Antibacterial Fluoroquinolones as a Treatment for Mycoplasma Conjunctivitis in House Finches

(Word Count: 4196)

Abstract

Mycoplasma conjunctivitis, a disease caused by the *Mycoplasma gallisepticum* bacteria, has caused a rapid decline in the eastern *Carpodacus mexicanus* (house finch) population since the disease first broke out in 1994. The disease is characterized by the formation of large eye lesions that hinder the eyesight of house finches as well as the development of respiratory issues. Many treatments have been tested to fight mycoplasma conjunctivitis, but none have been conclusively proven better than others. Most treatments for this disease fall into two categories of antibiotics: macrolides and fluoroquinolones. The purpose of this study was to compare the effectiveness of macrolides and fluoroquinolones in the treatment of mycoplasma conjunctivitis. PCR analysis results for both macrolide and fluoroquinolone treatment trials on house finches were extracted from academic papers and statistically analyzed. The number of birds infected with *M. gallisepticum* was reduced significantly for both macrolides and fluoroquinolones (p = 2.33E-06 and p = 5.87E-05 respectively). The recovery rates of birds treated with fluoroquinolones were significantly higher than those of birds treated macrolides (p = 0.003625). These results indicate the Fluoroquinolone treatment as more effective than macrolides in eradicating *M. gallisepticum*, and they should be implemented to slow the decline of wild house finch populations.

Introduction

Since the outbreak of mycoplasma conjunctivitis among house finches in 1994, the eastern house finch population has been cut in half (Clark 2013). In 1994, citizen scientists in the Washington D.C. area involved in Project Feederwatch with the Cornell Lab of Ornithology noticed that many house finches (*Carpodacus mexicanus*) had red, swollen eyes when visiting their feeders (Dhondt et al., 1998).

This disease caused by the bacterium *Mycoplasma gallisepticum,* has been nicknamed “House Finch Eye Disease.” Since then, the disease has spread all over the United States: north into Canada, south to Florida, and across the Rockies into the west coast. Outbreaks of the disease are typically seasonal, with increased prevalence in the spring and a drop in autumn (Hosseini et al., 2006). Studies show that many of the infected birds cannot survive due to blindness and difficulty finding food, especially in the winter when food is difficult to find. Finches with mycoplasma conjunctivitis also experience difficulty breathing and other respiratory symptoms. The disease passes from bird to bird through close proximity and bodily contact, creating a higher rate of occurrence in flocks. Other species have the ability to carry the disease, but most do not struggle with the physical symptoms faced by house finches. Due to the visitation of house finches to bird feeders, the close proximity of many birds in a flock leads to the spread of the disease (Adelman et al., 2013).

a.

b.

Figure 1: *a.* Healthy *Carpodacus mexicanus* (House finch) next to *b.* A bird infected with *Mycoplasma gallisepticum* (Hartup et al., 1998).

