Deaths Associated with Pneumonic Plague, 1946–2017

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The death rate for persons with treated pneumonic plague is often reported as 50%, but firm evidence for this figure is minimal. We conducted a meta-analysis of articles reporting the death rate for persons treated for pneumonic plague. The rate was 17%, substantially lower than the frequently cited 50%.

Yersinia pestis, the causative agent of plague, is a Tier 1 select agent because of the high case-fatality rate associated with pneumonic plague and its potential as a bioterrorism agent in aerosolized form (https://emergency.cdc.gov/agent/agentlist-category.asp). The death rate for persons with untreated primary pneumonic plague was reported to be almost 100% (*1*); the death rate for persons treated for primary pneumonic plague was 50% (*1*). Overall, the death rate for persons treated for primary pneumonic plague was high despite the sensitivity of *Y. pestis* to aminoglycosides, quinolones, and tetracyclines (*2*,*3*) and the relatively good penetration of some of these antimicrobial drugs into lungs (*4*,*5*). During the 2017 Madagascar pneumonic plague outbreak, the observed death rate for treated persons appeared to be substantially lower than that reported in the literature (*6*). Many articles that quoted a 50% death rate for treated primary pneumonic plague were cited in a 2000 study by Ratsitorahina et al. (*7*), which described a small outbreak in Madagascar in 1997. The article indicated that the data showed an overall death rate of 53% but did not state the number of deaths. However, the death rate for treated persons with confirmed or probable plague was 10%. On reviewing reports that cited Ratsitorahina et al., we identified 9 studies that referenced 50% of persons treated for pneumonic plague who died, 1 study that referenced 40%, and none referencing lower rates. One was a review cited 9 times about persons treated for primary pneumonic plague for whom the death rate was 50%. We identified 6 reports that stated but did not reference a 50% death rate for persons treated for pneumonic plague.

The Study

To address the lack of evidence supporting the frequently cited 50% death rate for persons treated for primary pneumonic plague, we conducted a systematic review and meta-analysis. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, http://www.prisma-statement.org) and MOOSE (Meta-analysis of Observational Studies in Epidemiology [*8*]) guidelines. The study was prospectively registered on PROSPERO (CRD42018086223) (https://www.crd.york.ac.uk/PROSPERO).

We searched PubMed and Embase covering 1946–2017 using the search terms "Yersinia pestis" or "plague" and "pneumon*" and limited our search to human data. We searched references and included articles describing death (within a 28-day period from illness onset) among patients with confirmed, probable, and suspected primary or undifferentiated (i.e., primary or secondary not distinguished pneumonic plague, 1999 World Health Organization case definition, https://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/). We did not restrict by study type, language, or minimum patient number.

Two authors reviewed and extracted data; a third author resolved any disagreements. Data fields extracted included year and country of the outbreak, number of patients who survived and died (stratified by antimicrobial drug status), number of patients receiving different antimicrobial

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drug classes, time to antimicrobial drug administration, and receipt of plague vaccination or prophylaxis (these patients were excluded). We calculated the risk from the number of events and participants in each group.

We performed a meta-analysis using a binomial-specific method. We assessed heterogeneity using the χ^2 test and quantified results with the I^2 statistic. In addition, we preplanned 2 sensitivity analyses to examine whether our estimation of death was influenced by the inclusion of specific articles (pneumonic plague was not confirmed as primary disease or patients with suspected and probable disease). We conducted statistical analysis using R version 3.6.0 (R Project, https://www.r-project.org).

We reviewed 362 articles (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/26/10/19-1270-App1.pdf). We described 1,107 patients in 44 articles (Appendix Table). Twenty-nine articles reported antimicrobial drug use in 108 patients with confirmed or probable pneumonic plague. For pneumonic plague patients receiving antimicrobial drug therapy, the pooled death rate was 17% (95% CI 8%–31%; I^2 = 47%) (Appendix Figure 2). Pneumonic plague patients who did not receive antimicrobial drug therapy had a pooled death rate of 98% (95% CI 73%–100%; I^2 = 47%) (Appendix Figure 3). Pneumonic plague patients for whom antimicrobial drug status was unknown had a pooled death rate of 46% (95% CI 32%–61%) (Appendix Figure 4). Heterogeneity was significant (I^2 = 91%; p<0.01). The pooled death rates were similar when sensitivity analysis was conducted (Table). Antimicrobial drugs in the reports were aminoglycosides (90 courses), quinolones (24 courses), sulfonamides (22 courses), chloramphenicol (16 courses), tetracyclines (14 courses), and cotrimoxazole (3 courses). Six reports described time to from admission to antimicrobial drug administration, but the nonstandardized reporting precluded stratification by this measure.

