Measles deaths in the United States, 1890–2016: Age profiles and sex differences help explain pre-vaccine mortality decline

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Abstract

One of the principal features of measles epidemiology in the United States is that mortality declined before the introduction of the vaccine. We present data on measles mortality in the United States from 1890 to the present day. Our analysis focuses in particular on 1933–63, which is the time period for which there are complete (i.e., nationwide) mortality statistics, and before the first use of the measles vaccine in the winter of 1963–64. Measles mortality decline pre-dated the vaccine, though accelerated after 1963 with the reduction of cases associated with immunization. We present data on the mean age of measles mortality, and of the sex ratio in measles mortality. Our analysis points to reduction in transmission, improvements in nutrition, use of antibiotics to treat complications, and use of convalescent serum as the reasons mortality fell before the vaccine.

Introduction

We document the decline of measles mortality in the United States, 1890–2016. Measles is a communicable disease caused by the measles virus, a Paramyxovirus (Burrell et al., 2017). It is characterized by upper respiratory symptoms, fever, and a blotchy rash. Measles often has pneumonia as a clinically-significant sequela (Bottomley, 1905; Clendening, 1918; Kohn and Koiransky, 1929, 1931, 1933). Through the mid-twentieth century, measles

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was a significant cause of child mortality in the United States (often killing through pneumonia). Prior to the licensure of the vaccine in 1963, nearly everyone got measles at some point in their life, usually childhood.

A longstanding question is that "measles mortality had been falling from the start of the [twentieth] century, and a puzzle continues to be posed as to the precise reasons for these decades of decline" (Cliff et al., 1998, p.328). We describe changes in the mean age of measles mortality, by sex, and use this information to help illuminate patterns and processes in the decline of measles mortality. The age- and sex-distributions of measles deaths reveal aspects of the underlying epidemiology, beyond the fact that death rates and counts fell throughout the century. To the best of our knowledge, the data we present on changes in measles mean age of mortality have not heretofore been documented.

The mean age of death data we present are based on published tabulations of causes of death, for 1890 and 1900–58, and on a census of digitized death certificates, 1959–2016.

RATES HARD TO CALCULATE BEFORE 1933 (but explain w.r.t. figure 1).

[[some capsule summary of what we find]]

[[where on earth does this ¶ go???]] In the heyday of measles mortality, physicians would have attributed pneumonia in the close wake of the rash to measles. For example: "[bacterial pneumonia] accounts for over 90 per cent of measles deaths" (Top, 1947, p.494). Even beyond this, there is a longer-term post-measles immunosuppressive phenomenon (Avota et al., 2010; Griffin, 2010; de Vries and de Swart, 2014). Thus, once the vaccine could prevent measles altogether, mortality declines were synergistic (Feachem and Koblinsky, 1983; Mina et al., 2015). This effect is more relevant to the introduction of the vaccine to high-mortality settings (f.e., Chen et al., 1994) than to the United States' case, however.

Results

Death rates

Figure 1 shows measles sex- and age-specific death rates for four age groups, 0, 1–4, 5–14, and 15–24, using data from U.S.Department of Health, Education, and Welfare (1956). These age groups encompass the vast majority of all measles deaths (well over 90% in most years). A number of patterns are noteworthy. Measles death rates declined profoundly throughout the cen-

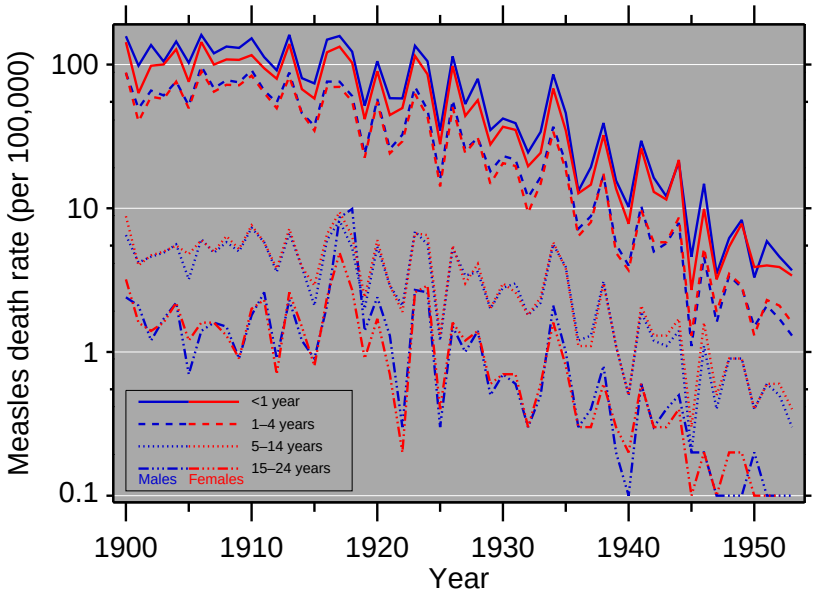

Figure 1: Measles sex- and age-specific death rates, United States death registration area, 1900–32, and United States, 1933–53.

tury. In just over 50 years, the highest death rates fell from the order of 100, to single digits (per 100,000). This fall pre-dated the measles vaccine, which was licensed in 1963 (Goddard et al., 1963; Terry, 1963). The secular trend is punctuated by epidemic years. Measles outbreaks follow a two-year cycle in a given locale (Hamer, 1906; Soper, 1929; Wilson and Burke, 1943; Wells, 1944; London and Yorke, 1973; Fine and Clarkson, 1982; Lau et al., 1992; Edmunds et al., 2000). The classic two-year cycle seen in monthly data from a single place becomes an annual cycle when summed over the entire United States (Murray and Cliff, 1977; Cliff et al., 1992*a*,*b*).

The data in figure 1 show more like a 3-year cycle, both by eye and from a periodogram analysis using the Butterworth filter (Gómez, 2001). These are annual data, and measles follows a winter-dominant pattern that does not nest into calendar years in the northern hemisphere. Annual data are therefore not ideal for studying measles periodicity. Binning into calendar years — an artificial construct as regards measles epidemiology — and converting to rates (which factors-in cycles in birth cohort size) results in a three-year cycle. Regarding the death rates in figure 1, note also that the age groups

are 1, 4, 10, and 10 years wide, which affects the raw number of deaths corresponding to each rate curve.

