RECENT INFECTIOUS DISEASE MORTALITY TRENDS IN THE UNITED STATES

by

Victoria Hansen

A Thesis Submitted to the Faculty of the

DEPARTMENT OF EPIDEMIOLOGY

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

2015
STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that an accurate acknowledgement of the source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Victoria Hansen

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

______________________________  ________________________
Heidi E. Brown                     Date
Professor of Epidemiology
ACKNOWLEDGEMENTS

I am grateful for the efforts of Sharia Smith, a FRONTERA summer intern at the University of Arizona in 2014, who first started looking at infectious disease mortality in the Arizona-Mexico border region and helped move the idea for this project forward. I am thankful for the unwavering support of my mom, dad, siblings, and friends throughout this journey. Lastly, I am eternally indebted to my committee, Dr Heidi E. Brown, Dr Eyal Oren, and Dr Leslie K. Dennis for their support and guidance. There are no disclosures to report.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATEMENT BY AUTHOR</td>
<td>2</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>3</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>4</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>5</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>7</td>
</tr>
<tr>
<td>METHODS</td>
<td>10</td>
</tr>
<tr>
<td>RESULTS</td>
<td>16</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>20</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>25</td>
</tr>
<tr>
<td>FIGURE LEGENDS</td>
<td>26</td>
</tr>
<tr>
<td>APPENDIX A</td>
<td>29</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>32</td>
</tr>
</tbody>
</table>
ABSTRACT

**Importance:** Infectious diseases present an ever-changing threat to public health. Analysis of pathogen-linked mortality trends is elucidatory to infectious disease burden.

**Objective:** To describe major shifts in United States infectious disease mortality trends from 1900-2013 with emphasis on recent changes for 1980-2013.

**Design:** Ecological study of infectious disease mortality in the United States.

**Setting:** Infectious disease deaths were summed from Vital Statistic Reports from 1900-1967. Infectious disease deaths from 1968-2013 were extracted from the Centers for Disease Control and Prevention Wonder database and tallied.

**Participants:** Deaths among United States residents from 1900-2013.

**Main Outcome Measures:** Crude and age-adjusted mortality rates for key infectious diseases including emerging infections, specifically human immunodeficiency virus and certain vector-borne diseases, re-emerging diseases, specifically, vaccine-preventable diseases and pathogens with drug-resistant strains, and newly defined infectious diseases such as cervical cancer due to human papilloma virus.

**Results:** While human immunodeficiency virus mortality has been declining since 1995 (average annual percent change=10.6%, 95% Confidence Interval (CI) [-13.1, -7.9]), recent years have seen an increase in infectious disease mortality related to vector-borne diseases. Specifically,
with the emergence of West Nile virus in the United States, vector-borne disease mortality increased from 34.5 deaths per year (1980-2001) to 141.7 deaths per year (2002-2013). Vaccine preventable disease mortality continues to decrease with an average annual percent change of 2.4%, 95% CI [-2.8, -2.0] from 1980-2013. Mortality due to drug-resistant strains of infectious diseases is increasing at an average annual percent change of 0.8%, 95% CI [0.1, 1.6] from 1980-2013. Finally, mortality due to a disease previously not classified as infectious, cervical cancer, has been decreasing at an average annual percent change of 1.4%, 95% CI [-1.7, -1.1] since 1980.

**Conclusions:** Despite the overall downward trends in infectious disease mortality, they still account for 43 per 100,000 deaths annually in the United States. Specific diseases and disease groups evaluated in this study show inconsistent, but concerning, trends across emerging, re-emerging, and newly defined infectious diseases, indicating that infectious diseases remain a public health concern.
INTRODUCTION

An infectious disease is defined as the invasion of a host by agents such as bacteria, viruses, fungi, or parasites and can be transmitted from one person to another, either directly or indirectly.\textsuperscript{1,2} Infectious disease continues to affect societies both globally and in the United States (US). Between 1998-2006, there were over 40 million hospitalizations due to infectious diseases in the US.\textsuperscript{3} Infectious disease mortality in the US showed a 4.8% annual increase from 1980-1996 in large part due to the human immunodeficiency virus (HIV) epidemic.\textsuperscript{4} Such emerging diseases, as well as the reemergence of previously eliminated or controlled diseases, and the reclassification of certain chronic diseases as having an infectious etiology, pose new health threats and challenges for public health officials.

