20% of visits for common childhood infections
Ladd (33)	Study utilizing retrospective cross-sectional data from NHAMCS and NAMCS databases to assess the prescribing practices of nurse practitioners compared to physicians and the factors that influence antibiotic prescribing in each group	14,198 patient encounters over a 5-yr period	loc, dx, year, sex, age, geo, race, ins, sup med	NPs have prescribing practices for viral upper respiratory tract infection similar to those of MDs; patient race and insurance type influenced NP antibiotic prescribing
Linder and Singer (47)	Prospective survey at the time of patient encounter to assess influence of patient desire for antibiotics on physician prescribing practices	310 patients with a mean age of 34 yr	pt exp, abs, ab ph	39% of patients wanted antibiotics; wanting antibiotics was associated with antibiotic prescription
Linder and Stafford (39)	Retrospective cross-sectional study using NAMCS database to examine antibiotic prescriptions for sore throat	1,852 patients above the age of 18 yr with a mean age of 38 yr	year, age, sex, race, ins, sp, geo, urb	Predictors of antibiotic use for sore throat were younger patient age and physician specialty being general practice

(Continued on following page)

TABLE 1 (Continued)

Study author and reference	Study description	No. and age of participants	Factor(s) examined[a]	Authors' conclusions and summary of key findings[b]
Mangione-Smith et al. (26)	Prospective nested cohort study of factors associated with inappropriate antimicrobial prescribing and parental satisfaction with the visit	306 parents of pediatric patients	race, pt inc, prev abx, otal, st, co, cmb, rhin, tm abn, pt exp, pppe, p att	Physicians were significantly more likely to inappropriately prescribe antibiotics if they believed a parent desired antimicrobials
Moro et al. (27)	Prospective cross-sectional survey of patients presenting to pediatricians with respiratory tract infections	4,352 patient encounters	age, imi, day care, pppe, ab ph, sin tn, otal, periorb, diar, tm abn, la, otor, fv, rhin, cmb, p age	No difference in the probability of antibiotic prescription was found between ambulatory practices and hospital emergency service pediatricians; the presence of an interviewer in the ambulatory practice was negatively associated with antibiotic prescription
Nyquist et al. (28)	Retrospective cross-sectional data from NAMCS database was used to look at factors affecting prescribing for children with acute respiratory illness	531 patients aged 0–18 yr	age, sex, race, geo, urb, ins, sp	Colds, URIs, and bronchitis accounted for over 20% of all antibiotic prescriptions provided by U.S. ambulatory physicians to children (<18 years) in 1992
Roumie et al. (31)	Retrospective cross-sectional study using NAMCS and NHAMCS data to assess factors associated with antibiotic prescription patterns	1,504 patients presenting to outpatient or emergency department with acute respiratory illness	loc, sp, hous st	Odds of receiving an antibiotic were greater in a visit to a non-physician clinician for respiratory diagnosis where antibiotics are rarely indicated; resident physicians prescribe fewer antibiotics for respiratory diagnoses where antibiotics are rarely indicated than physicians or non-physician clinicians
Rutschmann and Domino (40)	Retrospective cross-sectional review of NAMCS data to assess relationship between physician specialty and antibiotic prescribing for URI	956 patients over the age of 18 yr	age, sex, race, geo, urb, ins, sp, pcp, time, cxr, year	Antibiotics were still prescribed for more than 40% of the URIs seen in adult ambulatory practice between 1997 and 1999 in the U.S.
Smith et al. (46)	Retrospective cross-sectional assessment of NAMCS and NHAMCS data to assess factors affecting antibiotic prescription for acute rhinosinusitis	881 patients with a mean age of 46.2 yr	sp, age, cmb	First, antibiotics continue to be widely prescribed to treat ARS; second, when physicians prescribe antibiotics for ARS visits, they choose broad-spectrum antibiotics in the majority of cases; third, there are significant variations in antibiotic prescribing for ARS by physician specialties and patient age
Stanton et al. (41)	Prospective survey assessing relationship between smoking status and antibiotic prescription for acute cough	2,549 patients above the age of 18 yr	age, cmb, sm, dos	Primary care clinicians prescribed antibiotics more frequently to smokers than nonsmokers; this suggests that, despite differences in training and practice setting, clinicians have similar attitudes toward prescribing antibiotics for smokers

