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REVIEW ARTICLE

Effectiveness and Safety of Antibiotic Prophylaxis for Persons Exposed to Cases of Invasive Group A Streptococcal Disease: A Systematic Review

Faizan Khan,[1,2] Zemin Bai,[1,2] Shannon Kelly,[1,2] Becky Skidmore,[3] Catherine Dickson,[4] Alexandra Nunn,[4] Katie Rutledge-Taylor,[4] and George Wells[1,2]

[1]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Canada, [2]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada, [3]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, and [4]Centre for Immunization and Respiratory Infectious Disease, Public Health Agency of Canada, Ottawa, Canada

Among close contacts of patients with invasive group A streptococcal (iGAS) infection, the benefits and harms of chemoprophylaxis are uncertain. We conducted a systematic review of studies that reported on persons who, after being exposed to a case of laboratory-confirmed or probable iGAS, received any antibiotic prophylaxis for the prevention of GAS infection or carriage. Thirty-seven studies including 26 outbreak investigations and 11 case series or reports were included with predominantly descriptive information that suggested that antibiotic prophylaxis may be effective in preventing GAS infection or GAS carriage, with very few serious adverse events. However, current available evidence is scant (with limited information on contacts of iGAS cases) and largely based on studies with weak design and small sample size. Therefore, definitive conclusions on effectiveness of antibiotic prophylaxis cannot be drawn. Well designed prospective studies are required to establish the benefit-harm profile of antibiotic prophylaxis for secondary prevention of GAS disease among close contacts of iGAS cases.

Keywords. group A Streptococcus; antibiotic; prevention.

Group A streptococci (GAS) are Gram-positive bacteria that can cause a wide range of both noninvasive and invasive diseases and can colonize the throat and skin [1–3]. Invasive GAS disease (iGAS) occurs when these bacteria infect normally sterile sites (eg, blood, cerebrospinal fluid, joints, pleural or pericardial fluid) [4], and it can cause life-threatening diseases including necrotizing fasciitis, streptococcal toxic shock syndrome, pneumonia, and meningitis [4]. The incidence of iGAS has been reported to steadily increase from 2.8 cases per 100 000 in 2000 to 8.1 cases per 100 000 in 2019 in Canada, and from 4.0 cases per 100 000 in 2010 to 7.6 cases per 100 000 in 2019 in the United States, with the highest rates observed among infants and persons over 60 years of age [5, 6].

The risk of secondary iGAS infections among close contacts of iGAS cases has been reported in 2 household studies; the incidence of secondary iGAS infections among household contacts was 19-fold (United States study) and 200-fold (Canada study) higher than the rate of sporadic iGAS infections in the respective United States and Canadian surveillance catchment populations [7, 8]. Whereas iGAS outbreaks were previously most commonly reported in healthcare or long-term care settings, they have become more commonly reported in the community [9] and now seem to disproportionately affect vulnerable populations such as persons experiencing homelessness (PEH) [10, 11], persons who use or inject drugs [11–14], people living in overcrowded settings [14, 15], and mother-neonate pairs [15].

Many public health authorities in the world offer recommendations for public health management of iGAS; jurisdictions formulate their recommendations based on available evidence, resources available for contact management, and local public health context. The United States (2002) [16], Australia (2017) [17], Ireland (2006 and 2013) [18], and France (2005) [19] recommend that only close contacts with particular risk factors be considered for chemoprophylaxis, such as peripartum persons, neonates, older age groups, and those with comorbidities (ie, current or recent varicella, certain chronic diseases) or other risk factors. In 2006, the Public Health Agency of Canada (PHAC) published guidelines for the prevention and control of iGAS disease, developed through an expert consensus process [9]. Contact management recommendations, including recommendations regarding the use of chemoprophylaxis, were acknowledged to be based on expert opinion and very limited evidence. Specifically, the guidelines

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Correspondence: George A. Wells, PhD, Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Room H1281, 40 Ruskin Street, Ottawa, Ontario, Canada, K1Y 4W7 (gawells@ottawaheart.ca).

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cite the 2 aforementioned population-based studies from the late 1990s and early 2000s [7, 8] that showed an increased risk of iGAS among household contacts of cases relative to the rate of sporadic iGAS in the general population. The guidelines recommend that decisions about use of chemoprophylaxis must take into account individual and population risks and benefits, and they conclude that chemoprophylaxis can be offered to close contacts of confirmed severe cases of iGAS (as defined in the guideline) [9]. Chemoprophylaxis regimens are provided in the guidelines and are generally extrapolated from the treatment guidelines for acute GAS pharyngitis and from clinical trials for the eradication of pharyngeal GAS colonization. In 2019, in response to outbreaks in populations where the use of multidose postexposure prophylaxis regimens proved challenging, the Canadian province of Quebec introduced a recommendation for a chemoprophylaxis regimen of a single dose of azithromycin for persons experiencing unstable housing or homelessness who are close contacts of severe iGAS cases [20]. Canada's guideline does not currently include this provision.

Antibiotic stewardship and the risk associated with inappropriate use of antibiotics (ie, side effects and development of antimicrobial resistance) are of increasing concern. Moreover, the incidence of iGAS is steadily increasing in some countries. To this end, and recognizing the need for evidence synthesis to support guideline recommendations, we conducted a systematic review to (1) determine the effectiveness and safety of chemoprophylaxis for the prevention of GAS infection and GAS carriage in persons exposed to cases of iGAS disease, (2) investigate how the effectiveness and safety of chemoprophylaxis vary according to exposure to the severity of primary iGAS case, and (3) explore what current studies of effectiveness and safety report as barriers to chemoprophylaxis for the prevention of GAS in persons exposed to cases of iGAS.

METHODS

This systematic review was conducted in accordance with our study protocol that is available on the Open Science Framework (https://osf.io/bqjwx/). Our study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [21].

Search Strategy

An experienced information specialist (B.S.) developed a comprehensive search strategy in collaboration with the review team. The strategy utilized both controlled vocabulary (eg, "Streptococcal Infections", "Antibiotic Prophylaxis", "Anti-Bacterial Agents") and key words (eg, "iGAS", "PEP", "antibiotic"). Before execution, the MEDLINE strategy was independently reviewed by a second information specialist using the PRESS Checklist [22]. Using the multifile option and deduping tool in Ovid, the search was executed in Ovid MEDLINE ALL, Embase Classic + Embase, and the following EBM databases: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and NHS Economic Evaluation Database. Web of Science was also searched. All searches were performed on October 13, 2021. Results were downloaded and deduplicated using EndNote 9.3.3 (Clarivate). No language or date restrictions were applied, but, when possible, animal-only records and opinion pieces were removed from the results. The MEDLINE strategy is presented in the Appendix. We performed a gray literature search of trial registries, ie, ClinicalTrials.gov and WHO's ICTRP Search Portal. Reference lists of key relevant review articles identified through our search were manually scanned to ensure literature saturation.

Study Selection

Two reviewers (F.K. and Z.B.) independently screened titles, abstracts, and full-text publications using Distiller Systematic Review (DSR) software (Evidence Partners Inc., Ottawa, Canada). Disagreements were resolved by discussion or by consultation with a third reviewer (S.K.). Studies were eligible for inclusion if they were of any research design that reported on adults or children who, after being exposed to a person with laboratory-confirmed or probable iGAS (Box), received any antibiotic prophylaxis for the prevention of GAS infection or carriage. We excluded studies in which antibiotic prophylaxis was only prescribed to asymptomatic contacts with a positive GAS test (ie, carriers). Studies were not excluded on the basis of whether they reported the outcomes of interest.

Outcomes

All outcomes were evaluated among contacts (as defined by the individual studies) of iGAS cases. The primary effectiveness outcomes were laboratory-confirmed or probable iGAS disease (see Box for definition). Secondary effectiveness outcomes were any GAS infection, asymptomatic GAS carriage, severe disease in confirmed or probable iGAS (see Box for definition), or any GAS-related death (ie, GAS as a cause of or contributor to death). Safety outcomes were unintended harms, ie, adverse drug reactions, disruption of natural flora, and selection pressure for antibiotic resistance, injection site injury or soft tissue infection (for penicillin injections), allergic reaction, gastrointestinal side effects (such as nausea, vomiting, or diarrhea), and *Clostridium difficile* infection. Exploratory outcomes included (1) enablers and barriers to the provision of contact prophylaxis (including qualitative information) and (2) adherence to antibiotic prophylaxis.

Data Extraction

Using the DSR software [23], one of the 2 reviewers (F.K. and Z.B.) independently performed data extraction, while the other

reviewer verified the data. Disagreements were resolved by discussion. The following information was extracted from each eligible study: first author, year of publication, study design, study period, country/region(s), setting (eg, hospital, household, nursing home), number and type of iGAS contacts (eg, family members, hospital staff), definition of primary case of iGAS (including confirmed versus probable case), name and type (mass versus targeted) of antibiotic prophylaxis, number of contacts offered prophylaxis, and reported outcomes of interest.

Risk of Bias Assessment and Certainty of Evidence

Although specific tools to appraise the risk of bias in outbreak investigations are lacking, we considered several potentially applicable risk of bias tools available from the Joanna Briggs Institute (JBI), PHAC, CLARITY Group at McMaster University, and relevant review articles. We identified the following pertinent risk of bias tools: Critical Appraisal Tool (CAT) for descriptive studies (including outbreak investigations) and for case series or reports [24]; a modification of the JBI checklist for prevalence for outbreak investigations [25]; and the JBI checklist for case series [26]. Likewise, for grading of the evidence, we considered the following: Grading of Recommendations Assessment, Development and Evaluation (GRADE) handbook [27] and recent publications, including the GRADE approach used in developing the World Health Organization guidelines for management of H5N1 influenza virus [28] because of the similar nature of available evidence (ie, only small case series); and CAT for appraising the quality of evidence [24]. However, formal assessment of the risk of bias in included studies or grading of the evidence was not feasible (see Results and Discussion).