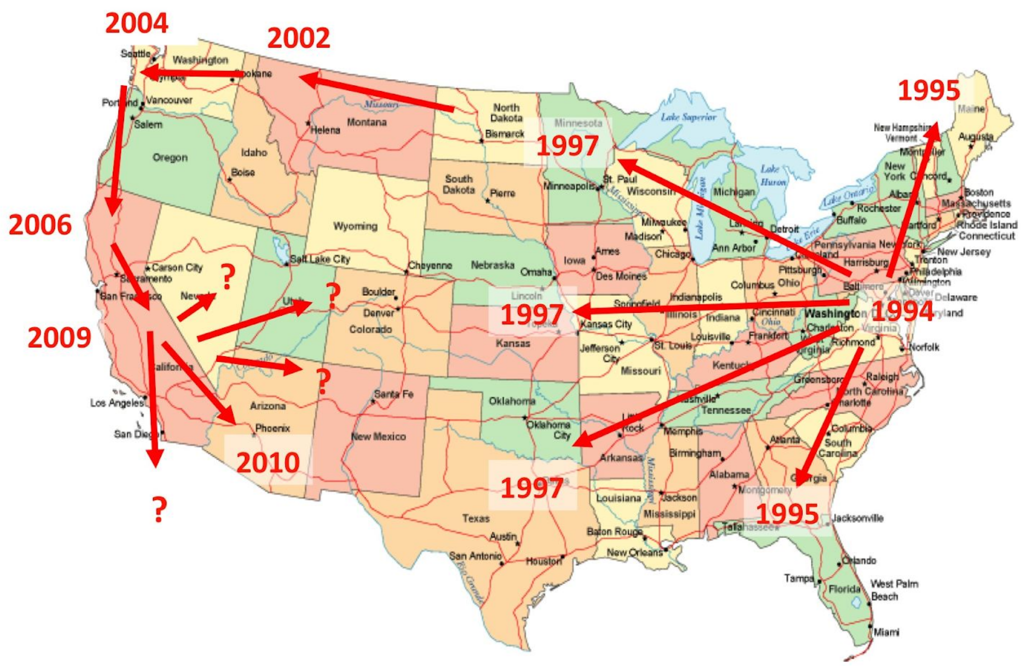


Figure 2: Retrieved from Project Feederwatch at the Cornell Lab of Ornithology. The spread of house finch eye disease from its breakout in 1994 through the year 2010. Cleary, the disease has spread all across continental United States and is currently affecting house finch populations throughout the country and into Canada and Mexico.

Although the wild strain of *M. gallisepticum* was first discovered in 1994, the majority of research conducted on the topic began in 1997 and has continued ever since. Researchers at North Carolina State University evaluated the known methods of treating the disease (Mashima et al., 1997). In the study, the researchers treated birds with two medications at a wildlife rehabilitation center, using tylosin tartrate as an oral drug combined with ciprofloxacin hydrochloride ophthalmic solution as topical eye drops. Sixteen of the birds treated showed no signs of the disease; no eye lesions were present, and PCR analysis showed no signs of *M. gallisepticum* remaining. These two medicines were proven effective and show evidence of possibly being the best treatment options available. In 1998, several studies aimed to identify patterns present with the disease in order to determine seasonal factors of the disease as well as the impact bird feeders have on the disease. Researchers at the Cornell lab of Ornithology conducted a survey of 778 volunteers, collecting information on the types of birds that visit their bird feeders, the health of these birds, and the types of feeders used. They concluded that tube style feeders used in winter months provided the strongest risk of passing the disease, and modifying bird feeding practices based on the time of year could help slow the spread of disease (Hartup et al., 1998). In another study later that year, researchers from the same University conducted a survey to determine the extent to which the disease is spreading. They found that the disease had affected the entire eastern house finch population’s territory by this time, and that house finch population levels declined in the winter in areas with a high concentration of the disease (Dhondt et al, 1998).

In 2001, researchers at the University of Minnesota tested alternative medications at a wildlife rehabilitation center. Twelve birds were admitted to the center and treated with oral enrofloxacin and ophthalmic gentamicin over a twenty-one day period. The visible eye lesions that characterize the disease were almost completely removed from the birds, but *M. gallisepticum* remained present as observed with PCR analysis (Wellehan et al., 2001). This indicates that these treatments are not completely effective. In another study that year, researchers at Auburn University maintained a flock of captive house finches experimentally infected with *M. gallisepticum.* Their objective was to see if the disease had changed since it was first discovered. They found evidence that the relationship between the bacteria and its host was evolving (Roberts et al., 2001).

By 2004, the disease had reached the west coast, and researchers at the Cornell Lab of ornithology set out to find patterns of how the disease changes seasonally. Compiling surveys from November 1994 to March 2001, they were able to conclude that outbreaks are most common in autumn months and carry into cold winter periods, when feeder use is high (Altizer et al. 2004). Researchers at the same University attempted to examine the infectious path of the disease by infecting birds kept in individual cages instead of in a flock. More birds survived than expected, but this was due to the constant environmental conditions and food supply provided to the birds (Kollias et al., 2004). Later that year, researchers at Auburn University conducted a similar study in which they observed the development of house finch chicks infected with *M. gallisepticum,* concluding that infected chicks took longer to leave the nest (Nolan et al., 2004).

