Letters

RESEARCH LETTER

Infectious Disease Mortality Trends in the United States, 1980-2014

From 1900 through 1996, mortality from infectious diseases declined in the United States, except for a 1918 spike due to the Spanish flu pandemic.[1] Since 1996, major changes in infectious diseases have occurred, such as the introduction of human immunodeficiency virus (HIV)/AIDS and West Nile virus into the United States, advances in HIV/AIDS treatment, changes in vaccine perceptions, and increased concern over drug-resistant pathogens. We investigated trends in infectious disease mortality from 1980 through 2014 to capture these changes.

Methods | Using *International Classification of Diseases* codes, overall and infectious disease mortality data were extracted, based on underlying causes of death, from the National Office of Vital Statistics reports from 1900 through 1967 and from the Centers for Disease Control and Prevention (CDC) WONDER database from 1968 through 2014.[2] The University of Arizona determined the study was exempt from review.

Crude mortality rates for infectious and noninfectious causes (per 100 000 population) from 1900 through 2014 were graphed along with selected infections from 1980 through 2014 based on overall burden (influenza, pneumonia) and emergence or reemergence (HIV/AIDS, vector-borne diseases, vaccine-preventable diseases, drug-resistant pathogens). Vaccine-preventable diseases included those for which vaccines are routinely provided in the United States. Pathogens with drug resistance were identified based on classification by the CDC.[3] Average annual percentage change (AAPC) was calculated using a 2-sided permutation test. Joinpoint Trend Analysis Software (National Cancer Institute), version 4.2.0,[4] was used to create a weighted regression of the time series. Segments were selected based on statistical significance (2-sided $P < .05$) except for HIV/AIDS (which was manually given a joinpoint in 1995 to capture the peak of the epidemic and AAPCs calculated before and after 1995) and vector-borne diseases (for which interannual variability made trend analysis inappropriate).

Results | Overall and infectious disease mortality decreased from 1900 through 1950 (except for the 1918 spike) and then leveled off (**Figure**, A).

From 1980 through 2014, infectious diseases composed 5.4% (95% CI, 5.1% to 5.8%) of overall mortality. Per 100 000 population, infectious disease mortality increased from 42.0 in 1980 to 63.5 in 1995, paralleling trends in HIV/AIDS mortality. A decline in overall and HIV/AIDS mortality in 1995 was associated with the introduction of antiretroviral therapy (Figure, B). The overall AAPC was 0.4 (95% CI, −0.4 to 1.2) from 1980 through 2014.

Most infectious disease deaths (38.3% [95% CI, 37.1%-39.4%]) from 1980 through 2014 were due to influenza or pneumonia (Figure, B and **Table**).

Prior to the introduction of West Nile virus (1980-1999), mean vector-borne disease mortality was 0.01 per 100 000 population (95% CI, 0.01-0.02); primarily from spotted fevers (Figure, C). Since 2002, the mean rate was 0.05 per 100 000 population (95% CI, 0.04-0.06).

Vaccine-preventable disease death rates decreased since 1980 (Figure, D and Table). In 2014, the rate was 0.8 per

Table. Summary of Infectious Disease Mortality Rates and Average Annual Percentage Change in the United States Over Time

	Mortality Rate (per 100 000 Population)		AAPC (95% CI)[a]
	1980	2014	1980-2014
All infectious causes	42.0	45.6	0.4 (−0.4 to 1.2)
Influenza or pneumonia	17.1	17.3	0.1 (−0.5 to 0.7)
Influenza	1.2	1.4	−1.1 (−3.3 to 1.1)
Pneumonia	15.9	15.9	0.1 (−0.4 to 0.6)
HIV/AIDS	0	2.1	
1980-1995			85.2 (66.9 to 105.6)
1995-2014			−10.4 (−12.7 to −8.0)
Vector-borne diseases	0.02	0.05	NR[b]
West Nile virus	0	0.03	NR[b]
Vaccine-preventable diseases	2.1	0.8	−2.4 (−2.8 to −2.1)
Pathogens with drug resistance	4.1	4.2	0.4 (−0.4 to 1.3)
Clostridium difficile	0	2.2	19.3 (15.2 to 23.5)
Other infectious causes[c]	18.7	21.1	0.8 (−0.2 to 1.7)

