A SYSTEMATIC REVIEW OF MURINE TYPHUS

A Thesis

by

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ABSTRACT

Murine typhus is a disease (brought on by infection with *Rickettsia typhi*) that has produced a surprising amount of morbidity when the relative dearth of literature on the subject is considered. Existing reviews of the subject are either relatively dated or surveys of all rickettsial disease with the majority of discussion dedicated to other agents, most often *Rickettsia prowazekii* or *Rickettsia felis*. This is likely due to the widespread consideration that Murine typhus is a "re-emergent organism" that was largely removed by the use of pesticides in the 1950s and has only recently re-emerged in much of the globe. I utilize a review of several databases to assess the literature regarding Murine typhus and to bring together summary information for a multitude of factors about the disease.

I found a remarkable heterogeneity of data regarding Murine typhus. Factors of specific note among the cases reviewed include the relatively high amount of probable exposures reported by patients, the difficulty at reaching the proper diagnosis experienced by physicians when attempting to ascertain the cause of symptoms, the many separate treatments used and differential efficacies of those treatments, and the disparate types of "severe" outcomes. This information may be of use in the coming years as Murine typhus continues to increase in incidence in many nations where it is present, and as it also appears in those nations where it has not been seen in the previous 50 years.

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Finally, thanks to my mother, Christine, and father, Kirby, for their encouragement and to my fiancée, Alexandra, for her patience and love.

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CHAPTER I

INTRODUCTION, METHODS, AND RESULTS

Murine typhus is a condition stemming from *Rickettsia typhi* (formerly *Rickettsia mooseri*) infection. This disease has been claimed to be "forgotten" or, alternatively, "re-emergent." While it is true that there was a sharp reduction in Murine typhus cases in most nations that used the pesticide DDT (dichlorodiphenyltrichloroethane) in the 1940s and 50s, this change was not necessarily a worldwide trend. Recently, an increase in interest in Murine typhus in scholastic research has corresponded with the increasing reports of the disease from many of those areas of the globe that had once been dubbed "typhus-free." The purpose of this study is to analyze newly available information and present summary statistics regarding recent trends in Murine typhus-related topics ranging from symptom presentation to treatment efficacy to the specific threats this resurgence poses to certain regions. A comprehensive, systematic review design was selected to accomplish this aim. The study presented here represents the first attempt the author has been able to find that analyzes Murine typhus cases over a long time period (from 1972-2014, 32 years). A previous study of nine years was located, as well as a summary representing seven years. This examination will also represent one of the larger non-serologic examinations of Murine typhus cases conducted, although no direct interventions are conducted. Previous studies have frequently been in response to outbreaks[1,2] or are reports of a single patient/manifestation/treatment of interest of the disease, and have been limited to either a single country or geographic region as well.

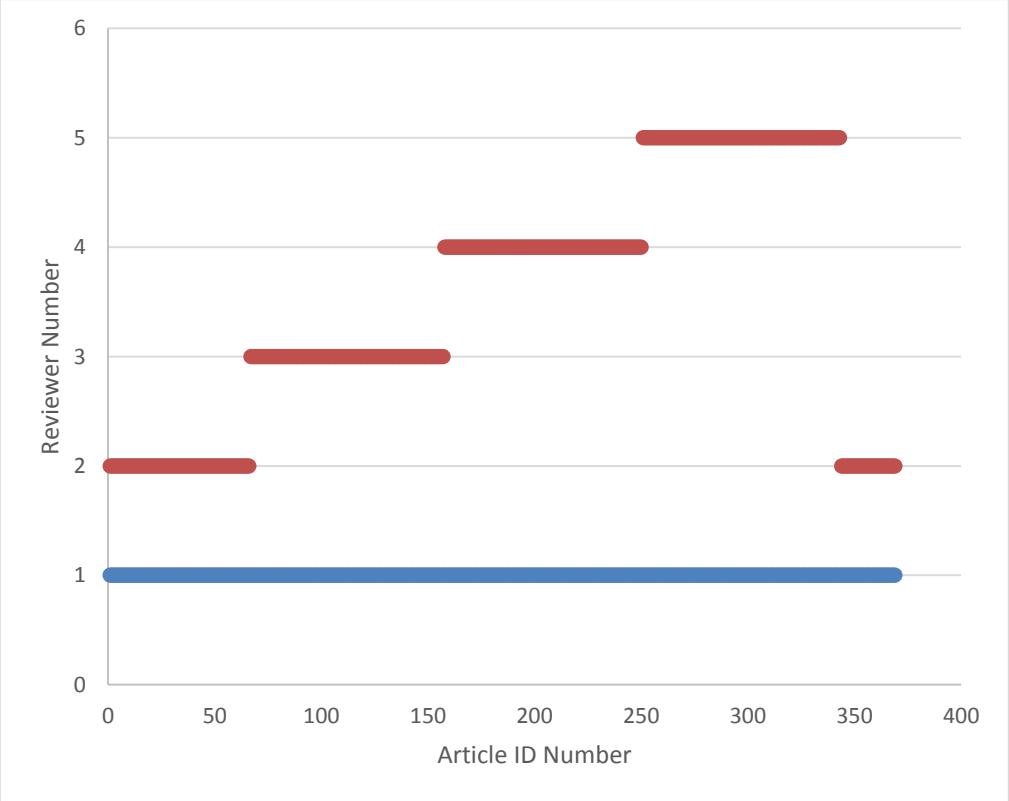
One advantage found in the multi-national plan detailed here is that I hope to eliminate national biases by bringing in data from multiple nations in several regions, another first as far as Murine typhus studies are considered. While there have been a number of large seroprevalence studies, I hope to provide some information (via summary statistics) on the way Murine typhus is studied, on the progression of the disease, on the way the disease is diagnosed and the effects an expeditious diagnosis has on the disease, and on the temporal-spatial trends of the disease over the previous 32 years.

I.1 METHODS

I conducted a systematic review of literature pertaining to Murine typhus by searching the MEDLINE, EMBASE, Global Health, and the Northern Light Life Sciences Conference Abstracts databases for articles. An external filter was applied to select only those studies that had occurred post-1972. After retrieval, each article was reviewed by two reviewers – one reviewer who reviewed every article to provide consistency and one reviewer who only analyzed 78 articles (Figure 1.1). These reviews were then compared with each other to determine inclusion or exclusion of a study. In those cases where a discrepancy occurred, both reviewers conferred with an additional reviewer and made a decision regarding the inclusion (or lack thereof) for the article. The following set of criteria was used when determining whether to exclude the article or not: Was the article in English? Was the article detailing Murine typhus infections? Did the article describe infections of humans? Geographic data were harvested from articles that met these criteria. A "second phase" of analysis occurred

afterwards in which each article was examined thoroughly to determine whether it was suitable for use in the building of summary statistics for the disease. The only criteria used for this step was the presence or absence of descriptions of the clinical characteristics of the case. While this step of abstraction used a slightly ambiguous definition, this kind of flexibility was necessary to ensure that larges studies that did not have information suitable for the development of summary statistics (for example, a seroprevalence study) would be excluded as necessary.

Figure 1.1: Graphical Representation of Reviewer Workload by Reviewer Number and Article Reference



I.1.1 Development of Phase 1 Data

"Phase 1" data refers to that data gathered using the aforementioned search and exclusion criteria with the exception of the "study design" criteria. This data was intended to provide a representation of regions where human Murine typhus is either being actively researched or reported in scholarly journals. Ten regions were selected for aggregated Murine typhus reporting: North America, Central America, South America, North Africa, Saharan and Sub-Saharan Africa, the Middle East, Europe, India, Asia, and Australia. These regions were selected based on pre-existing geographic convention. Additionally, data on year published was gathered and recorded. Multiple reviewers were used to select these articles, and corresponding inter-rater reliability (utilizing the Cohen's Kappa statistic[3] and Landis and Koch's criteria for assessment[4]) was calculated.