Emerging infections include both the identification of previously undetected diseases as well as the introduction of known diseases into new areas.\textsuperscript{5} For the US, this includes the detection of a previously unknown viral disease, HIV/Acquired Immune Deficiency Syndrome (AIDS) in 1979.\textsuperscript{6} By 2010, an estimated 1.1 million people were living with HIV and more than 650,000 deaths had occurred over the course of the epidemic.\textsuperscript{7} On the other hand, West Nile virus, a pathogen discovered in 1937 in Uganda, was introduced into the US in 1999, where it subsequently established itself across the continental US.\textsuperscript{8}
Reemerging diseases are defined as the return of a recognized disease after a decline in incidence. For the US, this includes both vaccine-preventable diseases and drug-resistant pathogens. Vaccination protects individuals against many childhood illnesses; however, a small minority of US parents now actively refuse to vaccinate their children, which potentially leads to increased transmission of these diseases. Despite the well-publicized annual vaccine for influenza, influenza and pneumonia hospitalize over 200,000 people per year (data from 1979--2001). Drug-resistant microbial pathogens, such as Clostridium difficile, have also come to the forefront of public health attention in recent years and may be classified as a reemerging infectious disease. In a study of 1,703 hospitalized patients with C. difficile in Quebec, Canada, in 2003, C. difficile was the primary causative agent in 117 (6.9%) patient deaths and a contributing factor among an additional 127 (7.5%) patients. The magnitude of concern regarding antimicrobial resistance was evident in German Chancellor Angela Merkel’s request for infectious diseases and antimicrobial resistance as major topics for discussion at the June 2015 G7 Summit and US President Barak Obama’s request to the US Congress for $1.2 billion for a five-year action plan against antibiotic-resistant "superbugs". These previously overlooked infections remain a significant cause of mortality.

Finally, recent scientific breakthroughs have forced researchers to rethink disease categorization with the discovery of infectious causes of chronic diseases. The 1983 linkage of cervical carcinoma, a chronic disease, with human papilloma virus (HPV), an infectious agent via person-to-person direct contact, added further complexity to the study of infectious diseases. Many other cancers are associated with human papilloma virus (HPV), but, at this time, cervical cancer is the only cancer for which HPV is considered a necessary cause for cancer development.
In this study, trends in US infectious diseases mortality from 1900 to 2013 serve to update the well-known Armstrong et al. graph with a primary focus on the years between 1980 and 2013. This time period is particularly relevant with respect to the peak of HIV/AIDS in 1995, invasions of new vector-borne disease and associated mortality, and changes in vaccine preventable disease and drug-resistant disease morbidity.
METHODS

Sources of Mortality Data

Infectious disease mortality rates for the US by cause of death from the years 1900 to 1967 were extracted from the Vital Statistic Reports published by the National Office of Vital Statistics.\textsuperscript{18-19} Annual number of deaths and US population data from 1968 to 2013 were obtained from the Centers for Disease Control and Prevention (CDC) Wonder database.\textsuperscript{20} The CDC Wonder's estimates of US population counts were used to calculate crude mortality rates. For both data sources, the International Classification of Diseases (ICD) was used to extract all infectious causes among underlying cause of death. This included all deaths in the "Infective and Parasitic Diseases" chapter of each ICD revision as well as inflammatory diseases of the central nervous system, diseases of the ear and mastoid process, acute rheumatic fever, acute respiratory infections, influenza, pneumonia, acute bronchitis, appendicitis, infectious and parasitic conditions in the mother, infections of the skin and subcutaneous tissue, acute osteomyelitis, deficiency of cell-mediated immunity (to account for HIV/AIDS from 1980-1987 [ICD-9]), SARS [ICD-10], and cervical cancer (data available from 1939-2013). Prion diseases are already defined by ICD as infectious (046 [ICD-9] and A81 [ICD-10]). All deaths of United States residents were included except deaths of US residents which occurred outside the United States.
From 1900 to 1960, annual crude death-rates reported in the Vital Statistic Reports for infectious causes were extracted and summed.\textsuperscript{18,21} From 1961 to 1967, mortality data were available as aggregated causes of death and infectious causes were likewise extracted and summed for each year.\textsuperscript{19} Non-infectious disease mortality was calculated as the difference between total mortality and infectious disease mortality. Annual rates per 100,000 were plotted by year. The age categories from the CDC Wonder database were collapsed to form five age groups (0-4 years, 5-24 years, 25-44 years, 45-64 years, and \( \geq 65 \) years).