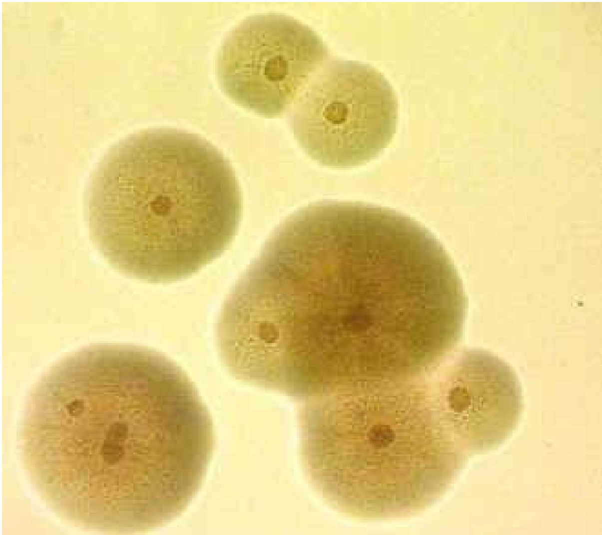


Figure 3: *Mycoplasma gallispticum* bacteria (Roberts et al., 2001).

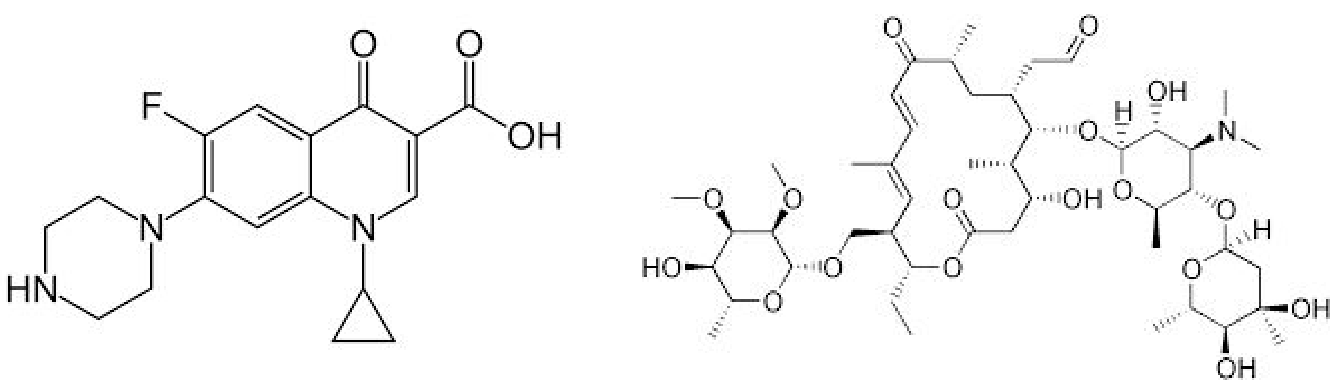
In 2008 researches at the Cornell Lab of Ornithology continued their research on this topic. In this study, house finches, house sparrows, and American goldfinches were captured and infected with *M. gallisepticum*. House sparrows were hardly affected at all, American goldfinches were able to carry the disease but did not show physical symptoms, and house finches were intensely infected (Dhondt et al., 2008). This shows that other species that house finches can contribute to spreading the disease. In 2010, researchers at the Cornell of Ornithology teamed up with researchers at North Carolina State University to determine if a different bacteria, *Mycoplasma sturni,* could also be a cause of conjunctivitis in house finches. Captive birds were experimentally infected with both bacterias, but *M. gallisepticum* remained the only bacteria to produce conjunctivitis (Ley et al., 2010).