I.1.2 Development of Phase 2 Data

"Phase 2" data refers to that data gathered from the Phase 1 data with the additional exclusion factor of study design. Because this review was designed to compare certain summary statistics (described in detail later in this section), large scale seroprevalence studies were excluded, as they do not typically enter into sufficient depth of analysis of cases to provide the necessary statistics. As a result, studies that did not detail the clinical course of the disease in humans were excluded from Phase 2 (generation of summary statistics) analysis. Once articles were selected for Phase 2, the following data was acquired from said articles if presented: patient age, gender,

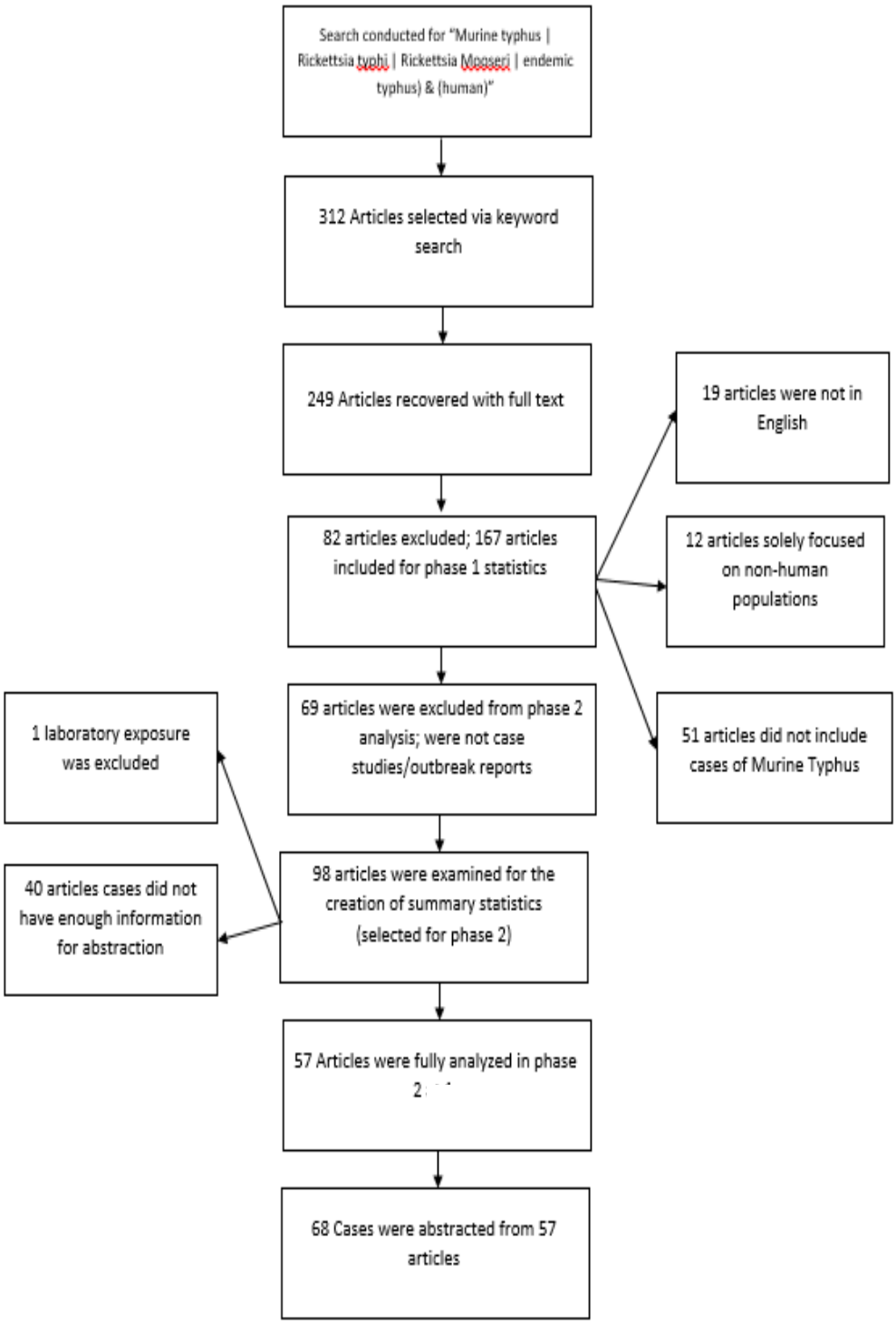
race/ethnicity, suspected exposure, total days from onset to end of symptoms, total symptomatic days (this number differs from total days from onset to end in cases with a relapse as mentioned in background), initial diagnosis, subsequent diagnoses, reported prior health history, initial treatments, final treatment, time from final treatment to resolution of symptoms (measured by release from hospital or first afebrile/otherwise asymptomatic day, whichever occurs first), oral fever temperature (in Celsius) at admission, maximum fever temperature (oral only, in Celsius), presence and type of rash, presence of headache during course of disease, additional symptoms (this box was kept free to accommodate as much freedom to record novel results as possible), and continuing symptoms (a measure of long term debilitation suffered by Murine typhus infection). If data could not be acquired for a minimum of eight of the 16 fields (the final two fields, additional and continuing symptoms, were not considered for inclusion criteria and were only included to facilitate a comprehensive analysis of unforeseen factors), the case was discarded for lack of information.

I.2 RESULTS

The search retrieved 312 unique articles (the data storage system automatically eliminated duplicated names, although there were four cases of articles with similar, although different names that otherwise described the exact same cases and were subsequently excluded). Sixty-one articles could not be recovered in a full-text format and were excluded from the study along with one copy each of the duplicated articles (for a total of 63 discarded). Fifty-one articles were excluded from analysis due to an

agent of interest other than Murine typhus. Twelve articles were excluded from analysis due to a focus on non-human populations. Nineteen articles could not be recovered in English. Sixty-nine articles were excluded from Phase 2 analysis for not reporting clinical information that would support the development of summary statistics but remained in Phase 1. Ninety-eight articles remained at the end of the exclusion phase. Of these, 40 articles were excluded due to lack of information of interest, and a single case was excluded as a laboratory exposure (the author did not feel this study was likely to represent an accurate portrayal of the course of the disease). Fifty-seven articles were used in the creation of summary statistics. Because Murine typhus articles sometimes include summaries of multiple cases, these 57 articles presented comprehensive information on 68 cases, an average of 1.17 cases per article. This search is described in an image in Figure 1.2.

Figure 1.2: Flowchart Describing Results of Selection Criteria



Analysis of inter-rater reliability was performed between reviewer one (who reviewed every article) and the other reviewers. This analysis was conducted using the inclusion/exclusion criteria for the Phase 1 statistics described previously (i.e., agreement between the two raters on the language of a document, whether or not the document assessed humans, whether the study design supported further analysis in Phase 2, and whether or not the document assessed Murine typhus). Cohen's Kappa method was used to assess agreement between the reviewers.[3] The subjective method of assessing results based on the paper by Landis and Koch was selected to assess IRR.[4] The results of the individual analyses can be found in Table 1.1. All Kappa scores fall well within the margin for "substantial" or "almost perfect" agreement, indicating a generally positive result for inter-rater agreement.