Data Synthesis and Analysis

We summarized the key characteristics of included studies, synthesized qualitative information on interventions, and reported outcomes stratified according to the setting. Because of the expected limited and descriptive nature of information available on outcomes among contacts of iGAS cases reported in the included studies, quantitative data synthesis using meta-analytic techniques was not feasible.

RESULTS

The literature search identified 4679 unique records. After screening titles and abstracts, 155 records (supplemented with 6 additional studies identified through scanning references of background articles) were deemed potentially relevant and eligible for full-text screening. After full-text review, 37 studies (25 with information on relevant effectiveness or safety outcomes) were included in the qualitative synthesis (Figure 1).

Characteristics of Included Studies

Among the 37 included studies [29–66] published between the years 1966 and 2020, 26 were reports of outbreak investigations (23 with relevant effectiveness or safety outcomes information) and 11 were case series or reports (2 with relevant effectiveness or safety outcome information) (Tables 1 and 2). Among the 26 studies reporting outbreak investigations [29–55], 14 were conducted in the United States, 5 were conducted in Canada, 3 were conducted in the United Kingdom, 2 were conducted in Australia, 1 was conducted in Spain, and 1 was conducted in New Zealand (Table 1). The setting reported among the outbreak investigations was hospital (6 studies), nursing home (6 studies), military barrack (5 studies), long-term care facility (4 studies), household (4 studies), childcare center (2 studies), homeless service facility (2 studies), and sports team activity (1 study) (Table 1).

Among the 11 case series or reports [56–66], 3 studies reported cases from United States, 3 studies reported cases from France, and 1 study each reported cases from Australia, Canada, and the United Kingdom, whereas 2 studies did not report on the country/region. The setting was reported in 10 studies; household (9 studies) and nursing home (1 study) (Table 2).

Among all included studies, the most frequently prescribed antibiotics were penicillin or azithromycin. The type of prophylaxis administered varied based on the setting. For example, facility-wide mass prophylaxis was generally offered at nursing homes, long-term care centers, and military barracks, whereas targeted prophylaxis (eg, to family members) was generally offered in households and hospitals. Among the 26 studies with information available on relevant effectiveness or safety outcomes, 19 studies reported on antibiotic prophylaxis for any GAS infection of which 7 studies reported on iGAS (including 4 studies reporting on severe iGAS and 2 studies reporting on laboratory-confirmed iGAS), 1 study reported on GAS-related death, 2 studies reported on asymptomatic GAS carriage, and 3 studies reported information on adverse drug reactions (Tables 1 and 2). The case definition of laboratory-confirmed, probable, or severe iGAS infection used in all included studies was comparable to that outlined in Box.

Risk of Bias Assessment and Certainty of Evidence

Due to the design of included studies and limited information on contacts of iGAS, it was not feasible to formally conduct a risk of bias assessment or evidence grading (see Discussion).

Effectiveness of Antibiotic Prophylaxis

Table 3 summarizes qualitative findings from the 25 studies reporting on antibiotic prophylaxis for GAS infection or GAS carriage, according to the setting. It is notable that there was only 1 study that quantified the effectiveness of antibiotic prophylaxis in the prevention of iGAS infection or carriage among

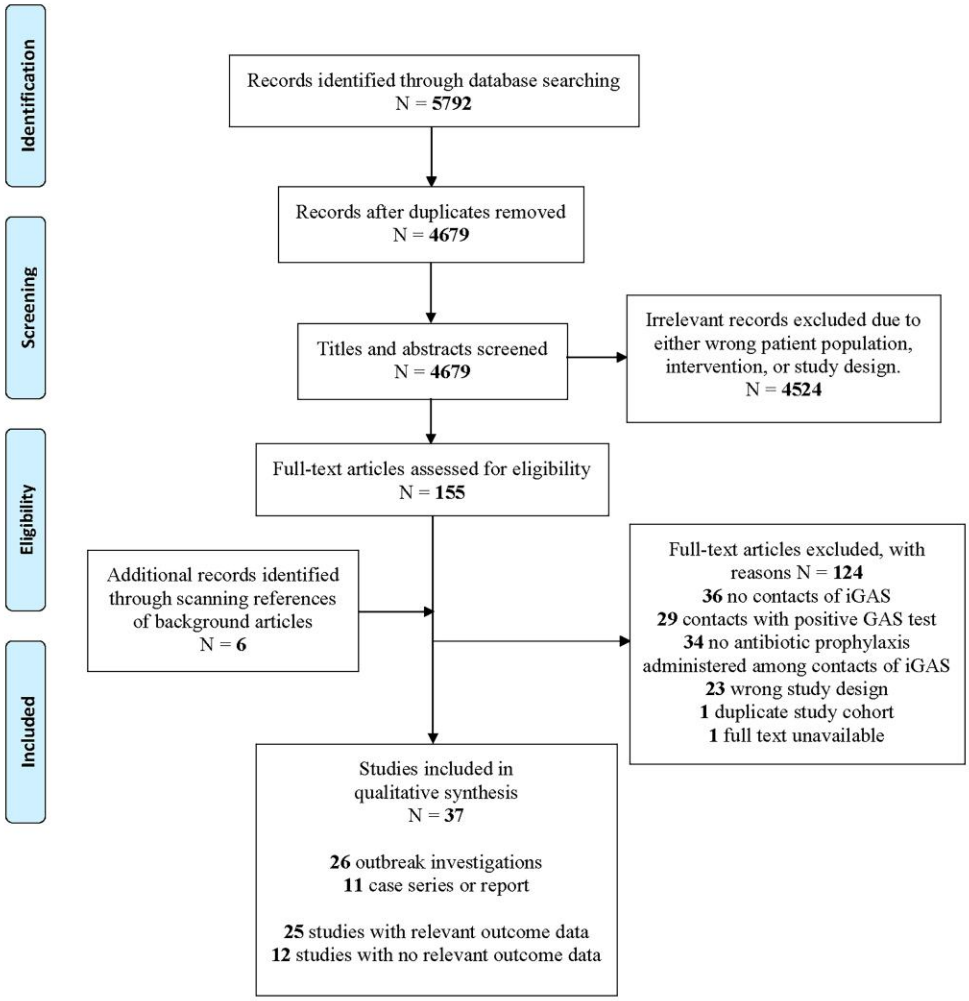

Figure 1. Flow diagram of study identification and selection. iGAS, invasive group A streptococcal.

PEH who were contacts of iGAS cases. In this outbreak investigation of emm26.3 iGAS infection conducted by Mosites et al [46] between July 2016 and April 2017 at 6 homeless service facilities in Anchorage, Alaska, 391 PEH were prescribed a single-dose 1 gram of azithromycin. In the 6 weeks before antibiotic prophylaxis, the incidence of emm26.3 iGAS infection was 1.5 cases per 1000 PEH per week, whereas in the 6 weeks after antibiotic prophylaxis, the incidence was 0.2 cases per 1000 PEH per week (incidence rate ratio, 0.1; $P = .01$). The prevalence of GAS colonization decreased from 9% (27 of 277) among participants in the baseline survey to 6% (19 of 287) among participants in the follow-up survey administered 4 weeks after provision of azithromycin ($P = .05$ for change from baseline) [46].

Qualitative information from 4 outbreak investigations [30, 38, 39, 43] reporting on severe iGAS (2 studies of which reported on GAS pneumonia) generally indicated that antibiotic prophylaxis might be effective in preventing severe disease in laboratory-confirmed or probable iGAS. For example, in an investigation of iGAS outbreak in a rural community of Native Americans in Arizona, United States, Harris et al [43] reported no additional cases at least 3 months after azithromycin prophylaxis among 58 household contacts who spent more than 24 hours with a case during the 7 days before the onset of illness. Likewise, Manning et al [39] reported no additional iGAS cases 10 months after antimicrobial prophylaxis with either penicillin and rifampin or azithromycin was recommended for 33 teammates and 5 coaches of a New York City high school varsity football team who had been exposed to 1 laboratory-confirmed and 1 probable case of iGAS.

Safety of Antibiotic Prophylaxis

Information on safety outcomes was available from 3 studies [34, 51, 54, 55], albeit limited and descriptive in nature. For example, based on findings from self-reported surveys conducted as part of an investigation of an iGAS outbreak at a Canadian Armed Forces military training facility, the majority of

Table 1. Characteristics of 26 Included Outbreak Investigations Included in Systematic Review