**Disease Categories**

In addition to overall infectious disease rates, three domains were created to focus on infectious diseases of current concerns today. These disease domains include emerging diseases (HIV/AIDS, which peaked since the last infectious disease summary,\textsuperscript{4} and vector-borne diseases), re-emerging threats (vaccine-preventable diseases and pathogens with drug-resistant strains), and infectious causes of chronic disease (cervical cancer since HPV is necessary for its development). Detailed analysis was limited to 1980 through 2013 in order to capture the recent shifts in infectious disease described above.

Data on HIV/AIDS deaths were defined as ICD code 279.1 ("cellular immune deficiency") for the years 1980 to 1986. Since 1987, the codes 042.0 to 044.9 [ICD-9] and B20 to B24 [ICD-10] were used. Vector-borne diseases included West Nile virus disease (A92.3 [ICD-10]), Lyme disease (088.81 [ICD-9] and A69.2 [ICD-10]), spotted fevers or tick-borne rickettsioses (082.0 [ICD-9] and A77 [ICD-10]), relapsing fevers (A68 [ICD-10]), malaria (084 [ICD-9] and B50-54 [ICD-10]), vector-borne encephalitis (A83-84 [ICD-10]), and other
arthropod-borne rickettsioses and protozoal diseases (060-066, 080-088 [ICD-9] and A75-79, A90-95, B50-57 [ICD-10]).

Vaccine-preventable diseases were limited to those for which a vaccine is routinely given in the US: measles (055 [ICD-9] and B05 [ICD-10]), mumps (072 [ICD-9] and B26 [ICD-10]), rubella (056 [ICD-9] and B06 [ICD-10]), pertussis (033 [ICD-9] and A37 [ICD-10]), diphtheria (032 [ICD-9] and A36 [ICD-10]), tetanus (037 [ICD-9] and A33-35 [ICD-10]), polio (045 [ICD-9] and A80 [ICD-10]), varicella/shingles (052-53 [ICD-9] and B01-02 [ICD-10]), hepatitis A (071.0-71.1 [ICD-9] and B15 [ICD-10]), hepatitis B (070.2-70.3 [ICD-9] and B16 [ICD-10]), meningococcal (036 [ICD-9] and A39 [ICD-10]), and pneumococcal (038.2, 320.1, 481 [ICD-9] and A40.3, G00.1, J13, J18.1 [ICD-10]).