[a] Abbreviations for patient-level factors: ab ph, abnormal pharynx; abs, altered breath sounds; age, patient age; ano, anorexia; chil, chills; cmb, patient comorbidity; cng, congestion; co, cough; cp, chest pain; cxr, chest X-ray performed; day care, child attendance at day care; diar, diarrhea; dos, duration of symptoms; dx, diagnosis; dx test, diagnostic tests ordered; fat, fatigue; fv, fever; gen, general symptoms; ha, headache; hr, high risk patient as determined by physician; htn, hypertension; hypox, hypoxia; imi, parents born abroad; inflam, signs of inflammation; ins, patient medical insurance type; la, lymphadenopathy; meds, other concurrent medications; mis wk, patient missed work; mya, myalgias; otor, otorhea/otalgia; pain, moderate to severe pain; p att, patient attitude toward antibiotic prescribing; p clin sc, physician clinical skills exam score; pd, percussion dullness; periorb, periorbital edema; pnd, postnasal discharge; ppc, perceived parental concern about child's illness; prev abx, previous antibiotics for similar illness; pt ask, patient asked physician for antibiotic; pt edu, patient level of education; pt exp, patient expectation for antibiotic; pt hp, patient hope for antibiotic; pt inc, patient income; pur ND, purulent nasal discharge; race, patient race; rhin, rhinorrhea; rr, elevated respiratory rate; se, patient concern about side effects of antibiotics; sex, patient sex; sin tn, sinus tenderness; sm, patient is a smoker; sob, shortness of breath; spm, sputum; st, sore throat; sup med, patient on supportive (nonantibiotic) medication; sv, severity of illness; tach, tachycardia; time, time spent with patient; tm abn, tympanic membrane abnormality; viral, viral diagnosis noted by physician; wait, patient waited >2 h to see physician; whz, wheeze. Abbreviations for provider-level factors: bact, physician belief that acute bronchitis and URI caused by bacteria; br spc, tendency of physician to use broad-spectrum antibiotics; fee, fee structure and billing; fu, follow up with physician; gpt, general practitioner special training; high rx, physician high prescriber; hm v, mean number of physician home visits; hous st, housestaff compared to staff physicians; img, international medical graduate; loc, physician practice location; mcq, physician score on infectious diseases component of licensing exam; non phy, patient seen by provider other than medical doctor; nontch, physicians at non-teaching hospitals compared to staff at teaching hospitals; n pt fv, number of patients in the physician's practice with fever; own, physician owns medical practice; p age, physician age; ph sex, physician sex; phy blf, physician belief about antibiotics for treatment of colds; p load, physician patient load; pppe, physician perception of patient expectations; p/t, physician works part-time; re, patient referral; solo, physician in solo practice; sp, physician specialty; spiro, availability of spirometry in physician office; sv pt pr, severity of other patients' illnesses within physician's practice; vol, physician practice volume; vol URI, volume of URI diagnosis in physician practice; yr in p, physician years in practice. Abbreviations for environment-level factors: bf gl, prior to guideline update compared to after; geo, geographic location; new, new patient; pcp, physician is patient's primary care provider; sea, season; urb, urban vs rural; year, year of visit.

[b] GP, general practitioner; NP, nurse practitioner; MD, medical doctor; ARS, acute rhinosinusitis.

TABLE 2 Direction of results by number of studies reporting each factor for factors investigated by 3 or more studies

Factor[a]	No. of studies with: Positive association	Negative association	No significant association	Total no. of studies
Patient level				
Age*	6		13	19
Male sex	1		9	10
Comorbidity	2		7	9
Medical insurance type*	1		7	8
Ethnicity*	1		6	7
Black vs white race		1	5	6
Fever	5		1	6
Bronchitis	5			5
Purulent sputum	5			5
Respiratory physical exam findings	5			5
Desire for antibiotics	3		1	4
Smoker	3		1	4
Cough	1		2	3
Duration of illness	1		2	3
Household income		1	2	3
Pharyngitis	3			3
Rhinorrhea		2	1	3
Sinus pain on exam	3			3
Tonsillar exudate	3			3
Tympanic membrane abnormality	3			3
Physician level				
Specialty*	6		2	8
Perception of desire for antibiotics	6			6
Severity of patient illness	4			4
High-vol practice	1		2	3
International medical graduate	2	1		3
Area-level				
Geographic location*	1		6	7
Rural vs urban	3		4	7
Yr of visit			4	4
Visit location (office, emergency department, hospital clinic)*	1		2	3

[a] An asterisk denotes a categorical variable with different possible reference groups; therefore, the direction of effect is not always comparable. We have categorized any study that found a statistically significant association in one direction as a positive association for illustrative purposes.

scription with these findings (Fig. 2b to f). Across the six studies that assessed abnormal respiratory exam (21–23, 25, 45, 47) (Fig. 2d), for instance, all showed a statistically significant positive association with antibiotic prescription in adjusted analyses, with aORs ranging from 3.0 to 19.9. Five of the seven studies assessing the association between purulent sputum or nasal discharge and antibiotic prescription described a statistically significant positive relationship (21, 22, 24, 25, 45) (Fig. 2c), while one found no relationship (36) and one had a 95% confidence interval very close to 1 (23).

Two of the studies that addressed fever were of children (20, 27), while the rest were of adults (22, 23, 47) (Fig. 2b). The fever association point estimates for aORs all were relatively low (ranging from just over 1 to less than 3) compared with those for some of the other factors identified. Each study developed a multivariable model with differing variables: all controlled for some set of physical symptoms, and five of the six studies also controlled for comorbid conditions (in various ways) (20–22, 27, 47).

The confidence intervals for three of the four studies that assessed the finding of an abnormal tympanic membrane were quite wide (23, 26, 47) (Fig. 2f), reflecting relatively small sample sizes and potentially few events, although the number of events was not reported.

Patient expectations. Of the four studies that addressed an association of prescribing with patient expectation of antibiotics, one (27) found a strong association (aOR of 9.9; 95% CI, 3.1 to 31.4), while the other three found weaker or no associations (Fig. 2g).

Prescriber-level factors. The specialization of the prescriber was the most commonly assessed factor in this category; however, designated reference groups differed across studies, making them difficult to compare.

