The possibility remains that the effect of aspirin on worldwide 1918 influenza mortality, if proven, may not have been trivial. Aspirin was widely used. In 1905, a British court struck down Bayer’s British patent and opened the aspirin market in the entire British Empire. In 1918, US manufacturers produced 172 million tablets [3]. During the pandemic, the Indian Surgeon General recommended gargling with diluted potassium permanganate and aspirin [4, p 89], and in Delhi, an eminent Indian surgeon “insisted that smart young doctors in Bombay were recklessly misusing it—on the basis, he said, that it weakened the heart (old canard) and actually brought on pneumonia as a consequence” [5, p 137]. In New Zealand, 1 Maori village, impressed by aspirin, honored the local health superintendent who had provided it; a baby there was named “Aspirin” [5, p 138]. In New South Wales, Aspro was at the top of the list of fixed price wartime commodities [5, p 138]. Unfortunately, a precise reckoning of the amount of aspirin produced, distributed, and used in various countries remains elusive. Yet, importantly, even if the etiologic fraction is small, in a country with a large extensive medical mystery, the extreme virulence of the 1918–1919 influenza pandemic. Her hypothesis, that the use of salicylates exacerbated the tendency of the infection to produce fluid in the lungs, has face validity and is supported by anecdotal evidence of widespread use of aspirin in the United States during the pandemic. The international characteristics of the pandemic make the salicylate hypothesis difficult to sustain as the primary explanation for the unusual virulence of the 1918–1919 influenza pandemic. Worldwide, an estimate of the mortality of the 1918–1919 pandemic is 50 million deaths, with a range of up to 100 million deaths [2]. Taking the 50 million figure, this was about 2.5% of the world population. By contrast, in the United States, mortality was on the order of 0.5%. Clearly, the rest of the world was struck more severely, on average, than the United States.

India serves as a useful vignette. Mortality in India was staggering, with estimates of 18.5 million persons dead [3] and higher [4]. Indeed, the Indian peasant population was so severely affected that economics Nobel laureate Theodore W. Schultz used the pandemic as a natural experiment in per capita agricultural output [5]. Given the huge number of deaths in India and the burden among subsistence agricultural workers, it is extremely implausible that salicylates played an exacerbating role in anything other than a trivial percentage of Indian mortality.

Thus, Starko’s intriguing hypothesis fails the test of dose-response. That is to say, in countries such as the United States, where salicylates were more available, mortality was much lower compared with regions where salicylates were less readily available. These observations are at the ecological level, and such comparisons are notoriously susceptible to confounding. However, if the salicylate hypothesis applies universally, then the ecological confounding would have to operate such that the salicylate-influenza connection is stronger in countries with less access to aspirin, which seems a priori unlikely. Indeed, the overwhelming majority of the millions of Indian peasants who were killed by the flu certainly had no access to salicylates whatsoever. If the salicylate hypothesis only works in the United States and in similar settings, then we question its validity given the worldwide scope of severe mortality in 1918–1919.

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Reply to Noymer et al

To the Editor—I understand the concern of Noymer et al [1] regarding the worldwide validity of the hypothesis that aspirin contributed to 1918 pandemic mortality [2]. However, worldwide use, as well as clinical, pathology, and physiology evidence of lung toxicity, indicate that aspirin may have played some role in mortality around the world.

I agree that aspirin is not the only risk factor for 1918 influenza mortality [2], yet the country “dose-response” test suggested fails to inform when competing risk factors are present. Potential competing factors, such as viral pathogenicity, bacterial colonization, immune response, smoking, preexisting conditions, and treatment, vary by locale; therefore, the role (etiologic fraction) of each factor is likely to vary by locale as well.

The possibility remains that the effect of aspirin on worldwide 1918 influenza mortality, if proven, may not have been trivial. Aspirin was widely used. In 1905, a British court struck down Bayer’s British patent and opened the aspirin market in the entire British Empire. In 1918, US manufacturers produced 172 million tablets [3]. During the pandemic, the Indian Surgeon General recommended gargling with diluted potassium permanganate and aspirin [4, p 89], and in Delhi, an eminent Indian surgeon “insisted that smart young doctors in Bombay were recklessly misusing it—on the basis, he said, that it weakened the heart (old canard) and actually brought on pneumonia as a consequence” [5, p 137]. In New Zealand, 1 Maori village, impressed by aspirin, honored the local health superintendent who had provided it; a baby there was named “Aspirin” [5, p 138]. In New South Wales, Aspro was at the top of the list of fixed price wartime commodities [5, p 138]. Unfortunately, a precise reckoning of the amount of aspirin produced, distributed, and used in various countries remains elusive. Yet, importantly, even if the etiologic fraction is small, in a country with a large

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population, the number of deaths attributable to aspirin could be substantial.

One step in proving or disproving the hypothesis is comparison of outcomes for those treated and those not treated with aspirin in 1918. Although I am unaware of any study of influenza with 1918 aspirin doses, a 1983 study of 47 college students with influenza A/Brazil/78 H1N1 comparing daily doses of 3.25 g aspirin to 100- and 200-mg doses of amantadine found worse symptom scores at 48 and 72 h in the aspirin and the 200 mg amantadine groups as well as a 35% discontinuation rate for bothersome symptoms in the aspirin group [6]. Meticulous records, such as those kept by the military in 1918, may be an excellent source of additional information.

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