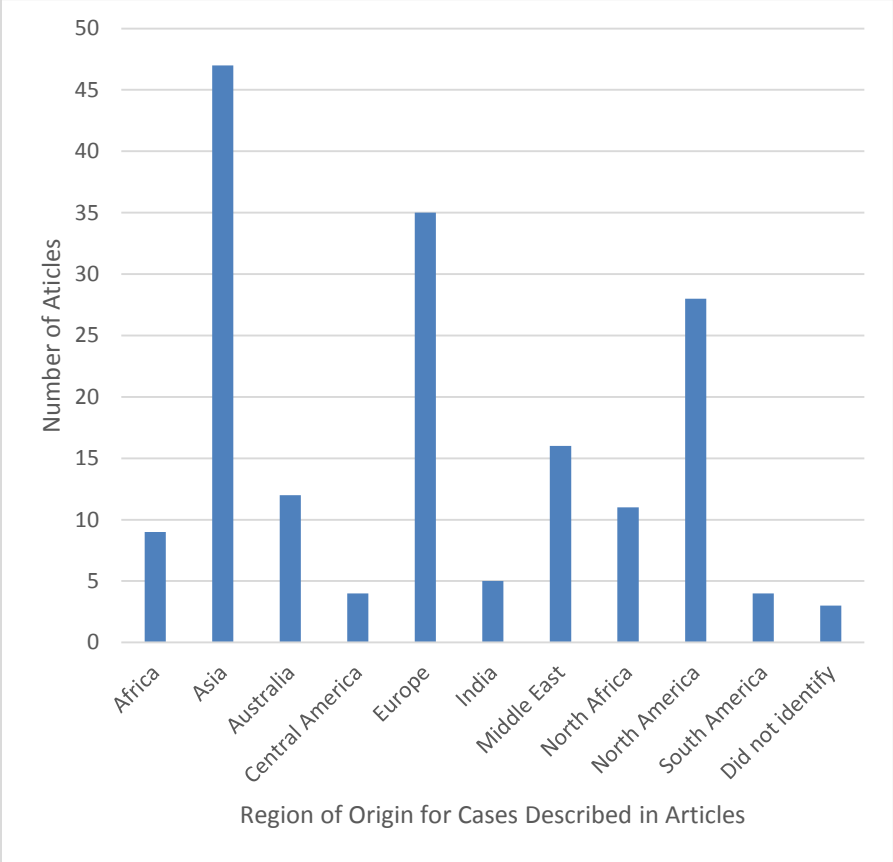
Table 1.1: Inter-Rater Reliability

Rater	1st rater:1	1st rater:1	1st rater:1	1st rater:1
Rater	2nd rater:2	2nd rater:3	2nd rater:4	2nd rater:5
Cohen's Kappa	.782	.611	.640	.828
Agreement Assessment by Landis and Koch[4]	"Substantial"	"Substantial"	"Substantial"	"Almost perfect"

I.2.1 Phase 1 Results

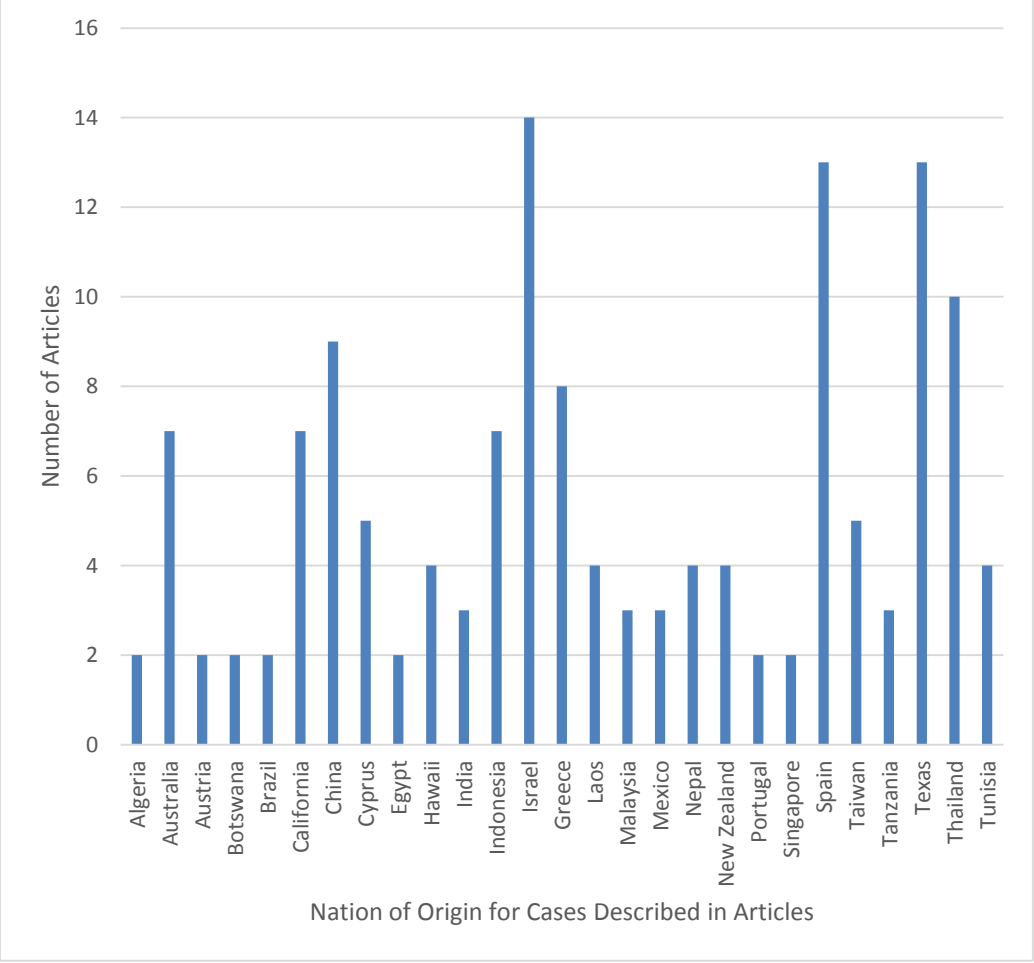
The regional results for the 167 articles selected for Phase one results are presented in Figure 1.3. The most common regions were Asia (46), Europe (31), and North America (26). Four articles were examinations of data comprised of two or more regions, and are reported as "did not identify."

Figure 1.3: Number of Articles by Region



Additionally, data on individual nation of origin was also acquired, and the nations that provide the primary source of Murine typhus articles are presented in Figure 1.4. Specific states of the United States are presented in independent columns due to variances in reporting. Only the most common reporting nations are presented in Figure 1.4.

Figure 1.4: Number of Articles by Nation



In terms of temporality, there has been an upward trend in Murine typhus publications yearly (with slight variances). This matches the upward trend in all medical literature observed over the study time of interest. After Winsorizing of top and bottom 2%, an approximately 300% increase since the beginning of the analyzed period was observed. This increase represented only 42% of the increase in total papers published in the corresponding databases. It is unknown as to why the increase was so much lower than might have been expected, but it may have to do with the relatively unknown nature of the condition.

I.2.2 Phase 2 Results

It is important to note that, at this phase of the study, reporting figures have shifted from the previously reported "articles" to the new figure "cases." This is due to the presence of multiple cases inside some articles. A single article may cover the course of disease, treatment, and recovery for two or more people. Indeed, one article has four well described cases and was included in all the statistics presented throughout this document. In an effort to most accurately report trends and to acquire as much data as possible, all cases with sufficient clinical data (at least eight/16 abstraction fields could be gathered) will be reported. Sixty-eight unique cases were selected for analysis based on the presence of sufficient data after abstraction. There was an average of 1.17 cases per report analyzed, as most Murine typhus reports contain only a single case. Race/ethnicity was only reported in 21% of cases, and so was excluded from later analyses. Similarly, subsequent incorrect diagnoses were reported for approximately

19% of cases, and thus were excluded from computation of summary statistics. Long term symptoms were relatively rare, but were considered an important clinical descriptor and were retained for description although no analysis of this variable was conducted.

Determining the characteristics of the population afflicted with Murine typhus is an important aspect of this project. The ages reported ranged from three – 81, with a mean of 38.42. The distribution of ages was approximately normal about the mean with a slight left skew. These factors were compared across region, but due to the relatively small sample size, it was difficult to determine specific regional trends. Fever at admission is notable in its constancy – while patients individually reached higher or lower temperatures, the means for regions remained remarkably similar. For example, North America had a 39.05 mean, Europe a 39.038, Australia a 39.07, and Asia a 39.069. Maximum fever temperature also was similar throughout the globe.

Further analysis of exposures reported is presented in Table 1.2. When multiple animal exposures were reported, each exposure was recorded and analyzed separately. Only animal exposures with supporting information in prior literature were included (there were three cases reporting injuries while swimming, three reporting contact with garbage or "unclean parts of the city", two reporting ill family members, one reporting mosquito bites. As none of these are supported by prior reports or by etiologic reasoning, and the reports are few in number, only those animal exposures that have been proposed as reservoirs/vectors for Murine typhus are reported formally). There was one interesting relationship discovered in this section – eight/12 (66%) of patients

who reported exposure to rats and mice were from North America. This represented 50% of all patients from North America who reported exposures.