Of the eight studies that assessed prescriber specialty, three were performed in exclusively pediatric populations and five in adult populations. In the pediatric studies, pediatricians were consistently less likely to prescribe an antibiotic than the reference group, which included emergency department physicians, general practitioners, and nonpediatric specialists. The aOR for pediatrician prescribing compared to non-pediatrician specialties ranged from 0.1 to 0.6 (20, 28, 43). Of the studies in adults, one study

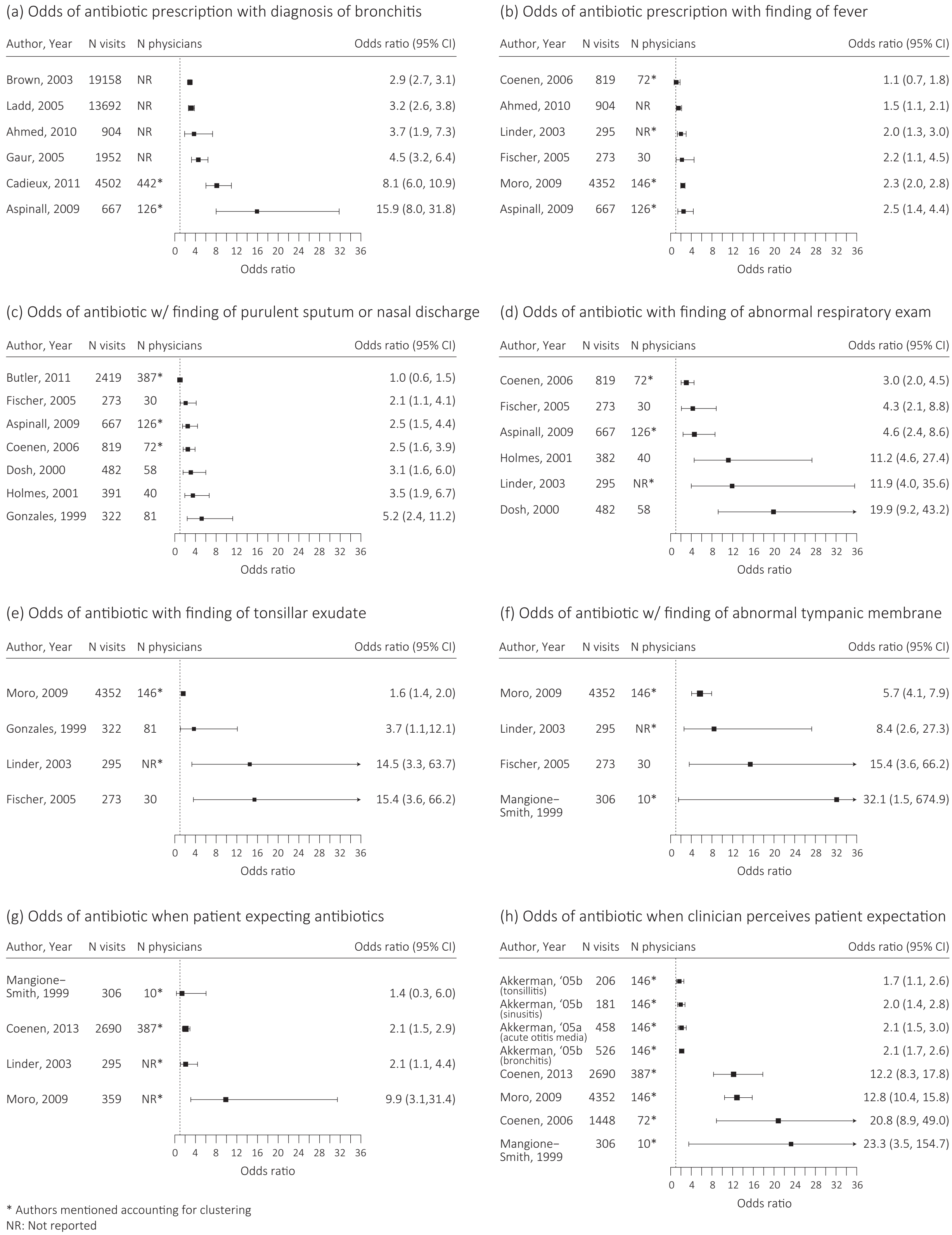

FIG 2 Forest plots of results for selected factors. (A) Odds of antibiotic prescription with diagnosis of bronchitis. (B) Odds of antibiotic prescription with finding of fever. (C) Odds of antibiotic prescription with finding of purulent sputum or nasal discharge. (D) Odds of antibiotic prescription with finding of abnormal respiratory exam. (E) Odds of antibiotic prescription with finding of tonsillar exudate. (F) Odds of antibiotic prescription with finding of abnormal tympanic membrane. (G) Odds of antibiotic prescription when patient expecting antibiotics. (H) Odds of antibiotic prescription when clinician perceives patient expectation. For each graph, the size of the point is proportional to the number of visits analyzed in each study, with larger points representing larger samples.

found no association of prescriber specialty and antibiotic prescription (11), and one study assessed other prescribers with otolaryngologists as the reference group and found that other groups prescribed significantly more than otolaryngologists (range of aOR, 3.9 to 7.9) (46). Of the remaining three, two studies found internists prescribed less than general practitioners and emergency room providers (aORs of 0.4 to 0.8) (21, 40), and one found no difference between internist and family practitioner prescribing (aOR, 0.9; 95% CI, 0.7 to 1.2) (39).

Five studies (in six reports) looked at the association between a clinician's perception that a patient expected an antibiotic and prescribing an antibiotic (Fig. 2h) (22, 26, 27, 29, 35, 44). All found statistically significant positive associations, ranging from an aOR of 1.7 to 23.3. All of these studies both reported the number of physicians in the sample and mentioned the use of a statistical technique to account for clustering.

Area-level factors. Geographic region was reported in 7 studies (11, 22, 28, 33, 38–40). Six of the 7 studies used the NAMCS or NHAMCS data from of the United States, which record geographic regions as south, northeast, midwest, and west (11, 28, 33, 38–40). Only one of these studies found any statistically significant differences, with lower odds of prescription in the south and west regions than in the northeast (38). The final study was from Dutch Belgium; the odds of an antibiotic prescription were statistically significantly higher in West Flanders (aOR, 3.95; 95% CI, 4.9 to 176.7) and Brussels (aOR, 29.2; 95% CI, 1.6 to 9.8) than Antwerp (22).