For pneumococcal disease there are two different vaccines for adults and children. In 1983, PPSV23 was licensed to protect adults against 23 of the most common strains. However, this vaccine was inconsistent in generating immunity in children. In 2007, PCV7 was licensed specifically for children to protect them against seven of the most common strains that cause severe childhood pneumococcal infections. In 2010, the pneumococcal conjugate vaccine (PCV13) was licensed to protect against 13 of the more than 90 serotypes of Streptococcus pneumonia. Strain specific information is not included in the ICD code, but we include S. pneumonia in the list of vaccine preventable diseases because of the highly efficacious vaccine which protects against the most common strains. Haemophilus influenzae type b (Hib) and rotavirus were not included due to indiscernible ICD grouping with all other serotypes of Haemophilus influenzae and other similar diseases, respectively. Finally, influenza is not included in the vaccine preventable diseases grouping because it is an annual vaccine with some years showing a markedly lower efficacy and was analyzed separately (see Appendix A). For
antimicrobial resistance, the ICD codes are not specific to drug-resistant pathogens, thus mortality due to any pathogens known to have drug-resistant strains was extracted. ICD codes for these pathogens were selected based on both the CDC and the World Health Organization (WHO) lists of pathogens with drug-resistant strains. According to the CDC, diseases/pathogens with drug-resistant strains include Enterobacteriaceae (008.0, 008.3, 038.42, 041.3, 041.4, 041.6, 482.0, 482.82 [ICD-9] and A04.0-A04.4, A04.6, A41.5, J15.0, J15.5, P23.4, P36.4 [ICD-10]), Nontyphoidal salmonella (003 [ICD-9] and A02 [ICD-10]), Shigella (004 [ICD-9] and A03 [ICD-10]), Neisseria gonorrhoeae (098 [ICD-9] and A54 [ICD-10]), Clostridium difficile (008.45 [ICD-9] and A04.7 [ICD-10]), Campylobacter (008.43 [ICD-9] and A04.5 [ICD-10]), Candida (112 [ICD-9] and B37 [ICD-10]), Salmonella typhi (002.0 [ICD-9] and A01.0 [ICD-10]), Enterococcus (041.04 [ICD-9] and A40.2, A41.81 [ICD-10]), Pseudomonas aeruginosa (008.42, 38.43, 041.7, 482.1 [ICD-9] and A41.52, J15.1, P23.5 [ICD-10]), Staphylococcus aureus (038.1, 041.1, 482.4 [ICD-9] and A41.0, A49.0, J15.2, P36.2 [ICD-10]), Streptococcus pneumoniae (038.2, 320.1, 481 [ICD-9] and A40.3, G00.1, J13, J18.1 [ICD-10]), Mycobacterium tuberculosis (010-018 [ICD-9] and A16-19 [ICD-10]), Streptococcus Group A & B (041.0, 482.3[ICD-9] and A40.0-40.1, J15.3, P23.3, P36.0 [ICD-10]), and Acinetobacter (no code). The WHO has a shorter list including Escherichia coli (008.0, 038.42, 041.4, 482.82 [ICD-9] and A04.0-04.4, A41.5, J15.5, P23.4, P36.4 [ICD-10]), Klebsiella pneumonia (041.3, 482.0 [ICD-9] and J15.0 [ICD-10]), and Staphylococcus aureus, Streptococcus pneumoniae, nontyphoidal Salmonella, Shigella, and Neisseria gonorrhoeae as per the CDC list (ICD codes above).

Data on cervical cancer deaths were defined using ICD-9 code 189 and ICD-10 code C53.
**Adjustments for ICD Revisions**

Comparability ratios were applied to account for changes in the underlying cause of death classification, where 1.0 signifies no differences, greater than 1.0 signifies the newer classification revision has a greater proportion of the underlying cause of death, and less than 1.0 means that the older classification revision has a greater proportion of the underlying cause of death. The comparability ratio was applied to diseases found to be significantly different between ICD-9 and 10, and included pneumonia, HIV/AIDS, salmonella, and tuberculosis.\(^{25}\)

**Analysis of Trends**

Temporal trends by disease category were analyzed using Joinpoint per National Cancer Institute.\(^{26}\) Joinpoint is a regression method to analyze trends over time by connecting short time segments to better fit an overall regression model. The permutation test was used with 4,499 randomly permutated data sets in order to obtain the most consistent P-values. P-values less than 0.05 were used for model selection. Both annual percent change (APC) and average annual percentage change (AAPC) were calculated. APC provides an estimate for each of the selected time segments while AAPC provides a weighted estimate of the overall time trend. APC and AAPC were calculated using log transformed data because rates change linearly at a constant annual percentage on a log scale.\(^{27}\) Break points were selected based on statistical best fit except for HIV/AIDS, where a 1995 break point was forced in order to capture the peak of the epidemic. AAPC was calculated for 1980-1995 for HIV/AIDS to account for the exponential growth in the first few years of the epidemic and the AAPC was also used to analyze the trends from 1995-2013. Overall, APC was used when the trend was relatively linear and AAPC was used for skewed trends.
SAS Statistical Software 9.4 (SAS Institute, Cary, NC) was used to calculate means and standard deviations and to develop graphs.
RESULTS

Overall Trends

Since 1900, with the exception of the Spanish flu pandemic, which killed millions of Americans, non-infectious causes have contributed more deaths annually in the US than infectious causes (Figure 1). From 1900 until 1936, infectious disease mortality in the United States declined at an APC of 2.7%, 95% Confidence Interval (CI) [-3.3, -2.2]. In 1935, the antibiotic era was shepherded in with the discovery and use of sulfa drugs which accelerated the decline of infectious disease deaths to an APC of 8.5%, 95% CI [-10.0, -11.2] from 1936 to 1955. From 1955 to 2013, the infectious disease mortality APC slowed to a decline of 0.4%, 95% CI [-0.7, -0.2]. Since the 1950s, non-infectious causes have accounted for 95% of US mortality (mean = 837 per 100,000, standard deviation (SD) = 46 deaths per 100,000) with infectious diseases accounting for the remaining 5% (mean = 50 per 100,000, SD = 12 deaths per 100,000). In 2013, the last year for which data were available, 43 deaths per 100,000 were attributed to infectious causes (Figure 1).

