Streptococcus pneumoniae outbreaks and implications for transmission and control: a systematic review

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Abstract

Background: Streptococcus pneumoniae is capable of causing multiple infectious syndromes and occasionally causes outbreaks. The objective of this review is to update prior outbreak reviews, identify control measures, and comment on transmission.

Methods: We conducted a review of published S. pneumoniae outbreaks, defined as at least two linked cases of S. pneumoniae.

Results: A total of 98 articles (86 respiratory; 8 conjunctivitis; 2 otitis media; 1 surgical site; 1 multiple), detailing 94 unique outbreaks occurring between 1916 to 2017 were identified. Reported serotypes included 1, 2, 3, 4, 5, 7F, 8, 12F, 14, 20, and 23F, and serogroups 6, 9, 15, 19, 22. The median attack rate for pneumococcal outbreaks was 7.0% (Interquartile range: 2.4%, 13%). The median case-fatality ratio was 12.9% (interquartile range: 0%, 29.2%). Age groups most affected by outbreaks were older adults (60.3%) and young adults (34.2%). Outbreaks occurred in crowded settings, such as universities/schools/daycares, military barracks, hospital wards, and long-term care facilities. Of outbreaks that assessed vaccination coverage, low initial vaccination or revaccination coverage was common. Most (73.1%) of reported outbreaks reported non-susceptibility to at least one antibiotic, with non-susceptibility to penicillin (56.0%) and erythromycin (52.6%) being common. Evidence suggests transmission in outbreaks can occur through multiple modes, including carriers, infected individuals, or medical devices. Several cases developed disease shortly after exposure (< 72 h). Respiratory outbreaks used infection prevention (55.6%), prophylactic vaccination (63.5%), and prophylactic antibiotics (50.5%) to prevent future cases. PPSV23 covered all reported outbreak serotypes. PCV13 covered 10 of 16 serotypes. For conjunctival outbreaks, only infection prevention strategies were used.

Conclusions: To prevent the initial occurrence of respiratory outbreaks, vaccination and revaccination is likely the best preventive measure. Once an outbreak occurs, vaccination and infection-prevention strategies should be utilized. Antibiotic prophylaxis may be considered for high-risk exposed individuals, but development of antibiotic resistance during outbreaks has been reported. The short period between initial exposure and development of disease indicates that pneumococcal colonization is not a prerequisite for pneumococcal respiratory infection.

Keywords: Streptococcus pneumoniae, Pneumococcus, Outbreaks, Transmission, Epidemic, Cluster, Pneumococcal vaccine

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Background
Discovered in 1881 independently by Louis Pasteur and George Sternberg [1], Streptococcus pneumoniae is a Gram-positive bacterial pathogen that may asymptptomatically colonize the upper respiratory tract and is capable of causing infections including conjunctivitis, otitis media, lower respiratory tract infections, bacteremia, and meningitis [2]. Those at particularly high risk for invasive disease are young children, older adults, and persons with underlying comorbidities [3, 4]. Among United States (US) adults ≥50 years, it is estimated that S. pneumoniae causes ≥500,000 cases of pneumonia and ≥25,000 deaths each year [5]. Previous publications describing pneumococcal disease state that nasopharyngeal colonization is a prerequisite for disease [2, 6, 7]. Colonization is “the presence and multiplication of microorganisms without tissue invasion or damage” [8]. Conversely, infection involves tissue invasion.

The objective of this review was to summarize the publications on outbreaks and inform the understanding of S. pneumoniae transmission in these outbreaks. The most recent review of general pneumococcal outbreaks was conducted in 2010 [9]. Since then, the Advisory Committee on Immunization Practices (ACIP) has revised its recommendations to include the use of 13-valent pneumococcal conjugate vaccine (PCV13) in adults [10]. Our review represents an important update to previous reviews, includes additional pneumococcal disease manifestations, and has over double the number of included articles from the previous review. This review informs the understanding of Streptococcus pneumoniae outbreak serotypes, transmission, and effective control measures.

Methods
A search of PubMed was conducted on July 18, 2017, for publications describing outbreaks of disease caused by S. pneumoniae. The following search terms were used: (“streptococcus pneumoniae” OR “pneumococcus”) AND (“outbreak” OR “epidemic”) with no date restrictions. Articles not available in the English language were excluded. All types of pneumococcal disease, year of outbreak, or location of outbreak were eligible for inclusion. To be considered an outbreak, at least one transmission event of pneumococcal disease had to occur. Pneumococcal carriage or surveillance studies were included if details of a pneumococcal outbreak were described. Each included article’s references and previous reviews [9, 11, 12] were screened for additional articles not identified.

The following information was extracted from publications. Case-patient ages were groups into five categories; toddler (0–2 years old), children (3–17), young adults (18–25), adults (26–49) and older adults (50+). S. pneumoniae were considered antibiotic susceptible or non-susceptible, where non-susceptible refers to intermediate or resistant. Specific antibiotic susceptibility information was extracted for penicillin, cefotaxime, erythromycin, tetracycline, levofloxacin, and vancomycin. The three general control measures considered were antibiotic prophylaxis, prophylactic vaccination, and infection prevention (i.e., hand-hygiene, isolation of cases, isolation of carriers, social distancing). Outbreak settings were categorized as occurring in hospitals, military, long term care facilities (LTCF), daycares, schools, jails, or workplaces. Settings falling outside these categories were grouped as “community” outbreaks. Pneumococcal lower respiratory tract infections were divided into three eras; pre-vaccine (pre-1977), pneumococcal polysaccharide vaccine (PPSV) only (1977–1999), and PPSV and PCV vaccines (2000–2017).

