

Supplementary Online Content

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Oral versus parenteral antibiotic classification.

Formulation^a	Antibiotic classes included^b
Oral	Penicillins, cephalosporins, macrolides, quinolones, lincomycin derivatives, sulfonamides, tetracyclines, urinary anti-infectives (e.g., nitrofurantoin), and linezolid
Parenteral	Aminoglycosides, carbapenems, nafcillin, oxacillin, penicillin G, ticarcillin/clavulanic acid, piperacillin, piperacillin/tazobactam, vancomycin, daptomycin, ceftriaxone, cefotaxime, ceftazidime, ceftizoxime, cefepime, ceftazolin, cefotetan, tigecycline, and colistin

^aData was not available on route of administration. Antibiotics supplied only in topical formulations were excluded. Oral antibiotics were defined as antibiotics with oral formulations, and parenteral antibiotics were defined as those antibiotics which are not made in oral formulations.

^bAntibiotics were coded in terms of their generic components and therapeutic classes using Lexicon Plus®, a proprietary database of Cerner Multum, Inc (Denver, Colorado).¹

eTable 2. Diagnostic categories by tier with corresponding ICD-9CM codes^a

Diagnosis	Corresponding ICD-9CM codes
Tier 1 diagnoses: Antibiotics almost always indicated	
Miscellaneous bacterial infections	010-018, 020-027, 030-033, 036- 041, 070-104, 130-139, 320-323, 383, 475 Various named infections including tuberculosis, zoonotic bacterial diseases, diphtheria, pertussis, rickettsial and venereal diseases, meningitis, mastoiditis, peritonsillar abscess
Pneumonia	481 Pneumococcal pneumonia [<i>Streptococcus pneumoniae</i> pneumonia], 482 Other bacterial pneumonia, 483 Pneumonia due to other specified organism, 484 Pneumonia in infectious diseases classified elsewhere, 485 Bronchopneumonia, organism unspecified, 486 Pneumonia, organism unspecified
Urinary tract infections (UTI)	590.1, 590.2, 590.8, 590.9, 595.0, 595.9, 599.0: Acute pyelonephritis, renal abscess, other pyelonephritis/pyelonephrosis, kidney infection (unspecified), acute cystitis, cystitis (unspecified), UTI (unspecified)
Tier 2 diagnoses: Antibiotics may be indicated	
Acne	706.0, 706.1 Acne, including vulgaris and varioliformis
Gastrointestinal infections	001-009, 787, 789 Intestinal infectious diseases, symptoms involving the abdomen or digestive system
Pharyngitis	462 Acute pharyngitis, 463 Acute tonsillitis, 034 Streptococcal sore throat and scarlet fever
Sinusitis	461 Acute sinusitis, 473 Chronic sinusitis
Skin, cutaneous and mucosal infections	680-686, 035, 110-111, 704.8, 728.0, 611.0, 771.5, 728.86, 380.0-380.1 Includes cellulitis, carbuncle/furuncle, impetigo, lymphadenitis, erysipelas, dermatophytosis, folliculitis, myositis, mastitis, necrotizing fasciitis, infective otitis externa
Suppurative otitis media	382 Suppurative and unspecified otitis media
Tier 3 diagnoses: Antibiotics not indicated	
Asthma, allergy	493 Asthma, 477 Allergic rhinitis, 995.3 Allergy, unspecified
Bronchitis, bronchiolitis	490 Bronchitis, not specified as acute or chronic, 466 Acute bronchitis and bronchiolitis, **Excludes visits in which the 2nd or 3rd diagnosis was chronic bronchitis (491), emphysema (492), or COPD (496).
Influenza	487 Influenza, 488 Influenza due to identified avian influenza virus
Miscellaneous other infections	042, 045-049, 050-059, 060-069, 112-129: Human immunodeficiency virus (HIV) infection, poliomyelitis and other non-arthropod-borne viral diseases and prion disease of central nervous system, viral disease accompanied by exanthema, mycoses, helminthiases, arthropod-borne viral diseases
Non-suppurative otitis media	381: Non-suppurative otitis media and Eustachian tube disorders
Other gastrointestinal conditions	520-579 Other conditions of the digestive system, not already included under gastrointestinal infections
Other skin, cutaneous and mucosal conditions	690-698, 700-709, 870-897, 910-919, 940-949, 360-379, 380-389 (excluding 380.0-380.1, 381, 382, 383), 782, 785.4, 785.6: Skin, cutaneous and mucosal conditions not already categorized as skin, cutaneous and mucosal infections: includes inflammatory and other skin conditions, open wounds, superficial injuries, burns, diseases of the eye/adnexa, ear diseases other than otitis media and mastoiditis, symptoms of skin/integumentary tissues (excluding acne), gangrene, enlargement of lymph nodes
Other genitourinary conditions	580-629, 788.1 (excluding UTI codes above and 611.0): Other genitourinary codes not already categorized as UTI, Other conditions of the genitourinary system, symptoms involving urinary system (including dysuria)
Viral pneumonia	480: Viral pneumonia
Viral upper respiratory infection (URI)	460: Acute nasopharyngitis [common cold], 464 Acute laryngitis and tracheitis, 465 Acute upper respiratory infections of multiple or unspecified sites, 786.2 Cough

