Epidemiological Isolation as a Mortality Risk Factor for Infectious Diseases in the late 19th to early 20th Centuries

G. Dennis Shanks MD, MPH[1-2]

[1] Australian Defence Force Malaria and Infectious Diseases Institute, Enoggera, Australia

[2] University of Queensland, School of Public Health, Brisbane, Australia

Corresponding author: Prof G. Dennis Shanks

ADF Malaria and Infectious Diseases Institute, Enoggera, 4051 QLD Australia

Phone: +61 7 3332 4931 fax: +61 7 3332 4800

dennis.shanks@defence.gov.au

Running title: Isolation as Mortality Risk Factor

Words 1938, abstract 100, references 15, figures 2

Abstract

It remains uncertain why most infectious disease mortality disappeared prior to modern medical interventions. Reconstruction of historical epidemiology using prospectively collected US Army data from the Civil (1860-61), Spanish-American (1898-99) and First World (1917-18) Wars suggests that epidemiological isolation was a major mortality risk factor. Morbidity and mortality due to common infections fell progressively from 1860-1918 except for influenza during the 1918 pandemic. Adult measles / mumps infections are indicative of isolated rural populations and correlated to disease mortality by US State. Experiencing infections prior to adulthood may equip the immune system to better resist infections and decrease mortality rates.

100 words

Background: Infectious disease mortality progressively declined over the 19th century prior to antibiotics or most vaccines with the exceptions of smallpox (early 19th century) and typhoid (early 20th century). Public health interventions improved after the discovery of micro-organisms as agents of disease (late-19th century) but cannot account for the majority of mortality changes.[1] Studying such historical changes often relies on military data as armies were critically interested in the health of their soldiers and prospectively collected information from groups scattered across the globe. Classical studies by Curtin indicated that the mortality cost of moving European soldiers into tropical environments progressively fell over the 19th century despite very limited therapeutic interventions (e.g. quinine for malaria) and few if any public health improvements during the colonization of Africa and tropical Asia.[2, 3]

Another factor influencing morality may have been decreasing epidemiological isolation as steamships and railroads revolutionized transport facilitating the mixing of human and pathogen populations.[4] This progressive acceleration of movement meant that even men growing up in isolated rural communities, were gradually drawn into larger populations with more circulating pathogens thus decreasing the number of military recruits who had not previously experienced common “childhood” infections such as measles and mumps. Epidemiological isolation was particularly characteristic of the southern US States that seceded from the Union during the US Civil War. War time devastation and economic depravation were only slowly reversed in this largely rural, agrarian region. Detailed medical morbidity and mortality data collected prospectively by the US Army from 1860 to 1918 were used to reconstruct changes that reflected survival prior to antibiotics and most vaccines.[5] It is important to better understand these determinants of historical infectious disease mortality given the threatened return to such a situation with few effective medical interventions as foreshadowed by increasingly multi-drug resistant pathogens.[4]

Methods: Annual reports of the US Army Surgeon General have been used to determine infectious disease-specific morbidity and mortality rates during the US Civil (excludes Confederate Army), Spanish-American and First World Wars. The first two years of these conflicts (1860-61, 1898-99, 1917-18) were used for comparison purposes as initial mobilization of a large army produced large recruit camp epidemics.[5] Although medical knowledge was rapidly improving over this period, common respiratory (measles, pneumonia, influenza, tuberculosis) and gastrointestinal/systemic infections (typhoid fever, malaria, diarrhea/dysentery, meningitis) were used for comparison purposes, admittedly with nearly all of these diagnoses occurring prior to the advent of diagnostic laboratory studies. There is no indication that clinical diagnostic criteria changed markedly during this era. The US Army had to account for every soldier every day, such that the military mortality data is detailed and quite complete.[5]

During the First World War the military officers charged with medical statistics came from the US Census Bureau and they used punch cards in the pre-electronic era to manage data with gravity-operated sorting machines.[6] Although the original cards no longer exist, thousands of pages of statistical graphs and tables were published in the US Army Surgeon General's Annual Reports as an enduring record of diseases during mobilization and war.[5] As military recruitment was state-oriented in the era prior to the growth of the US Federal Government, many of the disease data were reported by the US State of origin of the soldiers.