Results
The search identified 629 potential articles. After screening, 83 articles were identified as meeting the inclusion criteria. From references of included articles and other reviews an additional 15 articles were identified. A total of 98 publications detailing 94 unique S. pneumoniae outbreaks were identified (Table 1, Additional file 1: Figure S1). Thirteen reports were published from 1916 to 1946, and the remainder were published after 1980. Unique outbreaks by disease syndrome were as follows; 80 lower respiratory tract infection [12–97], 9 conjunctivitis [98–105], 3 otitis media [106, 107], 1 surgical site infection [108], and 1 lower respiratory tract infection and otitis media [109] (Fig. 1).

A majority of reported outbreaks occurred in hospitals (33.0%), community (26.6%), or military buildings (17.0%) (Fig. 2). The most common age categories for case-patients in outbreaks (n = 73) were older adults (60.3%), young adults (34.2%) and adults (28.8%). Case-patients were less commonly toddlers (20.5%) or children (19.2%). Most reported outbreaks were reported in the US (43.6%), the United Kingdom (24.5%), or Canada (7.4%). France, India, and Israel each reported four outbreaks (4.3%); Japan, Australia, Netherlands, and Hungary each reported two outbreaks (2.1%); and Tunisia, Poland, and Finland each reported one outbreak (1.1%).

Sixty-one outbreak investigations reported assessing S. pneumoniae strains by molecular typing. The most common methods used were pulse-field-gel-electrophoresis (PFGE) (23.2%), antisera methods (23.2%), and multi-locus-sequence-typing (MLST) (22.0%). Of outbreak reports published since 2007 (n = 18), MLST (40.6%) and PFGE (18.8%) were most commonly used. Of 52 outbreaks assessing antibiotic resistance, 73.1% of outbreaks reported some antibiotic non-susceptibility. Antibiotics chosen for susceptibility testing were inconsistent. Non-susceptibility to penicillin (28/50 outbreaks),
| Author         | Year published | Country | Type     | Setting            | Age Categories                  | Linkage | Serotype | Number colonized (%) | Number infected (%) | Case-Fatality Ratio |
|----------------|----------------|---------|----------|--------------------|---------------------------------|---------|----------|--------------------|---------------------|---------------------|
| McCrae T       | 1916           | Canada  | Respiratory | Community         |                                 |         |          |                    |                     |                     |
| Miller JL      | 1918           | United States | Respiratory | Military           |                                 |         |          |                    |                     |                     |
| Schröder MC    | 1930           | United States | Respiratory | School             | Children                        |         |          |                    |                     |                     |
| Smillie WG     | 1936           | United States | Respiratory | Hospital           |                                 |         |          |                    |                     |                     |
| Tilghman RC    | 1936           | United States | Respiratory | Community         | Toddler, Children, Young Adult, Adult, Older Adult |         |          |                    |                     |                     |
| Gilman BB      | 1938           | United States | Multiple   | Community         |                                 |         |          |                    |                     |                     |
| Smillie WG     | 1938           | United States | Respiratory | Hospital           |                                 |         |          |                    |                     |                     |
| Mackenzie GM   | 1940           | United States | Respiratory | Community         |                                 |         |          |                    |                     |                     |
| Hodges RG*     | 1946           | United States | Respiratory | Military           |                                 |         |          |                    |                     |                     |
| DeMaria A      | 1980           | United States | Respiratory | Community         |                                 |         |          |                    |                     |                     |
| Shayegani M    | 1982           | United States | Conjunctivis | Community       |                                 |         |          |                    |                     |                     |
| Shayegani M    | 1983           | United States | Conjunctivis | Military         |                                 |         |          |                    |                     |                     |
| Fenton PA      | 1983           | United Kingdom | Respiratory | Community         |                                 |         |          |                    |                     |                     |
| Shayegani M    | 1984           | United States | Conjunctivis | Community         | Adult, Older Adult               |         |          |                    |                     |                     |
| Davies AJ      | 1984           | United Kingdom | Respiratory | Hospital          |                                 |         |          |                    |                     |                     |
| Berk SL        | 1985           | United States | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
| Collingham RE  | 1985           | United States | Respiratory | Community         | Old Adult                       |         |          |                    |                     |                     |
| Mehtar S       | 1986           | United Kingdom | Respiratory | Hospital          | Toddler                         |         |          |                    |                     |                     |
| Davies AJ      | 1987           | United Kingdom | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
| Gould FK       | 1987           | United Kingdom | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
| Moore EP       | 1988           | United Kingdom | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
| CDC*           | 1989           | United States | Respiratory | Jail               |                                 |         |          |                    |                     |                     |
| Roach AM       | 1990           | United States | Respiratory | Daycare            | Toddler                         |         |          |                    |                     |                     |
| Bain M         | 1990           | United Kingdom | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
| Mercat A       | 1991           | France       | Respiratory | Community         | Young Adult, Adult, Older Adult |         |          |                    |                     |                     |
| Cartmill TDI   | 1992           | United Kingdom | Respiratory | Hospital          | Older Adult                     |         |          |                    |                     |                     |
Table 1 Characteristics of included pneumococcal publications (Continued)

