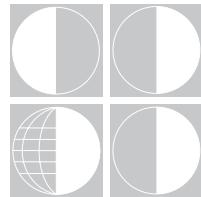


The 1918–19 Influenza Pandemic Affected Tuberculosis in the United States: Reconsidering Bradshaw, Smith, and Blanchard[†]



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Bradshaw, Smith, and Blanchard discuss a number of facets of the decline of tuberculosis and influenza, fascinating and important diseases. Bradshaw, Smith, and Blanchard (2008; hereinafter BSB) make a number of points opposing my 2000 *Population and Development Review* article with Michel Garenne. I will confine the present discussion to these points. It will be useful to begin with a summary of the relevant points of Noymer and Garenne (2000).

EARLIER FINDINGS

Noymer and Garenne (2000) (herein-after NG) started from the observation that the sex difference in life expectancy fell dramatically after 1918, and given the temporal coincidence, sought to determine

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whether this was related to the 1918–19 influenza pandemic. A falling differential in life expectancy indicates decreased female advantage (males were unable to turn the tables completely). A peculiar characteristic of the post-1918 drop in female advantage was persistence: the sex difference in life expectancy did not bounce back right away.

We concluded that the 1918–19 pandemic was the cause of the pattern in the life expectancy sex differential. The argument goes as follows. The influenza pandemic acted as a selector, killing, *in the aggregate*, people who were less healthy. In population biology (and sometimes in epidemiology), this phenomenon would be called a harvesting effect. In demography, it has been called selection, frailty, and cohort inversion. The flu pandemic was of course a massive episode of unhealthiness, but the post-flu population was healthier than the pre-flu population. We identified tuberculosis as having played a key role.

As we put it, “some of the huge losses of life resulting from the 1918 influenza epidemic were, in some sense, borrowed against future deaths from tuberculosis” (NG, p. 578). Tuberculosis deaths that would have occurred over the late 1910s

and early 1920s happened all-at-once, in 1918. Since people can only die once, post-1918 death rates were lowered relative to a continuation of pre-1918 trend. What is more, being a contagious disease, there is a catalytic effect of reduction of transmission.

What does this have to do with sex differences? The selector (influenza) acted more severely on males, so the effects of the selection are differential by sex. Figure 1 shows the age-mortality profile of the selector (influenza); as is customary, this is influenza and pneumonia combined. The two diseases are so intermingled in cause of death reporting, especially in 1918, that separate analysis is impractical. Males are plotted solid, females dotted—note the tremendous maleness of the selector, especially at the middle mode around age 30.

AGE, PERIOD, COHORT

Seemingly the most persuasive aspect of BSB's argument is that, using cohort data, they fail to replicate the findings of NG. The age, period, cohort (A-P-C) identity (Mason and Feinberg 1985)

means that rate analysis should give the same substantive results whether stratified by age and time (NG), or by cohort and age (BSB).

Is it better to look at cohort or period data? “*True* cohort data would be preferable but are unavailable” (NG, p. 574, emphasis added). Specifically, the ages affected by the pandemic get older over time—but the cohorts remain fixed, which is analytically convenient. The reason for preferring cohort data is not that they will give different results—by the A-P-C identity, the results must be equivalent—but it would be neater to have cohort data. Another matter entirely is whether separate effects of age, period, and cohort can be identified in linear models (see Mason and Smith 1985, and cf. also Mason 1991, p. 349, and Smith 2004, p. 114, for some later reflections).

Noymer and Garenne (2000) did not have cohort data, but neither do BSB. They have imputed cohort data from age- and period-specific data. Their explanation of the imputation is straightforward enough, though I believe BSB, in their example, meant age 5–14, not 10–14; historical mortality rates for the United

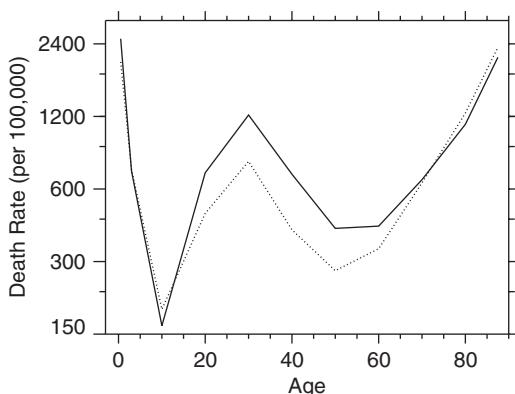


FIG. 1.—Influenza and pneumonia death rates, 1918. Males, solid; females, dotted. Data from U.S. Department of Health, Education, and Welfare (1956).