Measles death rates form a ladder by age, with infants highest and adults lowest (figure 1); the vertical axis is logarithmic, so the ladder is steep. For males, the rank order of the ladder is interrupted during the First World War, when death rates in the 15–24 age group exceed those of boys aged 5–14. While remarkable, this has a documented explanation, namely measles outbreaks in military camps (Cumming, 1921; Shanks et al., 2014; Morens and Taubenberger, 2015). Because it is the archetypal "crowd disease" (Black, 1959, 1966), with high force of infection (Grenfell and Anderson, 1985), measles is typically a childhood disease (Wilson and Worcester, 1941; Hope Simpson, 1952). Recruits from rural areas were susceptible to measles due to the inverse phenomenon; where populations were less dense, force of infection was lower, with higher average age of infection. Thus, outbreaks in the Army, fed by recruits from rural areas, were inevitable as long as bases were not completely sealed off from the rest of society: "Measles was from the start a disease of unseasoned rural troops" (Woolley, 1919, p.35). Moreover, the First World War military experience with measles among recruits fits neatly into a continuum going back to at least the Civil War (1861–65) (Black, 1976, p.307).

Sex differences are noteworthy in figure 1. Among infants, boys have consistently higher measles death rates than girls, mirroring all-cause sex differences in this age group (Ciocco, 1940*a*,*b*; Nathanson, 1984). Among children 1–4, boys have higher death rates in some years but in general there is more parity. At ages 5 and over, there is no important sex difference, apart from the male excess during the First World War.[1] These findings are not in perfect concordance with those of Garenne (1994) (explored further in Garenne and Lafon, 1998), although the geographic and temporal context is different.

Deaths

Now we turn to our principal analysis, of measles deaths by age and sex, 1890–2016. Data sources are listed in Appendix I. By working with age-

[1] In the age group 15–24, there is a female excess in 1939 and 1940 and a male excess in 1943 and 1944. The latter is plausibly explained by U.S. mobilization for the Second World War, along the lines discussed for the First World War. As tempting as it is to find explanations for these changes, measles death rates in this age group had fallen so much by this time that the absolute differences in rates were one part per million. There is a noise aspect when death rates are so low.

specific death counts, we obtain more precise estimates of the mean age of measles mortality than would be possible from working with the rate data in figure 1. In principle, we could back-out death counts from rates and data on population. By working with recorded death counts, we eliminate potential sources of error, for example ambiguities introduced when rates were rounded. This yields added precision by age, because deaths were recorded by single year of age in the first five years of life and in five year age groups thereafter, whereas figure 1 (U.S.Department of Health, Education, and Welfare, 1956) used less granular age categories.

Figure 2 shows measles deaths in the United States in 1890 and for 1900–2016 as a stacked bar chart (females on top of males). Because the scale makes it quite difficult to see the data after 1967, these are repeated as an inset. There are several important features of figure 2. The peak year in terms of recorded measles deaths was 1917, an epidemic year (not just on military bases), with 10,432 fatal cases. Total deaths are influenced not only by measles case fatality but by population growth, particularly that caused by natural increase, since many immigrants would have come to the United States having already experienced measles (and were therefore immune to it). The proportion of the population contracting measles also matters, but this is generally regarded as 100% (Black, 1959, 1962). The population at risk of measles infection was also increased by declines in other causes of infant mortality. The Death Registration Area (DRA) of the United States did not encompass the whole country until the addition of Texas in 1933 (Hetzel, 1997). Therefore, year-to-year changes in figure 2 are especially difficult to interpret in 1933 and before. The last year in which the United States recorded more than 5,000 measles deaths was 1934 (6,978 deaths). Despite increasing population throughout the twentieth century, measles deaths generally decline after 1934, a sign of decreasing case fatality rates (Gindler et al., 2004).