Other respiratory conditions	All remaining respiratory conditions (460-519) not coded above and 786.0-786.1, 786.3-786.4: Includes chronic bronchitis and bronchitis with a 2 nd or 3 rd diagnosis of chronic bronchitis, emphysema and COPD; other respiratory conditions; dyspnea; stridor; hemoptysis; abnormal sputum
All other codes not listed elsewhere	All remaining codes not listed elsewhere

^aDiagnostic categories adapted from Shapiro et al.² In assigning each visit a single diagnosis, priority was given to tier 1 diagnoses, then tier 2 diagnoses, then tier 3 diagnoses. If a visit had multiple diagnoses from a single tier, the first-listed diagnosis was assigned.

eTable 3. Clinical practice guideline recommendations for adults and children by diagnosis.

Diagnosis	Population	Summary of antibiotic treatment recommendations	References
Sinusitis	Children aged 1 to 18 years	<p>Prescribe antibiotics to children with acute bacterial sinusitis (diagnosed by strict criteria) with</p> <ul style="list-style-type: none"> • “Severe onset, i.e., fever $\geq 39^{\circ}\text{C}$ and purulent nasal discharge for at least 3 consecutive days” • “Worsening course, i.e., worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement.” <p>Either prescribe antibiotics or offer additional observation for 3 days to children with acute bacterial sinusitis (diagnosed by strict criteria) with</p> <ul style="list-style-type: none"> • “Persistent illness, i.e., nasal discharge or daytime cough or both lasting more than 10 days without improvement” 	Wald et al. American Academy of Pediatrics, AAP ³
	Children and adults	<p>Prescribe antibiotics to adults and children with acute bacterial sinusitis (diagnosed by strict criteria) with</p> <ul style="list-style-type: none"> • Severe onset: “high fever $\geq 39^{\circ}\text{C}$ and purulent nasal discharge or facial pain lasting for at least 3-4 days at beginning of illness” • Worsening course: “new onset of fever, headache, or increase in nasal discharge following a typical viral URI that lasted 5-6 days and were initially improving” • Persistent illness: “lasting ≥ 10 days without any evidence of clinical improvement” 	Chow et al. Infectious Diseases Society of America, IDSA ⁴
	Adults	<p>Either offer watchful waiting (without antibiotics) or prescribe initial antibiotics to adults with uncomplicated acute bacterial rhinosinusitis (diagnosed by strict criteria) with</p> <ul style="list-style-type: none"> • Symptoms or signs of acute rhinosinusitis “persist without evidence of improvement for at least 10 days beyond the onset of upper respiratory symptoms” • “Symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement” 	Rosenfeld et al. American Academy of Otolaryngology—Head and Neck Surgery, AAO-HNS ⁵
Suppurative otitis media	Children aged 6 months through 12 years	<p>Prescribe antibiotics to children with acute otitis media (diagnosed by strict criteria) with</p> <ul style="list-style-type: none"> • Severe signs or symptoms, i.e. fever $\geq 39^{\circ}\text{C}$, otalgia ≥ 48 hours, or severe otalgia • Children < 24 months old with bilateral acute otitis media <p>Either prescribe antibiotics or offer observation with close follow-up to children with acute otitis media who are</p> <ul style="list-style-type: none"> • < 24 months old with non-severe signs or symptoms and unilateral acute otitis media • ≥ 24 months old with non-severe signs or symptoms with either unilateral or bilateral acute otitis media 	Lieberthal et al. AAP ⁶

eTable 3. Clinical practice guideline recommendations for adults and children by diagnosis (cont.).