Table 1.2: Exposures by Animal Type and Number Reported

Animal exposure	Reported exposures
Rats and Mice	12
Cats	9
Insects (Fleas and Ticks and bites of the two organisms)	7
Dogs	3
Opossums	2
Cattle	2
Exotic	1
Goats	1
Sheep	1

Data regarding diagnoses were readily available for most articles. Table 1.3 reports the different diagnoses reported for these patients.

Table 1.3: Initial Diagnoses of Murine typhus Cases

Initial Diagnosis	Number
Viral Illness	8
Murine typhus	4
Upper respiratory infection	3
Dengue Fever	2
Influenza	2
Rickettsial disease	2
Bacterial Endocarditis	1
Bacterial illness	1
Kawasaki syndrome	1
Malaria or Salmonellosis	1
Mononucleosis	1
Pharyngitis	1
Pneumonia	1
Scrub typhus	1
Typhoid Fever	1
Enteric Fever	1

The most common initial diagnosis made is that of "viral illness/disease." This diagnosis is made 12% of the time. The accurate diagnosis was made in only 6% of reported cases, while a diagnosis of "rickettsial disease," which is technically accurate though perhaps less-than-useful, was made 3% of the time. Scrub typhus is also a very similar disease (*Orientia tsutsugamushi*, the causative agent, has been considered a member of the rickettsial diseases).[6] Dengue fever, Influenza, and upper respiratory tract infection are also common false diagnoses. The "proper diagnosis" was made only in California, China (PRC), and Brazil. None of these nations (or states) are considered true hotbeds of Murine typhus activity, although each have seen an increase in Murine typhus reports in the past 20 years. None of the cases correctly diagnosed were prescribed the same course of treatment. All cases initially diagnosed correctly were eventually administered Doxycycline and made full recoveries. There were no other important similarities between the cases properly diagnosed, with the exception that each had a rash. There were no meaningful correlations relating to diagnosis by region; with such small sample sizes, evaluation of such trends becomes difficult.

Little information was provided in the reports regarding pre-existing health outcomes, however, one important fact should be noted here that 6% of cases were pregnant at the time they were examined. This author completed an extensive review of literature and could find no proposed reason, nor could I determine any theoretical reason, for this consistency of reports of pregnancy. While it is known that certain insect species do attack pregnant women at a higher rate, I did not find any report of such an increase among *Xenopsylla cheopis* or *Ctenocephalides felis*, the primary vectors for the

disease.[5] It is also possible that there is a "publication bias" that would have caused a selection effect but that may be unlikely when it is considered that single cases of murine typhus seem to be unique enough to be published without a corresponding health effect. Additionally, the increased surveillance of pregnancy was considered, but not a single case was diagnosed at a regularly scheduled medical examination – all cases reported after at least two days of fever. The majority of pregnant cases were located in Europe. While this effect does not likely represent a meaningful trend, the importance of this special population compels me to mention it as an avenue for potential future study.

Treatments commonly prescribed for Murine typhus are mentioned below. Initial treatments were noted and reported for all patients (Table 1.4). Doxycycline (a tetracycline drug) was most common, followed by Amoxicillin and Ceftriazone. Only half of the Doxycycline patients were suspected of rickettsial disease, Scrub typhus, or Murine typhus. Amoxicillin is a common broad-spectrum antibiotic that is frequently prescribed in cases of known or suspected bacterial illness.

Table 1.4: Initial Treatment

Initial treatment	Percent of treatments
Amoxicillin	19.6%
Ampicillin	5.6%
Azithomycin	5.6%
Ceftriaxone	16.8%
Clarithomycin	2.8%
Acyclovir	2.8%
Methanesulfonamide	2.8%
Clavulanic Acid	5.6%
Doxycycline	28%
Erythomycin	2.8%
Minocycline	2.8%
Natural recovery	2.8%

Final treatments for patients were recorded and reported in Table 1.5. Doxycycline alone was most common (42%), followed by Doxycycline in conjunction with any other drug or combination of drugs, then non-specific tetracylines alone. Tetracyclines are a family of drugs that include Doxycycline and are widely considered the gold standard for Murine typhus treatment. Chloramphenicol, an often mentioned treatment for Murine typhus, was present as well. A mix of other drugs and natural recovery (two cases reported recovery and specifically mention no use of other treatments) made up the remaining 21%.

Table 1.5: List of Final Treatments

Final treatment	Number treated
Doxycycline alone	28 (42%)
Doxycycline with other drugs	13 (19%)
Non-Doxycycline tetracyclines alone	8 (12%)
Chloramphenicol	4 (6%)

The only other result of interest in this study was regarding rash presence or lack thereof. The prevalence of rash at any point in the illness was found to be 68%, a relatively high number, although within the bounds of previous studies. This is likely

due to the diagnostic value of a rash in Murine typhus diagnosis causing cases to be selected. More information is needed to properly assess this variable.

The following chapters present an analysis of the data acquired in the systematic literature search and attempt to fully review Murine typhus.

CHAPTER II

A REVIEW OF MURINE TYPHUS

Murine typhus (the disease caused by *Rickettsia typhi*) infection is caused when the Gram negative obligate intracellular bacterium enters a human body after transmission from an insect vector.[6] This bacterium is a member of the family that also includes the causal agents for epidemic typhus (*Rickettsia prowazekii*), Mediterranean spotted fever (*Rickettsia conorii*), and Rocky Mountain spotted fever (*Rickettsia ricketsii*).[6] Murine typhus begins to cause symptoms after the disease enters the bloodstream, where it infects endothelial cells. In some cases, the disease has been known to spread to organs and can cause numerous medical problems as described below. Patients frequently present with a fever and headache, and occasionally with a rash. Left untreated, the disease can cause organ failure and even death, although this outcome is usually seen in elderly patients only.

Murine typhus spreads using a relatively classic reservoir-vector-human victim cycle, with various warm blooded animals standing in as reservoirs and several insect species serving as vectors. Indeed, the name (Murine) is purposefully reminiscent of Muridae, the Latin name for the largest family of rodents. It is then appropriate that the Forest rat (*Rattus rattus*) and the Norwegian rat (*Rattus norvegicus*) are commonly named as vectors, although other animals have been shown to play a role as reservoirs as well.[7,8] Along with other rodents (the common striped field mouse *Apodemus agrarius* and *Crocidura lasiura),*[9,10] the common Opossum(*Didelphus Marsupialis*)[11] has been

shown to serve as a reservoir in some cases, and animals as varied as dogs,[12] cats,[13] goats and cattle,[14] and even sheep[15] have been shown to be serologically positive potential sources of Murine typhus as well. It is of note that at least one study found that presence of domestic dogs and cats in a house did not increase risks to attain Murine typhus, and the role of these organisms in the transmission of the disease is a matter of at least some debate.[16] Some evidence exists to suggest exotics to include the elephant, orangutan, and lion may be reservoir candidates as well, although empirical research into the role of such creatures in Murine typhus transmission is lacking.[17] As new hosts are continuing to be added to the list of "original suspects" (the rodent species), there is little doubt that the above list of reservoirs will continue to increase.