First Author, Year of Publication	Outbreak Period; Investigation Period	Country; Region(s)	Setting	Primary iGAS Cases No.	Type of Close Contacts	Close Contacts No.	Type of Prophylaxis and Number of Contacts Offered Prophylaxis	Name of Prophylaxis	Effectivenss or Safety Outcomes
Dillon, 1966 [29]	February to December 1964; April to December 1964	USA; Northern Alabama	Hospital	1 lab-confirmed; 1 probable	Infants in the nursery; hospital personnel; and family members	—	Mass prophylaxis to all infants with negative cultures	Penicillin	Any GAS infection
Basiliere, 1968 [30]	July 1964 to February 1966; July 1964 to February 1966	USA; San Diego	Military barrack	95 probable	Recruits in military training facilities	—	Mass prophylaxis to all recruits not known to be allergic to penicillin	Benzathine Penicillin	Severe iGAS disease (GAS pneumonia)
Nelson, 1976 [31]	November 1974 to February 1975; January 1974 to February 1976	USA; Dallas	Hospital	2 lab-confirmed	Newborns in the nursery	—	Targeted prophylaxis to all infants in the nursery on 2 separate dates, and all newborn infants during the subsequent 2 weeks, respectively.	Benzathine Penicillin G	Any GAS infection
Nicolle, 1986 [32]	January 17–23, 1983; —[a]	Canada; Calgary	Hospital	3 lab-confirmed	Patients in the ICU and hospital staff	—	Mass prophylaxis to all patients on the unit	Penicillin	Any GAS infection
Hansen, 1990 [33]	Winter, 1989–90; Winter, 1989–90	USA; Illinois, Kansas, North Carolina, and Texas	Nursing home	18 mixed	Residents and staff in the nursing home	591	Mass prophylaxis to all residents and staff in 3 of 4 nursing homes; but discontinuation in one due to negative culture results	Not reported	Any GAS infection
Auerbach, 1992 [34]	December 1989 to January 1990; August 1989 to February 1990	USA; North Carolina	Nursing home	12 mixed	Residents and staff in the nursing home	112	Mass prophylaxis to all nursing home residents and staff	Penicillin	Any GAS infection; Adverse drug reactions
Gunzenhauser, 1995 [35]	July 1989 in Fort Leonard Wood; Winter 1990–1991 in other 3 army training installations; July 1989 to June 1991	USA	Military barrack	3 mixed	Military trainee populations in 4 US army training installations	—	Mass prophylaxis to all persons in a defined population, involving all trainees at an installation. Targeted prophylaxis; newly arriving trainees	Benzathine Penicillin G	Any GAS infection
Barry, 1997 [36]	February 2–14, 1997; February 17–19, 1997	USA; Boston	Childcare center	2 lab-confirmed	Classmates and workers in childcare center; household contacts	137	Targeted prophylaxis to all carriers of GAS and all classmates of 2 cases regardless of culture results	Not reported	Any GAS infection
Smith, 2003 [37]	Outbreak 1: October 2000 to May 2001; Outbreak 2: November 2001 October 2000 to February 2003	Canada; Ontario	Long-term care facility; nursing home	6 lab-confirmed	Residents and staff in nursing home (Outbreak 1); residents and staff in a long-term care facility (Outbreak 2)	Outbreak 1: 521 Outbreak 2: 274	Mass prophylaxis to residents and staff in nursing home/long-term care facility	Outbreak 1: Cephalexin or penicillin; Outbreak 2: azithromycin	Lab-confirmed iGAS; Any GAS infection

Table 1. Continued

First Author, Year of Publication	Outbreak Period; Investigation Period	Country; Region(s)	Setting	Primary iGAS Cases No.	Type of Close Contacts	Close Contacts No.	Type of Prophylaxis and Number of Contacts Offered Prophylaxis	Name of Prophylaxis	Effectivenss or Safety Outcomes
Crum, 2005 [38]	November 1 to December 20, 2002; December 2002	USA; San Diego	Military barrack	7 lab-confirmed; 27 probable; 22 GAS pneumonia coinfected with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*)	Military recruits and staff personnel	4500	Mass prophylaxis to all 4500 military recruits and staff at the facility	Benzathine Penicillin or azithromycin	GAS pneumonia; Asymptomatic GAS carriage; Any GAS infection
Manning, 2005 [39]	October 20, 2003; October 24, 2003	USA; New York	Sports team/ activities (high school football team)	1 lab-confirmed; 1 probable	Teammates and coaches	38	Mass prophylaxis to all teammates and coaches	Penicillin, and rifampin; or azithromycin	Severe disease in lab-confirmed or probable iGAS
Chandler, 2006 [40]	January 27, 2003; January 29 to February 2003	USA; Portland	Hospital	1 lab-confirmed	Healthcare workers exposed to the index patient	103	Targeted prophylaxis to 6 healthcare workers	Not reported	Any GAS infection
Ortega-Mendi, 2008 [41]	March to April 2006; March to April 2006	Spain; Cantabria	Household; childcare center	3 lab-confirmed	Children and caregivers in the daycare, and people living in the same houses with them	258	Mass prophylaxis offered to all children, caregivers, and direct partners	Azithromycin	None reported
Dooling, 2013 [42]	Outbreak 1 (June to August 2009); Outbreak 2 (December 2010 to October 2011); Outbreak 3 (March to May 2012); Investigation 1 (January 2010); Investigation 2 (November 2011); Investigation 3 (June 2012)	USA; Atlanta	Nursing home	12 lab-confirmed	Residents and staff of nursing facility	— 240 residents and 205 staff	Mass prophylaxis facility wide	Benzathine Penicillin G and rifampin; or cephalexin	Any GAS infection
Harris, 2015 [43]	August 2012 to March 2013; Winter 2012–2013	USA; Arizona	Household	11 mixed	Household contacts of case patients with Native American ancestry	58	Targeted prophylaxis offered to household contacts who spent >24 hours with a case-patient during the 7 days preceding the onset of illness	Azithromycin	Severe disease in lab-confirmed or probable iGAS
Chalker, 2016 [44]	March to April 2013; 2013	UK; Oxfordshire	Long-term care facility	2 lab-confirmed	Residents and staff of long-term facility	—	Mass prophylaxis	Not reported	Any GAS infection

Table 1. Continued

First Author, Year of Publication	Outbreak Period; Investigation Period	Country; Region(s)	Setting	Primary iGAS Cases No.	Type of Close Contacts	Close Contacts No.	Type of Prophylaxis and Number of Contacts Offered Prophylaxis	Name of Prophylaxis	Effectivenss or Safety Outcomes
Gossain, 2016 [45]	May 2014 to March 2015; May 2014 to March 2015	UK	Long-term care facility	5 mixed	Residents and staff of long-term care facility	—	Mass prophylaxis to all staff and residents. Targeted prophylaxis to all residents in one unit	Not reported	Any GAS infection
Mosites, 2017 [46]	July 2016 to April 2017; July 2016 to April 2017	USA; Anchorage, Alaska	Homeless service facility	90 mixed	Homeless shelter staff, volunteers, residents	391	Mass prophylaxis in sites frequented by people experiencing homelessness living in Anchorage.	Azithromycin	Lab-confirmed iGAS; Asymptomatic GAS carriage
Hammond-Collins, 2018 [47]	December 2016 to May 2017; June to September 2017	Canada; St-Jean-sur-Richelieu, Quebec	Military barrack	6 mixed	Trainees and instructors in Military platoons	—	Mass prophylaxis to the entire platoon	Cefadroxil	Any GAS infection
Dickson, 2018 [48]	April 2016 to February 2018; May 2016 to February 2018	Canada; Ontario	Household; rural-urban community; marginalized populations (eg, drug users in homeless shelter)	156 lab-confirmed cases in 147 individuals	Household contacts of cases ≥4 hours/day or 20 hours/week, nonhousehold contacts sharing bed or having sexual relations with cases; people with direct contacts of mucous membrane or open skin lesion of cases	—	Targeted prophylaxis to individuals who had had close contact with people who use drugs and/or underhoused cases	Azithromycin	None reported
Nanduri, 2019 [49]	May 2014 to August 2016 Cluster 1 (May to July 2014); Cluster 2 (February to April 2015); Cluster 3 (June 2015 to February 2016); May 2014 to August 2016	USA; Illinois	Nursing home	19 lab-confirmed 12 lab-confirmed in Clusters 1 and 2; 7 lab-confirmed in Cluster 3 and afterwards	Residents and staff of nursing facility	—	Mass prophylaxis to facility-wide residents and staff (at the end of Cluster 2)	Benzathine penicillin G and rifampin; or cephalexin	Any GAS infection
Oliver, 2019[a] [50]	—; July 2016 to June 2018	Australia	Hospital	181 lab-confirmed	Family or other household contacts	—	Targeted prophylaxis to family and household contacts of 85 patients	Not reported	None reported
Leonard, 2019[b] [51]	—; January 2010 to December 2016	UK; London and South-East England	Hospital; household	155 mixed (134 mothers, 21 neonates)	Family (mothers and neonates)	16 asymptomatic mothers and 122 asymptomatic neonates requiring prophylaxis	Targeted prophylaxis to asymptomatic mothers and neonates	Penicillin, azithromycin, coamoxiclav for neonates	Adverse drug reactions

Table 1. Continued

First Author, Year of Publication	Outbreak Period; Investigation Period	Country; Region(s)	Setting	Primary iGAS Cases No.	Type of Close Contacts	Close Contacts No.	Type of Prophylaxis and Number of Contacts Offered Prophylaxis	Name of Prophylaxis	Effectivenss or Safety Outcomes
Vasant, 2019 [52]	September to November 2016; —	Australia; Queensland	Nursing home	3 lab-confirmed	Residents and staff of a residential aged care facility	—	Mass prophylaxis to all residents and staff	Phenoxymethylpenicillin, Cephalexin, or azithromycin	Lab-confirmed iGAS
Worthing, 2020 [53]	Phase 1: Late May to Early June 2014; Phase 2: Late July to mid of August 2014 Early July 2014 (Phase 1); Late July to Mid of November 2014 (Phase 2)	New Zealand; South Island	Long-term care facility	5 lab-confirmed 7 mixed	Residents and staff members in eldercare facility, and hospital staff members	All 75 residents and 30 hospital staff members	Targeted prophylaxis to all staff members, any resident who was unwell or had been in contact with a case-patient, and any resident from whom GAS was isolated.	Penicillin or amoxicillin	Any GAS-related death
Strauss, 2020 [54, 55]	Outbreak 2: February 11 to March 11, 2018; Outbreak 3: November 18 to December 9, 2018 Outbreak 2: March 7 to May 28, 2018; Outbreak 3: December 5 to 7, 2018	Canada; St-Jean-sur-Richelieu Quebec	Military barrack	6 mixed; 5 in Outbreak 2; 1 in Outbreak 3	Recruits and instructors at a military training facility	—	Mass prophylaxis to 11 293 recruits and 200 instructors	Penicillin or azithromycin	GAS pharyngitis; Severe GAS, iGAS; Asymptomatic GAS carriage Adverse drug reactions

Abbreviations: ICU, instensive care unit; iGAS, invasive group A streptococcal; lab, laboratory; UK, United Kindom; USA, United States of America.