Table. Sensitivity analysis of antimicrobial drug use and rates of pneumonic plague–related deaths, 1946–2017

Antimicrobial drug use	Confirmed cases, % (95% CI)	Total cases, % (95% CI)
Treated		
Primary plague	27 (14–47)	6 (1–31)
Undifferentiated	28 (6–72)	6 (1–31)
Not treated		
Primary plague	94 (82–98)	99 (22–100)
Undifferentiated	No data	100*
Unknown		
Primary plague	No data	29 (13–51)
Undifferentiated	42 (23–64)	51 (31–71)

*Crude analysis; model fails under this condition.

Conclusions

Our meta-analysis identified a 17% death rate for persons treated for pneumonic plague, in contrast to the 50% often reported in the literature. The death rate for the 2017 Madagascar outbreak was published after we completed our systematic review but is consistent with our findings (25% in confirmed cases) (*9*). These figures compare with 13.6% for patients who died in the hospital of community-acquired pneumonia; 12.3% who died of *Streptococcus pneumoniae* infection; 14.7% who died of *Legionella* species infection; and 32%–61% who died of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* species, or *Pseudomonas aeruginosa* infections (*10*). However, persons who died of other etiologic causes were predominantly elderly and had underlying conditions (*10*).

Our review indicated insufficient standardized data to stratify death by time from symptom onset to antimicrobial drug administration. The literature we assessed often stated that pneumonic plague is fatal in almost all patients who start antimicrobial drugs >24 hours after symptom onset. Generally, descriptions cite either 1 article, in which 11 patients treated within 24 hours survived and 2 treated after 24 hours died (*11*), or a handful of isolated case reports. However, case reports and series also exist in which patients survived despite starting antimicrobial drugs >24 hours after symptom onset (*12*–*14*).

An accurate estimate of death is crucial for several reasons. First, it is helpful for public health planning during outbreaks, including the allocation of healthcare resources and the development of social mobilization campaigns. The commonly reported high death rate associated with primary pneumonic plague contributes to fear and panic among healthcare workers and the public. For example, anecdotal reports indicating concerns during the Madagascar outbreak were the following: healthcare workers taking continuous antimicrobial drug prophylaxis, mass public use of over-the-counter antimicrobial drugs, asymptomatic persons visiting the hospital, and sick persons avoiding the hospital. Accurate assessment of death is also essential for clinical trial design. For example, the required sample size would be 134 (power 0.8, α = 0.025) for a binary outcome superiority trial in which the death rate in the control arm was 50% and the intervention was assumed to reduce death by 50% (similar to the assumptions in a clinical trial of gentamicin vs. doxycycline in Tanzania in 2002) (*15*). However, a sample size of 476 would be required in a trial in which the death rate in the control arm was 20%. A sample size renders a superiority trial unfeasible. Even during the Madagascar outbreak, the largest

outbreak of pneumonic plague this century, the final number of confirmed pneumonic plague patients was only 32 (*9*).

The major limitation of our meta-analysis is the sporadic reporting of clinical data and the relatively small number of cases for which antimicrobial drugs treatment status was described. Reporting bias in the literature also is likely, and pneumonic plague patients who survive are more likely than those who do not to be reported. Nonetheless, data indicate that the percentage of persons who die of treated pneumonic plague appears to be substantially lower than is frequently reported in the literature.