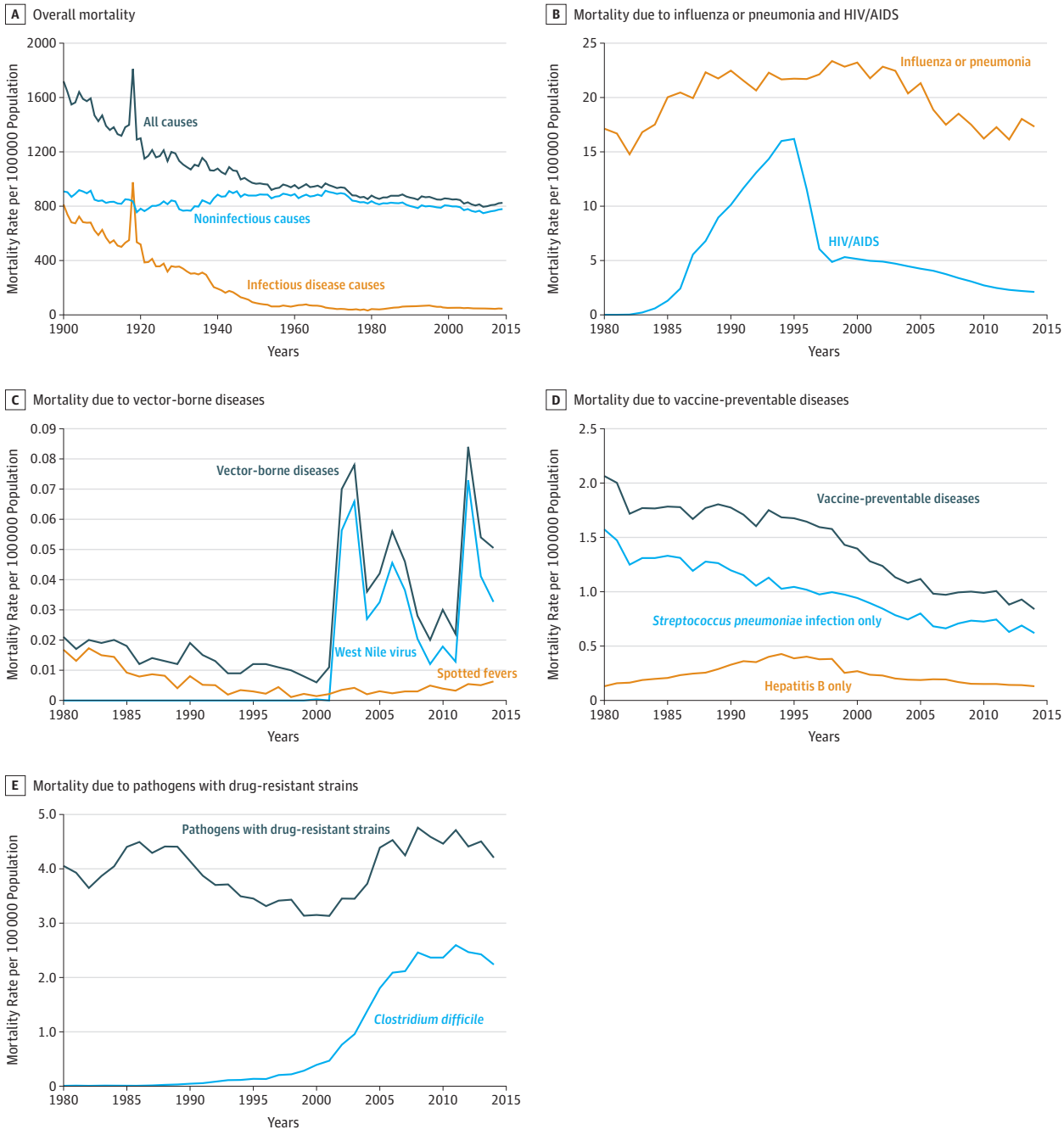
Abbreviation: AAPC, average annual percentage change; HIV, human immunodeficiency virus; NR, not reported.

[a] With the exception of HIV/AIDS, for which 1995 was selected as the joinpoint, AAPCs were calculated for 1980 through 2014.

[b] Not reported due to variability.

[c] Includes other infectious and parasitic diseases, including inflammatory diseases of the central nervous system, diseases of the ear and mastoid process, acute rheumatic fever, acute and subacute endocarditis, acute upper and lower respiratory tract infections, acute appendicitis, infections of the skin and subcutaneous infections, severe acute respiratory syndrome, and infections specific to the perinatal period.