Diagnosis	Population	Summary of antibiotic treatment recommendations	References
Pharyngitis	Children and adults	Prescribe antibiotics only to patients with proven acute group A streptococcal pharyngitis	Shulman et al. IDSA ⁷
Asthma	Children and adults	Antibiotic therapy is not recommended for acute exacerbations except as needed for comorbid conditions. There is insufficient evidence to recommend macrolides for long-term therapy	National Asthma Education and Prevention Program, ⁸
Bronchitis	Children	Antibiotic therapy is not recommended	Hersh et al. ⁹
	Adults	Routine antibiotic therapy of uncomplicated acute bronchitis is not recommended	Snow et al. American College of Physicians-American Society of Internal Medicine ¹⁰
	Adults	Routine antibiotic therapy of acute bronchitis is not recommended	Irwin et al. American College of Chest Physicians ¹¹
Bronchiolitis	Children 1 to 23 months of age	Antibiotic therapy is not recommended for infants and children with bronchiolitis unless there is a concomitant bacterial infection	Ralston et al. AAP ¹²
Influenza	Children and adults	When treatment is indicated, antiviral treatment should be used	Fiore et al. Advisory Committee on Immunizations Practices ¹³
Non-suppurative otitis media	Children aged 2 months through 12 years	Antibiotic therapy is not recommended for routine management	AAP ¹⁴
Upper respiratory infection (URI)	Children	Antibiotic therapy is not recommended	Dowell et al. ¹⁵ , Hersh et al. AAP ⁹
	Adults	Antibiotic therapy is not recommended	Snow et al, American College of Physicians-American Society of Internal Medicine ¹⁶
Pneumonia	Children older than 3 months	<p>Viral pneumonia</p> <ul style="list-style-type: none"> Antibiotic therapy is not routinely recommended in pre-school aged children with community-acquired pneumonia due to predominance of viral pathogens <p>Non-viral pneumonia</p> <ul style="list-style-type: none"> Antibiotic therapy is recommended in children with mild to moderate community-acquired pneumonia of suspected bacterial origin and children requiring hospitalization 	Bradley et al. AAP ¹⁷
	Adults	Antibiotic therapy is recommended.	Mandell et al. IDSA ¹⁸
Urinary tract infections	Children aged 2 to 24 months	Antibiotic therapy is recommended.	Roberts et al. AAP ¹⁹
	Adult women	Antibiotic therapy is recommended.	Gupta et al. IDSA ²⁰

eTable 4. Weighted mean annual rate of total visits and rate of visits with antibiotics prescribed (95% CI) per 1000 population^a, by diagnosis by US Census region and age, NAMCS/NHAMCS — United States, 2010–2011.

Age group, years	Northeast ^b		Midwest ^c		South ^d		West ^e		p-value ^f (for rate of total visits)	p-value ^g (for rate of visits with antibiotic prescriptions)
	Weighted mean annual rate of total visits per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of antibiotics prescribed per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of total visits per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of antibiotics prescribed per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of total visits per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of antibiotics prescribed per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of total visits per 1000 population (95% CI), 2010–2011	Weighted mean annual rate of antibiotics prescribed per 1000 population (95% CI), 2010–2011		
Suppurative otitis media										
0–19	215 (136–295)	169 (105–233)	160 (112–207)	138 (96–179)	205 (160–250)	161 (122–200)	169 (119–220)	148 (101–195)	0.43	0.82
20–64	19 (8–29)	*** ^h	13 (8–18)	10 (5–14)	10 (6–14)	6 (4–9)	12 (8–17)	8 (5–11)	0.38	0.09
≥65	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	NA ⁱ	NA ⁱ
Sinusitis										
0–19	87 (43–131)	67 (28–106)	62 (34–91)	59 (32–86)	84 (55–113)	70 (45–94)	70 (43–97)	60 (37–84)	0.69	0.93
20–64	79 (52–106)	51 (28–74)	91 (62–119)	69 (46–92)	92 (68–117)	66 (48–85)	41 (28–53)	27 (17–36)	<.001	<.001
≥65	76 (45–107)	*** ^h	72 (47–98)	44 (21–66)	101 (55–147)	53 (28–79)	65 (35–94)	37 (16–59)	0.64	NA ⁱ
Pharyngitis										
0–19	229 (133–325)	111 (56–165)	131 (105–157)	79 (56–101)	188 (143–232)	112 (86–137)	103 (68–137)	56 (39–73)	0.01	0.001
20–64	50 (31–69)	35 (18–52)	43 (32–55)	33 (24–42)	39 (26–53)	30 (19–41)	29 (19–39)	18 (9–27)	0.15	0.13
≥65	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	*** ^h	NA ⁱ
Asthma, allergy; bronchitis, bronchiolitis; influenza; non-suppurative otitis media; viral URI; and viral pneumonia										
0–19	527 (371–682)	94 (34–154)	358 (274–443)	63 (42–83)	428 (317–539)	112 (76–149)	416 (329–503)	75 (46–104)	0.29	0.15
20–64	184 (135–233)	52 (30–74)	146 (106–186)	53 (38–68)	141 (99–184)	56 (41–72)	149 (106–192)	43 (30–56)	0.57	0.63
≥65	206 (114–299)	*** ^h	193 (134–252)	67 (33–101)	163 (104–223)	55 (36–73)	283 (166–400)	*** ^h	0.34	NA ⁱ

