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Reply to letters to the Editor
Bellavite P. Factors that influenced the historical trends of tetanus and diphtheria. Donzelli A, Duca P. More than 70,000 deaths prevented by vaccination against three diseases in about 75 years? The estimation seems exaggerated

We thank Drs. Bellavite and Donzelli for their comments to our article on the evaluation of the impact of vaccination programs on morbidity and mortality in the last 115 years in Italy [1]. Many points raised are relevant and these enrich and expand the debate on the determinants of infectious disease, strengthening the different strategies to prevent them. However, there are several criticisms that we consider questionable.

In general, both letters argue that our estimates on tetanus and diphtheria vaccines impact on mortality are too optimistic. Actually, our estimates of prevented cases and deaths after vaccination of 74% and 86% for tetanus and of 82% and 45% for diphtheria, respectively, are consistent with analogous studies conducted in other countries such the USA, Croatia, and Iran [2–5]. Of course, our study and those published for other countries may have not controlled for all the factors that can affect historical trends. We made the assumption of attributing the entire difference between incidence rates during the pre- and post-vaccination periods to immunization programs [1]. We know that other factors, such as sanitation, lifestyles, environment, and increasing use of antibiotics on the incidence of specific infectious diseases could have been a positive impact on some of these diseases but their effect has not been quantified; thus, as reported in the study limits, we could not take them into account [1]. Moreover, these effects are likely having been, at least partly, counter-balanced by other factors, which were not accounted for in the analysis, such as diagnostic sensitivity improvements, access to care, and reduction of underreporting, which could have influenced the observed trends toward conservative estimates.

Regarding some specific comments of the projected estimates based on the time-series analysis we would like to give some details. In particular, both letters underline that the tetanus peak during the World Wars could have biased our estimates (see Fig. 1C [1]). However, we took into account of those potential effects. Specifically, a second-order autoregressive model (based on the information available at time t-2) was applied, including two time-periods which affected the temporal trend, the post-World War I (years 1919–1924) and a second peak between years 1944 and 1946 (the highest rate occurred in 1945). Moreover, it should be pointed out that, being a stationary time-series, the projected estimates do not increase, but tend to the mean value of the pre-vaccination period and, consequently, toward a plateau.

Regarding diphtheria, both authors highlight that the vaccine does not protect against the infection and found surprising the decline in morbidity (see Fig. 1B [1]). Actually, anti-diphtheria immunization consists in the administration of a toxoid vaccine, which protects against the disease and its lethal consequences. To this regard, it should be noted that surveillance systems collect information on the disease but not on infections, thus to observe a decline in disease incidence rates is expected. Dr. Bellavite suggests that vaccination would have limited the diffusion of toxigenic *Corynebacterium diphtheriae* strains, favouring those non-toxigenic, arguing that this did not happen because of widespread antibiotic use. To this regard, there are studies suggesting the rarefaction of these bacterial strains [6], which are apparently inconsistent with other studies showing that non-toxigenic strains have become increasingly recognised as emerging pathogens across Europe causing severe invasive disease [7]. Although only five cases of diphtheria due to non-toxigenic strains have been reported in Italy since the nineties [8], we cannot exclude that "non-toxigenic tox gene-bearing" strains, genotypically toxpositive, not expressing the protein, are circulating in Italy, with the theoretical risk of re-emerging toxin expression, given their possible role as a tox-gene reservoir. Moreover, scientific evidence on the impact of widespread antibiotic use on the circulation of different bacteria is limited or even lacking. However, as highlighted by Drs. Bellavite and Donzelli, all procedures improving health system could have minimized the risk of spread. Indeed, diphtheria infection can be treated with antibiotics, such as penicillin or erythromycin, which may also be used for prevention in those who have been exposed to the infection. Moreover, treatment is most effective in the early stages of the disease, decreases the transmissibility, and improves the course of the illness. Dr. Bellavite also states that the diphtheria pre-vaccination time series could have affected projection estimates of the morbidity rates. In Italy, in the pre-vaccination period, lower diphtheria morbidity rates were recorded between 1919 and 1924 as compared to the other time periods. This decrease was probably due to the reduction of newborns during the war, resulting in a lower susceptible population in the following years, because diphtheria mainly affected children. Similar patterns were observed also in other counties before vaccine introduction [2], and the disease has always been characterized by the occurrence of epidemic waves [9]. Specifically, diphtheria morbidity rates ranged from 48 to 75 per 100,000 between 1901 and 1918 (average annual incidence 55), from 30 to 42 between 1919 and 1924 (average annual incidence 33), and from 37 to 67 between 1925 and 1938 (average annual incidence 58). Consequently for the projected estimates, to take into account the lower values following the World War I, a first-order autoregressive model including 1914–1924 period effect was applied to the data, whereas, 1900–1913 and 1925–1938 presented similar patterns and comparable morbidity rates.

Finally, Drs. Donzelli and Duca ask explanations of the increasing projected estimates of pertussis morbidity rates in case of no vaccination (see Fig. 3B [1]). We feel that they misinterpreted

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our estimate, based on a third-order autoregressive model applied to reflect the fluctuation dynamics of pre-large-scale vaccination period when epidemic cycles occurred regularly. In fact, in their view of the increasing trend, they are substantially affected by the low estimated value in the years 1996 and 1997, reflecting the expected low phase of the cycle. Actually, our morbidity estimates in case of no vaccination shows fluctuations around a stable trend.

In conclusion, as already discussed in the article [1], other important elements, other than vaccination, such as lifestyles, disinfection, environment, antibiotics and early diagnosis could have influenced the temporal trend. More complex statistical models could help to provide more accurate estimates on the vaccination impact.

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