| Author | Year published | Country | Type | Setting | Age Categories | Linkage | Serotype | Number colonized (%) | Number infected (%) | Case-Fatality Ratio |
|--------|----------------|---------|------|---------|----------------|---------|----------|----------------------|---------------------|---------------------|
| Dawson S | 1992 | United Kingdom | Respiratory | Hospital | Older Adult | 6 | 1 | 5 | |
| PHLS | 1992 | United Kingdom | Respiratory | Hospital | 9 | 7 | 0.143 | |
| Quick RE | 1993 | United States | Respiratory | Long-term care facility | Older Adult | Quellung | 9 V | 2 (30%) | 7 (7.4%) | 0.710 |
| Gratten M | 1993 | Australia | Respiratory | Community | Young Adult, Adult, Older Adult | Antisera | 1 | 13 (17.3%) | 18 | |
| Denton M | 1993 | United Kingdom | Respiratory | Hospital | Older Adult | 14 | 8 | 0.125 | |
| Hoge CW* | 1994 | United States | Respiratory | Jail | Young Adult, Adult | Quellung | 12F | 11 (7.0%) | 46 (0.5%) | 0.043 |
| Cherian T | 1994 | United States | Respiratory | Daycare | Toddler | Ribotyping | 12F | 6 (100%) | 4 (66.7%) | 0 |
| Miller MR | 1994 | United Kingdom | Respiratory | Hospital | Older Adult | 9 | 0 (0%) | 10 (5.7%) | |
| Mandigers CMPW | 1994 | Netherlands | Respiratory | Hospital | Older Adult | Quellung | 9 | 18 | 0.556 | |
| Nims L | 1994 | United States | Respiratory | Daycare | Toddler | PCR | 19 | 3 | 14 | 0.500 |
| Raymond J | 1995 | France | Respiratory | Hospital | Toddler | RAPD | 23F | 2 | |
| Ertugrul N | 1997 | United States | Conjunctivis | Military | PFGE, PCR | Nontypeable | 561 | 0 | |
| Marton A | 1997 | Hungary | Otitis Media | Hospital | Toddler | | 0 | 6 | |
| Marton A | 1997 | Hungary | Otitis Media | Hospital | Toddler | | 3 | |
| Gillespie SH | 1997 | United Kingdom | Respiratory | Hospital | Older Adult | RFLP | 9 | 3 | 9 | 0.444 |
| CDC* | 1997 | United States | Respiratory | Long-term care facility | Older Adult | PCR | 14 | 10 (14.9%) | 0.200 |
| CDC* | 1997 | United States | Respiratory | Long-term care facility | Older Adult | PFGE | 23F | 17 (23.0%) | 11 (1.30%) | 0.270 |
| CDC | 1997 | United States | Respiratory | Long-term care facility | Older Adult | PCR | 4 | 14 (11.7%) | 0.200 |
| Musher DM | 1997 | United States | Respiratory | Military | Young Adult | | 1 | 128 (32%) | |
| Musher DM | 1997 | United States | Respiratory | Military | Young Adult | 7F / 8 | 44 (28.4%) | 14 (6.4%) | |
| Fiore AE* | 1998 | United States | Respiratory | Long-term care facility | Older Adult | PCR | 14 | 10 (14.9%) | 0.200 |
| Nuorti JP* | 1998 | United States | Respiratory | Long-term care facility | Older Adult | PFGE | 23F | 17 (23.0%) | 11 (1.30%) | 0.27 |
| Sheppard DC | 1998 | United States | Respiratory | Long-term care facility | Older Adult | PFGE | 14 | 0 (0%) | 15 (1.25%) | |
| Razzaq N | 1998 | United Kingdom | Respiratory | Community | Toddler, Older Adult | 12F | 2 | |
| Craig AS | 1999 | United States | Respiratory | Daycare | Toddler | PFGE | 14 | 15 (19%) | 3 (3.4%) | 0 |
| Author        | Year published | Country        | Type               | Setting                                      | Age Categories          | Linkage       | Serotype | Number colonized (%) | Number infected (%) | Case-Fatality Ratio |
|--------------|----------------|----------------|--------------------|----------------------------------------------|-------------------------|---------------|----------|----------------------|---------------------|---------------------|
| de Galan BE  | 1999           | Netherlands    | Respiratory        | Hospital                                      | Older Adult             | Quellung, RFEL| 15       | 36                   | 0.297               |                     |
| Kellner JD   | 1999           | Canada         | Respiratory        | Community                                     | Adult, Older Adult      | PFGE          |          | 6                    |                     | 0.167               |
| Leggadore RJ | 1999           | United States  | Respiratory        | Long-term care facility                        | Older Adult             | PFGE          |          | 4                    |                     | 3                   |
| Gleich S     | 2000           | United States  | Respiratory        | Long-term care facility                        | Older Adult             | PFGE          |          | 11 (5.5%)           |                     |                     |
| Dagan R      | 2000           | Israel         | Respiratory        | Community                                     | Adult                   | Ribotyping, PCR| 1        | 31 (4.8%)           | 5                   |                     |
| Nakashima T  | 2001           | Japan          | Otitis Media       | Daycare                                       | Children                | Antisera, RAPD| 19, 23, 6|                      |                     | 7                   |
| CDC*         | 2001           | United States  | Respiratory        | Long-term care facility                        | Older Adult             | PFGE          |          | 14                   | 9                   | 0.444               |
| Weiss K      | 2001           | Canada         | Respiratory        | Hospital                                      | Older Adult             | PFGE          | 2.3F     | 23                   |                     |                     |
| CDC          | 2002           | United States  | Conjunctivits      | School                                        | Children, Young Adult, Adult | PFGE, Nontypeable|          |                      |                     | 144                 |
| Melamed R    | 2002           | Israel         | Respiratory        | Hospital                                      | Toddler                 | RAPD          | 5        |                      |                     | 3                   |
| Martin M     | 2003           | United States  | Conjunctivits      | Community                                     | Young Adult             | PFGE, MLST, Nontypeable|          |                      |                     | 698 (13.8%)         |
| Tan CG*      | 2003           | United States  | Respiratory        | Long-term care facility                        | Older Adult             | PFGE          |          | 14                   | 9                   | 0.444               |
| Crum NF      | 2003           | United States  | Respiratory        | Military                                       | Young Adult             | Quellung, Latex Agglutination| 9 V / 4     | 13 (11.0%)           | 52 (1.5%)           | 0                   |
| Subramaniam D| 2003           | United Kingdom | Respiratory        | Hospital                                      | Older Adult             | PFGE          | 9 V      | 3 (5.5%)            | 9                   |                     |
| Sanchez JL   | 2003           | United States  | Respiratory        | Military                                       | Young Adult             | PCR           | 3, 6, 9, 14, 20, 22, 23| 30 (13.6%) | 30 (12.1%)          |                     |
| Crum NF      | 2004           | United States  | Conjunctivits      | Military                                       | Young Adult, Adult      | MLST, Nontypeable|          |                      |                     | 80 (2.3%)           |
| Banerjee A   | 2005           | India          | Respiratory        | Military                                       | Adult                   | MLST, RAPD    |          |                      |                     | 0                   |
| CDC          | 2005           | United States  | Respiratory        | Hospital                                      | Adult                   | PFGE          | 2.3F, 3 | 6 (3.1%)            | 7                   | 0.290               |
| CDC*         | 2005           | United States  | Respiratory        | Community                                     | Toddler, Young Adult, Adult, Older Adult | PFGE, MLST, MLST, MLBT| 12F | 46 (2.4%)           | 14 (0.1%)           |                     |
| Birtles A    | 2005           | United Kingdom | Respiratory        | Community                                     | Adult                   | MLST          | 8        | 2                    | 1                   |                     |
| Buck JM      | 2006           | United States  | Conjunctivits      | Community                                     | Toddler, Young Adult, Adult, Older Adult | PFGE, MLST, Nontypeable|          |                      |                     | 735                 |
| Herrick M    | 2006           | Canada         | Conjunctivits      | Community                                     | Toddler, Young Adult, Adult, Older Adult | AFLP, Nontypeable|          |                      |                     | 47                  |
| Hansmann Y   | 2006           | France         | Respiratory        | Long-term care facility                        | Older Adult             | Antisera, Urine| 4        | 1 (1.2%)            | 11 (1.7%)           | 0.273               |
| Singh PMP    | 2006           | India          | Respiratory        | Military                                       | Young Adult             | PCR, MLST     | 1        | 11                   | 0.182               |                     |
| Cashman P    | 2007           | Australia      | Respiratory        | School                                        | Children                |               | 1        | 25                  |                     |                     |
| Sheppard CL  | 2008           | United Kingdom | Respiratory        | Community                                     | Children, Young Adult, Adult | PCR, MLST     | 1        | 11                   | 0.182               |                     |
| Romney MG    | 2008           | Canada         | Respiratory        | Community                                     | Toddler, Young Adult, Adult, Latex Agglutination | 5 | 137 | 0.080 | | |
Table 1 Characteristics of included pneumococcal publications (Continued)