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Appendix

Articles Citing a 50% Mortality in Pneumonic Plague

Many articles that quote a treated mortality of 50% cite a 2000 Lancet paper by Ratsitorahina et al. (*1*), which describes a small outbreak of primary pneumonic plague in Madagascar in 1997. The mortality is not explicitly stated in the article, but the data show an overall mortality of 50%. However, the mortality amongst treated confirmed/probable cases is reported as only 10%. On reviewing publications that cited Ratsitorahina et al., we identified 9 that referenced a treated mortality of 50%, one of 40%, and none referencing other values (*2–11*). None of the articles explained how they derived this figure. One of these citations was a review paper published in the Lancet in 2007 (*11*). This review paper was also itself cited 9 times in relation to a treated mortality of 50% (*12–19*). Through examination of these publications' references, we identified a further 6 publications where a treated mortality of 50% was stated but not referenced (*20–25*), and only one publication mentioning a lower mortality (14%; source unreferenced) (*26*).

In the Ratsitorahina et al. paper, there were 18 cases in total. One patient (case 10) did not have plague. Therefore, there were 17 cases with plague. Of these, 10 appear to have received treatment (cases 6, 7, 8, 9, 11, 12, 13, 14, 15, 16 – as "eight patients with pneumonic syndrome were transferred" . . . "The patients were suspected to have pneumonic plague and thus were treated with streptomycin," and "The healer's brother died a few hours after admission"). Only 1 died out of these 10 (case 6). Eight patients did not receive treatment, and all died (cases 1, 2, 3, 4, 5, 17, 18). Therefore, the treated mortality is 10%, the untreated mortality is 100%, and the overall mortality is 53%.

Methods

We detailed whether confirmed cases alone, confirmed and probable cases together, or confirmed, probable, and suspected cases together were reported (and extracted numerical

data on the most specific classification available). Likewise, we noted whether articles included only primary pneumonic or undifferentiated pneumonic cases (defined by article authors using the term ‘primary’) and extracted data on the most specific measurement. Data on secondary pneumonic cases were not included. We defined antibiotic treatment as one or more doses of antibiotics currently or previously used for the treatment of plague: aminoglycosides, quinolones, tetracyclines, sulphonamides (alone), septrin, and chloramphenicol. Where data were duplicated in more than one publication, the largest of the overlapping cohorts that detailed antibiotic use were used. Data were reported as missing for each variable when they were not available in the article. Authors were not contacted for missing data. Where data were duplicated in more than one publication, the largest of the overlapping cohorts that detailed antibiotic use were used.

Descriptive statistics are presented as frequencies for categorical variables, means and standard deviations for normally distributed data, and median with range for other continuous variables.

Results

Antibiotics given included aminoglycosides (90 courses), quinolones (24 courses), sulphonamides (23 courses), chloramphenicol (16 courses), tetracyclines (15 courses), and septrin (3 courses). Six articles described the time to antibiotic administration in some detail, but the non-standardised way this was reported precluded stratification by this measure.