A few years later, in 2013, researchers at Virginia Tech investigated whether feeder use would cause an increase in mycoplasma infection. Birds were kept in an enclosed environment with feeders available that were covered in the *M. gallisepticum* pathogen. By altering temperatures in the enclosure, feeder use could be altered, as the birds would visit feeders more at colder temperatures and less at higher temperatures. The researchers could not conclude that there was a significant correlation between feeder use and infection of the bacteria (Adelman et al., 2013). The following year, researchers at the Cornell Lab of Ornithology conducted a large study in which they captured as many wild birds as possible and tested them for *M. gallispeticum* using PCR, regardless of the bird's species. In every bird species that was captured at least twenty times, *M. gallisepticum* was present in some amount (Dhondt et al., 2014). This shows that all bird species can be carriers for the disease. In 2015, the same researchers tried infecting black-capped chickadees with the disease, and once again, they found that species other than house finches can carry the disease but do not develop physical symptoms (Dhondt et al., 2015).

In 2015, researchers at Virginia Tech continued their research on the effects bird feeders and other factors have on house finch eye disease. This time, they were able to find conclusive evidence that feeder use encourages the spread of the disease. In the study, researchers held a captive flock and infected the birds that used bird feeders the most. When the disease spread to the rest of the flock, it was concluded the disease spread through the feeders (Adelman et al., 2015) In a different study that year by the same researchers, finches were kept in conditions that promoted aggression between birds, specifically by keeping two male finches together during breeding season. However, the increased aggression between the birds did not change how the finches reacted to the disease (Adelman et al., 2015). The majority of research on this topic is on the characteristics of the disease, but not on how this disease should be addressed and treated.

Several methods have been researched by ornithologists and field biologists to combat the disease, but none have been established and implemented on a large scale. Although removing bird feeders can reduce the close proximity of the finches, the removal of the food source may be just as damaging (Clark 2013). Another method tried is the use of oral medicine. Although this does not cure the disease, the physical symptoms are removed almost completely, which will give the birds nearly the same quality of life they had before ever being infected (Wellehan et al., 2001). Medicines tested include ciprofloxacin hydrochloride ophthalmic solution used in eye drops, tylosin tartrate, an oral medicine mixed with drinking water, oral enrofloxacin, and ophthalmic gentamicin eye drops, among many others (Mashima et al., 1997).

Most treatments for mycoplasma conjunctivitis fall into two categories of antibiotics: fluoroquinolones and macrolides. Examples of macrolides include tylosin and tulathromycin, and macrolides typically are named with -mycin suffixes. Examples of fluoroquinolones include enrofloxacin, danofloxacin, and ciprofloxacin, and fluoroquinolones are typically named with -oxacin suffixes. Both drug types are often used for veterinary purposes, usually in bovine, equine, porcine, and avian species. (Papich 2016). The objective of this research was to determine which antibiotic group proves most effective and to propose its implementation on a large scale to eradicate mycoplasma conjunctivitis.



a. **b.**

Figure 4: **a**. Ciprofloxacin, a fluoroquinolone (Hooper, 2001) **b.** Tylosin, a macrolide (Siegrist et al., 1981).

To determine which medicine is most effective against *M. gallisepticum*, systematic literature review was used to analyse peer-reviewed studies focussing on Polymerase Chain Reactions (PCR). This test (PCR) can be used to detect *M. gallisepticum* in house finches before and after medication is applied, and most studies on house finch eye disease use this test. Therefore, comparing PCR readings from different studies showed which medicine is most effective. The process of PCR analysis involves the amplification of DNA and the creation of millions of exact DNA replications. The DNA polymerase enzyme uses existing DNA as a template to generate new DNA strands. Then, a chain reaction makes enough DNA until the DNA is visible to the naked eye (Edwards et al., 1991). Papers referenced in this study used PCR to amplify DNA from eye swabs of house finches that have been infected with *M. gallispeticum.*

Currently, not much is being done to combat Mycoplasma Conjunctivitis. Since the discovery of its outbreak in 1994, many studies have been conducted to research the spread of the disease and the symptoms associated with it, as well as possible treatment. However, no single treatment has been agreed on and implemented on a major scale, due to the debate as to which treatment is most efficient in the elimination of the responsible bacterium. The majority of studies on this topic focus on how the disease is spread or how the disease develops once a bird is infected. Other studies focus on the effectiveness of a single treatment but do not compare them to other treatments. At this rate, many treatments will be discovered, but none will ever be implemented. This study aimed to determine the best medicine so that a single treatment can be agreed upon. Once this is accomplished, medicine can be used to save house finches and prevent further damage to the species.