DISCUSSION

This review compiles research on factors associated with antibiotic prescribing for RTI and finds that there is good evidence that factors beyond a clear bacterial diagnosis are associated with prescription decisions for RTIs. This is important because the majority of RTIs are viral and therefore do not improve with use of an antibiotic. A substantial proportion of antibiotic use for RTIs is, therefore, inappropriate and unnecessarily contributes to risk of adverse reactions as well as antibiotic resistance. By identifying factors that are associated with prescribing, antibiotic stewardship programs and interventions may be better able to target their activities.

Diagnosis and physical exam findings. A diagnosis of bronchitis was consistently associated with increased odds of antibiotic prescription, although most of the studies reporting this association did not account for clustering of patients among physicians. This practice may be indicative of a suspicion of underlying bacterial illness (15). However, guidelines and reviews commonly recommend against this method of management, as studies have shown that antibiotic prescription for acute bronchitis is minimally effective, resulting in a half-day reduction in cough but no reduction in functional impairment compared to the placebo and resulting in increased adverse events (13, 49, 50).

Several physical exam findings were associated with antibiotic prescription. The probable explanation for this association is the physician's belief that these findings are more indicative of a bacterial etiology for the patients' symptoms. Recent guidelines have addressed issues of presumptive distinctions between viral and bacterial upper RTIs (51). Some symptoms are suggestive of a possible bacterial diagnosis and therefore should lead to investigation of bacterial etiology; for instance, fever and patchy tonsillopharyngeal exudates are associated with bacterial group A streptococcal (GAS) pharyngitis (52). Suspicion of GAS pharyngitis, however, should initiate a throat swab to guide appropriate treatment, as the majority of pharyngitis cases remain viral in origin (53). Similarly, abnormal findings on chest auscultation may lead to suspicion of pneumonia; however, confirmation of the diagnosis with a follow-up chest X-ray should be performed prior to the administration of antibiotics (54).

Ultimately, differentiating definitively between bacterial and viral causes of RTIs based on signs and symptoms alone is seldom possible, and this imprecision and concern about missed bacterial diagnosis likely drives overprescription of antibiotics. Use of point-of-care tests and improved organism-prediction algorithms may be useful in a number of circumstances. While additional diagnostic tools may add some effort and cost, the price of continuing to use antibiotics for RTI as a safeguard rather than a directed therapy is likely greater.

Physician specialty. In general, we found that pediatricians tended to have better prescribing practices, with lower rates of antibiotic prescription for RTIs. A lower rate of antibiotic prescribing was also seen among internal medicine specialists, although not to the same extent. Conversely, front-line providers such as emergency department physicians, general practitioners, and family physicians generally had higher rates of antibiotic prescribing for RTIs. Reasons for higher prescribing rates may relate to physician training but more likely reflect the practice environment in which these providers see patients. Emergency departments and outpatient family medicine clinics are busy, high-volume environments and may not provide the opportunity for patient follow-up. This environment may tend to increase physician diagnostic uncertainty and concern about missing a diagnosis for which antibiotics are warranted, factors previously described as influencing prescriber treatment decisions (7).

Patient expectations. Physician perception of patient (or parent, in the case of pediatric patients) expectation for antibiotics was a more consistent predictor of antibiotic prescription than actual patient expectation of antibiotics. It should be noted that, among the studies assessing physician perception of patient/parent desire for antibiotics, while all of the studies reported positive associations, the set of analyses by Akkerman and colleagues (29, 35) reported lower point estimates and tighter confidence intervals. The lower variance could be due to these models controlling for fewer covariates than the other studies. Additionally, due to the conversion from log scale, higher point estimates will necessarily have wider confidence intervals. In fact, when expressed in logit, the width of the confidence intervals from the Coenen et al. (44) and Moro et al. (27) studies are not appreciably different from those of the Akkerman et al. studies.

The observed variability in point estimates between the Akkerman et al. study and the others could be due to differences in settings. The Akkerman et al. study was conducted in the Netherlands, where antibiotic use is the lowest in Europe (55). A culture of judicious use may moderate to some extent the effect of perceived pressure on physicians. This variability in point estimates suggests that we should not put too much emphasis on the magnitude of the association *per se* but rather the positive nature of the observed associations.

A qualitative study of physicians' strategies for managing perceived patient expectations for antibiotics noted that the physicians in the study were often reluctant to explicitly determine patients' expectations, as this could lead to direct confrontation if those expectations were not aligned with the physician's therapeutic recommendation (56). Instead, physicians preferred to assess perceived expectations and manage those. However, perceptions are not always accurately aligned with patient expectations (27, 45). Interestingly, in the study by Coenen et al., patients explicitly asking for antibiotics (as reported by the patient) did not have a significant effect on prescribing, and there was a trend toward reduced prescribing, in contrast to the physician perceiving that a patient was expecting an antibiotic, which was associated with prescribing (44). This suggests that by asking, the patient addresses directly the issue at hand, allowing for a discussion to ensue regarding the need for antibiotics. While these two variables (a patient expecting antibiotics and a physician perceiving that a patient expects antibiotics) may not be completely independent, the possible distinction is worth consideration.

Communication strategies of both patients and clinicians may shape clinicians' assumptions or perceptions regarding patient expectations for antibiotics (57, 58). In a systematic review of qualitative studies about how communication affects prescription decisions, the study of Cabral et al. discusses the opportunity for miscommunication that can arise when a patient/parent endeavors to justify the need for consultation, which can be perceived as an expectation of antibiotics by the clinician. Additionally, the clinician's use of minimizing and normalizing statements, which may be part of the clinical approach of reassurance and intended to pave the way for not prescribing antibiotics, may be interpreted by the parent/patient as questioning the need for consultation (57).