States are available in ten-year-wide age intervals above age 5. Thus, their cohort imputation for age 11 is a weighted average of observed age-specific death rates at ages 5–24 (and this is confirmed by the Excel spreadsheet that the authors kindly provided), and so on for older ages. That's an enormous age range for a value that is ostensibly a single year of age. It's not clear what this accomplishes apart from smoothing the data across a wide age range, thereby reducing the signal-to-noise, especially as regards the examination of sudden changes.

If smoothing in the period-to-cohort translation is the problem with BSB's analysis, then what happens when we don't smooth? Without imputation (smoothing), we no longer have cohort data. But we never really had cohort data in the first place, a point on which BSB and NG agree. Without smoothing, we have data on tuberculosis death rates, by single year of time, and mostly by ten-year groups of age, and for each sex. If we array all the available age-group time series, we can get the best approximation to a cohort picture as is possible without imputation. This is not exactly the same as having cohort data, but nothing is, except having the death certificates by year of birth instead of age of death (and knowing population denominators similarly). There is no way around that.

Figure 2 presents time series of death rates for tuberculosis at different ages. Each panel is a different age group, as indicated in the figure (i.e. the top panel is under 1 year, the middle panel is age 1–4, and the bottom panel is age 5–14). The vertical axes are death rates for tuberculosis (all forms) per 100,000 population, and the horizontal axes are year, 1900–45. Males are solid, females are dotted. Figure 3 presents ages 15–24, 25–34, and 35–44;

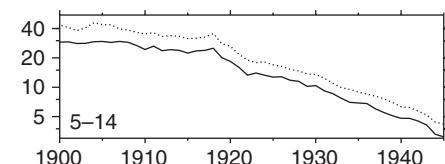
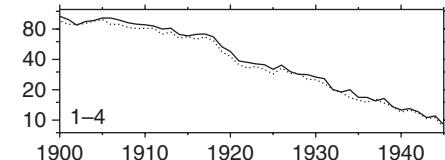
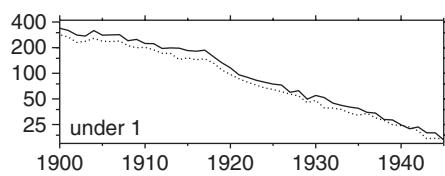


FIG. 2.—Tuberculosis death rates (per 100,000), 1900–45. Age group is indicated in each panel, lower left. Males, solid; females, dotted. Data from U.S. Department of Health, Education, and Welfare (1956).

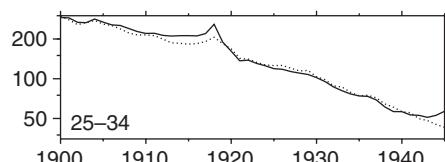
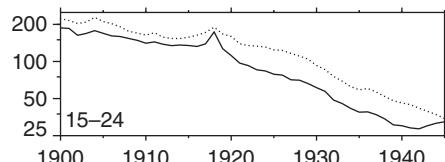


FIG. 3.—Tuberculosis death rates (per 100,000), 1900–45. Age group is indicated in each panel, lower left. Males, solid; females, dotted. Data from U.S. Department of Health, Education, and Welfare (1956).

figure 4 shows ages 45–54, 55–64, and 65–74; and figure 5 shows 75–84, and 85 and above.