[a]Descriptive cohort study.

[b]Cross-sectional retrospective study.

—, not available.

Table 2. Characteristics of 11 Included Case Series or Reports Included in Systematic Review

First Author, Year of Publication	Study Period	Country; Region(s)	Setting	Primary iGAS CasesNo.	Type of Close Contacts	Close Contacts No.	Type of Prophylaxis and Number of Contacts Offered Prophylaxis	Name of Prophylaxis	Outcomes
Schwartz, 1992 [56]	December 1990 to January 1991	USA	Nursing home	4 lab-confirmed	Residents and staff in Alzheimer's Disease Unit of nursing home	—	Targeted prophylaxis to individuals with positive cultures and several other residents of the unit.	Not reported	Any GAS infection
Gamba, 1997 [57]	—	—	Household	2 lab-confirmed	Family members and healthcare workers	—	Targeted prophylaxis to remaining family members not providing throat swab specimens	Penicillin	None reported
Husain, 2001 [58]	January 2001	Canada; Vancouver	Household	2 lab-confirmed	Family members	3	Targeted prophylaxis to parents and grandmother of the 2 cases	Cephalexin	None reported
Roy, 2003 [59]	1-week period in Spring	USA; Cleveland	Household	3 lab-confirmed; 2 probable	Family members and family friends	9	Targeted prophylaxis to 9 close contacts (5 family members, an aunt and uncle, and 2 family friends)	Amoxicillin	Any GAS infection
Dubrous, 2005 [60]	—	France	Household	1 lab-confirmed	Family members	2	Targeted prophylaxis to patient's wife and daughter	Amoxicillin/ clavulanic acid	None reported
Martinaud, 2010 [61]	—	France	Household	3 lab-confirmed	Family members	3	Targeted prophylaxis to 2 adults and 1 child	Not reported	None reported
Caillet-Gossot, 2011 [62]	—	France	Household	1 lab confirmed; 1 probable	Family members	2	Targeted prophylaxis to parents of the 2 cases	Azithromycin	None reported
Middleton, 2014 [63]	August 2011	Australia; remote Northern Territory community	Household	2 lab-confirmed	Family and household contacts	—	Targeted prophylaxis to family and household contacts of 2 cases who were twins.	Azithromycin	None reported
Howard, 2015 [64]	September 2012 to August 2014	UK; North East of England	—	24 probable (GAS infections in puerperium)	Infants of mothers with GAS infection in the puerperium	24	Targeted prophylaxis to infants of mothers with GAS infection in the 28 days after birth.	Not reported	None reported
Karmally, 2015 [65]	February to March 2015	USA; New York	Household	7 mixed	Household contacts	—	Targeted prophylaxis to all close household contacts.	Not reported	None reported
Sethness, 2018 [66]	—	—	Household	3 lab-confirmed	Household contacts	7	Targeted prophylaxis to 4 unsick household members	Amoxicillin	None reported

Abbreviations: iGAS, invasive group A streptococcal; lab, laboratory; UK, United Kindom; USA, United States of America.

—, not available.

individuals reported experiencing adverse events in the first week after administration of mass antibiotic priphylaxis. Serious adverse events requiring hospitalization were reported among 5 of the 2707 individuals who received mass antibiotic prophylaxis between March and May of 2018. These 5 serious adverse events included compartment syndrome (rhabdomyolysis with acute renal injury), anaphylaxis, cellulitis, hematoma at injection site, and excessive vomiting [54, 55]. Among individuals who received penicillin G benzathine, approximately 90% reported at least 1 adverse event, with localized pain at the injection site (lasting for approximately 3 days) being the most commonly reported adverse event [54, 55]. Among those who received azithromycin, approximately 70% reported experiencing at least 1 gastrointestinal symptom including diarrhea,

Table 3. Examples[a] of Qualitative Findings From Studies of Antibiotic Prophylaxis for GAS Infection or Carriage

Setting	Study Design	Number of Studies Reporting Outcome	Examples of Description of Intervention	Examples of Description of Outcome
Household	Outbreak investigations	1 [43]	"Azithromycin prophylaxis was offered to household contacts who spent >24 hours with a case-patient during the 7 days preceding the onset of illness"	"No additional cases were reported at least 3 months after the investigation and intervention."
	Case series or reports	1 [59]	"Nine other individuals in close contact with the index case (the remaining 5 family members, an aunt and uncle, and 2 family friends) were empirically given amoxicillin prophylaxis for 10 days; 1 contact was penicillin-allergic and was given erythromycin."	"Pharyngeal cultures were not obtained from these individuals, and none became clinically ill."
Hospital	Outbreak investigations	4 [29, 31, 32, 40]	"Many HCWs were taking antibiotics at the time of their exposure to the index patient (6 of the 90 questioned)."	"Although no information on the agent or indication was obtained, concurrent antibiotic use may have protected against the acquisition of disease, thereby limiting the extent of transmission."
Nursing home	Outbreak investigations	6 [33, 34, 37, 42, 49, 52]	"Failure of these actions to prevent new cases during cluster 2 prompted the facility to initiate mass antibiotic treatment for all staff and residents with a regimen of either benzathine penicillin G þ+ rifampin or cephalexin"	"Cases ceased briefly after facility-wide chemoprophylaxis of all residents and staff between April 28 and May 2, 2015"
	Case series or reports	1 [56]	"Antimicrobial agents were administered to the individuals for whom cultures were positive and were given prophylactically to several other residents of the unit."	"No further cases of streptococcal disease have been diagnosed."
Long-term care facility	Outbreak investigations	4 [37, 44, 44, 53]	"Mass chemoprophylaxis was initiated at home A the day after a second case was reported and at home B after GAS was confirmed in another resident."	"No further cases occurred after mass chemoprophylaxis and enhanced infection control"
Military barrack	Outbreak investigations	5 [30, 35, 38, 47, 54]	"Two types of penicillin programs were used for outbreak control: mass and tandem prophylaxis. Tandem prophylaxis was administered to trainees within 72 hours of their arrival at an installation."	"Mass and tandem benzathine penicillin G prophylaxis programs were extremely effective in interrupting epidemics and sustaining a disease-free environment"
Homeless service facility	Outbreak investigations	1 [46]	"Because case counts remained high, in February 2017, we carried out a mass antibiotic administration in sites frequented by PEH living in Anchorage. Sites included 2 shelters, 2 soup kitchens, and 2 supportive housing units. We offered a single dose of 1 gram of azithromycin. Participation was voluntary. Staff and volunteers at the homeless service facilities were also offered antibiotics. Consenting participants swallowed the azithromycin with water under the observation of a clinician."	"In March 2017, 4 weeks after the intervention, we recruited 287 participants into the follow-up survey, 95 (33%) of whom had also participated in the baseline survey. Swabs were collected from the OP of all participants from nonintact skin in 63 participants. Nineteen (6%) participants were colonized with GAS, including 4 (1%) colonized with emm26.3 (*P* value for change from baseline = .05)."
Childcare center	Outbreak investigations	1 [36]	"Prophylactic antibiotic therapy was recommended for all carriers of GAS and all classmates of patients 1 and 2 regardless of culture results. The specific antibiotic therapy was prescribed by the patient's physician."	"No GAS case was reported after February 2014."
Sports/team activities	Outbreak investigations	1 [39]	"To prevent additional cases of GAS, antimicrobial prophylaxis with either penicillin and rifampin or azithromycin was recommended for all varsity teammates and coaches."	"However, we received no additional reports of invasive GAS that were epidemiologically linked to this football team in the 10 months after the investigation."

Abbreviations: GAS, group A streptococcal; HCWs, healtcare workers; OP, oropharyngeal; PEH, persons experiencing homelessness.

[a]Examples are shown to underscore the vagueness of the descrption of interventions and outcomes among studies included in our review. We present here the most explicit descriptions available for each study design and setting.

stomach pain, nausea, and vomiting [54, 55]. The other 2 studies reported no adverse events associated with antibiotic prophylaxis [34, 51]. There was only 1 study that reported on antimicrobial susceptibility testing and found emm26.3 iGAS isolates to be susceptible to penicillin, erythromycin, tetracycline, levofloxacin, cefotaxime, and clindamycin [46]. However, the impact of prophylaxis on the proportion of antimicrobial resistance among all carriage isolates was not reported.

Enablers, Barriers, and Adherence to Antibiotic Prophylaxis

Seven studies [38, 40, 42, 44, 46, 47, 50] provided information on factors that enable the provision of contact prophylaxis, 8 studies [38, 39, 42, 44, 48–51] presented information on barriers to the provision of contact prophylaxis, and 4 studies [38, 47, 54, 64] provided information on adherence to antibiotics. Reported enablers to contact prophylaxis included strategies involving mass antibiotic campaigns (eg, facility-wide chemoprophylaxis) [42, 44], using a single-dose oral regimen [46], directly observing versus self-administering doses of antibiotic prophylaxis [38], and clinical recognition of the need to protect the vulnerable (eg, young children and the elderly cohabiting with iGAS patients) [50]. Reported barriers to antibiotic prophylaxis included the lack of consensus on a national recommendation resulting in geographic variation (eg, between

hospitals) in offering contact prophylaxis [50], physician preference to wait for GAS screening test results before making a decision on antibiotic prophylaxis [51], physicians' perception of the potential harms of antibiotic prophylaxis to be greater than the benefits [51], lack of recommendations regarding management of iGAS outbreaks in marginalized populations (eg, PEH or persons who use drugs) [48], and allergy to antibiotics [38]. Nonadherence to (self-adminstered) chemoprophylaxis was noted in 1 study [38].