eTable 4. Weighted mean annual rate of total visits and rate of visits with antibiotics prescribed (95% CI) per 1000 population^a, by diagnosis by US Census region and age, NAMCS/NHAMCS — United States, 2010–2011 (cont.)

All remaining conditions, excluding acute respiratory conditions, UTI and miscellaneous bacterial infections^j										
0–19	2887 (2294- 3479)	207 (138- 275)	2016 (1697- 2334)	171 (133- 210)	2253 (1771- 2735)	207 (168- 247)	2081 (1685- 2476)	137 (100- 174)	0.08	0.06
20–64	3623 (3215- 4032)	216 (173- 259)	3095 (2479- 3710)	232 (173- 291)	3182 (2627- 3737)	247 (198- 296)	2966 (2505- 3428)	180 (140- 220)	0.17	0.17
≥65	7128 (5984- 8272)	457 (299- 616)	6400 (5196- 7604)	383 (277- 488)	6554 (5379- 7729)	362 (272- 452)	7442 (6416- 8468)	436 (338- 534)	0.53	0.62

^a Population denominators are based on the July 1, 2010 and July 1, 2011, set of estimates of the civilian, noninstitutional population of the United States, as developed by the Population Division, U.S. Census Bureau.^{21,22} Figures are based on two-year averages.

^b Northeast region includes Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania.

^c Midwest region includes Ohio, Michigan, Indiana, Illinois, Wisconsin, Missouri, Iowa, Minnesota, Kansas, Nebraska, South Dakota, and North Dakota.

^d South region includes Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Florida, Georgia, Tennessee, Kentucky, Alabama, Mississippi, Louisiana, Arkansas, Oklahoma, and Texas.

^e West region includes Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Idaho, Washington, Oregon, Nevada, California, Alaska, and Hawaii.

^f p-values are for chi² test for heterogeneity for differences among regions in weighted annual rates of total visits

^g p-values are for chi² test for heterogeneity for differences among regions in weighted annual rates of visits with antibiotic prescriptions.

^{h****} Figure does not meet standard of reliability or precision.

ⁱ Not applicable (NA)

^j All remaining conditions except acute respiratory conditions (suppurative and non-suppurative otitis media; sinusitis; pharyngitis; pneumonia; bronchitis, bronchiolitis; upper respiratory infection; influenza, and asthma/allergy), urinary tract infections (UTI) and miscellaneous bacterial infections.

eTable 5. Sensitivity analysis with weighted mean annual antibiotic prescribing rates in 2010–2011 NAMCS/NHAMCS and estimated appropriate annual antibiotic prescribing rates per 1000 population using lowest regional rates for all diagnoses targeted for reductions and no changes targeted for pneumonia, UTI, and miscellaneous bacterial infections (e.g. pertussis and syphilis) by age group and diagnosis.