Figure. Crude Mortality Rates (per 100 000 Population) in the United States Over Time



The x-axis and y-axis scale is different for each panel. In panel D, vaccine-preventable diseases for which vaccines are routinely provided in the United States include measles, mumps, rubella, varicella, diphtheria, tetanus, pertussis, polio, *Streptococcus pneumoniae* infection, hepatitis A, hepatitis B, and meningococcal infection.

100 000 population for *Streptococcus pneumoniae* infection. Mortality due to hepatitis B alone showed an increase coincident with the HIV/AIDS epidemic (per 100 000 population: 0.13 in 1980 and 0.39 in 1995).

Mortality due to pathogens with drug-resistant strains remained stable since 1980 at about 4.0 per 100 000 population (95% CI, 3.80-4.13) (Figure, E and Table). Mortality from *Clostridium difficile*, a hospital-acquired infection with drug resistance, increased from almost none in 1989 (n = 74 deaths; 0.004 per 100 000 population) until reaching a plateau since 2007 (2.4 per 100 000 population [95% CI, 2.3-2.5]).

Discussion | Infectious diseases represented a small proportion of overall US mortality from 1980 through 2014, with influenza or pneumonia accounting for approximately 40% of infectious disease mortality. Major changes in mortality from

HIV/AIDS, West Nile virus, and *C difficile* occurred over this period. Mortality due to vaccine-preventable diseases declined, whereas mortality due to pathogens with resistant strains remained stable.

The study is limited to US mortality reported on death certificates, only partly capturing the true burden of these diseases. Globally, infectious diseases were the second (lower respiratory infections), fourth (diarrheal diseases) and fifth (HIV/AIDS) leading causes of lost disability-adjusted life-years.[5]

Grouping related diseases (eg, vector-borne disease) and using national-level data allow for the evaluation of general trends. However, trends in population subgroups and at the community level, such as measles outbreaks within low-vaccination communities, were not captured. Nonetheless, these trends illustrate the continued US vulnerability to infectious diseases.

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Concept and design: Hansen, Oren, Brown.
Acquisition, analysis, or interpretation of data: All Authors.
Drafting of the manuscript: All Authors.
Critical revision of the manuscript for important intellectual content: Oren, Dennis, Brown.
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Study supervision: Oren, Brown.

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COMMENT & RESPONSE

Cost-effectiveness of PCSK9 Inhibitor Therapy

To the Editor Cardiovascular disease (CVD) remains the leading cause of death in the United States. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an important treatment option for patients at highest risk of CVD who are unable to reach their lipid goals with current treatments. Dr Kazi and colleagues[1] suggested that use of PCSK9 inhibitors for patients with atherosclerotic CVD and heterozygous familial hypercholesterolemia is not cost-effective and that these medicines will increase costs to the US health care system. These findings depend on questionable assumptions that overestimate the calculated cost-effectiveness ratio and thus underestimate the value of PCSK9 inhibitors.

First, the background CVD risk was validated against data from randomized clinical trials, yet evidence suggests that CVD risk in real-world settings may be significantly higher.[2,3] The use of these risk estimates diminishes the potential benefit that PCSK9 inhibitor agents could provide.

Second, the effect of CVD events on patients' quality of life is underestimated and does not reflect the considerable disability associated with CVD events. Specifically, the model assigns little value to averting a CVD event, which in turn inflates the cost-effectiveness ratio.

Third, the cost of PCSK9 inhibitors used in the base-case analysis was overestimated as the analysis included the list price rather than the actual price paid because of discounts negotiated with payers. For example, rebates of approximately 25% have been provided for biologics for treatment of inflammatory conditions.[4] Moreover, use of the list price resulted in an inflated budget impact. This budget impact analysis also erroneously assumed that 100% of eligible patients will take PCSK9 inhibitors; this assumption is unrealistic and not supported by real-world data.

We are concerned that the findings from this report, which are similar to findings from the Institute for Clinical and Economic Review,[5] are misleading and will further support policies that place inappropriate restrictions on patient access to PCSK9 inhibitors and limit physicians' ability to treat patients with high unmet need for additional low-density lipoprotein cholesterol lowering.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Ms Mastey reported being an employee and stockholder of Regeneron Pharmaceuticals. Dr Johnstone reported being an employee and stockholder of Sanofi. Alirocumab (Praluent) is a PCSK9 inhibitor jointly marketed by Sanofi and Regeneron Pharmaceuticals.

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