House finches play an important role in their ecosystems. They eat primarily seeds and some fruits, which limits the growth of wild plant species (Beal, 1907). Cooper's and sharp-shinned hawks prey on house finches, while other bird species, rodents, and snakes eat the eggs of house finches (Cannings et al., 1987). A decline in house finches could hurt theses predators as well. Clearly, finding a cure to house finch eye disease proves an important task, for many groups would be affected by their extinction.

Purpose

Since the original outbreak of the *M. gallisepticum* conjunctivitis in 1994, much has been learned about the disease. The majority of research on the topic pertains to the spread of the disease in an attempt to predict how the disease will affect house finch populations in the future. Significantly fewer studies have investigated ways that people can help to combat and eradicate the disease. Several medications have been tested over the years, and many have been proven effective, but no single medication has been confirmed as the best choice. However, if there is ever a possibility for a medication to be implemented on a large scale, then one must be proven as the most effective and efficient option. The purpose of the present study was to compare the known medications and prove one as the best option for implementation to combat mycoplasma conjunctivitis in house finches.

Hypothesis

Initial Research Question:

Are antibacterial fluoroquinolones or antibacterial macrolides more effective in the eradication of mycoplasma conjunctivitis?

Null Hypothesis:

Both fluoroquinolones and macrolides are equally effective in treating mycoplasma conjunctivitis.

Alternative Hypothesis:

Fluoroquinolones will prove more effective than macrolides in the eradication of mycoplasma conjunctivitis.

Methods

Data for this study was collected using systematic literature review. This method of research was chosen due to the limitations of this being a high school project. In order for experimentation to be used in this project, live house finches would need to be captured with mist nets or some other method and kept in cages. The birds would then be tested for *Mycoplasma gallisepticum* and treated with different antibiotics. The biohazardous and ethical nature of this experiment would not be allowed in a high school setting, so a systematic literature review was conducted instead. Peer-reviewed scholarly articles retrieved from the internet acted as the main source of data. Peer-reviewed articles related to house finch eye disease were retrieved by searching in online databases such as Ebscohost, Google Scholar, Elsevier, BioOne, JSTOR, and PLOS, among others. Specifically, studies that used PCR (Polymerase Chain Reaction) analysis were used to measure the effectiveness of various medicines in lowering the quantity of *Mycoplasma gallisepticum* bacteria from the body of house finches. Since PCR is used in most studies involving mycoplasma conjunctivitis, PCR readings from different papers were used in order to draw conclusions on which medicines were most effective, even though data came from different studies. The time frame of the articles used for data ranged from when the disease was first discovered in 1994 until 2017.

In the papers used for data, PCR analysis was effective in amplifying DNA from the *M. gallisepticum* bacterium. If *M. gallisepticum* DNA was amplified and detected in PCR analysis, then the house finch was determined to be infected by the bacterium. The numbers of birds infected by *M.*

gallisepticum before and after treatment were extracted from papers for data. If a bird was not positive of *M. gallisepticum* by PCR after treatment, then it was determined that the bird was cured. When extracting data, the total number of birds infected at the beginning of treatment and the total of birds still infected after the treatment was completed in each study were recorded. If a study did multiple trials of the same treatment, then all trials were recorded.