Trends by Disease Category

Overall infectious disease mortality rose from 31.6 per 100,000 in 1979 to 63.5 per 100,000 at the height of the epidemic in 1995 (Figure 1). HIV/AIDS deaths increased at an
AAPC of 85.2%, 95% CI [66.9, 105.6] from 1980 until the introduction of anti-retroviral therapy (ART) in 1995 (Figure 2a). The effect of ART can be seen immediately, with an APC decrease of 40.2%, 95% CI [-54.4, -21.5] from 1995 through 1997. After the initial drop, overall mortality due to HIV/AIDS continued to decrease with an APC of 6.0%, 95% CI [-6.9, -5.0] from 1997 through 2013. The overall AAPC from 1995 through 2013 was -10.6%, 95% CI [-13.1, -7.9]. The age-specific analysis (see Appendix A) revealed a shift in the mortality rate related to ART introduction from the 25-44 to the 45-64 age groups (36.3 per 100,000 and 19.9 per 100,000, respectively in 1995, and 2.3 per 100,000 and 5.1 per 100,000, respectively, in 2013). In the last five years, there has been a significant decrease in APC of HIV/AIDS mortality by 8.0% ([−10.5, −5.3] 95% CI).

Before 1999, an average of 36 deaths per year (SD=8) in the US were attributed to vector-borne causes, (Figure 2b), the majority of which were a result of spotted fevers. However, since 2002, West Nile virus had been reported in all but five states of the continental US,29 and vector-borne diseases have averaged 141 deaths per year for the US (SD=64). While the annual mortality due to spotted fevers remains consistent (about 10 deaths each year), the majority (75%) of vector-borne disease deaths are now due to the West Nile virus disease (an average of 110 deaths each year). The AAPC for vector-borne disease mortality from 1980 to 2013 is 3.6%, 95% CI [-3.5, 11.2].

Vaccine-preventable deaths have been decreasing since 1980, with an AAPC of 2.4%, 95% CI [-2.8, -2.0] (Figure 2c). In 2013, over 3,000 deaths due to vaccine preventable diseases occurred in the US. Streptococcal pneumoniae has the largest influence on the trend, accounting for 72% (2,174 deaths) of vaccine-preventable disease mortality in 2013. Hepatitis B shows an APC increase of 8.7%, 95% CI [7.8, 9.7] from 1980-1994, that is coincident with the HIV/AIDS
epidemic (294 deaths in 1980 to 1027 deaths in 1995). Because children are historically an at-risk population and the subject of the current vaccination debate, we specifically looked at mortality in children under age five and calculated an overall AAPC of -3.5%, 95% CI [-4.9, -2.0] (see Appendix A). The majority of vaccine-preventable deaths in children under age five were due to pertussis (average 95% from 2003-2013) although a large measles epidemic from 1988-1990 killed 75 people, including 51 children; 40 children in 1990 alone. Over the time period evaluated here (1980-2013), a total of 79 children died of measles and 327 died of pertussis.

Influenza and pneumonia accounted for 41.5% of all infectious disease deaths in the US from 1980 to 2013 (mortality rates of 1.2 per 100,000 and 16.9 per 100,000, respectively, in 2013). The combined mortality rate for influenza and pneumonia has not changed since 1980 with an AAPC of 0.1%, 95% CI [-0.5, 0.8] (17.1 per 100,000 in 1980 compared to 18.0 per 100,000 in 2013) (see Appendix A).