DISCUSSION

In this comprehensive systematic review of 37 studies including persons receiving chemoprophylaxis after exposure to iGAS patients, we identified only 1 outbreak investigation [46] that evaluated risk reduction in GAS infection after administration of antibiotic prophylaxis. However, the generalizability of the findings from this single study are limited because the population was PEH. All other studies provided only qualitative data on effectiveness or safety of antibiotic prophylaxis. Although the predominantly descriptive information from outbreak investigations and case series or reports included in our study suggests that antibiotic prophylaxis may be effective in preventing GAS infection or GAS carriage, current available evidence is scant (with limited information on contacts of iGAS cases), largely based on studies with weak design and small sample size, and it does not allow for any definitive conclusions on effectiveness of antibiotic prophylaxis. Likewise, no firm conclusions could be drawn regarding the safety of antibiotic prophylaxis because a detailed description of adverse drug reactions was only reported in 1 outbreak investigation [54, 55]. Finally, there was insufficiently detailed information among the included studies to examine the effectiveness and safety of antibiotic prophylaxis according to exposure to the severity of the primary iGAS case. Thus, our systematic review emphasizes the need for well designed prospective studies to assess the benefits and harms of antibiotic prophylaxis among contacts of iGAS cases, including in clinically relevant subgroups (eg, extremes of age, severity of primary iGAS case, or emm type).

Despite the long interval since the publication of guidelines from the United States (2002), France (2005), and Canada (2006), the evidence base to inform guidelines for chemoprophylaxis of close contacts of severe iGAS cases remains poor. However, prevailing attitudes, new knowledge, and practice norms related to antibiotic stewardship have likely changed the nature and focus of dialog among clinical experts and public health practitioners.

Strengths of this systematic review include its rigorous methods and comprehensive search strategy. This system review was limited by a lack of available evidence from well designed studies. All but 1 study provided only qualitative information on outcomes of interest, precluding any meta-analyses to provide summary effect estimates of effectiveness and safety of antibiotic prophylaxis for secondary prevention of GAS infection or carriage. In the 1 study providing details on adverse events, investigators relied on self-reported surveys, which may have missed adverse events in general and/or mainly identified serious manifestatins. Moreover, given the paucity of available data, we could not comment on the length of follow-up period for contacts after exposure to an index patient during which antibiotic prophylaxis is provided and secondary infections are identified, nor could we analyze the effectiveness and safety of antibiotic prophylaxis in clinically relevant subgroups prespecified in our study protocol. Finally, due to the included studies' design and the limited information available on contacts of iGAS, it was not feasible to use existing tools to assess the risk of bias or perform evidence grading of the studies included in our review. After pilot testing (performed independently by F.K. and Z.B.), we determined that existing tools were unsuitable for assessing risk of bias in individual studies and the evidence grading for the following reasons: (1) the GRADE handbook [27] contains no information on quality assessment of outbreak investigations, whereas the PHAC CAT considers outbreak investigations with no group comparisons as descriptive studies with a weak strength of design [24]; (2) quality of evidence from case series or reports is classified as "very low" according to the GRADE handbook [27], whereas the PHAC CAT does not consider case series or reports to contribute to the evidence base; and (3) studies included in our systematic review were predominantly focused on primary iGAS cases, whereas information on iGAS "contacts" receiving antibiotic prophylaxis was very limited. As a result, many of the quality assessment domains in the identified risk of bias tools did not apply to outbreak investigations and case series or reports included in our review. The consequence of not performing a risk of bias assessment or evidence grading is that we are unable to comment on the strengths, limitations, and validity of the findings of individual studies, and the trustworthiness of the evidence underpinning the results and conclusions of our systematic review, which should be interpreted with caution.

CONCLUSIONS

In conclusion, this systematic review on effectiveness and safety of antibiotic prophylaxis in persons exposed to cases of iGAS disease demonstrates that currently available evidence is limited and largely based on studies with weak design and small sample size. There is insufficient information to confidently conclude whether the benefits of antibiotic prophylaxis outweigh its potential harms. Well designed prospective studies are needed (1) to establish the benefit-harm profile of antibiotic prophylaxis for secondary prevention of GAS

disease among close contacts and (2) to identify subgroups (eg, contacts over ≥65 years [67]) that will derive the most benefit. Until we have further evidence to inform practice, expert opinion is required to make recommendations about public health management of iGAS.

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APPENDIX

Literature Search Strategy for MEDLINE

1. iGAS.tw, kf. (293)
2. (invasi* adj3 GAS).tw, kf. (489)
3. (invasi* adj3 (group A adj1 strep*)).tw, kf. (597)
4. Streptococcal Infections/and invasi*.tw, kf. (2237)
5. Streptococcus pyogenes/and invasi*.tw, kf. (1401)
6. or/1-5 [iGAS] (3026)
7. Streptococcal Infections/(33045)
8. exp Streptococcal Infections/and (GAS or Group A).tw, kf. (5882)
9. ((strep or streptococc*) adj3 group A).tw, kf. (9854)
10. Streptococcus pyogenes/(13462)
11. ((strep or streptococc*) adj3 pyogenes).tw, kf. (8134)
12. "s. pyogenes".tw, kf. (2624)
13. ((h? emolytic or betah? emolytic or beta-h? emolytic) adj1 strep*).tw, kf. (6178)
14. (GAS and (strep or streptococc*)).tw, kf. (3098)
15. (GAS adj1 infecti*).tw, kf. (803)
16. (GABHS or BHGAS).tw, kf. (406)
17. or/7-16 [GROUP A STREP] (48214)
18. exp Sepsis/(123032)
19. bacter? emi*.tw, kf. (32966)
20. (sepsis or septic*).tw, kf. (152059)
21. ((bacteri* or toxic or endotoxi* or endo-toxic) adj2 shock).tw, kw. (9275)
22. (toxic adj2 forward failure).tw, kw. (0)
23. STSS.tw, kf. (1155)
24. ((blood or bloodstream* or blood stream*) adj2 (infection* or poisoning)).tw, kf. (16952)
25. (pyaemi* or pyemi* or pyohemi*).tw, kf. (241)
26. exp Arthritis, Infectious/(14462)
27. ((bacterial or infecti* or purulent or pyogenic or suppurative or viral) adj2 arthrit*).tw, kf. (2620)
28. (pyarthros* or pyoarthrit*).tw, kf. (151)
29. Fasciitis, Necrotizing/(2856)
30. fasciitis.tw, kf. (7896)
31. (necros#s or necroti#ing or necrotican*).tw, kf. (312662)
32. (myonecros#s or myo-necros#s or myonecrot* or myo-necrot*).tw, kf. (1641)
33. ((perimeningeal or peri-meningeal) adj3 infect*).tw, kf. (0)
34. flesh-eating.tw, kf. (102)
35. exp Meningitis/(55528)
36. (arachnoidit* or meningit* or meningoencephalit* or meningo-encephalit*).tw, kf. (68914)
37. (meningeal adj3 inflam*).tw, kf. (509)
38. Osteomyelitis/(20438)
39. osteomyelit*.tw, kf. (23410)
40. ((bone or bones) adj2 (infect* or inflam*)).tw, kf. (7280)
41. exp Pericarditis/(11710)
42. (pericardit* or pleuropericardit* or pleuro-pericardit*).tw, kf. (12355)
43. ((pericardial or peri-cardial) adj3 inflam*).tw, kf. (199)
44. (Pick* disease and heart?).tw, kf. (21)
45. exp Peritonitis/(27622)
46. peritonit*.tw, kf. (31880)
47. ((peritone* or intraperitone* or intra-peritone) and (infect* or inflam*)).tw, kf. (49919)
48. ((subphrenic or sub-phrenic or subdiaphragmatic or subdiaphragmatic) adj2 abscess*).tw, kf. (1083)
49. periviscerit*.tw, kf. (37)
50. exp Pneumonia/(103235)