| Author        | Year published | Country        | Type          | Setting          | Age Categories          | Linkage          | Serotype | Number colonized (%) | Number infected (%) | Case Fatality Ratio |
|---------------|----------------|----------------|---------------|------------------|-------------------------|------------------|----------|----------------------|---------------------|---------------------|
| Zegans ME     | 2009           | United States  | Conjunctivis  | Community        | Young Adult            | PFGE, MLST      | Non-typeable | 20 (8.1%)            | 698 (13.8%)         | 0                   |
| Vainio A      | 2009           | Finland        | Respiratory   | Military         |                         | MLST 7F         | 9 (20.9%)  | 5 (12.0%)            | 0                   | 0                   |
| Gupta A       | 2009           | United Kingdom | Respiratory   | School           | Children                | ELISA, Urine    | 1         | 1 (1.2%)             | 5                   | 0                   |
| Mehri-Zghal E | 2010           | Tunisia        | Respiratory   | Jail             |                         | PFGE            | 1         | 9 (45.0%)            | 150 (38%)           | 0                   |
| Balicer RD    | 2010           | Israel         | Respiratory   | Military         | Young Adult            | PFGE, MLST 5    | 35 (24.1%) | 34                   | 0                   | 0                   |
| Pichon B      | 2010           | United Kingdom | Respiratory   | Community        |                         | MLST            | 5         | 8                    | 0                   | 0                   |
| Dawood FS     | 2011           | United States  | Respiratory   | Military         | Young Adult            | Quellung 7F     | 16 (4.3%) | 74 (0.3%)            | 0.027               | 0                   |
| Vanderkooi OG | 2011           | Canada         | Respiratory   | Community        | Children, Young Adult, Adult, Older Adult | Quellung, MLST 5, 8 | 207 |
| Skoczynska A  | 2012           | Poland         | Respiratory   | Hospital         | Older Adult             | PFGE, MLST 14  | 6         | 11                   | 0                   | 0                   |
| Fleming-Duria K | 2012       | United States  | Respiratory   | Hospital         | Children, Young Adult  | PCR, MLST 15A  | 6         | 11                   | 0                   | 0                   |
| Guillet M     | 2012           | France         | Surgical Site | Hospital         |                         | 3               | 1         | 4                    | 0                   | 0                   |
| Zulz T*       | 2013           | United States  | Respiratory   | Community        | Toddler, Children, Young Adult, Adult, Older Adult | PFGE, MLST, MLBT 12F | 46 (2.4%) | 14 (0.1%)            | 0                   | 0                   |
| CDC           | 2013           | United States  | Respiratory   | Long-term care facility | Adult, Older Adult | 3               | 7 (50.0%) | 0.490               | 0                   | 0                   |
| Kuroki T      | 2014           | Japan          | Respiratory   | Hospital         | Older Adult             | PFGE, MLST 3    | 16 (83.9%) | 0.063               | 0                   | 0                   |
| Ben-David D   | 2014           | Israel         | Respiratory   | Hospital         | Young Adult, Older Adult | PFGE, MLST 19F, 23F | 21 (20.2%) | 66                   | 0                   | 0                   |
| Schillberg E  | 2014           | Canada         | Respiratory   | Community        | Children, Young Adult, Older Adult | Quellung, PFGE, MLST, MLVA 12F | 32 |
| Suryam V      | 2015           | India          | Respiratory   | Military         |                         |                 | 52        | 0                    | 0                   | 0                   |
| Thomas HL     | 2015           | United Kingdom | Respiratory   | Long-term care facility | Older Adult | Urinary, MLST 8 | 15 (650%) | 0.133               | 0                   | 0                   |
| Kunwar R      | 2015           | India          | Respiratory   | Military         | Young Adult             | Urinary, 6C    | 58 (11%)  | 0                    | 0                   | 0.231               |
| Sheppard CL   | 2016           | United Kingdom | Respiratory   | Hospital         | Older Adult             | Urinary, 6C    | 13        | 0                    | 0                   | 0.231               |
| Ewing J       | 2017           | United Kingdom | Respiratory   | Workplace        | Young Adult, Adult, Older Adult | WGS, MLST 4 | 25                   | 0                   | 0                   |
| Jauneikait E  | 2017           | United Kingdom | Respiratory   | Hospital         | Older Adult             | WGS, MLST 9V   | 4         | 0                    | 0                   | 0                   |