Mortality due to pathogens with drug-resistant strains based on the CDC list indicates a rising trend in mortality (AAPC 0.8%, 95% CI [0.1, 1.6] from 1980-2013) while the WHO list shows a stable trend (AAPC -1.9%, 95% CI [-3.2 -0.6] from 1980 – 2013; Figure 2d). The difference observed between the two lists is primarily due to the CDC's inclusion of tuberculosis and hospital-acquired infections. In particular C. difficile has been increasing since 1989 (74 deaths) until 2007 (6,374 deaths; APC of 26.9% increase, 95% CI [24.7, 29.1]). From 2007 to 2013, mortality due to C. difficile has stabilized, with no statistically significant APC in mortality due to these pathogens (APC 0.9%, 95% CI [-7.2, 9.8]). Since 1980, the AAPC of C. difficile is 20.0% (CI 95% [15.7, 24.5]) and in 2013, accounted for 2.4 deaths per 100,000.
Finally, to explore the impact of infectious causes of chronic disease on US mortality, we consider cervical cancer. Since 1980, cervical cancer mortality has decreased at an average annual percent change of 1.4%, 95% CI [-1.7, -1.2] (Figure 2e). Despite Pap smears being effective screening tool,\textsuperscript{31} over the last five years, there has been a statistically significant rise in APC of 1.13% (95% CI [0.1, 2.2]).
DISCUSSION

Infectious diseases continue to exact a significant burden in the United States, with 43 per 100,000 Americans dying from infectious disease in 2013. Over the last thirty years, the US has faced emerging diseases and re-emerging diseases, associated with an increase in travel and global accessibility, among other risk factors. The majority of US infectious disease mortality is due to influenza and pneumonia (average 41.5% from 1980-2013). This is consistent with the CDC estimates of 3,000 deaths to 49,000 deaths each year. It is important to remember that this manuscript looks at mortality only and not morbidity of these diseases, but morbidity and cost are also important metrics to consider. In 2003 the U.S. spent an estimated $10.4 billion in direct medical costs and $16.3 billion in indirect costs, plus an average of 610,660 life-years lost due to influenza and pneumonia. Nonetheless, the US mortality data provide a reliable metric by which to compare trends in emerging, re-emerging, and infectious causes of chronic disease.

Emerging pathogens continue to test US capacity to respond to infectious disease. With the sudden emergence of HIV/AIDS in the early 1980's, mortality increased with an AAPC of 85.2%, 95% CI [66.9, 105.6] from 1980 through 1995. The 1995 introduction of ART, HIV/AIDS mortality rates decreased rapidly with an APC of -40.2%, 95% CI [-54.4, -21.5] from 1995 through 1997. Despite the decline, there were an estimated 56,300 new infections in the US in 2006, and approximately 21% infected individuals are unaware of their disease status. In
addition to changes in the incidence and mortality due to HIV/AIDS, the risk groups have changed over the course of this epidemic; once a disease of men who have sex with men, the populations at risk have changed to also include high-risk heterosexuals and intravenous drug users.\textsuperscript{37} At the beginning of 2015, an HIV outbreak in Indiana was linked to intravenous drug users\textsuperscript{38} resulting in 181 cases (177 confirmed, 4 pending confirmation as of August 28, 2015).\textsuperscript{39} ART enables those infected with the virus to access medication to live longer\textsuperscript{40} but scientific research and continued public education of the risks associated with HIV/AIDS is still critical to reducing the incidence of this disease.

Between 2001 and 2002, vector-borne diseases increased by 625\%, from 32 deaths in 2001 to 200 deaths in 2002. Most of these were attributable to the emergence of West Nile virus in New York. By 2003, every state in the continental US reported West Nile virus, with the exception of Oregon, which would report its first case a year later.\textsuperscript{29} Between 1999-2010, there were an estimated 3 million cases in the US, with 780,000 of those resulting in illness.\textsuperscript{41} While the mortality rate of West Nile virus disease is low (3-15\% case fatality rate among those with severe WNV disease),\textsuperscript{42} it signifies a large financial burden. In 2005, Sacramento County, California experienced a West Nile virus outbreak of 163 cases that cost the county an estimated $2,979,037.\textsuperscript{43} With the complexity of vector-borne disease systems, increased human travel, and a changing climate, researchers are looking to predict the next vector-borne disease that might establish itself in the US. In December 2013, local transmission of mosquito-borne chikungunya virus was reported for the first time in the Western Hemisphere and by June 2014, 17 Caribbean countries reported local transmission.\textsuperscript{44} By mid-July of 2014, Florida too reported local transmission.\textsuperscript{45} These diseases represent a significant burden with respect to not only morbidity and mortality, but also economic burden. The precedent established with HIV, where new tests
and medications were effectively utilized within 15 years of recognizing the virus, provides hope that similar progress may be attainable with other emerging diseases if the necessary resources are available.