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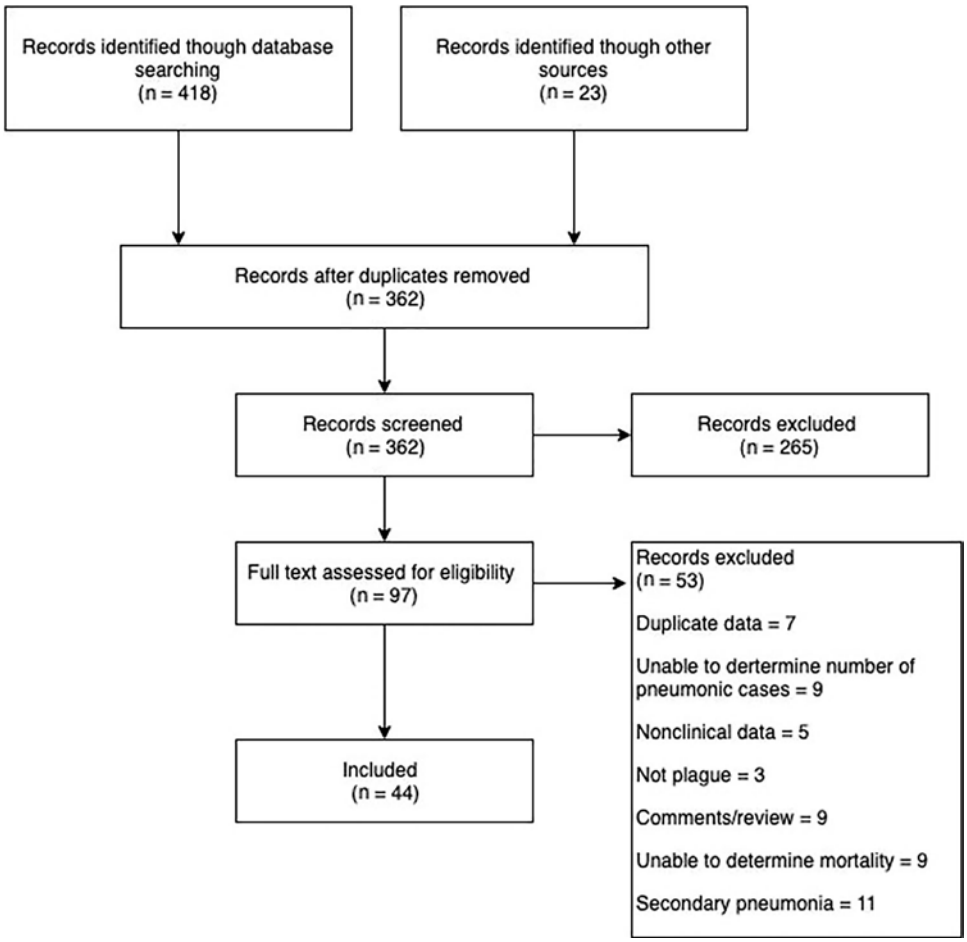
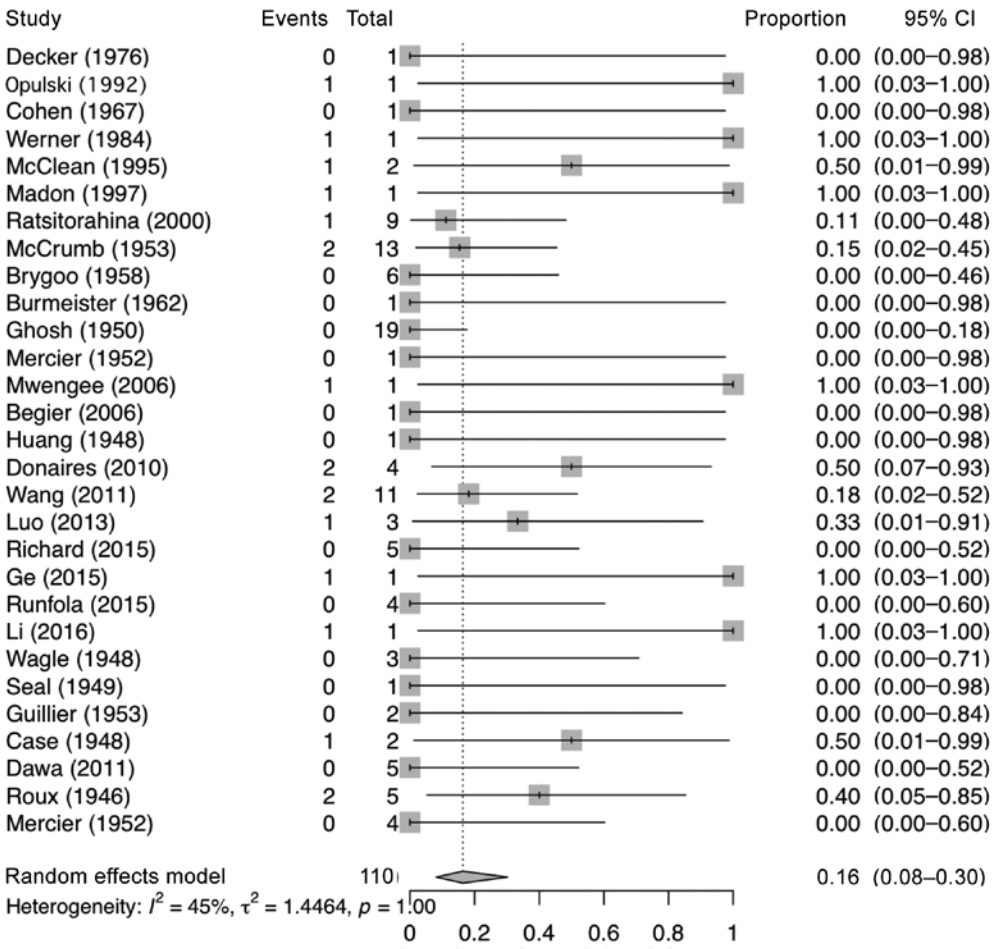
Appendix Table. Reports of pneumonic plague, 1946–2017*