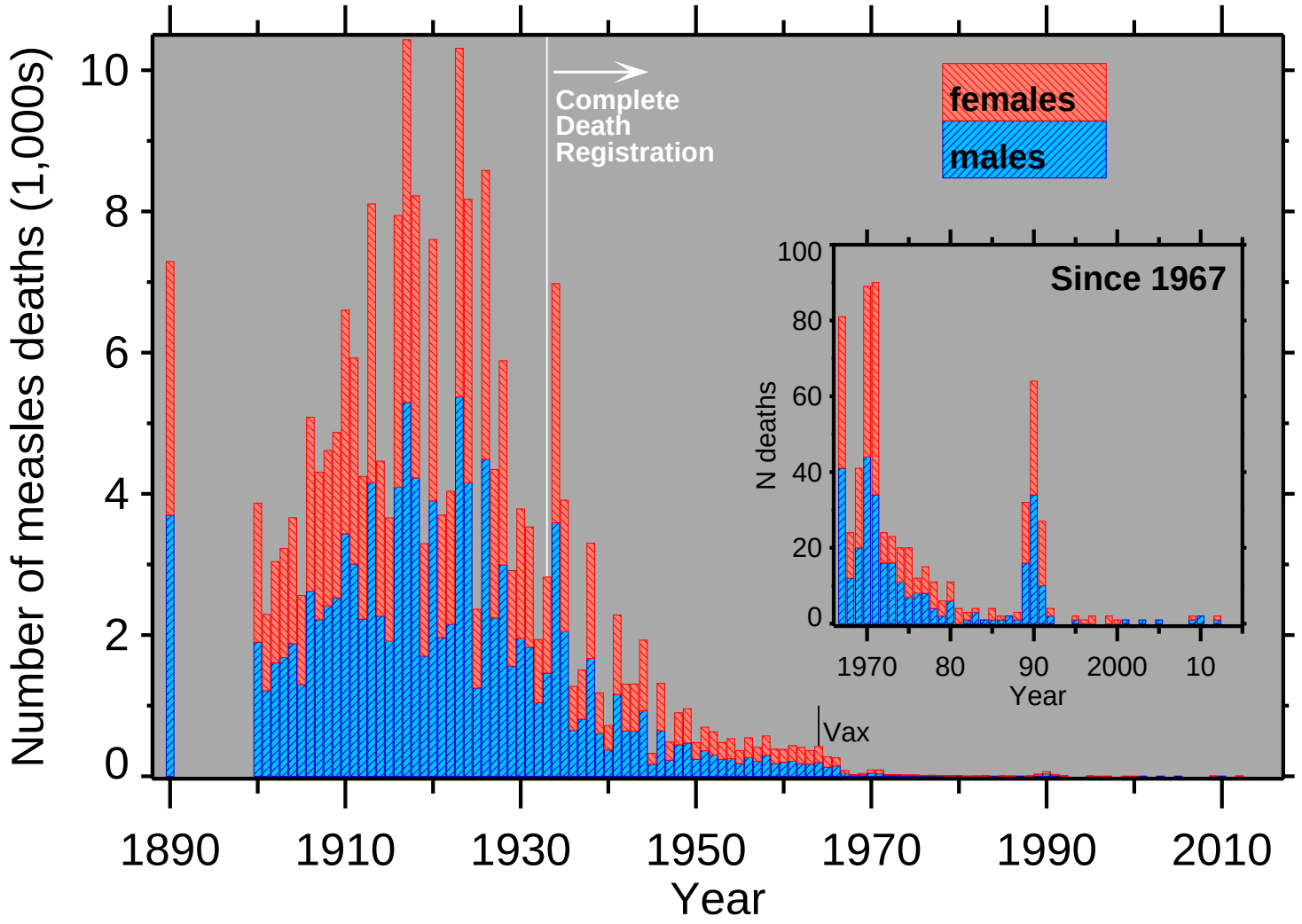

Figure 2: Measles deaths in the United States Death Registration Area, 1890, and 1900–32, and in the United States, 1933–2016.

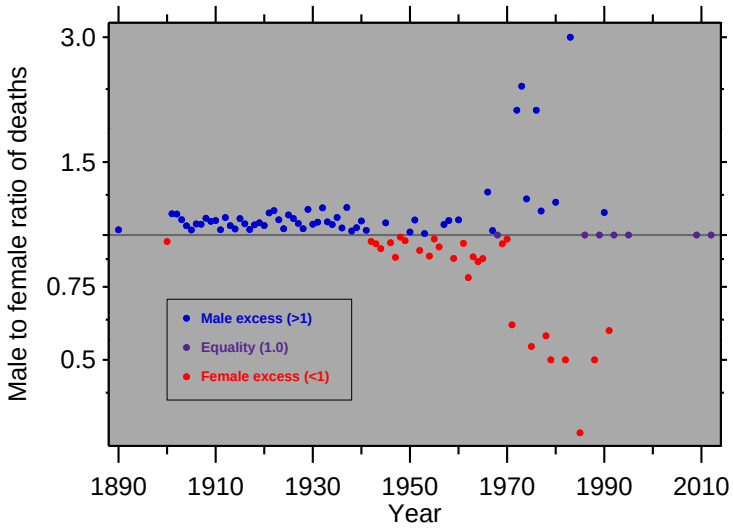

Figure 3: Sex ratio of measles deaths (male cases divided by female cases), in the United States Death Registration Area, 1890, and 1900–32, and in the United States, 1933–2016.

The licensure of the measles vaccine in 1963 is associated with a decline in measles deaths (by reducing cases), although by this time deaths had already fallen dramatically. Measles epidemics occurring after the introduction of vaccination are called *post-honeymoon* outbreaks (Corey and Noymer, 2016). The United States has seen a number of post-honeymoon measles epidemics, beginning just a few years after vaccination began (Dandoy, 1967; Landrigan, 1972; Pyle, 1973). As recently as 1990 (64 deaths), there were years with significant numbers of measles deaths (by the standards of the post-vaccine era). This was associated with a nationwide measles epidemic in 1989–91 (Atkinson et al., 1992; Gindler et al., 1992*a*,*b*), the last such epidemic of its scale prior to elimination of measles from the United States in 2000 (Samuel and Hinman, 2004). Elimination refers to the cessation of continuous chains of transmission; there still can be (and have been) post-elimination cases (and deaths), with the virus introduced by travelers (cf., for example, Halsey and Salmon, 2015).

Figure 3 displays the sex ratio (male/female) of measles deaths, from data in figure 2. Excluding 1900, all years through 1941 show a small (but, evidently, consistent over time) male excess measles mortality. This is not surprising, given that all-cause mortality has a sex ratio >1 (Clarke, 2000),

particularly at younger ages in which most measles mortality occurs. What is interesting is that from 1942 to 1963 (with the latter year chosen because it was the year of introduction of the vaccine), 7 of 22 years show male excess and 15 show female excess. As measles diminished as an important cause of child death, its sex ratio became less tethered to the male excess. One possibility is that boys enjoyed slightly preferential access to antibiotics in the treatment of complications of measles (or to convalescent sera in earlier stages of the disease); there does not appear to be any literature on this subject in the context of the United States in the relevant time period. Antibiotic use in measles was well-documented, and began with the sulfa drugs, and so pre-dated the penicillin era (Hodes et al., 1939; Gibel and Litvak, 1942; Swyer, 1943). Another explanation is that, net of antibiotics, measles became more a female cause of death, but not necessarily having anything to do with sex differences in prescription rates. Although the number of measles deaths declines, the changes in the sex ratio are not due to stochastic, small-N, effects (see Appendix II, p.19).

Mean age

Figure 4 presents a time series of the mean age of measles deaths, by sex. The data are shown as 95% uncertainty intervals (UIs) up to 1971, and as point estimates thereafter (without UIs, due to shrinking sample size). Measles mortality plummeted after 1971 (90 measles deaths), as the impact of vaccination became more profound and the early post-honeymoon epidemics burned out. The period 1972–1988 was relatively quiet — never more than 23 deaths (in 1973).

A large post-honeymoon epidemic occurred in 1989–91 (Atkinson et al., 1992; Gindler et al., 1992*b*; Watson et al., 1998). This saw 32, 64, and 27 annual measles deaths, and helped spur the transition to a two-dose vaccination schedule for measles in 1989 (Orenstein, 2006), which remains policy to the present day (McLean et al., 2013). This two-dose schedule paved the way for the elimination of measles from the US in 2000 (Orenstein et al., 2004), especially since there were fewer susceptible children in the wake of the 1989–91 epidemic. The first year in the history of the United States with no measles deaths was 1993 (1984 had seen only one measles death). In 1994 there were also no deaths, and 1998, 2002, 2004, 2006–08, 2011, and 2013–16 similarly saw no measles deaths. The most recent year (up to and including 2016) in which any measles deaths occurred was 2012 (2 deaths).