Some physicians have indicated that they prescribe antibiotics under likely unnecessary circumstances because it provides a quick resolution to the clinic visit and improves satisfaction of patients (59, 60). However, the amount of time spent with a patient has not been independently associated with antibiotic prescriptions (61, 62). Additionally, there is some evidence that patient satisfaction with a physician encounter is not dependent on having received antibiotics (63). This is important to note in the context of physicians prescribing based on perceived patient expectation, as presumably this phenomenon is intended to improve patient satisfaction. One study found that the odds of a patient reporting satisfaction with a physician visit for acute RTI were higher when the patient received information or reassurance than when they received an antibiotic (64). If, however, the patient was expecting antibiotics, the odds of satisfaction were similar among those who received information and those who received an antibiotic (64).

Limitations. The patient populations included in the studies in this review are diverse. While the benefit is that the factors identified stem from varied populations and as such are more representative, the consequence is that we are not able to identify factors associated with particular age groups or illnesses.

We decided to extract and report on adjusted effect estimates, as unadjusted estimates are too potentially confounded to be meaningful, and this is in line with recommendations from the Cochrane Handbook on Systematic Reviews of Interventions (65). However, this creates a challenge for interpretation, as each study controls for a different set of variables, and adjusted estimates are sometimes presented only for those variables that remain in the final model. Our findings then may be biased toward statistically significant associations. For instance, one study found that patient expectation was associated with antibiotic prescription on bivariable, but not multivariable, analysis controlling for a number of potential confounders, and the numeric value of the nonsignificant result was not reported (45). Similarly, a general publication bias would operate in the same direction.

Additionally, the definitions used to denote each factor were not standardized across studies. For instance, fever was specified dichotomously as $>$38°C or $\leq$38°C (22, 27), per degree Celsius above 37°C (47), or not defined/patient reported (20, 21, 23).

In studies where an adequate description of clustering techniques was not provided, the precision of point estimates should be interpreted with caution; in particular, point estimates that appear to be statistically significant but whose confidence limits are close to the null should be evaluated with care.

While we set out to identify factors at the levels of the patient, the prescriber, and the environment, our review ultimately focused mostly on those at the patient level, with just a few factors appearing at the physician level. At the environment level, geographic region, outpatient encounter setting, year of encounter, and urban versus rural location were the only factors identified, with most studies failing to demonstrate an association of these factors with prescribing practices. Additional studies that addressed factors at the level of the environment were excluded for not assessing individual-level prescriptions but rather area-level rates of prescribing. These studies are still important and are casting necessary light on higher-level influences on prescribing but could not be included here.

Most RTIs are viral, and antibiotics do not shorten the duration of illness or have other positive effects on viral infections. However, there are some situations where an antibiotic could be considered an appropriate treatment for an RTI. Our review does not distinguish between appropriate and inappropriate prescribing for RTI and instead assumes that most prescribing would be considered inappropriate. This was done because the assumption made by many of the studies included was that any antibiotic prescribing for RTI was inappropriate; however, few attempted to assess appropriateness in a systematic way.

Despite the typical drawbacks to this kind of review, we identified several main findings. First, we conclude that physicians can reflect on their own perceptions about patient expectation of antibiotics. Prescribers should feel justified to deflect perceived pressure from patients. Valuing the patient's experience, appreciating their time in coming in to seek advice about their symptoms, and providing clear information about how long symptoms might be expected to last and about what symptomatic treatment is recommended may help in reducing the unnecessary use of antibiotics. Second, a number of physical exam findings were independently associated with antibiotic prescribing, despite the lack of evidence that these signs and symptoms are indicative of bacterial infection. Third, there was limited data addressing potential associations between area-level factors and antibiotic prescribing at the individual level. This may be a fruitful area for further research.

Policy implications. Our findings suggest several possible policy directions. Continued education is warranted to highlight the viral etiology of most RTIs, in particular of acute bronchitis, and associated lack of benefit of antimicrobial treatment in these cases. Similarly, continued education should focus on signs and symptoms that are and are not associated with an increased risk of bacterial infection. Guidelines have been useful in reducing the volume of antibiotic use (66). While a number of guidelines pertaining to respiratory tract infections exist, it may be beneficial to enhance them with clear descriptions both of signs and symptoms that are, and are not, likely to be associated with bacterial infection. Improved access to point-of-care diagnostic aids for bacterial pneumonia may help relieve uncertainty about the diagnosis and therefore reduce the practice of prescribing antibiotics due to this uncertainty. Given the strong influence of physician perception of patient desire for antibiotics on prescribing practices, greater focus on communication strategies that physicians can use in negotiating the clinical encounter with a patient also may be useful.

There has been documented success with public policies to reduce antibiotic consumption, which are often educational campaigns aimed at the public and general practitioners (67). Further emphasis on knowledge levels among the general public should be a priority in an effort to reduce both actual and perceived patient demand for antibiotics. This public awareness effort could be expanded to encourage patients to engage in a dialogue with their physicians about the need or lack of need for antibiotics, such that the clinical encounter involves appropriate discussion and counseling and avoids practices based on unclear communication and perceptions.

Systematic reviews conclude that antibiotic stewardship programs show promise for optimizing antibiotic therapy both in hospital (68) and community settings (17, 69, 70). The components of these programs differ across implementations, and specific behavioral outcomes vary (e.g., decision to treat with antibiotics or not; choice of antibiotic when deemed appropriate; route, dose, and duration of antibiotic therapy), but in general these initiatives have been associated with improvements in the use of antibiotics. Further development and expansion, with thorough evaluation, of antibiotic stewardship programs for the outpatient setting could include individualized feedback on physician prescribing practices in relation to those of their peers (71) as well as increased regulatory control of pharmaceutical availability, with the hopes of improving guideline compliance and reducing unnecessary antimicrobial use.