Author/year	First year cases described	Country	Total		Antimicrobial drug use unknown		Treated patients		Untreated patients	
			Deaths	Patients	No. patient deaths	No, patients with unknown use	No. deaths	No. treated	No. deaths	No. patients
Begier (2006) (*27*)	2004	Uganda	1	2			0	1	1	1
Brygoo 1958) (*28*)	1957	Madagascar	35	41			0	6	35	35
Burmeister (1962) (*29*)	1959	USA	0	1			0	1		
de Ribes 1997) (*30*)	1989	Madagascar	52	91	52	91				
Cohen (1967) (*31*)	1966	Vietnam	0	1			0	1		
Cramer (1995) (*32*)	1995	USA	0	1	0	1				
Dawa (2011) (*33*)	2010	Tibet	0	5			0	5		
Decker (1976) (*34*)	1975	Zimbabwe	0	1			0	1		
Donaires (2010) (*20*)	2010	Peru	2	4			2	4		
Forrester (2017) (*35*)	2008	Uganda	8	18	8	18				
Gage (2000) (*36*)	1977	USA	2	5	2	5				
Ge (2015) (*37*)	2014	China	1	1			1	1		
Ghosh (1950) (*38*)	1950	India	0	19			0	19		
Guillier (1953) (*39*)	1948	Madagascar	0	2			0	2		
Gupta (2007) (*40*)	2002	India	4	16	4	16				
Huang (1948) (*41*)	1947	China	0	1			0	1		
Joshi (2009) (*42*)	2002	India	5	30	5	30				
Kamugisha (2007) (*43*)	1986	Tanzania	121	427	121	427				
Lewin (1948) (*44*)	1947	South Africa	1	2			1	2		
Li (2016) (*45*)	2014	China	3	3			1	1	2	2
Luo (2013) (*46*)	2005	China	2	5			1	3	1	2
Madon (1997) (*47*)	1995	USA	1	1			1	1		
McClean (1995) (*48*)	1993	Zambia	2	3			1	2	1	1
McCrumb (1953) (*49*)	1953	Madagascar	2	13			2	13		
Mercier (1952) (*50*)	1952	Madagascar	4	8			0	4	4	4
Mercier (1952) (*51*)	1951	Madagascar	0	1			0	1		
Mwengee (2006) (*9*)	2002	Tanzania	1	1			1	1		
Ogen-Odoi (2009) (*52*)	2006	Uganda	11	12	11	12				
Opulski (1992) (*53*)	1992	USA	1	1			1	1		
Ramasindrazana (2017) (*54*)	2015	Madagascar	6	14						
Ratsitorahina (2000) (*1*)	1997	Madagascar	7	17			1	9	7	7
Richard (2015) (*55*)	2011	Madagascar	15	20			0	5	15	15
Roux (1946) (*56*)	1946	Algeria	2	4			2	4		
Runfola (2015) (*57*)	2014	USA	0	3			0	3		
Seal (1949) (*58*)	1948	India	11	12	11	12				
Seal (1949) (*59*)	1948	India	13	14			0	1	13	13
Tieh (1948) (*60*)	1946	China	36	39					36	39
Trong (1967) (*61*)	1965	Vietnam	18	43	18	43				
Wagle (1948) (*62*)	1948	India	0	3			0	3		
Wang (2011) (*63*)	2009	China	3	12			2	11	1	1
Werner (1984) (*64*)	1980	USA	1	1			1	1		
Wong (2009) (*65*)	2007	USA	1	1					1	1
Wu (2011) (*66*)	2000	China	9	26	9	26				
Zhu (1993) (*67*)	1958	China	98	182	98	182				