The data for figures 2–4 (mean ages and UIs, as well as number of deaths) are in table 1; these were calculated using Stata v.13.1 (StataCorp LLC, Col-

lege Station, TX). The final column of table 1 is the p-value for the test of males and females having different ages (the same data are presented with a UI approach in figure 5, discussed below). In 1959, the data change from tables in printed books, to a database of all deaths; this is indicated with a white vertical line in figure 4. The decline in average age of mortality in 1959 and thereafter is partly an artifact of increased precision afforded by the electronic data. For example, before 1959, we have counts of measles deaths at ages 5–9, 10–14, and so on. These are assigned to age 7.5, 12.5, et cetera. Most measles deaths in the 5–9 range are closer to 5 than to 9; using 7.5 introduces an upward bias. However, lacking any basis to assign these deaths to an age other than the midpoint of the group, we use 7.5. Starting in 1959, each measles death is known with precision of 1 year (for infant deaths, age is known in months).

In 1963, vaccination was introduced, indicated by a gray vertical bar in figure 4. Starting in the winter of 1963–64, the epidemiology of measles in the United States changed dramatically in response to the vaccine. The general upward increase in the mean age of measles deaths in 1964 and thereafter is associated with vaccination. With most children vaccinated, and therefore immune, cases (and deaths) occurred more among older individuals who missed the roll-out of the vaccine. In the 1970s and 1980s, this trend continued, with two factors synergistically contributing to older cases (and deaths). As the force of measles transmission waned, the average age of infection naturally increased (Grenfell and Anderson, 1985), meaning measles cases among primary vaccine failures[2] would be older. At the same time, secondary vaccine failures,[3] which by definition take time to appear, increased the mean age of the susceptible population. In the period since 1971 in which figure 4 does not show the UIs, due to small sample size, there are wild swings in the mean age of measles mortality, driven by extremely small sample sizes.[4]

[2] Primary vaccine failures are cases in which an individual received the vaccine but did not become immune.

[3] Secondary vaccine failures are the waning of vaccine-induced immunity in individuals who were successfully immunized.

[4] Specifically, after 1971 (and excluding the epidemic of 1989–91) there were on average 3.75 female measles deaths per year (excluding years with no deaths), and 3.65 deaths per year for males.

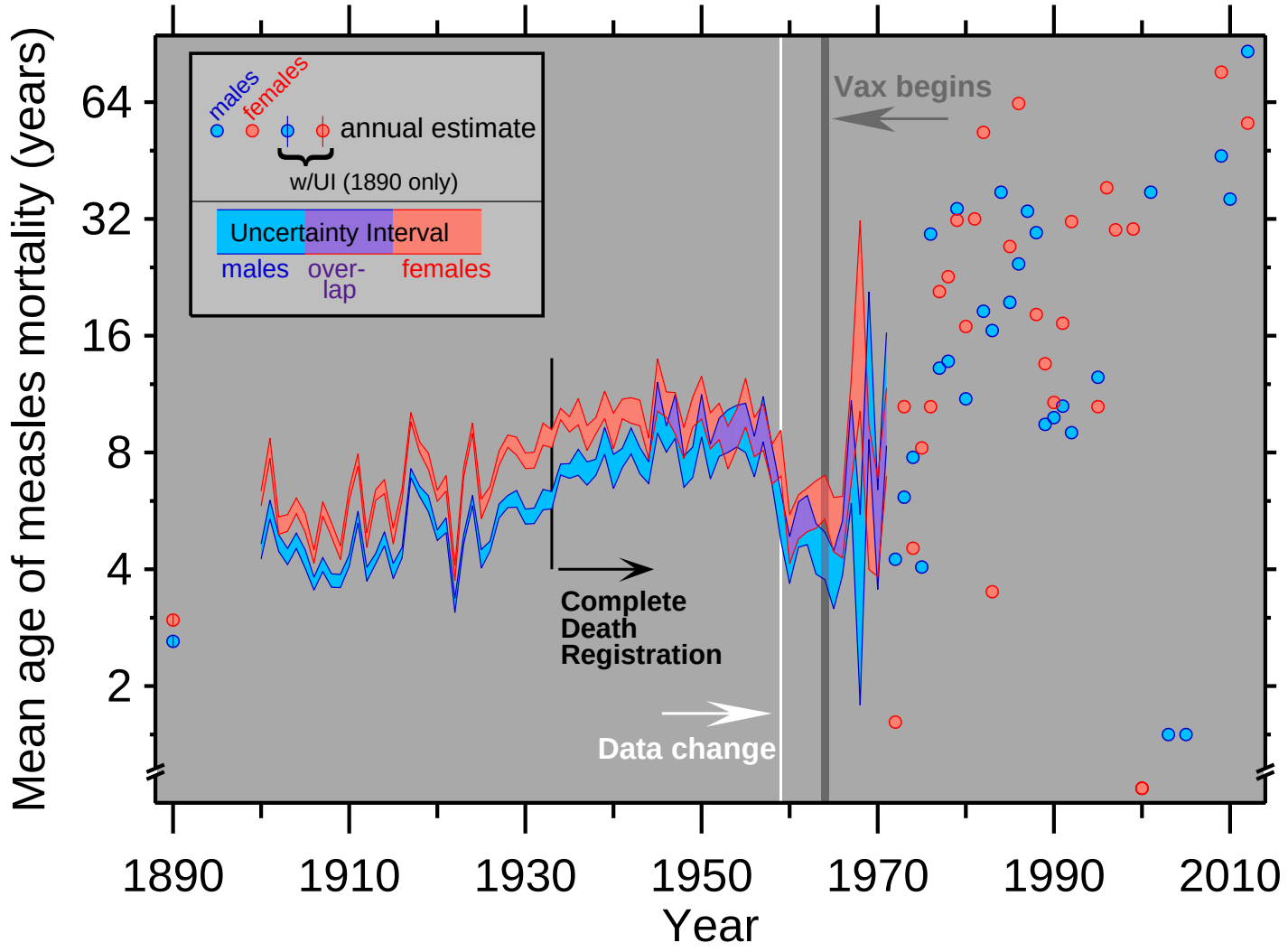

Figure 4: Mean age of measles deaths (as 95% uncertainty interval through 1971), by sex, United States Death Registration Area (1890, 1900–32), and United States (1933–2012).