Conclusions. While it is difficult to distill the clinical encounter into discrete factors, this review highlights broad areas that can be integrated into future efforts to promote judicious use of antibiotics. Reinforcement of signs and symptoms of viral respiratory illnesses, as well as supporting clear communication between physicians and patients, may be useful areas of focus.

ACKNOWLEDGMENTS

Rachel McKay is supported by a Canadian Institutes of Health Research Doctoral Award. Michael R. Law received salary support through a Canada Research Chair in Access to Medicines and a Michael Smith Foundation for Health Research Scholar Award.

REFERENCES

1. **World Health Organization.** 2014. Antimicrobial resistance. World Health Organization, Geneva, Switzerland.
2. **Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, Bartlett JG, Edwards J, the Infectious Diseases Society of America.** 2008. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis **46:**155–164. http://dx.doi.org/10.1086/524891.
3. **Hillier S, Roberts Z, Dunstan F, Butler C, Howard A, Palmer S.** 2007. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. J Antimicrob Chemother **60:**92–99. http://dx.doi.org/10.1093/jac/dkm141.
4. **Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, Smith S, Crook DW, Mant D.** 2007. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. BMJ **335:**429–429. http://dx.doi.org/10.1136/bmj.39274.647465.BE.
5. **Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M.** 2014. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis **14:**13. http://dx.doi.org/10.1186/1471-2334-14-13.
6. **Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O.** 2013. Antibiotic resistance–the need for global solutions. Lancet Infect Dis **13:**1057–1098. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.
7. **Calbo E, Alvarez-Rocha L, Gudiol F, Pasquau J.** 2013. A review of the factors influencing antimicrobial prescribing. Enferm Infecc Microbiol Clin **31**(Suppl 4):S12–S15.
8. **Lopez-Vazquez P, Vazquez-Lago JM, Figueiras A.** 2011. Misprescription of antibiotics in primary care: a critical systematic review of its determinants. J Eval Clin Pract **18:**473–484.
9. **Hersh AL, Shapiro DJ, Pavia AT, Shah SS.** 2011. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics **128:**1053–1061. http://dx.doi.org/10.1542/peds.2011-1337.
10. **British Columbia Centre for Disease Control.** 2010. British Columbia annual summary of antibiotic utilization. British Columbia Centre for Disease Control, British Columbia, Canada.
11. **Gonzales R, Steiner JF, Sande MA.** 1997. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA **278:**901–904. http://dx.doi.org/10.1001/jama.278.11.901.
12. **Lee GC, Reveles KR, Attridge RT, Lawson KA, Mansi IA, Lewis JS, Frei CR.** 2014. Outpatient antibiotic prescribing in the United States: 2000 to 2010. BMC Med **12:**96. http://dx.doi.org/10.1186/1741-7015-12-96.
13. **Blondel-Hill E, Fryters S.** 2012. Bugs & drugs: an antimicrobial/infectious diseases reference. Alberta Health Services, Alberta, Canada.
14. **Hersh AL, Jackson MA, Hicks LA, the Committee on Infectious Diseases.** 2013. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics **132:**1146–1154. http://dx.doi.org/10.1542/peds.2013-3260.
15. **Kenealy T, Arroll B.** 2014. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev **6:**CD000247.
16. **Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group.** 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med **6:**e1000097. http://dx.doi.org/10.1371/journal.pmed.1000097.
17. **Ostini R, Hegney D, Jackson C, Williamson M, Mackson JM, Gurman K, Hall W, Tett SE.** 2009. Systematic review of interventions to improve prescribing. Ann Pharmacother **43:**502–513. http://dx.doi.org/10.1345/aph.1L488.
18. **Bai A, Shukla VK, Bak G, Wells G.** 2012. Quality assessment tools project report. Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada.
19. **National Institutes of Health's National Heart, Lung and Blood Institute.** Quality assessment tool for observational cohort and cross-sectional studies. NIH National Heart, Lung, and Blood Institute, Bethesda, MD.
20. **Ahmed MN, Muyot MM, Begum S, Smith P, Little C, Windemuller FJ.** 2010. Antibiotic prescription pattern for viral respiratory illness in emergency room and ambulatory care settings. Clin Pediatr (Phila) **49:**542–547. http://dx.doi.org/10.1177/0009922809357786.
21. **Aspinall SL, Good CB, Metlay JP, Mor MK, Fine MJ.** 2009. Antibiotic prescribing for presumed nonbacterial acute respiratory tract infections. Am J Emerg Med **27:**544–551. http://dx.doi.org/10.1016/j.ajem.2008.04.015.
22. **Coenen S, Michiels B, Renard D, Denekens J, Van Royen P.** 2006. Antibiotic prescribing for acute cough: the effect of perceived patient demand. Br J Gen Pract **56:**183–190.
23. **Fischer T, Fischer S, Kochen MM, Hummers-Pradier E.** 2005. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. BMC Fam Pract **6:**6. http://dx.doi.org/10.1186/1471-2296-6-6.
24. **Gonzales R, Barrett PHJ, Steiner JF.** 1999. The relation between purulent manifestations and antibiotic treatment of upper respiratory tract infec-