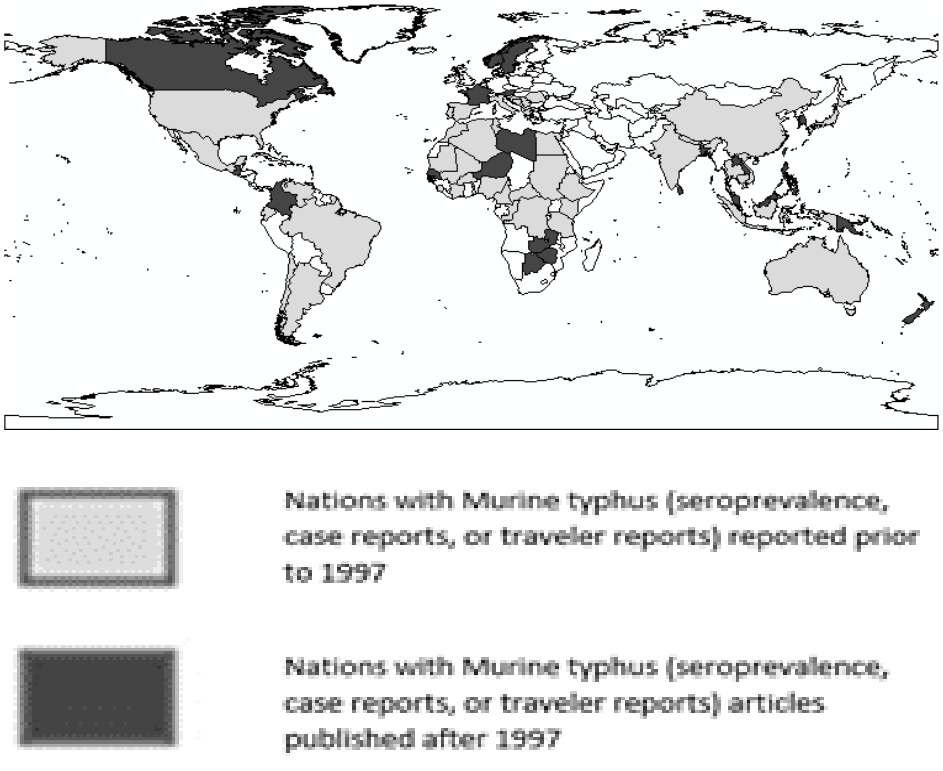
While these reservoirs are an important piece of the Murine typhus puzzle, the disease cycle is not fully understood until the arthropod vectors are taken into consideration. For much of history, the rat flea (*Xenopsylla cheopis*) was held to be the primary vector of Murine typhus.[18] This flea has shown the ability (in lab settings) to transfer the infection within seven days after taking a meal from an infected rat, although evidence exists to show that the disease transmission is modulated by temperature.[19] In recent years, an increasing number of studies have found that the cat flea (*Ctenocephalides felis*), often in conjunction with the opossum, also plays a role in the spread of the disease.[20,21] Another flea species, *Leptopsylla segnis,* has also been shown to carry the disease but does not readily parasitize humans.[22] This species may pose a special threat, however, in that is known to cause the accumulation of significant amounts of fecal matter on host rats.[23] This accumulation presents the possibility that a

limited range aerosolized version of the disease can emerge opening the possibility of airborne transmission. (The theory proposed in a 1983 study suggests that, the crushed fecal matter could enter the air in a powdered state and be inhaled, leading to infection).[24] Additional vectors include *Ctenophthalmus congeneroides*, *Rhadinopsylla insolita*, and *Neopsylla bidentatiformis*, which have been associated primarily with various species of mice.[25]

Murine typhus is a relatively ubiquitous and certainly overlooked condition. Estimates exist that suggest between one in three and one in eight persons with the disease will present themselves for medical assistance. This is likely due to the relatively mild symptoms many patients experience. A fever and headache are symptomatic of many conditions that are commonly ignored by the populace every day. The disease is interesting in that it is further complicated by the frequency with which patients experience "relapses" – periods of seeming recovery followed by a return of difficult symptoms.[26] While this phenomenon may be linked to the drug prescribed for treatment, patients without any treatment used can still experience a relapse. Seroprevalence surveys have found antibodies to *Rickettsia typhi* in significant fractions on every continent and in many countries as well, and cases have been reported clinically in these same locations.[27-32] A map from a study conducted in the 1990s was located, with a list of nations with positive seroprevalence studies, indigenous cases, or cases from travelers.[33] This map becomes more impressive when the implications are considered for the populace in these nations. The countries that reported Murine typhus contained an approximate

population of 5.1 billion.[33] A similar map (Figure 2.1) was generated (using ArcMap 10.2 ESRI Redlands, California) with information from the cases abstracted in the study as previously described. Areas indicated in grey were added from the previous source, and areas in black were new areas with Murine typhus (defined as a seroprevalence study, case report, outbreak, or case report of a traveler). The newly added nations add approximately 970 million persons, bringing the total world population living in nations with Murine typhus reports to more than 6 billion.

Figure 2.1: Murine typhus Worldwide



The disease itself presents in a troublingly inconsistent manner. Common symptoms, once referred to as the classic triad of Murine typhus, are present in 49% of patients.[34] The classic triad has been identified as a fever, headache, and rash, but these symptoms are not very useful in discriminating between diseases as they are associated with multiple conditions.[34] Additionally, the frequency with which these symptoms occur seems to be subject to a great deal of variance. Two relatively large studies in Greece and Cyprus, which have a relatively small geographic distance between them, revealed that 71% and 29% of patients showed a rash, respectively.[35,36] This sort of wild variance in presentation is indicative of Murine typhus, and it is very rare that any two of the limited large studies indicate the same proportion of patients with identical symptoms. This variance makes the diagnosis of the disease very difficult, and it is a well-known fact that earlier diagnoses allow the selection of desirable treatments more quickly which in turn makes treatment easier and can reduce debilitating symptoms.[37] Murine typhus shares certain symptoms (to include the presence of high fever for a long period of time) with Kawasaki syndrome, a fact which can further complicate diagnoses; however, a recent study found no association between Murine typhus and Kawasaki syndrome.[38,39] Certain other relatively minor symptoms to include myalgia, arthraglia, chills, nausea, among others also occur relatively frequently. The worst Murine typhus symptoms can be very debilitating indeed, with such negative outcomes as splenic rupture,[40-42] hearing loss,[43,44] cardiovascular conditions,[45] localized paralysis,[46] optical complications,[47,48] kidney failures,[49] pulmonary embolism,[50] intestinal difficulties to include obstruction,[51] liver complications,[52,53] and death.[30,54] There are reports of

Murine typhus in persons of virtually every age, both genders, and a myriad of racial/ethnic identities. Little information has been presented regarding socioeconomic status - while many cases are found in relatively poor regions, many instances of the disease are found in world travelers, a presumably wealthy population subset. While the disease is rare enough that little information on prior medical history of concern is available, several case reports exist of Murine typhus in pregnant women, and the association between the disease and pregnancy outcomes needs exploring.[55-57]

Murine typhus diagnosis is a matter of some debate as well. While it is widely accepted that a quicker diagnosis leads to a better progression from symptomatic to asymptomatic, making this diagnosis is quite difficult. A review of Murine typhus cases in Texas in the 1980s reported 20 diagnoses (not counting minute differences such as different forms of neoplasms and the reported "no diagnosis") in 80 patients with confirmed cases (a ratio of .25 diagnoses per case).[58] In modern case reports, diagnosis is often made on the basis of presenting symptoms confirmed by a serological report. The serological report of choice in recent years is the use of an IGG/IGM titer, a method that analyses antibody prevalence. The titer is exposed to Murine typhus antigen and then analyzed again. A four-fold increase in titer response is usually accepted as proof of the disease when taken along with expected symptoms, but there is some concern regarding the cross reactivity of the IFA titration system (most notably with *Rickettsia prowazekii*, epidemic typhus, and Rocky mountain spotted fever). Unfortunately, because this method takes more than a week to perform, it is rarely of use at the time an

initial diagnosis is needed, and is more frequently used to confirm presumptive diagnoses.

Several treatment options exist for Murine typhus. Choices of treatment can be debated, but the most common, and a widely accepted choice of treatment, is Doxycycline. Doxycycline is a member of the tetracycline antibiotic family, and is also frequently prescribed as a malaria prophylactic and as a treatment for acne and facial blemishes. Other treatments used have included Chloramphenicol,[26] Moxifloxacin,[59] Ciprofloxacin,[60] and the (relatively new) macrolide family of drugs.[61] The argument has been made that cases with rickettsial disease are likely to experience relapses when treated with non-tetracycline drugs; specifically Chloramphenicol.[26] More information on treatment choices is presented in the following chapter.