All data used came from experiments that used either antibacterial macrolides or antibacterial fluoroquinolones to treat mycoplasma conjunctivitis in house finches. Data on the treatment and PCR results of birds treated with macrolides and fluoroquinolones were recorded separately in Table 1. Recovery rates of the birds in each treatment were calculated by dividing the number of birds that were not infected at the end of treatment by the total number of birds that were treated. This data was recorded in Table 2.

In order to evaluate the effectiveness of each treatment, statistical analysis was conducted for each treatment. Paired t-tests were conducted for both macrolides and fluoroquinolones to determine the effectiveness of each treatment and to determine whether there was a significant difference between the number of birds infected before treatment and the number of birds still infected after treatment. To compare the two treatments to each other, a two-sample T-test assuming unequal variances was conducted with the recovery rates of each treatment. A $p < 0.05$ was considered statistically significant for each of the T-tests. All statistical analysis was carried out using Microsoft Excel 2007.

Results

Data was found on both macrolide and fluoroquinolone antibiotics that were used against the *M. gallisepticum* bacterium . Macrolide drugs included primarily tylosin, along with tiamulin and tylvalosin. Fluoroquinolone drugs used included enrofloxacin, danofloxacin, and ciprofloxacin. Data was collected from 8 groups treated with macrolides and 8 groups treated with fluoroquinolones. The number of birds positive by PCR before each treatment and then after each treatment were recorded (Table 1). The number of birds positive of *Mycoplasma gallisepticum* decreased significantly when treated with macrolides (p = 2.33E-06), as well as when treated with fluoroquinolones (p= 5.87E-05).

The number of birds that recovered as a result from each treatment session was calculated from subtracting the number of birds infected with *Mycoplasma gallisepticum* after treatment from the number of birds infected before treatment. Recovery percentages were then calculated from these values (Table 2). The average recovery percentage of birds treated with macrolides and the average recovery percentage of birds treated with fluoroquinolones were 67.825% and 90.675% respectively (Figure 3). The recovery percentages of birds treated with fluoroquinolones were significantly higher than those of birds treated with macrolides (p = 0.003625). The standard deviation of the percentages of birds treated with macrolides was 15.31766021, and the standard error of these percentages was 5.415610703. The standard deviation of the percentages of birds treated with fluoroquinolones was 13.75964597, and the standard error of these percentages was 4.864769485.

Table 1: Persistence of *Mycoplasma gallisepticum* in PCR detection through two antibiotic treatment types.

Antibiotic Type	Birds Positive by PCR Before Treatment	Birds Positive by PCR After Treatment	Data Source
Antibacterial Macrolides	45	14	Tanner et. al
	45	18	Tanner et. al
	50	20	Jordan et. al.
	50	16	Jordan et. al.
	45	25	Migaki et. al
	45	14	Migaki et. al
	45	1	Migaki et. al
	36	9	Forrester et. al
Antibacterial Fluoroquinolones	45	0	Tanner et. al
	45	5	Tanner et. al
	12	4	Wellehan et. al
	50	14	Jordan et. al
	45	1	Migaki et. al
	45	0	Migaki et. al
	45	0	Migaki et. al
	25	0	Stanley et. al

Table 2: Percentages of bird recovery from ailments caused by *Mycoplasma gallisepticum* determined by PCR analysis.

Antibacterial Macrolides	Antibacterial Fluoroquinolones	Data Source
68.9	100	Tanner et. al
60	88.9	Tanner et. al
60	66.7	Jordan et. al., Wellehan et. al
68	72	Jordan et. al
44	97.8	Migaki et. al
68.9	100	Migaki et. al
97.8	100	Migaki et. al
75	100	Forrester et. al, Stanley et. al