Diagnosis	2010–2011 weighted mean annual rate of antibiotic prescriptions per 1000 population (95% CI)	Estimated appropriate annual rate of antibiotic prescriptions per 1000 population ^a	Potential percent reduction in annual antibiotic prescription rates
0–19 years			
All acute respiratory conditions^b	421 (369–473)	337^c	-20%
Sinusitis	65 (51–79)	59	-9%
Suppurative otitis media	154 (131–177)	138	-10%
Pharyngitis	91 (76–105)	56	-38%
Asthma, allergy; Bronchitis, bronchiolitis ^e ; influenza; non-suppurative otitis media; URI; and viral pneumonia	90 (71–108)	63	-30%
Pneumonia	22 (16–27)	22	0%
Other conditions^d	225 (197–252)	180^f	-20%
UTI	23 (17–28)	23	0%
Miscellaneous bacterial infections	20 (13–26)	20	0%
Remaining non-acute respiratory conditions ^g	182 (160–205)	137	-25%
Total^h	646 (571–721)	517	-20%
20–64 years			
All acute respiratory conditions^b	150 (129–170)	99^c	-34%
Sinusitis	55 (45–64)	27	-51%
Suppurative otitis media	9 (7–11)	6	-33%
Pharyngitis	29 (23–35)	18	-38%
Asthma, allergy; Bronchitis, bronchiolitis ^e ; influenza; non-suppurative otitis media; URI; and viral pneumonia	52 (43–60)	43	-17%
Pneumonia	5 (4–7)	5	0%
Other conditions^d	269 (239–298)	227^f	-16%
UTI	35 (30–41)	35	0%
Miscellaneous bacterial infections	11 (9–13)	11	0%
Remaining non-acute respiratory conditions ^g	222 (197–248)	180	-19%
Total^h	418 (372–464)	326	-22%

eTable 5. Sensitivity analysis with weighted mean annual antibiotic prescribing rates in 2010–2011 NAMCS/NHAMCS and estimated appropriate annual antibiotic prescribing rates per 1000 population using lowest regional rates for all diagnoses targeted for reductions and no changes targeted for pneumonia, UTI, and miscellaneous bacterial infections (e.g. pertussis and syphilis) by age group and diagnosis (cont.).

≥65 years			
All acute respiratory conditions^b	136 (111–162)	118^c	-13%
Sinusitis	44 (32–57)	37	-16%
Asthma, allergy; Bronchitis, bronchiolitis ^e ; influenza; non-suppurative otitis media; URI; and viral pneumonia	66 (48–84)	55	-17%
Pneumonia	12 (7–17)	12	0%
Other conditions^d	480 (418–543)	441^f	-8%
UTI	64 (51–77)	64	0%
Remaining non-acute respiratory conditions ^g	401 (346–456)	362	-10%
Total^h	617 (544–689)	559	-9%
All Ages			
All acute respiratory conditions^b	221 (198–245)	166	-25%
Other conditions^d	284 (256–313)	242	-15%
Total^h	506 (458–554)	408	-19%

^aTargets based on low-prescribing regions for all diagnoses targeted for reduction: sinusitis; suppurative otitis media; streptococcal pharyngitis; asthma, allergy; bronchitis, bronchiolitis; influenza; non-suppurative otitis media; URI; and viral pneumonia. No reductions targeted in antibiotic prescribing for pneumonia, UTI and miscellaneous bacterial infections (e.g. pertussis and syphilis).

^bAll acute respiratory conditions include suppurative and non-suppurative otitis media; sinusitis; pharyngitis; pneumonia; bronchitis, bronchiolitis; URI; influenza, asthma, allergy, and viral pneumonia.

^cDifference between the current antibiotic rate for all acute respiratory conditions and sum of the differences between the 2010–2011 and estimated appropriate antibiotic rate for each acute respiratory condition.

^dOther conditions excluding acute respiratory conditions listed above.

^eBronchitis, bronchiolitis includes visits with bronchitis, not specified as acute or chronic and acute bronchitis and bronchiolitis but excludes visits in which the 2nd or 3rd diagnosis was chronic bronchitis, emphysema, or chronic obstructive pulmonary disease.

^fDifference between the current antibiotic rate for other conditions and sum of the differences between the 2010–2011 and estimated appropriate antibiotic rate for UTI, miscellaneous bacterial infections and remaining other conditions.

^gRemaining other conditions exclude acute respiratory conditions, UTI and miscellaneous bacterial infections.

^hSum of acute respiratory conditions and other conditions.

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