Vaccine preventable diseases provide yet another challenge to public health - communication of success and the time period 1980-2013 is particularly pertinent as it captures some important changes in vaccine perception despite the continued decline in mortality. Since measles was declared eliminated from the US in 2000, the US experienced measles outbreaks in 2008, 2011, 2013, 2014, and 2015, with over 1400 individuals contracting this preventable disease since 2010. Failure to reach sufficient vaccine coverage may partially explain these outbreaks. While vaccination of at least 90% of the population is needed to achieve herd immunity for measles, vaccination rates below 90% were reported for preschool aged children in 17 US states in 2015. Although mortality from vaccine-preventable diseases has been consistently declining, it is important to note that this decline may not reflect the trend in morbidity. For children born between 1994-2013, routine vaccination is estimated to prevent 322 million illnesses, 732,000 premature deaths from vaccine-preventable diseases, and to save $1.38 trillion in costs ($295 billion in direct costs). The persistence of vaccine-preventable deaths among children under age five might be explained by the poor efficacy of the current pertussis vaccine. An acellular pertussis vaccine is currently recommended; however, the protective immunity from the vaccine wanes after 4-12 years.

Since the introduction of antibiotics to the general public in the 1940's, bacteria and other pathogens have evolved resistance to a number of once-effective drugs, and we are now seeing increasing mortality rates caused by pathogens once thought to be defeated. In 2008, the Antibiotic Resistance Genes Database collected resistance information on over 200 species and
over 100 genera.\textsuperscript{53} Hospital-acquired infections kill more than 63,000 patients in the US every year, 70\% of these drug-resistant strains.\textsuperscript{52} Rapid development of drug-resistant pathogens may be due to improper diagnosis, incorrect prescribing, and poor patient compliance, and microbial evolution.\textsuperscript{54} Another reason for increasing drug-resistance is the use of antibiotics in agriculture. Although it is difficult to compare antibiotic use in humans to use in animals, it is estimated that more antibiotics are used for food animals than for humans.\textsuperscript{55} The final major obstacle contributing to drug resistance is that only one novel class of drug has come on the market since the 1960's, lipopeptides (1983).\textsuperscript{56} While the data used here are not specific to resistant strains, and include all pathogens known to have resistant strains, the CDC list indicates an increase in drug resistance while the WHO list illustrates a stable trend, mostly due to the inclusion of tuberculosis and hospital-acquired infections.

Perhaps the most profound shift in the conceptualization of infectious diseases over the last three decades has been the recognition of infectious causes of chronic diseases. An estimated 99.7\% of cervical cancer can be attributed to HPV infection.\textsuperscript{17} Currently, over 4,000 Americans die each year from this disease.\textsuperscript{57} In our study, we see a continued decline in mortality due to cervical cancer. While its contribution to overall mortality in the US is small (Figure 1, inset), it is remarkable that the discovery of HPV as a necessary cause for cervical cancer changes our perception of infectious diseases. In 2006, the Advisory Committee on Immunization Practices recommended that 9-26 year old females should be vaccinated against HPV to prevent cervical cancer.\textsuperscript{58} Subsequently, in 2011, they recommended that males aged 9-26 should also be vaccinated.\textsuperscript{59} We expect the rates of cervical cancer mortality to continue to decrease in the coming decades as this cohort ages. HPV is also linked to anal cancer,\textsuperscript{60} oropharyngeal cancers,\textsuperscript{61} vaginal cancers,\textsuperscript{62} vulvar cancers,\textsuperscript{63} and penile cancers,\textsuperscript{64} which were not included in
this revised assessment of infectious disease mortality in the US since it is not considered necessary for these cancers and due to limitations of the data. The link between the bacteria *Helicobacter pylori* and gastric cancer is still being studied, but studies indicate that those infected with *H. pylori* are six times more likely to develop non-cardiac gastric cancer than individuals who do not carry the bacteria. As infectious causes of chronic diseases are recognized, new tools to prevent mortality may be possible. The 1950's saw the highly successful introduction of the Pap smear, a screening tool against cervical cancer, which has been shown to lower cervical cancer mortality by over 50%. Although, mortality has been consistently declining since the pap smear became commonplace, the HPV vaccine recommendation since 2006 is likely to further decrease overall incidence and thus mortality even if the benefits are not seen for a few more decades as younger generations are vaccinated and age into their 20s. As science improves our understanding of disease etiology, major epidemiologic shifts in diseases classified as either infectious or chronic are likely to be observed.
CONCLUSIONS