51. (bronchopneumonia* or broncho-pneumonia* or pneumonia* or pneumonit*).tw, kf. (184163)
52. Puerperal Infection/(3143)
53. ((puerper* or postpartum or post-partum or postnatal* or post-natal*) adj3 infection?).tw, kf. (2323)
54. Soft Tissue Infections/(3597)
55. ((soft tissue? or nonskeletal tissue? or non-skeletal tissue?) adj3 infect*).tw, kf. (8461)
56. or/18-55 [GAS-RELATED INFECTIONS] (937033)
57. 17 and 56 [GAS & GAS-RELATED INFECTIONS] (15424)
58. 6 or 57 [iGAS, GAS & GAS-RELATED INFECTIONS] (16998)
59. exp Disease Transmission, Infectious/(68819)
60. (transmi* adj3 (autochthonous* or auto-chthonous* or horizontal* or pathogen*)).tw, kf. (12350)
61. ((contact* or expos* or transmi*) adj3 (disease* or infect*)).tw, kf. (93808)
62. ((contact* or expos* or transmi*) adj3 (GAS or iGAS or GABHS or BHGAS or strep* or group A)).tw, kf. (4522)
63. (contact* adj3 manag*).tw, kf. (791)
64. Carrier State/(21647)
65. carrier state? .tw, kf. (3857)
66. Community-Acquired Infections/(14191)
67. Cross Infection/(56519)
68. ((cross or communit*) adj3 infection*).tw, kf. (10587)
69. (transmi* adj3 communit*).tw, kf. (1304)
70. or/59-69 [DISEASE TRANSMISSION/EXPOSURE] (259610)
71. 58 and 70 [iGAS, GAS & GAS-RELATED INFECTIONS - DISEASE TRANSMISSION/EXPOSURE] (1431)
72. Antibiotic Prophylaxis/(13894)
73. Chemoprevention/(5982)
74. Post-Exposure Prophylaxis/(1248)
75. (prophyla* or chemoprophyla* or chemo-prophyla* or chemoprevent* or chemo-prevent*).tw, kf. (191328)
76. exp Streptococcal Infections/pc [prevention & control] (9906)
77. prevent*.tw, kf. (1442394)
78. protect*.tw, kf. (806486)
79. (transmi* adj3 control*).tw, kf. (6297)
80. PEP.tw, kf. (7861)
81. or/72-80 [Abx prophylaxis] (2250955)
82. 58 and 81 [iGAS, GAS & GAS-RELATED INFECTIONS - Abx PROPHYLAXIS] (2670)
83. Anti-Bacterial Agents/(334336)
84. (antibiotic* or anti-biotic* or Abx).tw, kf. (348513)
85. (antibacterial* or anti-bacterial*).tw, kf. (80079)
86. (antimycobacterial or anti-mycobacterial*).tw, kf. (4795)
87. (antiinfecti* or anti-infecti*).tw, kf. (7945)
88. beta-Lactamase Inhibitors/(2965)
89. (beta-lactam* adj2 (inhibitor? or antagonist?)).tw, kf. (3287)
90. exp Cephalosporins/(42512)
91. cephalospor*.tw, kf. (23049)
92. exp Cephalexin/(3326)
93. (airex or alsporin or anxer or apo cephalex or bandax or biocef or bloflex or cefablan or defacin-m or cefadal or cefadin or cefadina or cefalex or cefalexin or cefalexine or cefaporin or cefaseptin or cefax or cefaxin or ceforal or cefovit or cefrin or celexil or celexin or cepastar or cepexin or cephalen or cephalexcin or cephalexin or cephalexine or cephalexinum or cephalexyl or cephaloxin or cephanmycin or cephia or cepo 1000 or cepol or ceporex or ceporexin or ceporexine or ceprax or cromlex or difagen or durantel or erocetin or falexin or farmalex or felexin or fexin or hi 89 or ialex or ibilex or inphalex or kefacin or kefalex or kefalospes or kefaxin or kefexin or keflet or keflex or kefloridina or keforal or keftab or kemolexin or larixin or lc-lexin or lenocef or lonaxel or lonflex or madlexin or mamalexin or medolexin or montralex or neokef or novolexin or nufex or oracef or oriphex or ospexin or ospexina or paferxin or palitrex or panixine or pactril or pharmexin or pondnacef or pyasan or pyassan or refosporen or respinal or rofex or s 6437 or s6437 or salitex or sanaxin or sefasin or sencephalin or sepexin or septilisin or servicef or servispor or sialexin or sigmacef or sinlex or sinthecillin or sofilex or sorlex or sporahexal or sporicef or sporidex or syncl or syncle or tepaxin or tokiolexin or uphalexin or velexin or voxxim or zeplex or zucoflaxin).tw, kf. (2995)
94. (cefadroxil or adroxef or alxil or ancefa or baxan or bidicef or bidocef or biodroxil or biodroxyl or biofaxil or BL-S 578 or BL-S578 or camex or cedrox or cedroxim or cefadroxil or cefalom or cefamox or cefaroxil or cefat or cefaxil or cefoxil or cefra-om or cefroxil or ceoxil or cephadroxyl or cephos or cepotec or cipadur or crenodyn or curisafe or cyclomycin-k or dacef or doxef or drocef or droxicef or droxil or droxyl or drozid or duracef or duricef or egobiotic or ethicef or evacef or fadrox or gruencef or gruncef or kefloxcin or kefroxil or kelfex or kleotrat or konicef or lappicef or lesporina or likodin or lydroxil or medicefa or mjf 115 67 3 or moxacef or nefalox or nor-decef or odoxil or omnidrox or oracefal oradroxil or qualidrox or rafemox or sedoral or sedral or sofidrox or teroxina or ucefa or ultracef or urocef or vepan or versaatic or vidcef).tw, kf. (688)
95. (cephradine or anspor or bactocef or broadcef or cefadrine or cefirex or cefra or cefradin or cefradur or cefrasol or cefril or cefro or cephadrine or cepharadine or daicefalin or dexef or duphratex or dynacef or eskacef or folzep or forticef or gramcep or kelsef or lenzacef or lisacef or lovecef or maxisporin or megacef or nakacef or nicef or opebrin or qualisef or racep or safdin or sefril or sephros or skf d 39304 or skf d39304 or solphride or sq 11436 or sq11436 or sefril or septacef or taicefran or u-save or v-cefra or vamocef or velocef or velodyne or velosef or veracef or zeefra).tw, kf. (700)
96. (cefotiam or abbott 48999 or alospor or ceradolan or ceradon or cgp 14221 e or cgp 14221e or cse 963 or cse963 or haloapor or halospor or pansporin or sce 963 or sce963 or spizef).tw, kf. (650)
97. (cefpodoxime or r 3746 or r3746 or r 3763 or r3763 or ru 51746 or ru51746 or ru 51763 or ru51763 or u 76253 or u76253).tw, kf. (806)
98. (cefuroxime or alporin or altacef or anaptivan or aprok or aprokam or biocefal or cefoxurime or cefumax or cefuroxim or cefoxima or cefuroxime or ceplus or ceroxime or curocef or curoxim or curoxima or curoxime or eroxmit or froxal or fucerox or furoxime or iceca or intracef or kefazol or kefurim or kefurox or kesint or ketocef or lxinat or maxil or polixima or prokam or sn 107 or sn107 or supacef or ucefaxim or ultraoxim or uroxime or vekfazolin or ximaract or zinacef or zinocef).tw, kf. (4511)
99. (benaxima or biosint or cefotaxim or cefotaxime or cefradil or cephotaxim or claforan or fotexina or "HR-756" or kendrick or klaforan or primafen or "Ru-24756" or taporin).tw, kf. (8966)
100. (benaxona or cefatriaxone or cefaxona or ceftrex or ceftriaxon or ceftriaxona or lendacin or longacef or longaceph or "Ro 13-9904" or "Ro13-9904" or rocefalin or rocefin or rocephin or rocephine or tacex or terbac).tw, kf. (388)
101. (ceftazidime or ceptaz or fortaz or fortum or "GR-20263" or "LY-139381" or tazidime or tazicef).tw, kf. (9193)
102. (anticepim or axepime or bacteripime or bmy 28142 or bmy28142 or cefepim or cefepime or cefepitax or ceficad or cepim or cepimax or cepimex or ceptaz or critipeme or "forzyn beta" or gencef or maxcef or maxfrom or maxinject or maxipime or verapime or zefipime).tw, kf. (3466)
103. (ceftaroline or teflaro or "ppi-0903M" or "t-91825" or "TAK-599").tw, kf. (727)
104. Amikacin/(4133)
105. (akacin or akicin or amic or amicacina or amicasil or amicin or amiglymide or amika-synto or amikacin or amikacina or amikacinas or amikacine or amikacinum or amikacyna or amikafur or amikalem or amikan or "Amikason's" or amikayect or amikin or amiklin or amiktam or amikozit or amiktam or amitracin or amixin or amukin or apalin or arikace or arikayce or "BB-K 8" or "BB-K8" or bbk8 or belmaton or biclin or biklin or biodacyna or biokacin or briclin or briklin or brucelin or chemacin or cinmik or dramigel or fabianol or farcyclin or flexelite or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or mediamik or miacin or migracin or mikan or mikasome or nekacin or onikin or oprad or orlobin or

pediakin or pierami or purutetsushin or riklinak or romikacin or rovericlin or savox or selaxa or selemycin or tybikin or uzix or "vs 107" or vs107 or xylanal or yectamid).tw, kf. (11963)