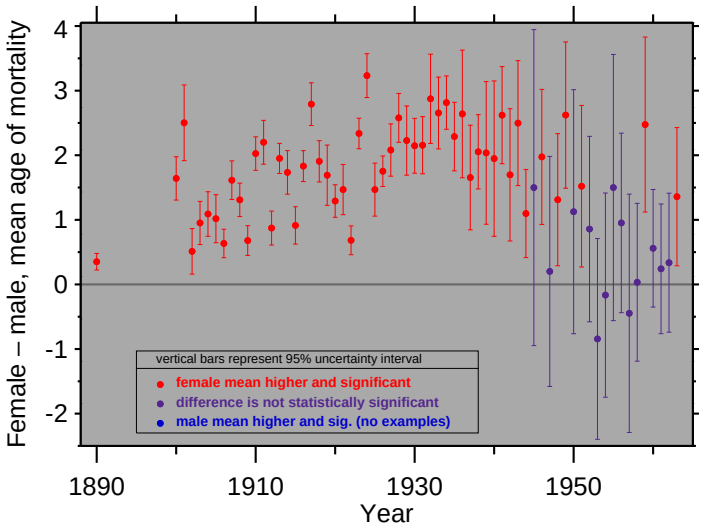

Figure 5: Sex difference in mean age of measles mortality, 1890, 1900–63.

The most prominent aspect of figure 4 is that the mean age of measles mortality was higher for females during most of the pre-vaccine era (all years except three). The older female mean age was usually statistically significant, as shown by the completely non-overlapping UIs in most years. Another major feature is the slow (and noisy) increase in the mean age of measles mortality, 1890–1958. As noted above, when the data change to electronic records in 1959, there is a break in the comparability and then there are only five years before the effect of the vaccine becomes evident in 1964. We speculate that the increase in mean age throughout the century is due to improvements in transportation which made rural America progressively more connected to metropolitan areas.

Rural areas have lower population density and therefore less intense measles transmission, with older mean ages of infection; the 1917 outbreaks among military recruits (discussed above) are a perfect example of this. The improvements of transportation networks (particularly automobiles and highways) throughout the century increased rural-urban contact, creating a situation similar to the rural troops coming to Army encampments, albeit at a slower pace. This would result in a gradual increase in measles mortality at older ages, driving up the mean.

Figure 5 shows the sex difference in mean age of measles mortality, from 1890 to 1963 (the start of vaccination). Whereas figure 4 shows each sex,

Table 1: The data for figure 4. * denotes that 1972 was a 50% sample of deaths.

	Males				Females				*p*-value,
	mean	95% UI		*N*	mean	95% UI		*N*	sex
year	age	lower	upper	deaths	age	lower	upper	deaths	diff.
1890	2.61	2.52	2.69	3,698	2.96	2.86	3.06	3,592	<0.0005
1900	4.45	4.25	4.65	1,899	6.09	5.82	6.36	1,969	<0.0005
1901	5.70	5.39	6.03	1,213	8.20	7.73	8.71	1,078	<0.0005
1902	4.67	4.45	4.90	1,609	5.18	4.92	5.46	1,432	0.004
1903	4.31	4.11	4.53	1,681	5.27	5.01	5.53	1,544	<0.0005
1904	4.74	4.53	4.96	1,878	5.83	5.56	6.10	1,784	<0.0005
1905	4.25	4.03	4.49	1,298	5.27	4.99	5.57	1,262	<0.0005
1906	3.67	3.53	3.81	2,621	4.31	4.14	4.48	2,464	<0.0005
1907	4.11	3.95	4.29	2,218	5.73	5.49	5.98	2,089	<0.0005
1908	3.74	3.59	3.89	2,414	5.05	4.84	5.27	2,199	<0.0005
1909	3.73	3.59	3.88	2,527	4.41	4.24	4.59	2,342	<0.0005
1910	4.21	4.07	4.35	3,435	6.24	6.02	6.46	3,169	<0.0005
1911	5.45	5.26	5.65	3,006	7.65	7.38	7.94	2,919	<0.0005
1912	3.88	3.72	4.05	2,227	4.76	4.55	4.97	2,021	<0.0005
1913	4.26	4.13	4.39	4,159	6.21	6.02	6.41	3,948	<0.0005
1914	4.80	4.60	5.00	2,269	6.53	6.26	6.81	2,194	<0.0005
1915	3.96	3.78	4.14	1,913	4.87	4.65	5.10	1,746	<0.0005
1916	4.41	4.28	4.55	4,095	6.25	6.05	6.45	3,847	<0.0005
1917	7.08	6.89	7.27	5,296	9.87	9.61	10.15	5,136	<0.0005
1918	6.35	6.16	6.54	4,227	8.25	8.00	8.51	3,994	<0.0005
1919	5.90	5.62	6.18	1,703	7.59	7.22	7.97	1,591	<0.0005
1920	4.90	4.75	5.05	3,902	6.19	5.99	6.39	3,701	<0.0005
1921	5.19	4.97	5.43	1,963	6.66	6.36	6.98	1,736	<0.0005
1922	3.23	3.09	3.37	2,155	3.91	3.74	4.09	1,882	<0.0005
1923	4.78	4.66	4.91	5,374	7.12	6.92	7.32	4,938	<0.0005
1924	6.02	5.84	6.20	4,158	9.25	8.97	9.54	4,015	<0.0005
1925	4.26	4.03	4.50	1,249	5.72	5.40	6.07	1,117	<0.0005
1926	4.59	4.46	4.73	4,487	6.34	6.15	6.54	4,094	<0.0005
1927	5.65	5.42	5.89	2,243	7.73	7.41	8.07	2,103	<0.0005
1928	5.98	5.77	6.20	2,994	8.56	8.25	8.87	2,891	<0.0005
1929	6.08	5.78	6.39	1,560	8.31	7.87	8.76	1,353	<0.0005
1930	5.47	5.23	5.72	1,950	7.61	7.27	7.97	1,836	<0.0005
1931	5.49	5.25	5.75	1,828	7.65	7.29	8.02	1,702	<0.0005
1932	6.05	5.69	6.43	1,041	8.92	8.36	9.53	895	<0.0005
1933	6.03	5.73	6.34	1,461	8.68	8.23	9.16	1,358	<0.0005
1934	7.23	7.00	7.47	3,591	10.05	9.71	10.39	3,387	<0.0005
1935	7.17	6.87	7.49	2,051	9.46	9.04	9.90	1,860	<0.0005
1936	7.55	6.99	8.15	649	10.19	9.42	11.02	624	<0.0005
1937	7.06	6.59	7.57	811	8.72	8.09	9.39	696	<0.0005
1938	7.32	6.98	7.68	1,669	9.38	8.93	9.84	1,632	<0.0005
1939	8.58	7.92	9.30	602	10.62	9.79	11.52	578	<0.0005
1940	7.14	6.46	7.91	373	9.09	8.18	10.10	345	0.001
1941	7.74	7.31	8.20	1,157	10.36	9.77	10.98	1,127	<0.0005
1942	8.57	7.93	9.26	641	10.26	9.51	11.07	664	0.001
1943	7.62	7.05	8.23	638	10.11	9.38	10.91	670	<0.0005
1944	7.09	6.65	7.56	928	8.19	7.70	8.71	1,001	0.002
1945	10.44	8.98	12.15	168	11.94	10.21	13.96	157	0.227
1946	8.66	8.01	9.35	644	10.63	9.86	11.47	672	<0.0005
1947	9.90	8.70	11.27	228	10.10	8.94	11.41	258	0.825
1948	7.14	6.51	7.83	447	8.45	7.71	9.27	452	0.011
1949	7.55	6.90	8.26	471	10.17	9.30	11.12	486	<0.0005