Finally, some mention of time in hospital and the associated costs needs to be made here. Of the Murine typhus cases analyzed in this study, it was found that the mean time (after outliers of more than 1 standard deviation were excluded) from admission to discharge was 10.82 days. This compares to a US national average of 4.8 days for all inpatients.[62] While there are innumerable factors that could be considered in determining the cost of this increased inpatient time, a very conservative estimate suggests that the financial costs of a day of inpatient stay in the United States averages around $2,100.[63] This means that an average of $12,600 in excess of the average cost of a hospital stay is incurred by the patient with Murine typhus. The aforementioned lack of surveillance prevents me from being able to make a yearly estimate of the annual financial burden of Murine typhus, but it is certainly well into the millions of dollars in

Texas alone. These costs do not include the loss of productivity incurred by the period of debilitation, the loss to quality of life for the sick individual and the community, or any of the special costs associated with an infectious disease. Given that a Murine typhus patient usually undergoes a comprehensive battery of tests during the diagnostic process, it is virtually certain that the costs of Murine typhus are higher than the average quoted above. A simplistic analysis might find that that time is largely due to the slow process of making a Murine typhus diagnosis – the mean time to recovery for the cases reviewed in this study once treatment begins is approximately 3.7 days when utilizing a tetracycline regimen. This could be interpreted to mean that 7.2 days are attributable to the inability to quickly decide which drug is necessary, which in turn stems from the previously mentioned diagnostic difficulties, in which case $14,700 could be attributed per case of Murine typhus to the inability to provide expeditious diagnoses. When combined with the significant morbidity and previously described suffering experienced by both the individual and their community, it becomes obvious that improving diagnostic capabilities should be a priority for public health in regard to Murine typhus.

CHAPTER III

A COMPARISON OF DRUG TREATMENT METHODOLOGIES FOR MURINE TYPHUS

There is a great degree of variability involved in the progression of Murine typhus. Patients develop symptoms, are diagnosed, treated, and respond differently than others with similar determinants. While making a proper Murine typhus diagnosis has been demonstrated to be difficult, deciding on a treatment regimen afterward may be equally difficult. There are several possible treatments for Murine typhus, and the debate as to the best treatment still rages in some corners.[26,59,60,64]

When assessing drug treatments, it is perhaps best to begin by considering the biological processes of the drugs themselves. The most popular drug family for treatment of Murine typhus is undoubtedly tetracyclines. The members of the tetracycline family that pertain to Murine typhus include Doxycycline (also known as vibramycin), the presumptive "gold standard" of Murine typhus treatment, Tigecycline, and Minocycline. This family has been in use for many years and efficacy data for these drugs, at least when used to treat Murine typhus, is readily available (studies have indicated significantly reduced risk of negative outcomes for each day earlier Doxycycline treatment is begun in patients with rickettsial disease).[65] Only one case of Murine typhus relapse occurred when tetracycline treatment was used. The family is also commonly used for such various treatments as acne, certain types of sexually transmitted diseases, and as a prophylaxis for malaria prevention.[66-68] Potential side

effects include rash, nausea, vomiting, and may cause teeth discoloration and bone growth inhibition in children.[69] One article of those generated in the review described in previous chapters documented possible resistance to the effects of Doxycycline against Murine typhus.[70]

While the tetracyclines are a well-known family for treatment of rickettsial disease, another almost equally well known family is the Amphenicol family. Chloramphenicol carries the standard for this family when it comes to Murine typhus as it has been a treatment used for the disease since its introduction in the 1940s.[71] It was noted in this early introductory study that "no highly satisfactory chemotherapeutic agent existed for the treatment of the rickettsial disease of man."[71] This same study also noted that, when studying cases of typhoid fever, (caused by *Rickettsia prowazekii*, a close relative of *Rickettsia typhi*) relapses of the disease occurred in two of ten patients tested.[71] This result was mimicked in the performance of Chloramphenicol recently in a study of the drug's efficacy against Murine typhus and Mediterranean spotted fever.[26] Chloramphenicol is also used against salmonellosis and certain streptococcus infections, although many organisms have emerged with resistance to the drug.[72,73] The drug has many side effects, although they are rarely of a severe nature and include diarrhea, headaches, and inflammation at various body sites.[74]

The quinolones are yet another family with some evidence of successful treatment for rickettsial disease. Moxifloxacin and Ciprofloxacin (members of this family) both have been used against Murine typhus, although opinions and results are varied.[59,60,64] The quinolone family (Moxifloxacin and Ciprofloxacin in particular) have

been used against *Escherichia coli*, *Klebsiella pneuomoniae*, Salmonella, and other organisms.[75,76] The risk of disease relapse when used against Murine typhus is negligible. Resistance has emerged against this family (and against these drugs in particular) in many organisms, and the minimum inhibitory concentrations of these drugs needed to prevent certain infections as well as the prevalence of any sort of resistance among organisms has increased rapidly in the past two decades among varied organisms and in several geographic locations.[77,78] Side effects to these drugs are usually rare but potentially extremely severe; neurologic complications can occur and in 2013, the FDA ordered that a warning of "possible permanent nerve damage" be placed on fluoroquinolones to include Ciprofloxacin and Moxifloxacin.[79,80]

Finally, the macrolides are another family of drug that has some effects against rickettsial disease in particular and against Murine typhus in specific.[61] This family includes Erythromycin, Azithromycin, and Clarithromycin, as well as others, although the first two were the only members of the macrolide family used in the review conducted as previously described. All cases of Murine typhus in pregnancy located in this review described previously were treated with a drug from this family (usually Erythromycin although one case was treated with Azithromycin).[55-57] These also encompassed all final treatments solely with macrolide drugs as the drugs were often used for initial treatment although later discarded. This class of drugs has seen relapses when used against Murine typhus, but this is rare (one example in the articles abstracted in the previously described review). Outside of Murine typhus, macrolides are also used to treat a variety of diseases including various skin disorders and sometimes asthma.[81,82]

Resistance to macrolides has been observed, especially in Europe and Asia.[83,84] Gastrointestinal disturbances and rare cases of "transient" deafness are observed side effects, although the possibility for hepatic conditions exists.[85]

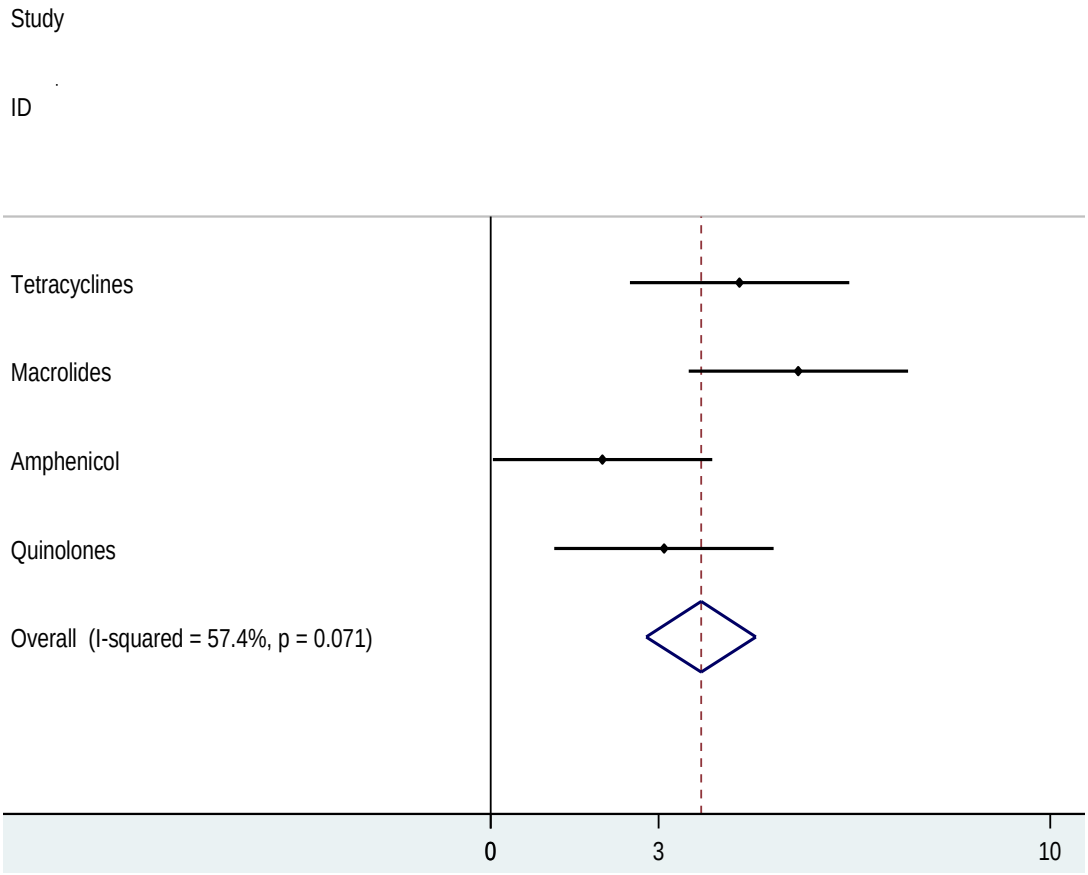
Using data from studies involved in the review conducted previously, the following Forest plot graphics were created using STATA 13.1 (STATACORP, College Station, Texas). The average time to recovery (defined as either defervescence, report of relief of symptoms, or release from hospital) for each drug type is reported in Table 3.1. Only single-use drugs were included and any treatments involving combinations of drugs were excluded.