PCR polymerase chain reaction, RAPD random amplified polymorphic DNA, PFGE pulse-field gel electrophoresis, RFLP restriction fragment length polymorphism, RFEL restriction fragment end labeling, MLST multilocus sequence type, AFLP amplified fragment length polymorphism, ELISA enzyme-linked immunosorbent assay, MUBT multilocus boxB sequence typing, MLVA multiple loci variable-number tandem repeat analysis, WGS whole genome sequencing.

Age categories are defined as follows: toddler (0–2 years old), children (3–17), young adult (18–25), adult (26–49), and older adult (50+).

Settings falling outside the other indicated categories were considered as "Community" settings. These included transmission among families, homeless shelter outbreaks, outbreaks in socially disadvantaged groups, and transmission occurring generally within geographical regions.

*Outbreaks that were described in multiple publications. See supplement data set containing unique identifiers for each outbreak report.
erythromycin (20/38), and tetracycline (11/20) were reported. Fewer outbreaks reported non-susceptibility to cefotaxime (5/13) or levofloxacin (3/11). Non-susceptibility to vancomycin was not reported for any outbreak (n = 17).

**Disease types**

**Lower respiratory tract infection**

A total of 81 unique reported outbreaks involved lower respiratory tract infection with pneumococcus, with 9 in the pre-vaccine era, 41 in the PPSV era and 31 in the PPSV/PCV era.

**Pre-vaccine era** Within the pre-vaccine era, outbreaks occurred in community (4/9), military (2/9), hospital (2/9), and a school (1/9) settings. Interestingly, 3 of the outbreak reports mentioned concocting a vaccine from pneumococcal polysaccharides [16, 18, 20].