continues

	Males				Females				*p*-value,
	mean	95% UI		*N*	mean	95% UI		*N*	sex
year	age	lower	upper	deaths	age	lower	upper	deaths	diff.
1950	9.95	8.77	11.29	241	11.08	9.76	12.58	237	0.241
1951	7.58	6.84	8.40	362	9.10	8.17	10.13	333	0.016
1952	8.75	7.82	9.80	301	9.61	8.63	10.71	328	0.242
1953	9.08	8.00	10.31	240	8.24	7.25	9.35	238	0.286
1954	9.35	8.26	10.59	250	9.19	8.17	10.33	281	0.837
1955	9.26	8.00	10.71	180	10.76	9.31	12.43	184	0.152
1956	7.80	6.92	8.81	264	8.76	7.79	9.84	282	0.179
1957	9.75	8.52	11.16	211	9.31	8.10	10.69	199	0.635
1958	7.42	6.63	8.32	297	7.46	6.63	8.40	274	0.957
1959	5.50	4.75	6.36	180	7.97	6.95	9.14	205	<0.0005
1960	4.22	3.67	4.85	198	4.78	4.13	5.53	182	0.225
1961	5.21	4.56	5.97	212	5.46	4.78	6.22	222	0.637
1962	5.36	4.63	6.20	180	5.69	5.00	6.48	228	0.541
1963	4.52	3.89	5.25	171	5.87	5.10	6.76	193	0.012
1964	4.33	3.76	4.98	195	6.14	5.39	6.99	226	<0.0005
1965	3.76	3.16	4.46	129	5.21	4.44	6.13	147	0.007
1966	4.53	3.85	5.33	146	5.14	4.28	6.16	115	0.318
1967	8.03	5.92	10.91	41	9.09	6.67	12.40	40	0.577
1968	3.14	1.78	5.53	12	18.02	10.24	31.74	12	<0.0005
1969	13.40	8.65	20.77	20	6.13	3.99	9.40	21	0.012
1970	4.77	3.55	6.41	44	5.13	3.83	6.87	45	0.732
1971	11.65	8.32	16.30	34	9.03	6.95	11.73	56	0.241
1972*	4.24	2.12	8.49	8	1.61	—	—	4	—
1973	6.14	3.76	10.01	16	10.50	5.01	22.02	7	0.236
1974	7.77	4.30	14.04	11	4.53	2.36	8.71	9	0.230
1975	4.05	1.93	8.50	7	8.22	4.77	14.16	13	0.132
1976	29.25	14.63	58.49	8	10.50	—	—	4	—
1977	13.20	6.60	26.39	8	20.79	9.91	43.60	7	0.380
1978	13.75	—	—	4	22.71	10.83	47.63	7	—
1979	34.00	—	—	2	31.75	—	—	4	—
1980	11.00	4.94	24.48	6	16.90	—	—	5	—
1981	—	—	—	0	32.00	—	—	4	—
1982	18.50	—	—	1	53.50	—	—	2	—
1983	16.50	—	—	3	3.50	—	—	1	—
1984	37.50	—	—	1	—	—	—	0	—
1985	19.50	—	—	1	27.17	—	—	3	—
1986	24.50	—	—	1	63.50	—	—	1	—
1987	33.50	—	—	2	—	—	—	0	—
1988	29.50	—	—	1	18.15	—	—	2	—
1989	9.45	5.79	15.43	16	13.55	8.30	22.11	16	0.309
1990	9.84	7.03	13.77	34	10.77	7.53	15.40	30	0.719
1991	10.53	5.67	19.58	10	17.22	10.71	27.70	17	0.217
1992	9.00	—	—	2	31.50	—	—	2	—
1995	12.50	—	—	1	10.50	—	—	1	—
1996	—	—	—	0	38.50	—	—	1	—
1997	—	—	—	0	30.00	—	—	2	—
1999	—	—	—	0	30.15	—	—	2	—
2000	—	—	—	0	0.12	—	—	1	—
2001	37.50	—	—	1	—	—	—	0	—
2003	1.50	—	—	1	—	—	—	0	—
2005	1.50	—	—	1	—	—	—	0	—
2009	46.50	—	—	1	76.50	—	—	1	—
2010	36.00	—	—	2	—	—	—	0	—
2012	86.50	—	—	1	56.50	—	—	1	—

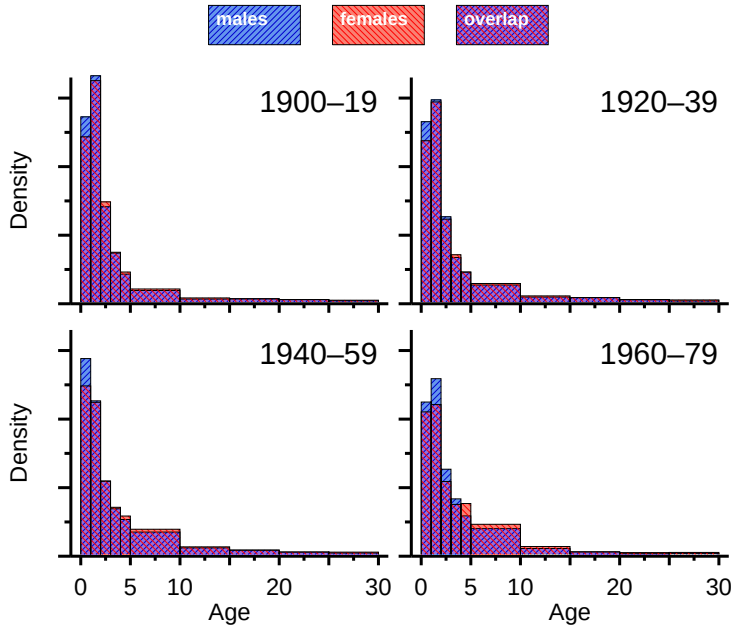

Figure 6: Histograms of measles deaths by age and sex, using data from table 1, aggregated into 20-year spans, 1900–1979.