While infectious diseases have represented a small contribution to US mortality for the past 30 years, they remain a significant cause of death. In 2013, over 130,000 Americans died of infectious causes. Recent history has shown that new diseases will continue to emerge, some with high mortality and others with greater morbidity. Diseases once controlled by vaccination and medication have re-emerged, the latter with disconcertingly increasing trends. Diseases once billed as chronic will now also be considered “infectious”. As new hurdles present themselves with time, the battle against infectious disease continues to wage on.
FIGURE LEGENDS

**Figure 1**: Crude Mortality Rates per 100,000 for All Causes (solid line), Noninfectious Causes (dashed line), and Infectious Diseases (dotted line). Infectious diseases include cervical cancer deaths from 1939 onward. The inset shows overall infectious disease mortality 1980-2013 without (solid line) and with cervical cancer (dotted line).

**Figure 2**: Crude Mortality Rates for Three Disease Domains and associated examples: a) Human immunodeficiency virus/ acquired immunodeficiency syndrome mortality; b) vector-borne diseases; c) vaccine-preventable deaths for diseases routinely provided vaccines in the US (measles, mumps, rubella, varicella/shingles, diphtheria, tetanus, pertussis, polio, Hepatitis A, Hepatitis B, meningococcal, and pneumococcal). Not included among the plotted vaccine preventable diseases, though recommended US vaccinations are deaths due to influenza, rotavirus, and *Haemophilus influenzae* type b; d) deaths due to pathogens with drug resistant strains; e) cervical cancer. Notice that the x-axis is consistent across all 5 images while the y-axis is not.
Figure 2:
HIV/AIDS Mortality by Age

When looking at HIV/AIDS mortality by age groups, it is apparent that at the beginning of the epidemic until 2003, 25-44 year olds (solid line) carried the majority of the burden of disease. In 2003, there is a shift from the 25-44 year old age group to the 45-64 year old age group (dashed line). This shift could be due to ART allowing people with HIV/AIDS to live longer. Also, the 65 and older age group (dotted line) is the only age group that has been increasing. This could be because ART is allowing infected people to live longer, such that they are more likely to eventually die in an older age group.
Although vaccine-preventable deaths in children under five years of age are fairly rare, it is still important to look at trends since this age group is the most susceptible to disease and relies on herd immunity more than any other age group. The solid line is the total rate of vaccine-preventable deaths in children under five which includes measles, mumps, rubella, diphtheria, tetanus, pertussis, varicella, polio, hepatitis A, and Hepatitis B. The overall AAPC is -3.5%, 95% CI [-4.9, -2.0]. The spike at 1990 is a result of a measles outbreak in California, where 40 children died from measles in that year alone. The dashed line shows the trend of chicken pox deaths. In 1995 the introduction of the varicella vaccine highlights the success of the vaccine. Lastly, the dotted line shows pertussis deaths that has a nonsignificant AAPC of 6.1%, 95% CI [-3.5, 16.7] indicating a stable rate over these 33 years. After the year 2000, pertussis accounts for nearly all vaccine-preventable deaths in children under five.
Influenza and pneumonia remain the leading cause of death of all infectious diseases accounting for 41.5% of all infectious disease deaths in the US from 1980 to 2013 (mortality rates of 1.2 per 100,000 and 16.9 per 100,000, respectively, in 2013). Although there have been fluctuations in mortality from year to year, the rate has remained stable (AAPC of 0.1%, 95% CI [-0.5, 0.8]) within a narrow range (16.1 to 23.3 per 100,000). Influenza vaccines usually provide moderate protection with some years showing a markedly lower effectiveness.\textsuperscript{24}
REFERENCES


48. Centers for Disease Control and Prevention. Provisional cases of selected infrequently reported notifiable diseases (<1,000 cases reported during the preceding year), United States, week ending August 29, 2015 (WEEK 34). *MMWR Morb Mortal Wkly Rep.* 2015.