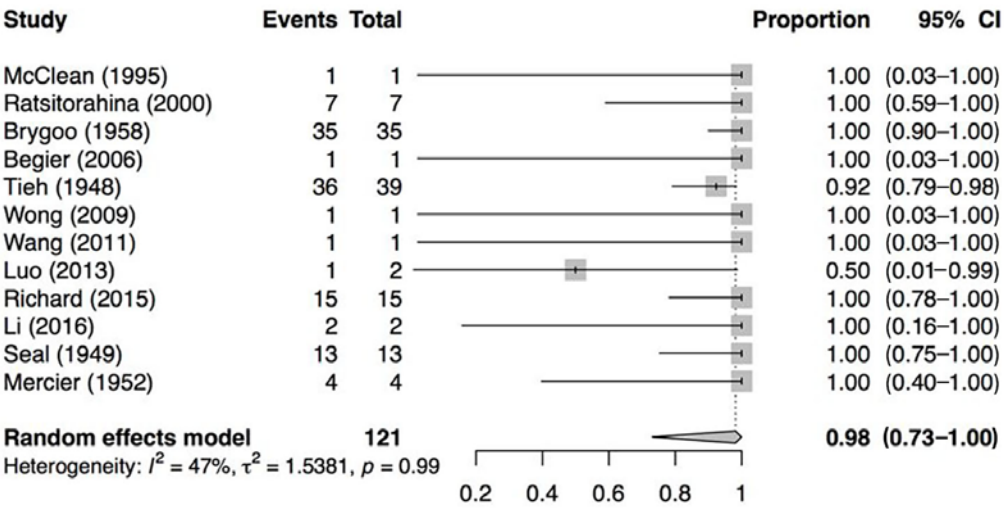
*Blank cells indicate data not available.



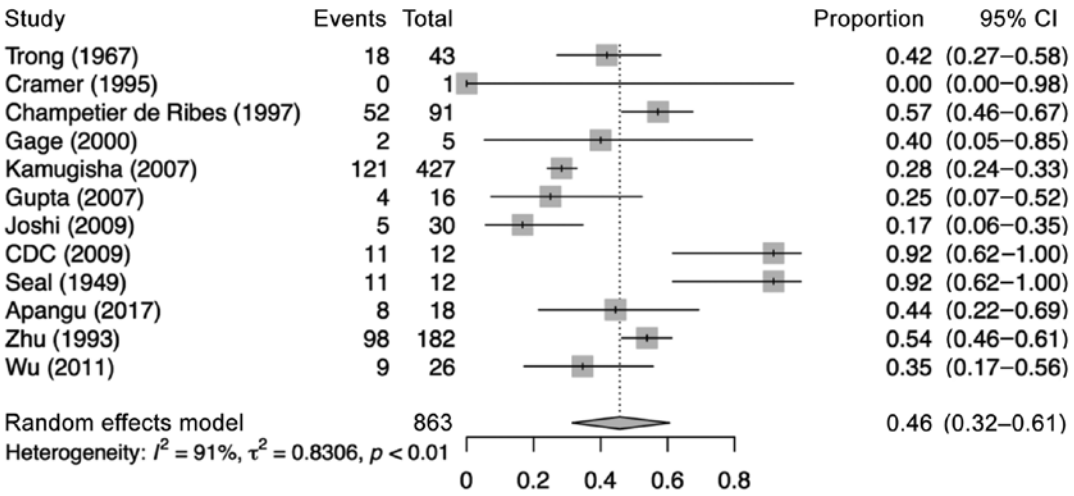
Appendix Figure 1. Overview of 362 reports of pneumonic plague, 1946–2017.



Appendix Figure 2. Forrest plot for death of all patients receiving antibiotics treatment for pneumonic plague in various countries, 1946–2015.



Appendix Figure 3. Forest plot for death of all patients with untreated pneumonic plague in various countries, 1967–2017.



Appendix Figure 4. Forest plot for pneumonic plague patients where antibiotic status was unknown, 1949–2016. Refer to Appendix Table for full citations.