separately, as UIs, figure 5 provides the point estimate of the sex difference (with a 95% UI). Girls and women die from measles older, on average, than boys and men in all years but three. Through 1944, the sex difference in mean age is always statistically significant. In 1945 and thereafter, there is a mix of statistically significant and not significant differences, as shown by the UIs which cross zero. None of the three years (1953, '54, '57) in which the sex difference is negative (i.e., males have a higher average age of measles death) are statistically significant. While more males than females typically die of measles (figure 3), females die (on average) at older ages. Recall that the loss of significance (and sign reversal, in three years) begins in the 1940s — as measles death rates (figure 1) and absolute number of deaths (figure 2) fell, and the sex ratio of the deaths became more female in some years (figure 3).

To give a feel for the age distribution of measles deaths — as opposed to a single summary statistic (the mean age of death) — figure 6 shows histograms of measles mortality by age and sex. Four two-decade time pe-

riods are shown (1900–19, 1920–39, 1930–59, 1960–79); since 1980, due to vaccination, there are fewer deaths (figure 2) and they are older than the typical measles mortality pattern (figure 4). These histograms have positive skew, and illustrate well that the vast majority of measles deaths occur below age 10, and with no mode at older ages. In all four panels (i.e., time periods), there is male excess among infants. This makes sense in two ways. First, boys have higher infant mortality for all causes (Pongou, 2013, 2015), so it is not surprising that this should also extend to measles. Second, this partly accounts for the older female mean age of measles mortality seen in figure 5. Males experience more measles mortality in infancy, bringing down the mean age relative to females. As infant mortality and especially measles mortality fell, the excess measles deaths among infants exerted less influence on the mean.

Factors affecting mortality decline before the vaccine

One of the salient features of figure 2 is the enormous drop in measles deaths, even before the vaccine. Measles surveillance and serology studies show that the mortality decline was not a reflection of a reduction in cases (Collins, 1924; Black, 1959). Prior accounts have stressed the role of antibiotic therapy for measles complications, and childhood nutritional improvements (Babbott and Gordon, 1954; Barkin, 1975; Gindler et al., 2004). Reduced residential crowding can lower the average size of the infectious dose. This has been proposed as a factor in the reduction of measles case fatality (Aaby, 1988), albeit not specifically in the United States. We endorse a multicausal explanation for the pre-vaccine decline in measles mortality. The aggregate data we analyzed are not well-suited to assignment of percentages to each category. Nonetheless, in this subsection we thumbnail the evidence on antibiotics and nutrition, and highlight another factor: the use of measles immune globulin.

The medical literature featured a number of articles on the use of antibiotics to treat measles; "sulfadiazine and penicillin are of value in the treatment of measles complications caused by secondary invaders" (Top, 1947, p.496). The first antibiotics, the sulfonamides (Lesch, 2007), were enthusiastically put to use against measles as soon as they were available (Thompson and Greenfield, 1938; Hodes et al., 1939; Gibel and Litvak, 1942; Swyer, 1943). We do not know of any estimates of the number of doses of sulfa drugs that were used specifically to treat measles. Jayachandran et al. (2010) argue that sulfa drugs significantly impacted all-cause mortality, so their role in measles mortality decline was plausibly large. When penicillin

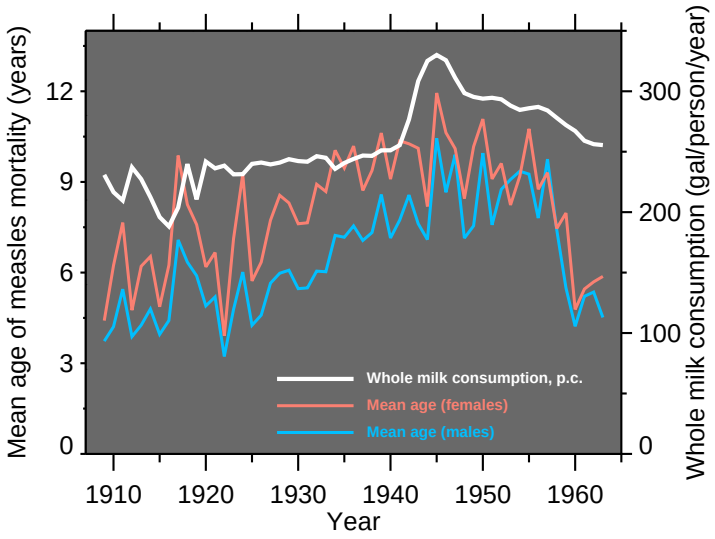

Figure 7: Mean age of measles mortality; male and female (left y-axis) are the point estimates from figure 4. And whole milk consumption, per capita (right y-axis).

became available to the civilian population after the Second World War, it was likewise used in measles patients (Karelitz et al., 1954, 1959).

Use of convalescent serum to prevent measles in exposed children goes back to 1916 (Zingher, 1924). This substance, sometimes (mostly later) called immune globulin (e.g. Anonymous, 1948), is an injection of human serum — i.e., blood spun in a centrifuge to separate cells from plasma and clotting factors.[5] Measles convalescent serum was available as a commercial medical product from Lederle Antitoxin Laboratories, Pearl River, NY, in 1925 if not before (U.S.Public Health Service, 1925). Antibodies from prior infections are present in large numbers in serum, especially in the case of measles, which elicits a strong humoral immune response. Measles was a ubiquitous infection in this ear, so there was no shortage of raw material for serum production. Prior to the vaccine, serum was used as post-exposure prophylaxis, especially in boarding schools, and (less successfully) as a treatment for symptomatic measles (Townsend, 1926; Picken, 1931; Hunter, 1933; Hobson, 1934, 1938; Gallagher, 1935; Elkington, 1936; Le Fleming, 1937; Gray,

[5] Attempts to make heterologous measles sera (i.e., using blood from animals intentionally exposed to measles) did not prove successful (Barenberg et al., 1930).

1938; Gunn, 1938; Lempriere, 1939; Top and Badger, 1941; Cockburn et al., 1948; Hartley et al., 1950; Bettag et al., 1955).