**PPSV era** During the PPSV era, reported outbreaks occurred in hospitals (43.9%), community (19.5%), LTCF (17.1%), daycares (9.8%), military (7.3%) or jail (2.4%) settings. Within hospital settings, outbreaks occurred in geriatric, pulmonary, oncology, maternity, and “AIDS-care” units. Community outbreaks included homeless shelter outbreaks, transmission between family members, and outbreaks occurring within socially disadvantaged groups. Of the 39 outbreaks that reported serotypes, the most common pneumococci were serogroup 9 (15.4%), serotype 1 (15.4%), serotype 23F (12.8%), and serotype 14 (12.8%) (Fig. 3). Of the 17 studies that reported colonization data, the median percent of colonized individuals was 9.3% (IQR: 3.0%, 19.0%). For 15 studies with a denominator, the median attack rate was 7.4% (IQR: 4.4%, 12.8%) with a median case-fatality ratio of 25.0% (IQR: 11.5%, 36.1%) from 24 studies. Twenty-six studies reported conducting testing for resistance to at least one antibiotic. Non-susceptibility was reported for the following antibiotics: penicillin (18/25), cefotaxime (5/9), erythromycin (9/19), tetracycline (8/11), levofloxacin (2/3), and other antibiotics (13/17). No vancomycin non-susceptibility was reported in 13 publications. Seven outbreaks reported sufficient information to calculate the vaccination coverage of the source population with the following
coverages; 2% [110], 3% [55], two with 4% [52, 110], 7% [42], and 24% [70]. One study reported an unadjusted vaccine effectiveness (VE) of 0.87 (95% CI: -0.03, 0.98) for those who received PPSV before the outbreak [70]. For hospital outbreaks with reported control measures (11/18), infection-prevention practices alone (54.5%), vaccination alone (9.1%), infection-prevention and vaccination (18.2%), infection-prevention and prophylactic antibiotics (9.1%), and all three (9.1%) were used to mitigate outbreaks. Only two outbreaks (infection control alone [64], all three control measures [70]) reported control measures as unsuccessful. Both outbreaks described the development of antibiotic resistance over the course of the outbreak [64, 70]. LTCF reported infection-prevention and vaccination (2), infection-prevention and antibiotics (1), and all three (1) as control measures with cases discontinuing after implementation. Two of three daycare centers that used antibiotics alone reported failure of control measures to eradicate carriage of the outbreak strain. For outbreaks designated as within communities, a homeless men’s shelter controlled an outbreak successfully using vaccination. None of the other community outbreaks reported using control measures.

PPSV/PCV era From 2000 to 2017, outbreaks were reported in hospitals (25.8%), military settings (25.8%), communities (22.6%), LTCF (12.9%), schools (6.5%), a workplace (3.2%), and a jail (3.2%). Hospital outbreaks occurred in geriatric, pulmonary, ear/nose/throat, and a pediatric psychiatry ward. Community outbreaks included a homeless shelter outbreak, transmission among children, and a socially disadvantaged group. Of outbreaks with recorded case-patient ages (n = 29), 55.2% were older adults, 48.3% were young adults (37.9%) were adults, 27.6% were children, and 10.3% were toddlers. Twenty-seven outbreaks reported serotypes, with serotype 5 (18.5%) and serotype 1 (14.8%) most commonly reported (Fig. 3). Of 10 outbreaks with a denominator for colonization, the median colonization percentage was 8.2% (IQR: 2.9%, 20.7%). The median attack rate was 7.7% (IQR: 1.2%, 40.5%) for the ten outbreaks that provided attack rates. The case-fatality ratio was 4.5% (IQR: 0%, 21.9%) for 18 reports. Seventeen studies reported testing for antibiotic resistance with 64.7% reporting resistance to at least one antibiotic. Reported antibiotic non-susceptibility included; penicillin (5/16), erythromycin (5/11), tetracycline (2/5), levofloxacin (1/4), and other antibiotics (5/9). No non-susceptibility was reported for cefotaxime (n = 3) and vancomycin (n = 2). Twelve studies assessed whether case-patients had ever received either pneumococcal vaccine before the outbreak [62, 66, 67, 71, 73, 74, 82, 88, 89, 91, 93, 97]. Of the studies that provided enough information to calculate vaccination coverage of the source population of cases, two reported 0% coverage [66, 88], one reported 7% [89], and one reported 57% [93]. At least one vaccine failure was reported for 6 studies [71, 74, 88, 91, 93, 97]. Two reports described one case-patient vaccine failure of a vaccine received within five years of the outbreak [71, 74]. Two studies reported PPSV VE among older adults; 1.00 (95% CI: 0.30, 1.00) [63] and ~ 0.41 (95% CI: -2.33, 0.40) [93]. The poor VE and the outbreak occurring despite 57% vaccination coverage was partially attributed to “waning immunity” by the authors, since all case-patients received the vaccine more than 7 years prior to the outbreak [93]. Of hospital outbreaks with reported control measures (6/8), the following measures were used; infection-prevention alone (16.7%), vaccination alone (16.7%), infection-prevention and prophylactic antibiotics (50%), and vaccination and prophylactic antibiotics (16.7%). None of the six outbreaks reported the control measures failing to control the outbreak. Military outbreaks were effectively controlled by antibiotics alone (1), infection control alone (1), antibiotics and vaccination (3), infection-prevention and antibiotics (3) or all three (1). All five LTCF outbreaks were controlled with vaccination paired with infection control (2), antibiotics (2), or both (1). Community outbreaks reporting control measures (5/7), all used vaccination alone. All outbreaks except one were reported as being successfully controlled.

Conjunctivitis Eight publications describing nine conjunctivitis outbreaks have been published since 1982. All of these outbreaks are attributed to non-typeable strains. Two pneumococcal outbreaks were MLST sequence type 448 [101, 104]. Interestingly, this pneumococcal strain, identified in the 2002 Dartmouth and 2003 Minnesota outbreaks, was related to a strain isolated in 1980’s outbreaks in New York, California, and Illinois [98, 99, 101, 104]. Noteworthy is the development of non-susceptibility to penicillin, erythromycin, and tetracycline between 1980 to 2003 in this strain. Four of six outbreaks reported non-susceptibility to at least one antibiotic [98, 100, 103, 104]. Non-susceptibility was observed for erythromycin (4/6), penicillin (2/6) and tetracycline (1/4). Outbreaks occurred in the community (N = 6) or military settings (N = 3). Three of the community outbreaks were associated with universities, with two large outbreaks occurring in this setting. Furthermore, all outbreaks with reported ages (n = 5) included young adult case-patients. Outbreaks of conjunctivitis were generally larger than respiratory outbreaks (median: 561 cases; range 80, 735). There was no reported mortality associated with these outbreaks. Five outbreaks reported using infection-prevention to control outbreaks and led to a subsequent decline in cases [100, 101, 103–105].
However, for three of the four outbreaks related to schools, the decline occurred after school breaks [100, 101, 105], complicating the attribution of infection-prevention strategies as ending the outbreak.