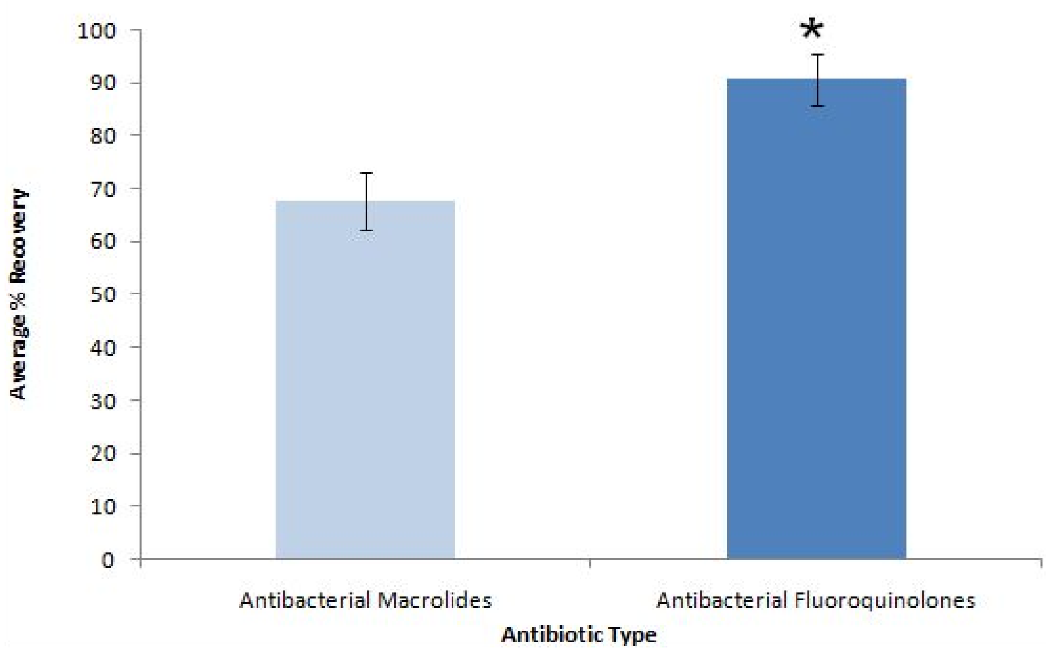


Figure 5: This Figure shows the average percent recovery of house finches treated with two different types of antibiotics with standard error bars.

Discussion

Data shows that the most effective treatments for mycoplasma conjunctivitis are antibacterial fluoroquinolones. These treatments are effective in eradicating the *Mycoplasma gallisepticum* bacteria from the house finch body completely, as shown by PCR analysis. The bird recovery rates of birds treated with fluoroquinolones was significantly higher than those of birds treated macrolides. Therefore, it is clear that medications such as enrofloxacin, danofloxacin, ciprofloxacin, and other fluoroquinolones should be implemented to treat mycoplasma conjunctivitis to preserve the house finch species and slow mortality rates. Since antibacterial fluoroquinolones proved more effective than antibacterial macrolides in eliminating conjunctivitis, these medicines should be implemented to cure house finch populations.

The reason fluoroquinolones are more effective than macrolides in eradicating *M. gallisepticum* is unclear, but the main difference between each antibiotic group is their mechanisms of action. Fluoroquinolones fight bacteria by inhibiting the actions of the topoisomerase, an enzyme that overwinds or unwinds DNA strands. The topoisomerase allows for the DNA polymerase to effectively copy and replicate DNA, which is necessary for the reproduction of bacteria (Hooper, 2001). Since fluoroquinolones inhibit the reproduction of bacteria, they are effective in destroying bacteria populations, including populations of *M. gallisepticum*. Macrolides on the other hand fight bacteria by inhibiting the function of the peptidyl transferase, and enzyme that generates peptide bonds between amino acids and creates amino acid chains to form proteins. Since macrolides prevent the creation of new proteins, they inhibit bacterial reproduction (Siegrist et al., 1981). Fluoroquinolones are more effective in eradicating *M. gallisepticum* than macrolides, so it may be possible that inhibiting the topoisomerase is more important than limiting the peptidyl transferase in fighting the *M. gallisepticum* bacteria.