Results: Morbidity and mortality rates per 1000 US Army soldiers are shown in Figure 1 for respiratory infections such as measles, pneumonia, influenza, tuberculosis as well as typhoid fever, malaria, diarrhea/dysentery, meningitis. Except as noted in the discussion morbidity and mortality rates decreased over the 58 years between the US Civil War and the First World War consistent with global trends that occurred in the absence of major medical interventions excepting the compulsory use of typhoid vaccine in the US Army from 1910.

Geographic-specific disease data by US State was available from the US Army of the First World War.[5] Epidemiological isolation largely due to rural origin was reflected by soldiers developing measles and mumps when mixed into large groups in recruit camps. Measles and mumps infections correlated strongly by US state. (Figure 2A) Both infections were also correlated to all-cause disease mortality during the war despite measles (2455) but not mumps (161) causing many deaths. (Figure 2B and 2C) Measles infection correlated to the fraction of a US State's population classified as rural by the US Census of 1920. (Figure 2 D) This was largely due to the southern US States which is shown in the reproduced map from *The Medical Department of the United States Army in the World War* shown in Supplemental figure 1.[6]

Discussion: Measles mortality fell markedly from the US Civil War to the Spanish-American War largely because urbanization pushed the age of measles infection below military recruitment age in all but the most isolated rural communities. The somewhat increased mortality during 1917-18 was probably due to the greater mobilization of manpower in the First World War as well as the large number of secondary bacterial pneumonias following measles analogous to what was seen during the 1918 influenza pandemic.(Morens) Nearly 7% of the US Army soldiers of 1917-18 developed clinical mumps infection also indicative of epidemiological isolation in areas where respiratory pathogens only occasionally circulated.[5]

Typhoid fever was the great killer during the Spanish-American War (2450 deaths) but much of the Civil War typhoid is likely lost in the diarrhea/dysentery category. Whole cell, killed typhoid vaccine accounts for the marked decrease in mortality (158 deaths) by 1917-18.[5] Smallpox vaccine was commonly used during the US Civil War even though the quality of the "lymph" was often questionable. In spite of no changes in the smallpox vaccine itself, case fatality rates in the US Army fell from 29% in 1860-61 to 1% in 1917-18.

The remarkable increase in pneumonia/influenza morbidity and mortality during the First World War is certainly due to the 1918 influenza pandemic.[7] Secondary bacterial pneumonia following influenza was unusually common in 1918 military recruit camps which in the pre-antibiotic era had approximately 30% mortality. This increased mortality pattern in young adults as opposed to adolescents or elders has not reoccurred, neither has it ever been satisfactorily explained.[8]

If public health interventions could be said to have had any effect during this period it would have been with diarrhea/dysentery and malaria. The rejection of miasmas in favor of micro-organisms as the cause of infections only became universal in the 20th century. Safe disposal

of feces and locating military camps away from river valleys breeding mosquitoes likely did result in fewer illnesses and deaths. Tuberculosis mortality fell over the 58 years reported even though infection was common and chemotherapy remained decades into the future. Although meningitis cases were not common, up to half of them died, a situation which did not improve until the arrival of antibiotics in the 1930-40s.