106. exp Gentamicins/(18987)
107. (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam or duragentamicin or epigent or frieso gent or g-mycin or garabiotic or garalone or garamicin or garamicina or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or genta 20 or genta 50 or genta grin or genta-globens or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame or gentamedical or gentamen or gentamerck or gentamicin* or "g-myticin" or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin or genticina or genticyn or gentiderm or gentimycin or genticin or genticina or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or megental or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocumycin or ocugenta or oftagen or ophtagram or opthagen or opti-genta or optigen or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or terramycin or u-gencin or versigen or yectamicina).tw, kf. (28725)
108. exp Tobramycin/(4277)
109. (ak-tob or aktob or artobin or bethkis or bralifex or bramitob or brulamycin or eyebrex or gernebcin or ikobel or ixotic tobryne or kitabis pak or l 47663 or nebacin or nebcin or nebcina or nebicin or "nebramycin factor 6" or obracin or ocumicin or ocuracin or tenebra or tirselon or tobacin or tobi or tobra gobens or tobracin or tobradistin or tobral or tobralex or tobramaxin or tobramicin* or tobramycin* or tobrasol or tobrex or tobrimin or tobrin or toravin or trazil or tymbrineb or vantobra).tw, kf. (7119)
110. exp Ciprofloxacin/(13425)
111. (acire or alcon cilox or bacquinor or bactiflox or baflox or "bay-09867" or "bay 9867" or "bay o 9867" or "bay o9867" or "bay q 3939" or "bay q3939" or bay09867 or bay9867 or baycip or bernoflox or ciprinol or c-flox or c-floxacin or cetraflux or cetraxal or ciclodin or cidroxal or ciflo or ciflox or cifloxin or cifran or cilab or ciloquin or cilox or ciloxan or ciloxin or cimogal or cinaflox or cipflox or cipide or cipio or ciplox or ciplus or cipocin or ciprecu or ciprinol or cipro or ciprobac or ciprobay or ciprobid or ciprobiotic or ciprocan or ciprocep or ciprocin or ciprocinol or ciprodar or ciproflox or ciprofloxacin or ciprofloxacino or ciprogis or ciproglen or ciprok or ciprolet or ciprolin or ciprolkan or ciprolon or cipromycin or ciropharm or ciproquin or ciproquinol or ciproval or ciprox or ciproxacol or ciproxan or ciproxin or ciproxina or ciproxine or ciproxino or ciproxyl or ciriax or cirok or cirokan or cirox or ciroxin or citeral or citopcin or cobay or corsacin or cosflox or cycin or cyfloxin or cypral or cyprobay or cysfec or droll or eprocin or estecina or fimoflox or flociprin or floroxin or floxager or floxantina or floxbio or globuce or gonning or grifociprox or "h-next" or holdestin or ibixacin or inciflox or infectocipro or iprolan or isotic or jayacin or k-sacin or kenzoflex or kinoves or kipocin or lofucin or loxan or medociprin or mitroken or neofloxin or nivoflox or oftacilox or opthaflox or otiprio or otosec or probiox or procin or profloxin or profloxin or proksi or proquin or proxacin or qilaflox or qinosyn or quilox or quinobiotic or quinolide or quintor or qupron or rigoran or rofcin or sarf or septicide or septocipro or sifloks or siprogut or sophixin ofteno or spitacin or superocin or unex or unicexal or uniflox or uroxin or zipra or zumaflox).tw, kf. (26465)
112. Macrolides/(12301)
113. (macrolide* or macrotetrolide*).tw, kf. (16402)
114. Erythromycin/(13789)
115. (abomacetin or acneryne or acnesol or akne mycin or aknederm ery gel or aknemycin or anamycin or bonac gel or c-solve-2 or cliniderm or deripil or duraerythromycin or e mycin or e-base or e-glades or e-solve 2 or emgel or emu v or emu-ve or emuvin or emycin or eriecu or erimycin-t or eriprodin or eritimix or eritrex or eritrocina or eritromicina or erixyl or ermycin or ermysin or ery maxin or ery-b or ery-diolan or ery-taba or eryacne or eryacnen or eryc or erycen or erycette or erycin or erycinum or eryderm or erydermec or erydermer or eryfluid or erygel or eryhexal or erymax or erymaxin or erymed or erysafe or erystrat or erytab or eryth mycin or erythelan or erythmycin or erythomycin or erythra-derm or erythran or erythro 200 or erythro teva or erythro-statin or erythrogan or erythrogel or erythrogran or erythroguent or erythromid or erythromycin or erythromycine or erythromycinum or erythroteva or erytop or erytrarco or erytrociclin or etinycine or etrolate or etromycinn or ilocap or ilocaps or iloticina or ilotycin or inderm gel or labocne or latotryd or lederpax or mephamycin or oftamolets or pantodrin or pantomycin or pharyngocin or primacine or r-p mycin or robimycin or romycin or roymicin or rp mycin or rythocin or sans-acne or sansax or skid gel e or staticin or stiemycin or stimycine or t-stat or theramycin).tw, kf. (21750)
116. Clarithromycin/(6282)
117. (a-56268 or a56268 or abbotic or aeroxina or bactirel or baxin filmtab or biaxin or biclar or bicrolid or binoklar or bremon or brevil od or c-clarin or carimycin or celex or clacin or clacine or clambiotic or clapharma or clari or claribid or claridar or clarikan or clarimac or claripen or clarith or clarithromycin or clarithromycina or clarithromycine or claritrol or claroma or clormicin or crixan or cylind or cyllind or dicupal or er 36469 or er36469 or gervaken or hecobac or heliclar or helitic or klacid or klacina or klaciped or klaribac or klaricid or klaridex or klaridia or klarin or klerimed or kofron or lagur or lekoklar or macladim or macladin or maclar or macrobiol or makcin or maksin or mavid or monoclarium or monozeclar or naxy or soriclar or "te 031" or te031 or veclam or winclar or zeclar).tw, kf. (9337)
118. Azithromycin/(5243)
119. (azithromycin* or "9 deoxo 9a aza 9a methyl 9a homoerythromycin a" or "9a aza 9 deoxo 9a methyl 9a homoerythromycin a" or aruzilina or atizor or azadose or azasite or azatril or azenil or azibiot or azimin or azithral or azitrocin or azitromax or azitromicin or azitromicina or aziwok or azomyne or aztrin or azydrop or azyter or azythromycin or bazyt or "cp 62933" or cp62993 or "erythromycin a,9 deoxo 9a aza 9a methyl 9a homo" or forcin or goxal or hemomycin or inedol or infectoazit or "isv 401" or isv401 or kromicin or macrozit or mezatrin or misultina or mixoterin or octavax or ordipha or ribotrex or setron or sumamed or sunamed or tobyl or toraseptol or tromix or trozocina or trulimax or ultreon or vinzam or xithrone or "xz 450" or xz450 or zaret or zarom or zentavion or zetamax or zeto or zibramax or zifin or zimericina or zistic or zithrax or zithromax or zithrox or zitinn or zitrim or zitrobifan or zitrocin or zitromax or zitrotek or zmas or zmax).tw, kf. (8983)
120. Clindamycin/(5714)
121. (antirobe or aquadrops or chlolincocin or chlorlincocin or cleocin or cleocine or clinda-ipp or clinda-saar or clindamycin or clindamycine or clindasol or clindomycin or clinimycin or dalacin or cleocin or dalacin or sobelin or sobeline or u 21251 or u 21251f or u21251 or u21251f or zindaclin).tw, kf. (10708)
122. exp Fluoroquinolones/(32876)
123. (chinolone derivative? or fluoroquinolone* or haloquinolone derivative? or quinolone derivative? or quinolones).tw, kf. (23881)
124. (levaquin or levofloxacin or ofloxacin or quixin).tw, kf. (13906)
125. exp Carbapenems/(11660)
126. carbapenem*.tw, kf. (15592)
127. (meropenem or carbonem or carnem or mepenox or merem or merocon or meronem or meropen or merosan or merobat or meromax or meromer or meroza or merotrol or merrem or neopenem or penro or ronem or zwipen).tw, kf. (6885)
128. ((imipenem and cilastatin) or primaxin).tw, kf. (1313)
129. (ertapenem or invanz).tw, kf. (1599)