A possible path for implementing fluoroquinolones to treat mycoplasma conjunctivitis is to use fluoroquinolones to treat infected house finches at wildlife rehabilitation centers across the united states. This is how most birds were treated in the papers referenced for this study. Another possible pathway would be to add small doses of ciprofloxacin or other weak fluoroquinolones into bird seed at birdfeeders. The *M. gallisepticum* bacteria can spread from house finch to house finch through bird feeders (Adelman et al., 2013). Many bird seeds have added vitamins and minerals to benefit wild birds. Since fluoroquinolones are oral drugs, then it may be possible for medication to be mixed into commercially sold bird seed. However, more research would need to be conducted on the safety and feasibility of this method for the implementation of fluoroquinolones.

House finches play an important role in their ecosystems. They eat primarily seeds and some fruits, which limits the growth of wild plant species (Beal, 1907). Meanwhile, Cooper's and sharp-shinned hawks prey on house finches, while other bird species, rodents, and snakes eat the eggs of house finches (Cannings et al., 1987). A decline in house finches could hurt theses predators as well. Birdwatching and bird feeding are some of the most popular hobbies in the united states. The market size for wild bird seed and feeders in the United States is valued at $6.3 Billion (Industry Facts, 2014). Many companies, such as Wild Birds Unlimited and Duncraft, depend on bird feeder and bird seed sales. House finches are one of the most common bird feeder visitors in the United States, so bird feeder companies could suffer from their absence. By 2013, the eastern house finch population was cut in half from fatalities linked to mycoplasma conjunctivitis (Clark, 2013). Since then, little has been done to slow this epidemic of mycoplasma conjunctivitis that is rapidly spreading through the United States as shown in figure 2. The status of the house finch species is in a perpetual decline. It is imperative that house finch eye disease is eradicated so that the species can thrive.

Conclusion

Fluoroquinolones were significantly more effective than macrolides in the antibiotic treatment of mycoplasma conjunctivitis. PCR analysis showed that house finches recover from mycoplasma conjunctivitis at a higher rate with fluoroquinolones than macrolides. Fluoroquinolones are a better treatment for house finch eye disease, and it should be implemented on a large scale. House finches play a vital role in their ecosystem, but the bird's population has been declining dramatically since mycoplasma conjunctivitis first broke out in 1994. In order to combat this deadly disease, fluoroquinolones could be used extensively to treat house finches and slow mortality rates.

Further Work

Current research shows that fluoroquinolones are more effective than other treatments for mycoplasma conjunctivitis. Thus, more research must be done to determine which specific fluoroquinolones work best. Ciprofloxacin, enrofloxacin, danofloxacin, ofloxacin, pradofloxacin, orbifloxacin, difloxacin, marbofloxacin, moxifloxacin, and norfloxacin are all fluoroquinolones that have the potential to treat mycoplasma conjunctivitis. A similar study to this one could be conducted comparing different fluoroquinolones to narrow down treatment options to a single medication.

More research could also be conducted on implementation methods for fluoroquinolones. Most treatment currently done for house finches infected with mycoplasma conjunctivitis takes place in wildlife rehabilitation facilities, where house finches are held for several days and then released into the wild. Although this has been proven effective in treating birds, this may not be feasible to treat a nationwide population of house finches. Therefore, other methods of implementation, such as mixing fluoroquinolones into food at bird feeders could be investigated and studied.

It is recommended that further work must be done to study why fluoroquinolones are more effective than macrolides at eliminating the *M. gallisepticum* bacteria specifically. Both medicines are antibiotics that interfere with cell reproduction, but it is unclear why fluoroquinolones are more effective for mycoplasma conjunctivitis in house finches. It may be possible that the bacteria is more sensitive to fluoroquinolones, or it is possible that fluoroquinolones work better for the anatomy and bodily functions of house finches. It is known that species other than house finches are capable of carrying the *M. gallisepticum* bacteria without showing physical signs of conjunctivitis, such as eye lesions or respiratory health issues (Dhondt et al., 2014). Research could be conducted on whether fluoroquinolones can prevent the spread of mycoplasma conjunctivitis from bird to bird regardless of the species.

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