These changes in mortality rates can thus be explained, but what about the mega-trend downwards of infectious disease mortality that was not specific to any military group or country? It cannot be due to Darwinian selection for resistance genes as it occurred over the space of two to three generations which is insufficient to greatly change any genetic factor.[9] Improved public health practices did occur in the USA but their penetration was highly variable and they cannot be invoked to explain the very similar simultaneous mortality changes that were occurring the British and French colonial armies; no one claims that Bengal or Algeria suddenly became better sanitized in the 19th century.[3] Although improved nutrition has been suggested as a possible factor decreasing infectious disease mortality, it is doubtful that it applied to US Army soldiers who were selected on strict height and weight standards and served a diet that was a least sufficient in calories.[1]

Any explanatory mortality risk factor(s) has to meet the minimum criteria of changing consistently over the course of the 19th century, being global in scope with variable penetration as well has making a very substantial improvement in mortality due to many different infectious diseases. Isolated populations with exposure to a very limited number of pathogenic organisms are known to be at risk of highly lethal epidemics when even ordinary respiratory infections such as influenza or measles are first introduced into a population. This was most dramatically seen in the depopulation of the Americas in the 15-17th centuries and Pacific Islands in the 18-19th centuries but 20th century examples such as measles on the Polynesian Island of Rotuma in 1911 are well described.[4, 10] Extreme lethality was not

pathogen-specific during these first-contact epidemics but appears to have depended on how the host responded to infection. The 1918-19 influenza pandemic was caused by the same or at most only a few very closely related H1N1 viruses yet islands as comparable as New Zealand and Tasmania had mortality rates that differed by up to two orders of magnitude.[11]

Isolated populations respond differently to infectious diseases than those who have experienced a wide variety of pathogens. Smallpox and measles only cause a single infection in a life-time yet the mortality rates are very different in isolated compared to urban populations. Measles was a major military medical problem in the 19th century and during the US Civil war *rubeola negra* (black measles) was described as a highly lethal, hemorrhagic fever which had apparently disappeared by the 20th century.[12] Measles mortality and case fatality rates progressively fell over the century after the Civil War such that very few US soldiers of the Second World War and none during the Vietnam conflict died of measles; this all occurred prior to the wide-spread use of measles vaccine.[13] The 1918 influenza pandemic preferentially killed US Army soldiers recruited from rural areas as a dim reflection of the destruction of a fifth of population on the isolated island of Samoa.[14] US soldiers from urban areas and those who had been in the front lines in Europe usually had unremarkable influenzal illnesses; mortality in 1918 was largely limited to recent recruits with 78% of all deaths occurring in the first 6 months in the US Army.[7, 14]

If epidemiological data on infectious deaths in isolated populations during the 19th century is sparse, then immunological information is nearly non-existent. Some recent pediatric studies in West Africa are, however, suggestive that a dysfunction of innate immunity may be involved. Newborns immunized with BCG vaccine have considerable survival advantage not due to any protection from tuberculosis but apparently from improved ability to resist other common infectious agents.[15] This extends to other live vaccines such as measles but not toxoid vaccines such as tetanus. Such “trained” innate immunity appears to alert the first-

responder macrophages such that the critical gap between infection and effective host response is considerable shortened. No one received BCG in the 19th century, but a natural equivalent might have been early childhood infections with ordinary respiratory viruses.

Globalization created by improved transportation networks during the Industrial Revolution increased the speed of pathogen circulation and would have provided such a putative survival advantage first to urban children followed by those in more isolated communities. Growing up on a farm in 19th century America was probably not an ideal environment to prepare an adult to resist common infections and may explain the terrible mortality seen in Civil War military recruit camps that spontaneously disappeared prior to the introduction of most medical interventions in the 20th century.[12] Despite our inherent desire to see human survival being improved by progressive medical science, it may more appropriately be seen as an immune adaptation to a changing pathogen pattern. Let us hope our dynamic immune system is also capable of dealing with the not so futuristic threat of pathogens against which we have no appropriate antibiotics.

Contributors: GDS conceived the epidemiological study, collected the data, did the analyses and wrote the manuscript.

Conflicts of interest statement: The author does not claim any conflict of interest.

Funding: GDS is an employee of the Australian Defence Organization. No specific funding was given for this epidemiological study.