One has to bear in mind that as they age, surviving individuals are subject to

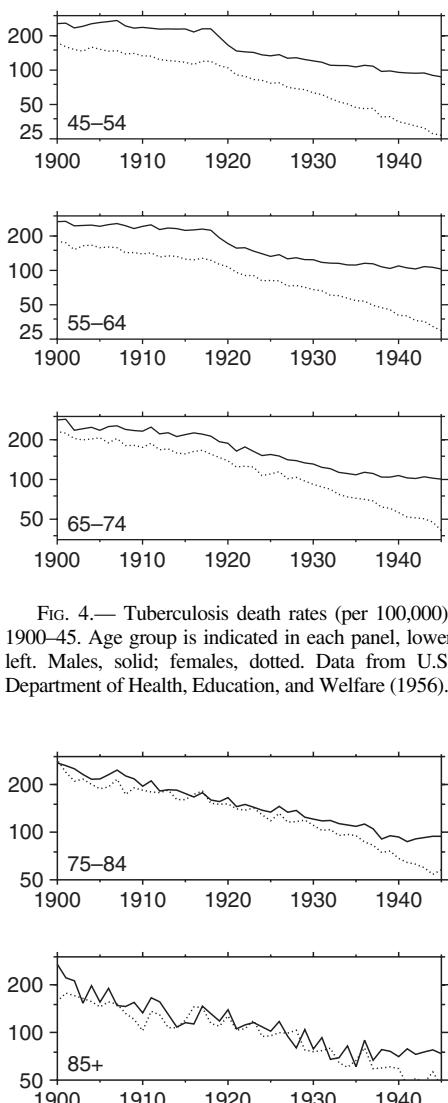


FIG. 4.—Tuberculosis death rates (per 100,000), 1900–45. Age group is indicated in each panel, lower left. Males, solid; females, dotted. Data from U.S. Department of Health, Education, and Welfare (1956).

FIG. 5.—Tuberculosis death rates (per 100,000), 1900–45. Age group is indicated in each panel, lower left. Males, solid; females, dotted. Data from U.S. Department of Health, Education, and Welfare (1956).

the rates plotted in different panels. This is the essence of why this array of period data is not the same as true cohort data. Nonetheless, when we stack the data this way, we are doing graphical period \times age analysis, which is as best as we can do cohort analysis without smoothing.

As these figures show, tuberculosis death rates were in broad decline throughout the period 1900–45. Note the post-1918 drops from pre-1918 trend; these are especially clear at ages 15–24 to 45–54. These declines occurred in all age groups for which influenza mortality was unusual in 1918, and, like the 1918 flu (figure 1), were more pronounced for males than females. This post-pandemic downturn in tuberculosis did not occur in ages where the 1918 influenza death rates were like a typical flu year (cf. BSB figure 3). The groups affected by the 1918 flu responded with lower tuberculosis death rates; the groups unaffected saw no such amelioration of tuberculosis death rates. This becomes clear when, as in figures 2–5, the data are stratified by age and, insofar as the flu was differential by sex, by sex. The changes were large enough to be apparent even when superimposed on the secular decline of tuberculosis. That, in a nutshell, is the selection effect.

Bradshaw, Smith, and Blanchard are dismissive of the selection effect and propose in its stead a series of ad hoc arguments to explain various aspects of the data. Moreover, BSB focus on sex differentials in tuberculosis, while it is sex differentials in the 1918 flu that are crucial to the changes seen in figures 2–5. Bradshaw, Smith, and Blanchard are correct in stating that NG “believed that tuberculosis was more prevalent in the male population”. In this time period, there were more male than female tuberculosis deaths every year (U.S. Department of Health,

Education, and Welfare 1956). And we are all in agreement that tuberculosis deaths give a reasonable proxy for prevalence, at least to first order.

The sex difference of the selector (flu) being aligned with the sex difference of the selected trait (tuberculosis) made for some synergy, so both diseases are relevant, but the selector matters more. There were some age groups in which females had higher tuberculosis death rates. Nonetheless, the patterns seen in the tuberculosis time series in *all* age groups are consistent with the selection effect as outlined in NG and as thumbnailed above.

Bradshaw, Smith, and Blanchard argue for the importance of troop mobilization for wartime changes in tuberculosis. Only the pattern seen in the Second World War is consistent with mobilization. In the early 1940s, there are increases in tuberculosis among 15–24 and 25–34 year-olds, and for males not females (figure 3). This is consistent with wartime mobilization—males only, military ages. On the other hand, the changes ca. 1918 are consistent with the selection effect (both sexes, not only military ages, changes in proportion to influenza).

Commenting on the concomitant increase of tuberculosis during the 1918 flu pandemic, BSB write, “there was some increase in tuberculosis mortality in both sexes, but the sharper increase was among males”. And this is because of the maleness of the selector (again, cf. figure 1). Bradshaw, Smith, and Blanchard’s comment that “it seems likely that any unusual rise in female tuberculosis mortality from 1916–18 may be attributable to the rise of influenza, and any excess of male over female mortality may be attributable to the mobilization and deployment of men for the First World War” does not explain why the changes seen in

tuberculosis overlay so well with the age- and sex-specific contours of the unusual flu mortality (figure 1). As comparison to the early 1940s shows, mobilization for the First World War may have also played a role, but the rise among females in 1918 requires the intercession of the flu pandemic, and it is not clear why this should not have applied also to males, especially at non-military ages.