**Otitis media**

There were four reported otitis media outbreaks in three publications. The first was an otitis media outbreak occurring simultaneously with a pneumococcal lower respiratory tract infection outbreak in a US community in 1937 [109]. This study was unable to directly link the two manifestations of pneumococcal disease. Two outbreaks occurred in hospitals in Hungary during 1993–1994 and 1996 [106]. No carriers were reported among healthcare personnel and transmission was believed to occur between patients in the hospital since case-patients shared rooms. The other outbreak occurred in 1997 in a Japanese daycare center among seven children with serogroup 6 (n = 1), and serotypes 19 (n = 4), and 23F (n = 2) [107]. Otitis media occurred in at least one case-patient during two pneumococcal lower respiratory tract infection outbreaks [48, 61]. Non-susceptibility was reported for penicillin (3/3) and erythromycin (2/2). None of the publications reported instituting control measures.

**Surgical-site**

One publication detailed four surgical site infections transmitted by a surgeon with nasopharyngeal carriage to four prostatic surgery patients [108]. Pneumococcal infection occurred at skin and soft tissue near the surgical site of case-patients. Transmission was attributed to the surgeon persistently wearing a poorly fitting mask.

**Transmission**

In the reviewed outbreak articles, we found evidence for multiple modes of transmission. Aside from transmission attributable to nasopharyngeal carriers, there were pneumococcal lower respiratory tract infection outbreaks suggestive of device-associated transmission (infant resuscitation device [30]; inhaler [50, 97]), and infection transmission without any carriers detected [27, 28, 33, 39, 46, 65, 97]. While it is near impossible to ever fully rule out transient nasopharyngeal colonization as the source, these outbreaks found no evidence that carriers contributed to transmission. There is also evidence that droplet transmission occurs for *S. pneumoniae*. In a neonatal intensive care unit, transmission occurred between two neonates 2 meters apart who had no overlapping nursing staff, no contact between families, no carriage among family member, and infection of the transmitting neonate occurred before admission [65]. Studies also reported co-circulation of other viral [51, 76, 87, 91, 95] or bacterial respiratory tract pathogens [44, 59, 84, 87] preceding or during a pneumococcal outbreak. For conjunctivitis outbreaks, direct droplet, or indirect (i.e. environment or hand contamination) transmission may also have occurred, because having a roommate with conjunctivitis was associated with developing conjunctivitis [101]. In four outbreaks, time from exposure to infection in several outbreaks was less than 72 hours for at least one case-patient [27, 28, 65, 97]. Serotype 1, 5, and 9 V exhibited short times between exposure and disease.

**Discussion**

In our review, we found multiple outbreaks attributable to *S. pneumoniae* reported in the first half of the 1900s. In the beginning of the antibiotic area, there were no publications regarding pneumococcal outbreaks. One explanation for this observation is that outbreaks went unreported or unrecognized due to widespread antibiotic use while antibiotics were exquisitely effective. After the 1980’s, outbreaks began being reported regularly, with most reporting non-susceptibility to at least one antibiotic. A majority of pneumococcal outbreaks are linked to lower respiratory tract infection but several large conjunctivitis outbreaks due to non-typeable strains have recently occurred. Most reported lower respiratory tract infection outbreaks have occurred in hospitals, perhaps due to observation bias. Conjunctivitis outbreaks have mostly occurred in community settings, specifically universities. Regarding transmission, this review supported the view of *S. pneumoniae* transmission as a complicated process occurring by multiple modes (Fig. 4), and droplet precautions may be warranted for symptomatic patients due to the evidence of droplet transmission occurring [65]. Recommendation for droplet precautions is in line with American Public Health Association for patients with antibiotic-resistant pneumococcus [111], but differs from US Centers for Disease Control and Prevention’s (CDC) and Red Book’s recommendation of standard precautions for pneumococcus cases [112, 113]. For infection progression in individuals, we reviewed several studies that development of pneumococcal disease occurred with 72 h of initial exposure to *S. pneumoniae* [27, 28, 65, 97]. Such a short time between exposure and infection suggests that colonization is not a prerequisite for pneumococcal disease, and infection can progress directly from initial exposure. Based on these observations, we propose a new conceptual model for pneumococcal lower respiratory tract infection progression within an individual (Fig. 5). After initial exposure, an individual may develop infection directly or become colonized. A colonized individual can either develop disease or develop immunity to the pneumococcal serotype. After this point, pneumococcal
respiratory infection progresses as has been described previously [2].