tions. J Gen Intern Med 14:151–156. http://dx.doi.org/10.1046/j.1525-1497.1999.00306.x.
25. **Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R.** 2001. Symptoms, signs, and prescribing for acute lower respiratory tract illness. Br J Gen Pract 51:177–181.
26. **Mangione-Smith R, McGlynn EA, Elliott MN, Krogstad P, Brook RH.** 1999. The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. Pediatrics 103:711–718. http://dx.doi.org/10.1542/peds.103.4.711.
27. **Moro ML, Marchi M, Gagliotti C, Di Mario S, Resi D, Progetto Bambini a Antibiotici.** 2009. Why do paediatricians prescribe antibiotics? Results of an Italian regional project. BMC Pediatr 9:69.
28. **Nyquist AC, Gonzales R, Steiner JF, Sande MA.** 1998. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 279:875–877. http://dx.doi.org/10.1001/jama.279.11.875.
29. **Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJM.** 2005. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. J Antimicrob Chemother 56:569–574. http://dx.doi.org/10.1093/jac/dki257.
30. **Brown DW, Taylor R, Rogers A, Weiser R, Kelley M.** 2003. Antibiotic prescriptions associated with outpatient visits for acute upper respiratory tract infections among adult Medicaid recipients in North Carolina. N C Med J 64:148–156.
31. **Roumie CL, Halasa NB, Edwards KM, Zhu Y, Dittus RS, Griffin MR.** 2005. Differences in antibiotic prescribing among physicians, residents, and nonphysician clinicians. Am J Med 118:641–648. http://dx.doi.org/10.1016/j.amjmed.2005.02.013.
32. **Stone S, Gonzales R, Maselli J, Lowenstein SR.** 2000. Antibiotic prescribing for patients with colds, upper respiratory tract infections, and bronchitis: a national study of hospital-based emergency departments. Ann Emerg Med 36:320–327. http://dx.doi.org/10.1067/mem.2000.109341.
33. **Ladd E.** 2005. The use of antibiotics for viral upper respiratory tract infections: an analysis of nurse practitioner and physician prescribing practices in ambulatory care, 1997-2001. J Am Acad Nurse Pract 17:416–424. http://dx.doi.org/10.1111/j.1745-7599.2005.00072.x.
34. **Cadieux G, Tamblyn R, Dauphinee D, Libman M.** 2007. Predictors of inappropriate antibiotic prescribing among primary care physicians. Can Med Assoc J 177:877–883. http://dx.doi.org/10.1503/cmaj.070151.
35. **Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJM.** 2005. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. J Antimicrob Chemother 56:930–936. http://dx.doi.org/10.1093/jac/dki283.
36. **Butler CC, Kelly MJ, Hood K, Schaberg T, Melbye H, Serra-Prat M, Blasi F, Little P, Verheij T, Molstad S, Godycki-Cwirko M, Edwards P, Almirall J, Torres A, Rautakorpi U-M, Nuttall J, Goossens H, Coenen S.** 2011. Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection. Eur Resp J 38:119–125. http://dx.doi.org/10.1183/09031936.00133910.
37. **Cadieux G, Abrahamowicz M, Dauphinee D, Tamblyn R.** 2011. Are physicians with better clinical skills on licensing examinations less likely to prescribe antibiotics for viral respiratory infections in ambulatory care settings? Med Care 49:156–165. http://dx.doi.org/10.1097/MLR.0b013e3182028c1a.
38. **Gaur AH, Hare ME, Shorr RI.** 2005. Provider and practice characteristics associated with antibiotic use in children with presumed viral respiratory tract infections. Pediatrics 115:635–641. http://dx.doi.org/10.1542/peds.2004-0670.
39. **Linder JA, Stafford RS.** 2001. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989-1999. JAMA 286:1181–1186. http://dx.doi.org/10.1001/jama.286.10.1181.
40. **Rutschmann OT, Domino ME.** 2004. Antibiotics for upper respiratory tract infections in ambulatory practice in the United States, 1997-1999: does physician specialty matter? J Am Board Family Med 17:196–200.
41. **Stanton N, Hood K, Kelly MJ, Nuttall J, Gillespie D, Verheij T, Little P, Godycki-Cwirko M, Goossens H, Butler CC.** 2010. Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit? An observational study in 13 European countries. Eur Resp J 35:761–767.
42. **Altiner A, Wilm S, Wegscheider K, Sielk M, Brockmann S, Fuchs A, Abholz H-H, der Schmitten JI.** 2010. Fluoroquinolones to treat uncomplicated acute cough in primary care: predictors for unjustified prescribing of antibiotics. J Antimicrob Chemother 65:1521–1525. http://dx.doi.org/10.1093/jac/dkq151.
43. **Kozyrskyj AL, Dahl ME, Chateau DG, Mazowita GB, Klassen TP, Law BJ.** 2004. Evidence-based prescribing of antibiotics for children: role of socioeconomic status and physician characteristics. Can Med Assoc J 171:139–145. http://dx.doi.org/10.1503/cmaj.1031629.
44. **Coenen S, Francis N, Kelly M, Hood K, Nuttall J, Little P, Verheij TJM, Melbye H, Goossens H, Butler CC, GRACE Project Group** 2013. Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough. PLoS One 8:e76691.
45. **Dosh SA, Hickner JM, Mainous AG, Ebell MH.** 2000. Predictors of antibiotic prescribing for nonspecific upper respiratory infections, acute bronchitis, and acute sinusitis. A UPRNet study. Upper Peninsula Research Network. J Fam Pract 49:407–414.
46. **Smith SS, Kern RC, Chandra RK, Tan BK, Evans CT.** 2013. Variations in antibiotic prescribing of acute rhinosinusitis in United States ambulatory settings. Otolaryngol Head Neck Surg 148:852–859. http://dx.doi.org/10.1177/0194599813479768.
47. **Linder JA, Singer DE.** 2003. Desire for antibiotics and antibiotic prescribing for adults with upper respiratory tract infections. J Gen Intern Med 18:795–801. http://dx.doi.org/10.1046/j.1525-1497.2003.21101.x.
48. **Gelman A, Hill J.** 2007. Data analysis using regression and multilevel/hierarchical models. Cambridge University Press, Cambridge, United Kingdom.
49. **Smith SM, Smucny J, Fahey T.** 2014. Antibiotics for acute bronchitis. JAMA 312:2678–2679. http://dx.doi.org/10.1001/jama.2014.12839.
50. **Snow V, Mottur-Pilson C, Gonzales R, American Academy of Family Physicians, American College of Physicians–American Society of Internal Medicine, Centers for Disease Control, Infectious Diseases Society of America.** 2001. Principles of appropriate antibiotic use for treatment of acute bronchitis in adults. Ann Intern Med 134:518–520. http://dx.doi.org/10.7326/0003-4819-134-6-200103200-00020.
51. **Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, Nelson CE, Rosenfeld RM, Shaikh N, Smith MJ, Williams PV, Weinberg ST.** 2013. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics 132:e262–e280. http://dx.doi.org/10.1542/peds.2013-1071.
52. **Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C.** 2012. Clinical practice guideline for the diagnosis and management of group a streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis 55:e86–e102. http://dx.doi.org/10.1093/cid/cis629.
53. **Bennett JE, Dolin R, Blaser MJ.** 2015. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Saunders, Philadelphia, PA.
54. **Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Musher DM, Niederman MS, Torres A, Whitney CG, Infectious Diseases Society of America, American Thoracic Society.** 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72. http://dx.doi.org/10.1086/511159.
55. **Ferech M.** 2006. European surveillance of antimicrobial consumption (ESAC): outpatient antibiotic use in Europe. J Antimicrob Chemother 58:401–407. http://dx.doi.org/10.1093/jac/dkl188.
56. **Mustafa M, Wood F, Butler CC, Elwyn G.** 2014. Managing expectations of antibiotics for upper respiratory tract infections: a qualitative study. Ann Fam Med 12:29–36.
57. **Cabral C, Horwood J, Hay AD, Lucas PJ.** 2014. How communication affects prescription decisions in consultations for acute illness in children: a systematic review and meta-ethnography. BMC Fam Pract 15:63. http://dx.doi.org/10.1186/1471-2296-15-63.
58. **Lucas PJ, Cabral C, Hay AD, Horwood J.** 2015. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. Scand J Prim Health Care 33:11–20. http://dx.doi.org/10.3109/02813432.2015.1001942.
59. **Dempsey PP, Businger AC, Whaley LE, Gagne JJ, Linder JA.** 2014. Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. BMC Fam Pract 15:194. http://dx.doi.org/10.1186/s12875-014-0194-5.
60. **Teixeira Rodrigues A, Roque F, Falcão A, Figueiras A, Herdeiro MT.**