Table 3.1: Treatments for Murine typhus by Mean Time to Recovery

Drug name or class	Uses	Mean time to recovery
Tetracyclines	37	4.45
Macrolides	3	5.5
Amphenicol	4	2
Quionolones	5	3.1
Overall weighted average of individual drugs in time to defervescence	49	4.18

A graphical representation of the times mentioned above is shown in Figure 3.1. A value of three is supplied as this was the previous average time to defervescence found in a large study of Murine typhus utilizing only the tetracycline and amphenicol families.[58]

Figure 3.1: Graphical Representation of Recovery Time by Drug Used



I did not have enough cases to properly analyze any drug and would hesitate before making a recommendation for any of them on the basis of the data harvested in the systematic review described previously. In lieu of unwarranted analysis, a table containing the (subjective) properties of Murine typhus treatments is included in Table 3.2

Table 3.2: A Brief Subjective Description of Treatment Options for Murine typhus

Drug name or class	Time to recovery	Side effect severity	Side effect frequency	Resistant organisms	Relapse frequency
Tetracyclines	Moderate	Severe in children and pregnancies,	Common in children and pregnancies,	Rare	Rare
Macrolides	Longest	Mild	Common	Common	Rare
Amphenicol	Shortest	Mild	Common	Common	Very Common
Quionolones	Moderate	Extreme	Rare	Common	Unknown

A further analysis of tetracycline was conducted, as it is the drug of choice for Murine typhus treatment in the United States. Tetracycline cases with no listed time to recovery were excluded from this analysis. The value 4.45 days to recover, as mentioned in Figure 3.1, has already been reported. This number was very dissimilar to the 1980s figure of three days to recovery.[58] Further analysis removed the three outliers greater than one standard deviation from the mean and the data was reanalyzed. These cases were removed and a new analysis revealed that the time to defervescence mean for Murine typhus with tetracyclines dropped from 4.45 days/case to 3.7 days/case. This still, however, represented a 22% increase in time to treat over the previously reported mean of three.[58] This previous study was selected as it was the largest available Murine typhus study with recorded treatments and contained both tetracycline and Chloramphenicol treatments.[58] A brief examination using Student's t-test revealed that this difference was classically significant with a p-value of .01. Unfortunately, the sample size involved in this analysis is likely too small to be of much use in determining any interesting information about this trend; however, more research into why this apparent increase has occurred could be fruitful.

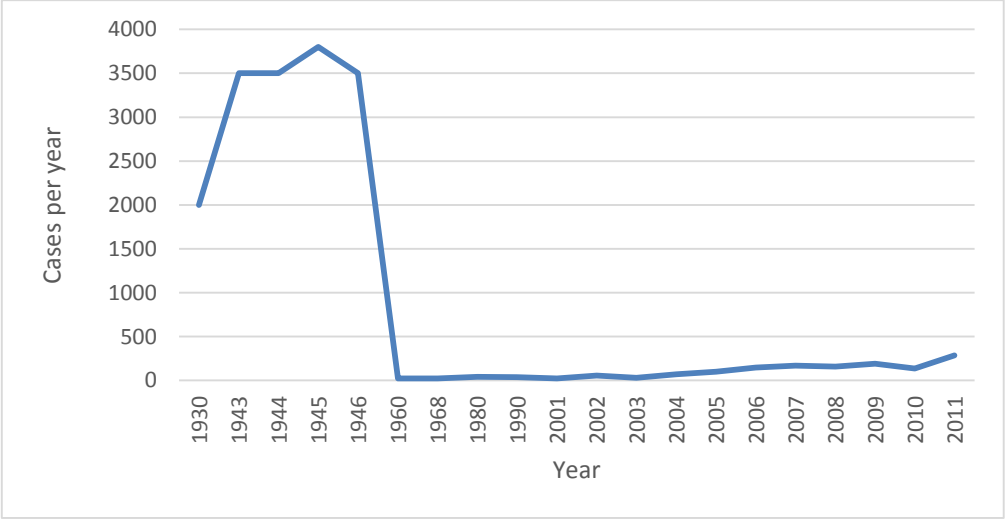
Murine typhus remains a difficult to diagnose and perhaps more difficult to treat disease, and treatment choices, once abundant, are becoming more limited as resistances continue to become more common to most of the treatments. Vigilant surveillance to detect any emergent resistance phenomena in Murine typhus is recommended.

CHAPTER IV

MURINE TYPHUS: AN EMERGING PUBLIC HEALTH THREAT FOR TEXAS

That Murine typhus is on the rise in many regions and nations is not under debate. Recent outbreaks have been reported in Hawaii,[86] California,[87] and Texas (most notably Austin),[88] while cases described as "the first report of Murine typhus from" or "Murine typhus in a place it was not expected" continue to be seen.[17] Texas experienced a thirteen times increase in Murine typhus cases from 2001-2011.[89] Figure 4.1 shows a visualization of Murine typhus in Texas from the estimates of 1930 to the decrease in the late 1940s and on to present day. The obvious decrease in the 1940s was likely due to the introduction of DDT as mentioned earlier and discussed further in this chapter.

Figure 4.1: Murine typhus Cases in Texas



The Texas Department of State Health Services (DSHS) mentions this increase as being attributable to two causes; increased surveillance on border counties (Mexico is an area of relatively high endemicity for the disease and there is a potential for movement of the disease)[89,90] and migration of Murine typhus into areas where it has not appeared before. Texas, like many regions in similar latitudes, offers an environment of sufficient warmth for the disease to flourish.[19] That Murine typhus is emerging in new counties in the state is widely accepted. From 2006 to 2010, the number of counties with clinically and serologically confirmed murine typhus reports rose from 13 to 18.[90] It is important to note that these cases could have been acquired in different counties than the county of residence for the reported cases. With this in mind, the trend reported should be considered, but the author hesitates to state that these specific counties are endemic areas for Murine typhus (a notable exception can be made for the counties on the border with Mexico, as this region of endemicity has been a consistent reporter of murine typhus in Texas).

While the reasons for this increase are difficult to identify definitively, it is worth a moment to mention the decline and subsequent ban on the use of the insecticide DDT at this juncture. A pre-DDT implementation paper found that after a first application of DDT in two counties in the United States, rats that were seroprevalent to Murine typhus decreased greatly when compared to those in a neighboring county that was untreated as well as to prior numbers.[91] A decrease from a high of greater than 60% of rats sampled yielding a positive seroprevalence test to a high of less than 20% in one county, and a decrease from a high of 50% to a high of approximately 10% in the other county was

reported.[91] The same study suggested that human Murine typhus cases reduced "considerably" and later "significantly," but no analysis was presented in quantitative terms.[91] The same paper stated that harvested numbers of *Xenopsylla Cheopis* (one of the main vectors of Murine typhus infection) did not return to the level prior to use of DDT within three years (unfortunately no further data was available).[91]

DDT was almost universally sprayed in the United States prior to 1972.[92] Many other nations, both industrialized and non-industrialized, used the chemical during the same time period to one degree or another. This may have resulted in a protective effect of sorts against the insects that harbor the disease, as DDT remains in the soil for years.[93] Even at the relatively low depth of only six inches, 30% of DDT applied can be found 15 years later, and the Environmental Protection Agency has estimated the half-life of DDT in soil to be 15 years.[93] It is possible that the protective effects of the insecticide have now dissolved to a sufficient level to allow for a rise in vectors and a subsequent rise in cases noted in the increased number of Murine typhus reports and surveillance data presented above.