The notion that “any unusual loss of tuberculous males . . . attributable to the 1918 influenza pandemic must have been brief, and probably no different than among persons ill with other chronic conditions” (BSB) is not well founded. The loss was concomitant with the flu pandemic, and therefore brief. The subject at hand is whether the epidemiology of tuberculosis was affected. As discussed by NG, the difference between tuberculosis and other contemporary chronic conditions is the age at which they occurred. Tuberculosis was a disease of middle age, and was different from other chronic conditions in this respect. What was unusual about the 1918 pandemic mortality, compared to annual flu seasons, was how it struck at middle age.

Bradshaw, Smith, and Blanchard note that “if tuberculous persons were selectively killed by the 1918 influenza pandemic, then either the influenza attack rates or case fatality rates, or both, should have been higher among the tuberculous than among the non-tuberculous”. These factors are possibly sufficient but not necessary to produce the selection effect. The selection effect only requires that enough people with tuberculosis were killed—preferentially or not—in the 1918 pandemic, to affect the subsequent epidemiology.

In sum, figures 2–5 show tuberculosis death rates by age groups, for each sex

and over time by single year of time. These are raw data that have not been smoothed. The patterns seen in these graphs are highly consistent with the selection explanation proposed by NG. The failure of BSB to reproduce these findings is due to the fact that their imputed cohort data are heavily smoothed, which severely biases against finding the sort of sudden changes seen in the raw data.

RAYMOND PEARL'S DATA

Raymond Pearl (1919) published an article on influenza incidence among the tuberculous in 1918 in Baltimore. These data were touched upon in NG, where the difficulties of using non-randomized data were noted, though for whatever it's worth, the data do show higher influenza incidence rates among the tuberculous. On the other hand, BSB point out that Pearl himself felt "that this difference was not statistically significant" (quoting BSB).

Pearl's sampling frame was highly nonrandom. It was households containing at least one case of tuberculosis registered with the health department. Being tuberculous in the dataset means being registered as such. This selects in favor of longer-standing TB infections, and also in favor of more severe infections (since clearly not each and every tuberculosis case in Baltimore in 1918 would have been registered). People with longer-standing and, especially, more severe cases of tuberculosis, would have been more likely to be housebound and therefore less at risk of community-acquired influenza. This biases toward the null.

All-in-all, I have my doubts about how definitively Pearl's data can adjudicate the question of influenza incidence

among the tuberculous. Pearl himself was unsure. What he wrote was that the "difference is small and *probably* not statistically significant" (Pearl 1919, p. 539, emphasis added). The percentages quoted by BSB may be verified in table 1. The odds ratio of this table is $(595 \times 6,849) \div (1,971 \times 1,780) = 1.16$, a slightly higher influenza attack rate among the tuberculous. Table 2 gives some logistic regression results. Model (1) corresponds to table 1, and the z-statistic is the same as a two-sample test of proportion. Models (2)–(4) add the conditioning variables of other cases of flu in the household (indicator), and household size. The differences seen in Pearl's dataset, though modest, are statistically significant.

MULTIPLE CAUSES OF DEATH

Bradshaw, Smith, and Blanchard look for associations between tuberculosis and influenza in underlying and contributory causes of death in 1917 and 1925. In these years, deaths from these diseases (i.e., as underlying causes) for the most part did not overlap (figure 6). The overlap is not zero of course, but comparing the total numbers of deaths of each disease without regard to age-stratification invites Simpson's paradox-like pitfalls. The preponderance of influenza deaths in these years were among the very young, and very old.

TABLE 1
RAYMOND PEARL'S TUBERCULOSIS
AND INFLUENZA DATA

INFLUENZA	TUBERCULOSIS	
	YES	NO
YES	595	1,971
NO	1,780	6,849
percent	25.05%	22.35%

TABLE 2
LOGISTIC REGRESSION OF PEARL'S DATA. ODDS RATIOS AND Z-STATISTICS; SEE TEXT.

ODDS RATIO OF INFLUENZA	(1)	(2)	(3)	(4)
Tuberculosis	1.162*	1.486***	1.448***	1.433***
	(2.78)	(6.44)	(5.95)	(5.77)
Other cases		13.01***	13.42***	13.64***
		(39.8)	(39.6)	(39.6)
HH-size			0.969*	0.859**
			(-2.78)	(-3.18)
$(\text{HH-size})^2$				1.008*
				(2.61)
N	11,195	11,195	11,195	11,195

z statistics in parentheses; ***p < 0.0005, **p < 0.005, *p < 0.01.