2012. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. Int J Antimicrob Agents **41:**203–212.
61. **Linder JA, Singer DE, Stafford RS.** 2003. Association between antibiotic prescribing and visit duration in adults with upper respiratory tract infections. Clin Ther **25:**2419–2430. http://dx.doi.org/10.1016/S0149-2918(03)80284-9.
62. **Coco A, Mainous AG.** 2005. Relation of time spent in an encounter with the use of antibiotics in pediatric office visits for viral respiratory infections. Arch Pediatr Adolesc Med **159:**1145–1149. http://dx.doi.org/10.1001/archpedi.159.12.1145.
63. **Tonkin-Crine S, Anthierens S, Francis NA, Brugman C, Fernandez-Vandellos P, Krawczyk J, Llor C, Yardley L, Coenen S, Godycki-Cwirko M, Butler CC, Verheij TJM, Goossens H, Little P, Cals JW, GRACE INTRO Team.** 2014. Exploring patients' views of primary care consultations with contrasting interventions for acute cough: a six-country European qualitative study. NPJ Prim Care Respir Med **24:**14026.
64. **Welschen I, Kuyvenhoven M, Hoes A, Verheij T.** 2004. Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. Fam Pract **21:**234–237. http://dx.doi.org/10.1093/fampra/cmh303.
65. **Reeves BC, Deeks JJ, Higgins JP, Wells GA, Cochrane Non-Randomised Studies Methods Group.** 2011. Including non-randomized studies, chapter 13. *In* Higgins JPT, Green S (ed), Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011). The Cochrane Collaboration, London, United Kingdom.
66. **Drekonja DM, Filice GA, Greer N, Olson A, MacDonald R, Rutks I, Wilt TJ.** 2015. Antimicrobial stewardship in outpatient settings: a systematic review. Infect Control Hosp Epidemiol **36:**142–152. http://dx.doi.org/10.1017/ice.2014.41.
67. **Filippini M, Ortiz LGG, Masiero G.** 2013. Assessing the impact of national antibiotic campaigns in Europe. Eur J Health Econ **14:**587–599. http://dx.doi.org/10.1007/s10198-012-0404-9.
68. **Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M.** 2013. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev **4:**CD003543.
69. **Arnold SR, Straus SE.** 2009. Interventions to improve antibiotic prescribing practices in ambulatory care (review). The Cochrane Collaboration, London, United Kingdom.
70. **Ranji SR, Steinman MA, Shojania KG, Gonzales R.** 2008. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. Med Care **46:**847–862. http://dx.doi.org/10.1097/MLR.0b013e318178eabd.
71. **Dormuth CR, Carney G, Taylor S, Bassett K, Maclure M.** 2012. A randomized trial assessing the impact of a personal printed feedback portrait on statin prescribing in primary care. J Contin Educ Health Prof **32:**153–162. http://dx.doi.org/10.1002/chp.21140.