The mixture of early-stage natural infection and external antibodies from serum can both prevent symptomatic measles and generate a long-lasting immune response, "rendering [sub-clinical] infections effectively vaccine-like" (Zinkernagel, 2002, p.117). Note that in serosurveys, such survivors would be indistinguishable from those who survived symptomatic infection. We do not know of any estimates of the number doses of immune globulin (also called gamma globulin) that were administered in the United States. Given the prevalence of accounts in the medical literature of its use, especially in schools, we believe that its impact was significant, even at the population level. For example, a contemporary medical editorial (Anonymous, 1945) urged: "We have an ample, supply of gamma globulin, containing immune substances, for 1945–1946. We should use it to the full extent."

Various factors could have increased the mean age of measles infection from 1900 to the advent of the vaccine in 1963. Anything that reduces the force of infection of a ubiquitious disease, such as measles, will increase the average age of its acquisition (Anderson and May, 1991). Decreases in housing density and the use of serum to squelch school epidemics would both have reduced the force of infection. Also, the falling cost of transportation, and the related transformation of rural areas into suburbs, would have increased the mean age of measles infections by exposing rural populations to measles virus. As the the aforementioned experience in Army camps demonstrates, the relative isolation of these populations made them an exception to the rule that everyone gets measles in childhood.

The increase in the average age of measles infection would have two secondary effects on measles epidemiology. First, it would increase the mean age of measles deaths. Measles deaths are not a random sample of measles infections — deaths are drawn from severe cases. However, it would have required highly unusual selection effects for the mean age of mortality to remain stable in the face of upward movement of the age distribution of measles cases. Second, it would decrease the number of measles deaths, because the case fatality rate (CFR) of measles declines with age (Picken, 1921; Barkin, 1975; Black, 1976; Walsh, 1983; Cutts, 1990; Wolfson et al., 2009). Before the vaccine, everyone (for all intents and purposes) got measles at some point in their life (or had a case suppressed through well-timed immune globulin). Therefore, declines in the force of measles transmission shifted the mean age but did not — in the long run — affect the number of cases. The sustained decrease in the number of deaths (figure 2) therefore

comes in part from the age-CFR relationship, since upward age shifts reduce mortality.

Sex differences in measles mortality undergo some noteworthy flips in the pre-vaccination era. Figure 3 and table 1 show that, with the sole exception of 1900, until 1942 there were always more male measles deaths. From 1942 until the start of vaccination, only seven years see a male excess in measles deaths; appendix II discusses how this is extremely unlikely to have been a statistical artifact of declining numbers of measles deaths. It is well understood that boys' infant and child mortality rates are higher than those for girls (CITE), so it is not surprising that there are more measles deaths among boys. It seems to be no coincidence that the mean age of measles mortality during the period of male excess (roughly, 1900–40) was significantly higher for females. The excess male deaths occurred at younger ages (figure 6). As the force of measles transmission declined, the mean age of deaths went up (figure 4), and the sex difference of mean age of mortality became insignificant (figure 5). As the overall measles CFR fell due to the age-related effects, it became harder for sex differences to remain significant. Moreover, the use of immune globulin in boys' boarding schools may have induced a sex bias big enough to sustain the observed differences. The boarding school effect is plausible — the absolute sex difference in numbers of measles deaths in the post-war era was not large.[6]

discuss figure 7

Conclusion

WE ARE HERE

summarize paper

and say how social patterns are relfected in meas data

Deaths declined before the vaccine because... recap pp.15–17

Emphasize our contribution: globlulin and decline in λ inferred by the mean age of mortality...

Say something somewhere, about maternal antibodies.

[6]For example, 1945–1960, inclusive, there were nine years in which males had fewer measles deaths than females, but by this era, so few people died of measles that the sex difference in these nine years was 20.3 ± 10.4 deaths per year (mean $\pm$SD). Thus small factors, such as boys' greater enrollment at boarding schools with use of immune globulin, could have been enough to drive the effects.

Appendix I: Data sources for counts

Dates	Source
1890, 1900–58	*Vital Statistics of the United States* (*VSUS*), annual volumes: www.cdc.gov/nchs/products/vsus.htm
1959–67	NCHS mortality MCD data files: www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html
1968–2016	NCHS mortality MCD data files: www.cdc.gov/nchs/data_access/vitalstatsonline.htm

Appendix II: The change in the sex ratio of deaths

The sex ratio of measles deaths starts out being predominantly male on an annual basis, but becomes more female after 1940 (figure 3, the data for which are caclculated from figure 2). The sample size of deaths also declines over time. If one flipped a coin 10,000 times and got 60% heads, it would be easy to conclude that it was an unfair coin. Suppose the coin was returned to its owner, who, later, supplied a coin — possibly the same coin — for testing, except this time, only 10 flips are allowed. Due to the smaller sample size, getting four heads would not be sufficient to conclude that it is a different coin. Assuming the coin is the same (i.e., biased 60:40 in favor of heads), the binomial probability of getting four or fewer heads in 10 tries is about 17%. Similarly, the change in measles sex ratio could be due to diminished sample size, because the number of deaths had declined by 1940.

We tested this by simulation. For the period 1890–1939 (excluding 1891–99), there were 40 years in which there was a male excess. In the period that followed, up to the start of vaccination (1940–62), only 9 of the 23 years had a male excess. By simulating the earlier period 100,000 times per candidate sex ratio, we find that the smallest (i.e., least male) sex ratio that is consistent with the data is 1.0451. If the sex ratio is this value, then getting the observed outcome (viz., 40 years with a male sex ratio) is at the 97.5 percentile of the simulated distribution — i.e., it is at the edge of plausibility with a two-sided test and $\alpha = 0.05$. This is an estimate of the smallest plausible sex ratio that is consistent with the data; the most likely sex ratio is more male.

If the sex ratio continued to be 1.0451 in the period 1940–62, the chance of seeing 9 or fewer male-majority years was 0.00132 in a second simulation, of 1.5 million runs of this time span. We conclude that it is extremely unlikely that the change in the sex ratio was due to the diminished sample

size. This approach assumes a constant sex ratio in the period 1890–1939, and then tests whether that sex ratio remained the same, 1940–62. Reality is probably much closer to the sex ratio being a different realization of a random variable in each year. Nonetheless, these simulations show that the changes are extremely unlikely to have been due to stochasticity driven by the diminished sample sizes in the fashion of the coin example. The simulation exercise treats the observations as an ensemble; within a given year, uncertainties can be cacluated (without simulation) using binomial variance.

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