Of the serotypes reported in pneumococcal lower respiratory tract infection outbreaks, the reported strains are considered high risk for serious disease manifestation [114]. Specifically, increased empyema/parapneumonic effusion (serotype 1), meningitis (serotypes 12, 23F), and fatality (serotypes 14, 23F). These strains have continued to be reported in the PPSV/PCV era. Outbreak strains in lower respiratory tract infection outbreaks are included within PCV13 but are covered more fully by PPSV23 (Fig. 3) [115]. Along with the observation that most outbreaks occurred where vaccination/revaccination rates were low suggests that effective vaccination programs play a key role in preventing outbreaks. Providing vaccination is particularly vital in highly susceptible populations, like individuals in LTCF. Primary adult pneumococcal vaccination is recommended for healthy adults 65 years or older, immunocompromised individuals, and those with certain chronic diseases [115, 116]. Providing a 5-year PPSV23 revaccination, if indicated per US CDC recommendations, should be considered to retain sufficient immunity [117–121]. In regards to conjunctivitis, vaccination likely has no role in prevention since these strains do not express capsules, the antigenic target of the current vaccines.

The nasopharyngeal carrier state is an important feature in transmission of S. pneumoniae strains both within households and across regions. There is recognition that carrier-attributed transmission is important among families, with children acting as a reservoir [122–125]. In a global view, large events offer opportunities for widespread dissemination of S. pneumoniae strains. Events like the Hajj, the annual Islamic pilgrimage to Mecca, can lead to acquisition of new S. pneumoniae strains in attendees [126]. While the colonization has been important in dissemination of S. pneumoniae, in outbreaks we found evidence of additional transmission from other sources. Furthermore, there is a need to
explore the transmission dynamics of *S. pneumoniae* with other respiratory pathogens, and the role of the time-order of co-infections [127]. Pneumococcal infection severity has been observed to increase with influenza in murine models [128], and influenza and other respiratory viruses have been associated with increased pneumococcal colonization and infection [129, 130]. In outbreak settings, interventions targeted at preventing or treating co-infections has potential to interrupt transmission. The CDC provided an interim recommendation for the use of PPSV23 as an adjunctive intervention during the 2009 influenza pandemic [131]. Data supports the use of pneumococcal vaccine in future influenza pandemics [132]. Additionally, annual influenza vaccination has potential to mitigate pneumococcal risk [133]. However, interventions targeted specifically for pneumococcus are still required to prevent pneumococcal outbreaks, as evidenced by a pneumococcal outbreak occurring in a military barrack with comprehensive infection-prevention measures should be taken (i.e. droplet precautions). While use of prophylactic antibiotics have had success in controlling outbreaks, the risk of antibiotic resistance developing should be considered carefully. Antibiotic non-susceptibility has previously developed secondary to antibiotic prophylaxis [70]. Rather, it may be appropriate to limit antibiotic prophylaxis to exposed contacts who are at high-risk of disease. Use of prophylactic antibiotics should be evaluated in light of the outbreak size, the pace of new cases, existing antibiotic resistances, and other contextual features. In conjunctivitis outbreaks, prevention efforts should focus on infection-prevention, since vaccination confers no protection against this disease manifestation.

The major strength of our review involves fewer restrictions on inclusion, allowing a more expansive assessment compared to prior pneumococcal outbreak reviews. We updated prior reviews with more recently published outbreaks. Our review also explored features of transmission and infection dynamics in *S. pneumoniae*, which has not previously been commented on in prior outbreak reviews. Lastly, since we could not report every possible combination of variables that may be of interest to readers, we have provided a data file containing all of the information extracted from the articles (Additional file 2: Table S1).

There are several limitations to our review. While our search terms were general, it is possible that our review missed articles of interest. We attempted to minimize this by searching through the references of included articles and other review articles. Some of these further identified articles were in journals not indexed by PubMed and would not have been identified regardless of search terms. One article not identified by our search reported a serotype 5 outbreak among unaccompanied minors in the US during 2014 [136]. Our conclusions are consistent with the unidentified article and this article provides further evidence for co-infection transmission. Our search was limited to only including articles available in English, but only 8 non-English were identified via abstracts. Lastly, our review is limited to published outbreaks. However, our conclusions regarding transmission and infection progression remain valid, because only one example is needed to show this can occur.

**Conclusion**

*S. pneumoniae* causes outbreaks of various clinical manifestations. There is sufficient evidence that *S. pneumoniae* colonization is not an obligate prerequisite for disease. To prevent the initial occurrence of outbreaks, maintaining high vaccination rates and revaccination per US CDC/ACIP recommendations is likely to be effective. Once an outbreak occurs, efforts should be directed to infection-prevention strategies, like droplet precautions, and vaccination. The usage of prophylactic antibiotics for exposed individuals may lead to development of antibiotic resistance, and is not currently recommended by
the CDC. In scenarios of pneumococcal infection co-circulating with another pathogen, interventions targeted at the co-circulating infections may mitigate pneumococcal transmission. Interestingly, conjunctival pneumococcal outbreaks have been linked to bacteria that do not express a capsule and would therefore not be covered by the currently-licensed pneumococcal vaccines. Despite being discovered over 100 years ago, there is still much to uncover regarding S. pneumoniae.

Additional files

Additional file 1: Figure S1. Article exclusion flow diagram. (PNG 22 kb)

Additional file 2: Table S1. Data extracted from reviewed articles. (XLSX 28 kb)

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Author’s contributions
Literature search: PNZ, JDG. Article review: PNZ. Data extraction: PNZ. Drafting of Manuscript: PNZ, JDG, SIB-D, DJW. All authors performed a critical review of the manuscript. All authors read and approved the final manuscript.

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