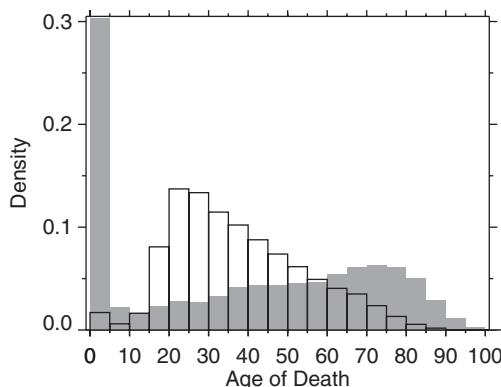


FIG. 6.—Histogram of deaths by age, US death registration area, 1925. Solid bars: influenza (following BSB, this is: "influenza (with pulmonary complications)", "influenza (other and unspecified)", "bronchopneumonia", "capillary bronchitis", "lobar pneumonia", "pneumonia (unspecified)"); Superimposed outlines: pulmonary tuberculosis. Both sexes combined. Data from Bureau of the Census (1927).

Nearly one-third of all influenza deaths were among those age 0–5. Most tuberculosis deaths were among middle-aged people. There is no reason to expect a whole lot of overlap between influenza and tuberculosis as contributory causes unless these diseases have an unusual tendency to act as contributory in ages other than in which they act as underlying causes.

Moreover, as BSB note, tuberculosis was not a very often-assigned contributory cause in 1917 and 1925, except among its own various forms. That only

goes to show that tuberculosis was such a dreaded disease that it was not generally regarded as being worthy of assignment to anything other than the underlying cause.

The selection effects postulated by NG pertain to co-morbidity among 1918 flu deaths, for which BSB present a paucity of data. And the quality of contributory cause coding in the height of the pandemic charitably can be described as dubious. The whole point of the influenza and tuberculosis selection argument is that the 1918 pandemic brought these two

diseases together in an unusual way. Bradshaw, Smith, and Blanchard use data from 1917 and 1925 to argue the case for what happened in 1918, but it makes no sense to interpolate 1918 data from these years—the pandemic was totally unlike either of these years.

LATENT TUBERCULOSIS

Tuberculosis latency is infection without active disease. To this day there is no gold standard test for latent tuberculosis infection (Shams et al. 2005). In tuberculosis, “the risk of active disease is generally greatest within the year following receipt of infection; it then decreases fairly promptly to a low level *but never disappears as long as living tubercle bacilli are present within the host*” (Comstock 1980, p. 208, emphasis added). In high-prevalence environments, such as the early twentieth century, reactivation of latent cases clearly played an important role in tuberculosis epidemiology. This was one of the points of Wade Hampton Frost’s classic 1939 article on tuberculosis decline. As discussed in NG (pp. 573–4), latency can play a role in the selection effect. People with latent tuberculosis can appear healthy, but if they were killed in the 1918 flu, then their risk of subsequent reactivation drops to zero. With over half a million deaths, how could a sizable number not have been tuberculosis-latent? Even nowadays, about 5% of the US population is skin-test positive for tuberculosis (Bennett et al. 2008). These considerations attenuate BSB’s concerns about primary versus contributory causes

of death. Latent cases of tuberculosis would not show up as contributory, but their deaths are still relevant for the selection effect.

CONCLUSION

That BSB’s “findings do not support the Noymer and Garenne conclusion that the fall of tuberculosis mortality can be attributed to the influenza pandemic” is correct in a literal sense. This is because BSB use imputed cohort data where the signal has been smoothed away, or examine data that don’t speak to the issue. The data—the death rate time series with no adjustment or smoothing—are presented in figures 2–5 herein. Nothing in BSB provides a compelling explanation for these patterns. Noymer and Garenne (2000) explained it as influenza as a selector, which is consistent with all the vital statistics data. The greater ambiguity in BSB’s graphs, which they interpret as nullifying the selection explanation, is due to their approach, which assumes that grouped age×period data can be reshaped into single-year cohort data with no loss of precision or, for that matter, accuracy.

Bradshaw, Smith, and Blanchard’s suggestion that their findings impeach the selection effect proposed by Noymer and Garenne (2000) is untenable. In the United States, the 1918–19 influenza pandemic accelerated the decline of tuberculosis. The mechanism was a selection effect. A large number of people with tuberculosis were killed in a short time span; these deaths would have, in equilibrium, occurred over a long period.

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