130. Aztreonam/(1429)
131. (azactam or azenam or aztreonam or "az-threonam" or azthreonam or corus 1020 or corus1020 or dynabiotic or primbactam or "sq-26,776" or "sq 26776" or "sq26,776" or sq26776 or urobactam).tw, kf. (3217)
132. Linezolid/(2966)
133. (anozilad or antizolid or bagrizidine or dilizolen or grampolid or gramposimide or ilenozyd or lineurlub or lineza or linezan or linezolid or linezolide or linox or linxyd or livegramide or lizedia or lorezogram or lynvox or natlinez or pneumolid or pnu 100766 or pnu100766 or synzolid or tanturb or "U 100766" or u100766 or zetalid or ziloxon or ziplemol or zolic or zolinid or zyvox or zyvoxa or zyvoxam or zyvoxid).tw, kf. (6007)
134. exp Penicillins/(80576)
135. penicillin*.tw, kf. (60493)
136. (aminopenil or banzacillin or beacillin or benacil or bencelin or benzacillin or benzanil simple or benzathine benzylpenicillin or benzetacil or benzethacil or benzilfan or bicillin or brevicilina or cepacilina or cillenta or debecillin or debecyclin or debecyclina or debecycline or debecylin or debycillin or diaminocillina or dibencil or dibenciline or dibencillin or durabiotic or duropenin or extencillin or extencilline or isoject permapen or lentocillin or lentopenil or liquocillin or longacilina or longicid or lutecilina or moldamin or neolin or pen di ben or penadur or pencom or pendepon or pendi ben or penduran or penduzan or pendysin or penicillindamin or penidural or penidure or penilente or penretard or permapen or pheliquin or pheliquine or provipen benzatina or tardocillin or tripenadur or wycillina or zalpen).tw, kf. (344)
137. (amdinocillin or amidinopenicillin or coactin or FL-1060 or fl1060 or hexacillin or mecilinamo or mecillinamum or mecillinam or melysin or "ro 10 9070" or "ro 109070" or "ro10 9070" or ro109070 or selexidin).tw, kf. (611)
138. (cyclacillin or aminocyclohexylpenicillin or amino-cyclohexylpenicillin or amino-cyclohexyl-penicillin or aminocyclohexyl-penicillin or calthor or ciclacillin or cyclapen or cyclocillin or ultracillin or Wy-4508 or wycil).tw, kf. (123)
139. (amcill or aldribid or aletmicina or alpha aminobenzylpenicillin or alfasilin or aminobenzylpenicillin or aminobenzyl penicillin or alphacin or ambiopi or amblocin or amblosin or amcill or amcillin or amficot or amfipen or aminobenzylpenicillin or amipenix or amoxi or amoxine or ampcillin or ampecu or ampen or ampenolet or ampensaar or ampexin or ampibex or ampiblan or ampicher or ampicil or ampicilin or ampicilina or ampiciline or ampicillin or ampicilline or ampicin or ampicyn or ampidar or ampifen or ampiflex or ampiger or ampilag or ampilin or ampillin or ampimedin or ampipen or ampitenk or ampivral or ampkid or amplacilina or amplibin or ampliblan or amplital or amplivacil or ampolin or ampycin or amsapen or anglopen or anhypen or "antibiotic KS-R1" or apo-ampi or austrapen or "ay 6108" or ay6108 or bayer 5427 or binotal or biocil or bremcillin or bridopen or britapen or "brl 1341" or brl1341 or "c 10575" or c10575 or camicil or cetampin or cimexillin or citicil or clovillin or copharcilin or dhacillin or diferin or doktacillin or doltirol or domicillin or dotirol or duacillin or dumopen or eracillin or eurocin or excillin or extrapen or fontapen or gramcil or h-ambiotico or helvecillin or herpen or "hi 63" or hi63 or hostes or ibimycin or ikacillin or intramed or iwacillin or jenampin or julphapen or "ks r1" or marticil or mecil-n or neosensitabs or nuvapen or omnipen or pamecil or panacta or penbristol or penbritin or penicillin aminobenzyl or penicline or penodil or penstabil or pentrex or pentrexil or pentrexyl or petercillin or polycillin or picylin or polycillin or polyflex or polypen or pricillin or primapen or princillin or principen or radiocillina or redicillin or rimacillin or roscillin or semicillin or servicillin or shacillin or sintelin or standacillin or standcillin or synpenin or synthocilin or synthocillin or tolimal or totacillin or totapen or trafarbiot or tricil or trifalicina or trihypen or trilaxin or ukapen or usampi or vacillin or viccillin or vidopen or virucil or vitapen).tw, kf. (23863)
140. (amoxicillin or abdimox or acilina or acimox or actimoxi or adbiotin or agerpen or agram or alfamox or alfoxil or almodan or almorsan or alphamox or amagesen solutab or ameclina or amitron or amoflamisan or amo-flamsian or amocillin or amoclen or amodex or amoflux or amohexal or amolin or amonex or amopen or amophar or amosine or amoval or amoxa or amoxal or amoxapen or amoxaren or amoxcil or amoxicilline or amoxil or amoxcillin or amoxcin or amoxibasan or amoxicilina or amoxycillin or amoxicilline or amoxiclin or amoxicot or amoxidal or amoxidin or amoxidrops or amoxihexal or amoxil or amoxillin or amoxina or amoxipen or amoxipenil or amoxisol or amoxivan or amoxivet or amoxy or amoxycillin or amoxycilline or amoxypen or ampliron or apo-amoxi or ardine or aroxin or azillin or bacihexal or bactamox or bactox ge or beamoxy or betamox or bimox or bintamox or biomox or biotamoxal or bioxidona or bioxyllin or bristamox or "BRL-2333" or brl2333 or broadmetz or cabermox or cilamox or clamox or clamoxyl or clearamox or clonamox or coamoxin or damoxicil or dispermox or doxamil or draximox or edamox or efpinex or erphamoxy or eupen or farconcil or fisamox or flemoxin or flemoxine or fluamoxina or foxolin or fullcilina or gexcil or gimalxina or glamox or glassatan or gomcillin or grinsul or grunamox or hamoxillin or hiconcil or hidramox or hipen or hosboral or hydroxyampicillin or ibamox or ibiamox or ikamoxil or imacillin or imaxilin or inamox or infectomycin or intermox or isimoxin or izoltil or julphamox or jutamox or kamoxin or ladoxillin or lamoxy or larocilin or larocin or larotid or macromox or magnimox or maxamox or maxcil or medimox or meixil or metifarma or mopen or morgenxil or moxacin or moxaline or moxarin or moxilen or moxilin or moximar or moxitab or moxtid or moxylin or moxypen or moxyvit or neogram or novabritine or novamox or novamoxin or novenzymin or novoxil or nuvosyl or optium or oramox or ospamox or pamocil or pamoxicillin or pamoxin or panvilon or pasetocin or penamox or penbiosyn or pentyloxycillin or pharmoxyl or piramox or polymox or pondnoxcill or rancil or ranmoxy or ranoxil or ranoxyl or robamox or romoxil or ronemox or saltermox or sawacillin or sawamezin or servamox or shamoxil or sia-mox or sigamopen or sil-a-mox or silamox or simoxil or sintopen or solamocta or solpenox or sumox or superpeni or teramoxyl or tolodina or tormoxin or triafamox or triamoxil or trifamox or trimox or uro clamoxyl or uroclamoxyl or utimox or vastamox or velamox or vistrep or widecillin or winpen or wymox or xiltrop or zamocillin or zamox or zamoxil or zerrsox or zimox).tw, kf. (18073)
141. (methicillin or azapen or belfacillin or "brl 1241" or brl1241 or celbenin or celpilline or cinopenil or dimethoxyphenecillin or dimethoxyphenylpenicillin or dimocillin or flabelline or lucopenin or mechicillin or metcillin or meticillin or methicilline or methycillin or metin or penistaph or staficyn or stafylopenin or staphcillin or synticillin).tw, kf. (35469)
142. (nafcillin or nafcil or nallpen or naphcillin or naphcillineor naphthamidopenicillin or unipen or vigopen or "w 663989" or w663989).tw, kf. (712)
143. (amoxicillin or actimoxi or amoxicilline or amoxil or amoxycillin or "BRL-2333" or clamoxyl or hydroxyampicillin or penamox or polymox or trimox or wymox).tw, kf. (17943)
144. (oxacillin or bactocil or bactocill or bristopen or cryptocillin or dicloxal or isoxacillin or methylphenyl isoxazolylpenicillin or oksin or oxacil or oxacillin or oxacilline or oxazocilline or oxcillin or pactocil or penstapho or prostafilina or prostaphlin or resistopen or stafcil or staficilin or staficillin or stapenor or staphcillin or wydox or cloxacillin or chloroxacillin or syntarpen or tegopen).tw, kf. (6372)
145. (dicloxacillin or brispen or "brl 1702" or brl1702 or "c 10651" or c10651 or cilpen or cloxydin or dacocilin or dichlor stapenor or dichloro oxacillin or dichloroxacillin or dichlorstapenor or diclex or diclixin or diclocil or diclopen or diclox or dicloxaciclin or dicloxacillin or dicloxallin or dicloxin or dicloxman or dicloxno or dicloxsig or dicloxacycline or dicloxsig or didoxacillin or diloxin or diocloxacillin or distaph or ditterolina or dixalin or dycill or dynapen or infectostaph or methyldichlorophenylisoxazolylpenicillin or novapen or "p 1011" or pathocil or pen sint or pensint or posipen or sodium dicloxacillin or stampen or staphcillin a or syntarpen or uniclox or veracillin or ziefmycin).tw, kf. (708)

146. (brl 2039 or brl2039 or flopen or floxacillin or floxapen or flucil or flucloxacillin or fluorochloroxacillin or heracillin or stafoxil or staphylex).tw, kf. (880)
147. (doripenem or doribax or finibax).tw, kf. (671)
148. Rifampin/(17873)
149. (ba 41 166 or ba 41166 or ba 41166e or ba41166 or ba 41166e or benemycin or doloresum or eremfat or finamicina or kalrifam or l 5103 or lositril or manorifcin or medifam or nsc 113916 or nsc 113926 or orifam or prolung or ramfin or ramicin or rhymactan or rifa or rifacilin or rifadin or rifadine or rifagen or rifaldin or rifamax or rifampicin or rifampicine or rifampin or rifampycin or rifapiam or rifarad or rifasynt or rifcap or rifcin or rifodex or rifoldin or rimactan or rimactane or rimapen or rimpacin or rimpin or rimycin or ripin or ripolin or rofact or sinerdol or tubocin or tuborin).tw, kf. (24692)
150. exp Streptomycin/(22419)
151. (distampin or evolin or "nsc 14083" or nsc14083 or strepolin or streptaquaine or streptinomycin or streptomycine or streptomyxin or streptomycin? or estreptomicina or strepto-fatol or strepto-hefa or stryzolin).tw, kf. (25232)
152. (roxithromycin or assoral or biaxsig or claramid or "er 42857" or er42857 or forilin or infectoroxit or macrosil or overal or rossitrol or rotesan or rotramin or roxibeta or roxid or roximin or roxigamma or roxigrun or roxithromycine or roxihexal or roxithro-lich or "ru 28965" or "ru 965" or ru28965 or ru965 or rulid or rulide or roxidura or surlid).tw, kf. (1513)
153. or/83-152 [Abx] (753244)
154. 71 and 153 [Abx - GROUP A STREP - DISEASE TRANSMISSION/EXPOSURE] (832)
155. 82 or 154 [GAS - ABX PROPHYLAXIS] (3185)
156. exp Animals/not Humans/(4718368)
157. 155 not 156 [ANIMAL-ONLY REMOVED] (2752)
158. (comment or editorial or news or newspaper article).pt. (1430807)
159. (letter not (letter and randomized controlled trial)).pt. (1084300)
160. 157 not (158 or 159) [OPINION PIECES REMOVED] (2660)

Box: Definition of Laboratory-Confirmed, Probable, and Severe iGAS Disease According to the Public Health Agency of Canada [9].

Laboratory-confirmed iGAS infection with or without clinical evidence of invasive disease*

- isolation of group A *Streptococcus* (*Streptococcus pyogenes*) from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, deep tissue specimen taken during surgery [eg, muscle collected during debridement for necrotizing fasciitis], bone or joint fluid excluding the middle ear and superficial wound aspirates [eg, skin and soft tissue abscesses]).

Probable iGAS disease

- clinical evidence of invasive disease* in the absence of another identified etiology, and with non-confirmatory laboratory evidence of infection: isolation of group A *Streptococcus* from a non-sterile site or positive group A *Streptococcus* antigen detection.

Severe disease in confirmed or probable iGAS

- streptococcal toxic shock syndrome, characterized by hypotension (systolic blood pressure $\leq$90 mmHg in adults or $<$5th percentile for age in children) and at least 2 of the following signs:
  - (i) renal impairment (creatinine level $\geq$ 177 µmol/L for adults)
  - (ii) coagulopathy (platelet count $\leq$ 100 000/mm^3 or disseminated intravascular coagulation)
  - (iii) liver function abnormality (SGOT [AST], SGPT [ALT] or total bilirubin$\geq$2 times the upper limit of normal)
  - (iv) adult respiratory distress syndrome
  - (v) generalized erythematous macular rash that may desquamate;
    - soft-tissue necrosis, including necrotizing fasciitis, myositis or gangrene;
    - meningitis;
    - GAS pneumonia;
    - iGAS-related death;

*Clinical evidence of invasive disease is defined as conditions listed under severe disease in confirmed or probable iGAS. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; iGAS, Invasive Group A Streptococcal Disease; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.