While DDT was supremely effective, new insecticides have been developed in the past 50 years. Specifically, Fipronil has been shown to be effective in several ways – it can be applied directly to an animal and fleas will then ignore the animal. If this treatment lasts long enough (one or more years), widespread use of this chemical may lead to a significant reduction in eligible reservoirs for Murine typhus and a subsequent decrease in cases of the disease.[94] Several other non-chemical methods to prevent Murine typhus exist as well. Campaigns to promote public awareness about fleas, the

warning signs/how to identify flea bites, and how to prevent animals from coming into contact with fleas may also be of use. Finally, most major cities have rodent control programs. Improved rodent surveillance and disposal methods may be able to reduce the burden of Murine typhus in and of itself.

An increase in reported cases of any disease in a similar manner to that found in Murine typhus in Texas would be cause for concern. When considered with regard to the relatively unique difficulties that are accompanied by Murine typhus, this increase could represent a grave threat indeed. One of the major difficulties with Murine typhus is obtaining a proper diagnosis. An analysis of 80 patients in South Texas found that there were 20 unique diagnoses (not including "no diagnosis" and proposed differential causes of neoplasms).[58] Murine typhus represented 11% of the diagnoses made.[58] The analysis in this document showed an even lower number – only 5.8% of diagnoses were correct. Diagnostic ability has not increased since 1980 either. While Texas represented approximately 10% of the cases in phase 2 analysis presented earlier in Table 1.3, not a single case diagnosed properly on first attempt was located in Texas. Diagnostic efficiency increases are important due to the fact that early treatment with Doxycycline (not a commonly used antibiotic without suspicion of rickettsial illness) decreases risk of certain severe complications in rickettsial disease (to include death) by 20%.[65] Reasons for the difficulty of diagnosis are difficult to come by, but many answers have been theorized to include the relative ubiquity of common symptoms (fever, headache, and rash are not unique to Murine typhus), the long time delay required for appropriate analysis of a seroprevalence test (seroprevalence assays have been shown to have

confirmed 100% of Murine typhus diagnoses in a South Texas study within 15 days after presentation of symptoms), and the lack of attention granted to tropical diseases in general.[92]

While an increasing total number of Murine typhus cases is undoubtedly a worrying trend, a change in the geographical prevalence of Murine typhus cases merely compounds this concern. One additional potential difficulty concerns the treatments used for Murine typhus themselves. While Doxycycline has been accepted as the drug of choice for Murine typhus in recent years, there are problems associated with this drug. Doxycycline (along with many other tetracyclines, which are also efficacious against Murine typhus) has experienced shortages in recent years.[95] With an increasing number of Murine typhus cases, this could lead to a shortage at a time of great potential need. Doxycycline is contraindicated for use for pregnant women, who may or may not be at greater risk for Murine typhus acquisition, but are definitely a population with specific health concerns of interest to public health planners. Further, if supported by future research, the trend of decreased Doxycycline efficacy presented previously could also add to the list of problems Murine typhus poses for Texas.

Texas is a state blessed with many resources. However, the presence of a long border with an area of relatively high endemicity, an environment desirous to both vectors and reservoirs of Murine typhus, and the existence of the aforementioned trends and problems in Murine typhus management mean that the potential for a public health problem caused by Murine typhus is relatively high. Fortunately, all of the problems that the state faces (outside of the favorable environment and geography for Murine

typhus) can be addressed. An improvement in diagnostic ability does not seem impossible – an increased presence of rickettsial disease knowledge can help address some of the diagnostic problems immediately simply by raising awareness. A 2006 study found that a lack of knowledge was the third leading cause of certain missed diagnoses, and the diagnoses in question were primarily those much more common (cancer, heart disease, etc) than the currently rare Murine typhus.[96] While no small undertaking, improving knowledge in any population can be done in a relatively expeditious manner. The potential to incorporate Bayesian statistics, a set of methods well known for defining causality in the process safety world, may be useful to help improve diagnostic abilities. Additionally, as more studies are conducted regarding the organism, the amount of information available will continue to rise and new understandings of the way the disease presents itself and is diagnosed will likely follow. New pesticides to replace DDT have been developed and have been used in many areas. Drug shortages can be managed and alleviated with increased production or possibly simply better management of resources. Other drugs have been shown to be effective against Murine typhus – Chloramphenicol, Ciprofloxacin, and Moxifloxacin all have promise for use as treatments for Murine typhus, although at least some drawbacks exist.[26,37,59]

Murine typhus has the potential to pose a major threat to the state of Texas in the coming years. This threat may also "pass in the night" and never manifest as more than a few hundred cases a year. Regardless, continued research into Murine typhus, in conjunction with proper public health planning and surveillance, is important to maintain

the level of knowledge and readiness we now possess and to improve upon these qualities to reduce the potential for Murine typhus to present a public health threat to Texas.

CHAPTER V

CONCLUSIONS

The difficulties that Murine typhus poses for Texas, and for the world as a whole, cannot be understated. An increasing incidence, combined with the spread of the disease to new geographic regions means that there will be few nations not affected by the disease in the coming years. Difficulties with surveillance and pest control will continue to be a problem as well, as a pesticide with similar efficacy to DDT does not exist. If future research, both epidemiologic and on a microbial/biochemical basis substantiates the aforementioned observations with regard to decreasing treatment efficacy, another problem will have emerged. Additionally, the lack of ability to procure quick and accurate diagnoses of cases of Murine typhus will only exacerbate these other problems.

However, one advantage of a public health problem is the impetus that it gives to research. With Murine typhus, research is not so much a matter of "filling in the gaps" as it is establishing a base structure. One article reviewed eloquently described Murine typhus as "forgotten, but not gone."[97] This is an excellent summary of the situation with regard to Murine typhus. Many of the studies cited here were conducted in the 1940s. There is a great deal of room for innovation with regard to Murine typhus and the problems it poses, and many new studies will be needed to address these problems. Specifically, a large scale statistical study of Murine typhus treatments could substantiate the trends found in the section on drug use in Murine typhus. Additionally, an analysis of the minimum inhibitory concentrations of various drugs on Murine typhus

is likely to reveal some changes in the organism. The rise in tools of molecular epidemiology is encouraging, as inferences from these tools have allowed the tracing of strains of disease responsible for specific trends, and these tools could also be applied to help make similar determinations about Murine typhus.

Epidemiologically, analyses of certain populations (the young, elderly, groups of varying socioeconomic status and race, and especially pregnant women) are likely to be exceptionally fruitful. While this author chose not to formally present any findings concerning pregnant women, it is very likely that they are disproportionately affected by Murine typhus on the basis of their over-representation in the articles reviewed in this study. Research into prevalence of the disease and outcomes in pregnant women could be very productive.

Finally, a word should be spoken about the potential that Bayesian statistics holds with regard to further research into this organism. The prevalence of this methodology in the world of process analysis, combined with unique problems posed by Murine typhus, makes this the most likely way to address the aforementioned problems with diagnostics. The author attempted to form such an analysis of predictors of hospital stay length as a crude predecessor to a more properly designed Bayesian analysis of factors that influence hospital stay length. While the small sample size yielded an overly specific analysis that was of little use, these statistics remain likely the best way to analyze and improve the weaknesses found in identifying Murine typhus cases (barring a rapid analysis for the disease).

Murine typhus represents an emerging public health threat, but the world scholastic community is well equipped to meet this challenge. All that needs to be done is a bit of redirection of effort and the threat posed by Murine typhus can again be reduced until the disease is truly "gone, but not forgotten."

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