Acknowledgements: The author thanks many un-named historians, medical librarians and archivists who have unselfishly provided data and ideas for this paper.

Disclaimer: The opinions expressed are those of the authors and do not necessarily reflect those of the Australian Defence Force or the US Department of Defense.

References:

1. McKeown T. The origins of human disease. Oxford, UK: Basil Blackwell, **1988**.

2. Curtin PD. Death by migration: Europe's encounter with the tropical world in the nineteenth century. Cambridge University Press, **1989**.

3. Curtin PD. Disease and empire: The health of European Troops in the Conquest of Africa. Cambridge University Press, **1998**.

4. McNeill WH. Plagues and peoples. New York: Doubleday, **1998**.

5. Ireland M. Report of the Surgeon General. Vol. 2. Washington: GPO, **1920** (War Department Annual Reports, 1919).

6. Siler J. Inflammatory disease of the respiratory tract (bronchitis, influenza, bronchopneumonia, lobar pneumonia). In: Charles Lynch C, Weed F, McAfee L, eds. The Medical Department of the United States Army in the World War Vol. IX Communicable and Other Diseases. Washington DC: GPO, **1928**.

7. Vaughn V, Palmer G. Communicable disease in the United States Army during the summer and autumn of 1918. J Lab Clin Med **1919**; 4:647-86.

8. Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. Lancet Infect Dis **2006**; 6:303-12.

9. Penman BS, Gupta S, Shanks GD. Rapid mortality transition of Pacific Islands in the 19th century. Epidemiol Infect **2017**; 145:1-11.

10. Shanks GD, Lee SE, Howard A, Brundage JF. Extreme mortality after first introduction of measles virus to the polynesian island of Rotuma, 1911. Am J Epidemiol **2011**; 173:1211-22.

11. Shanks GD, Wilson N, Kippen R, Brundage JF. The unusually diverse mortality patterns in the Pacific region during the 1918-21 influenza pandemic: reflections at the pandemic's centenary. Lancet Infect Dis **2018**; 18:e323-e32.

12. Woodward J. Outlines of the Chief Camp Diseases of the United States Armies. Philadelphia: J B Lippincott, **1863**.

13. Cliff AD, Haggett P, Smallman-Raynor M. Measles: an historical geography of a major human viral disease: from global expansion to local retreat, 1840-1990. Citeseer, **1993**.

14. Paynter S, Ware RS, Shanks GD. Host and environmental factors reducing mortality during the 1918-1919 influenza pandemic. Epidemiol Infect **2011**; 139:1425-30.

15. Roth A, Gustafson P, Nhaga A, et al. BCG vaccination scar associated with better childhood survival in Guinea-Bissau. International journal of epidemiology **2005**; 34:540-7.

Legends:

Figure 1: Epidemiology of infectious diseases in the US Army during the first two years of the Civil (1860-61), Spanish-American (1898-1899) and First World (1917-18) Wars. Respiratory (measles, pneumonia, influenza, tuberculosis) pathogens are shown as A. Morbidity and B. Mortality; gastrointestinal/systemic (typhoid fever, malaria, diarrhea/ dysentery, meningitis) pathogens are shown as C. Morbidity and D. Mortality, all are rates per 1000 soldiers.

Figure 2: Epidemiology of measles and mumps as markers of epidemiological isolation in the US Army during the First World War (1917-18) based on US State of recruitment / origin of soldiers. A. US States' infection rates (all per 1000 soldiers) with measles and mumps were highly correlated. B. US States' measles infection rates relationship to all-cause disease mortality. C. US States' mumps infection rates relationship to all-cause disease mortality. D US States' measles infection rates relationship to fraction of US State classified as rural in US Census of 1920.

Supplemental Figure 1: Map of US States showing measles morbidity and mortality in the US Army of the First World War (1917-18). Taken from figure 48 of *The Medical Department of the United States Army in the World War*.