Comment on "Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality"

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Abstract

Mina *et al.* (Ref. [1]) use population-level statistical analysis to argue that measles infection results in a 2 to 3 year immunomodulation, implicating measles in substantially more child mortality than previously thought. We show using both simulation and data from Iceland that the statistical approach used may be confounded by the 2 year periodicity of measles incidence in the areas studied.

Measles vaccine introduction has been shown to coincide with decreases in child mortality substantially larger than what would be expected based solely on deaths attributed to measles [1, 2, 3]. Understanding the mechanism underlying this observation is a topic of current research with significant policy implications for measles burden control and eradication [2, 3].

Based on analysis of measles incidence and child mortality in the U.K., U.S., and Denmark, Mina *et al.* [1] offer measles-induced long-term immunomodulation, where host resistance is compromised for a period of 2 to 3 years, as a possible mechanism for measles vaccine's impact. Under this hypothesis, vaccination decreases mortality typically attributed to non-measles diseases by preventing opportunistic infection and increasing polymicrobial herd immunity [1].

Ref. [1] focuses on vaccine introduction, but a 2 to 3 year immunomodulation's effect on mortality must also be observable when measles is imported into an unexposed community. In this regard, Iceland is a useful study area: measles has been imported and subsequently burned out 16 times from 1904-74 [4], the island population ($\sim 200,000$) is large enough for statistical analysis [5], and other aspects of health infrastructure are comparable to the U.K., U.S., and Denmark.

Iceland's monthly measles incidence (black) and all-cause child mortality (red) are plotted in Fig. 1(a). The incidence trace shows two distinct regimes: pre-1945, when the island was only accessible by boat and road leading to more isolated and violent outbreaks, and post-1945, when the island became accessible by air leading to more frequent outbreaks [4]. Previous analysis of this data [6] has shown that there is a significant change in measles transmission seasonality in the two eras, and in the post-1945 regime, the seasonality closely follows that of the U.K. and U.S.

The effect of measles importations on mortality can be tested by computing the annual mortality rate difference between the years before and after measles outbreaks while accounting for the overall decrease in child mortality over time. We find that the average detrended mortality rate difference is -0.19 ± 1.59 deaths per 1000 1 to 9 year olds, effectively zero, demonstrating that measles importation did not yield a statistically significant increase in child mortality in Iceland. Given the apparent magnitude of the effect in Ref. [1], where measles is argued to be implicated in up to 50% of all childhood deaths in the U.K. before vaccine introduction, this is a surprising null result.

To understand this discrepancy we further analyze the Iceland data by applying the method of Ref. [1] to the post-1945 era when we can reasonably expect to obtain results which agree with those from the U.K. and U.S. More specifically, we use the additive approximation to the integral transformation described in [1] to construct hypothetical immunomodulation prevalence traces, $S(t)$, from measles incidence for given suppression durations, d. Regressing these traces against childhood mortality results in the set of R^2 values plotted in Fig. 1(b), showing that correlation is maximized at $d^* = 47$ months but with an R^2 value of only 0.21 (Fig. 1(c)), giving insignificant support for a roughly 4 year measles-induced immunomodulation.

The presence of this optimum at 4 years highlights mathematical properties of the method developed in Ref. [1]. Analysis of the method itself can be carried out analytically if we idealize the situation by assuming that the measles trace, $M(t)$, has a definitive periodicity P with even symmetry about $P/2$, and that the death-rate is a simple linear function of time, $y(t) = mt + b$.

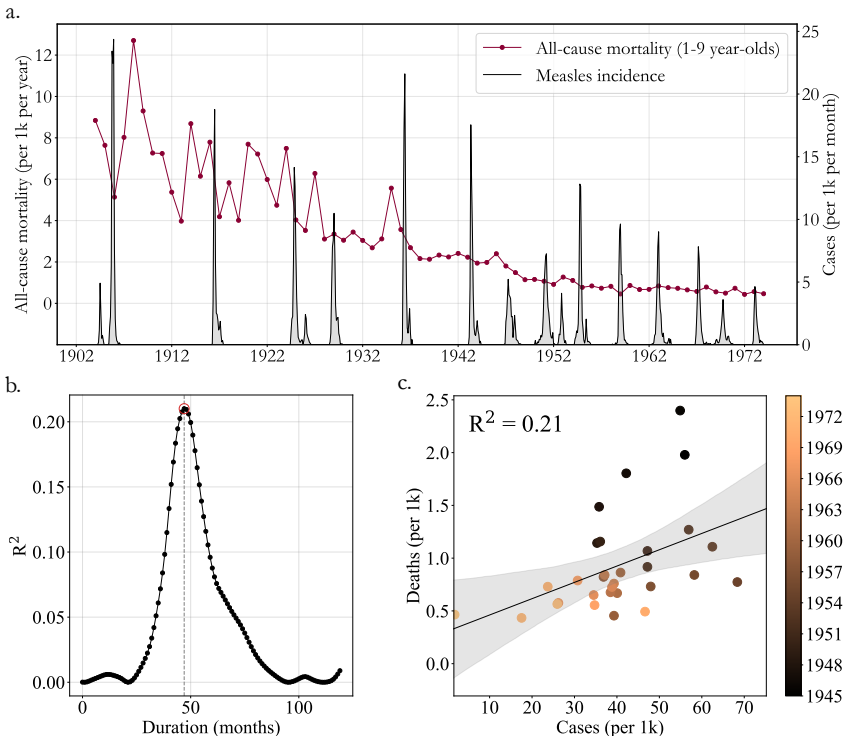

Figure 1: Measles in Iceland. (a) Monthly measles incidence per 1000 population (black) and 1 to 9 year old all-cause mortality (red) from 1904-1974 can be used to test measles importation's effect on mortality. (b – c) While we find no statistically significant mortality increase in the years after measles outbreaks, applying the method of Mina *et al.* offers weak support ($R^2 = 0.21$) for a 47 month immunomodulation duration following measles infection.

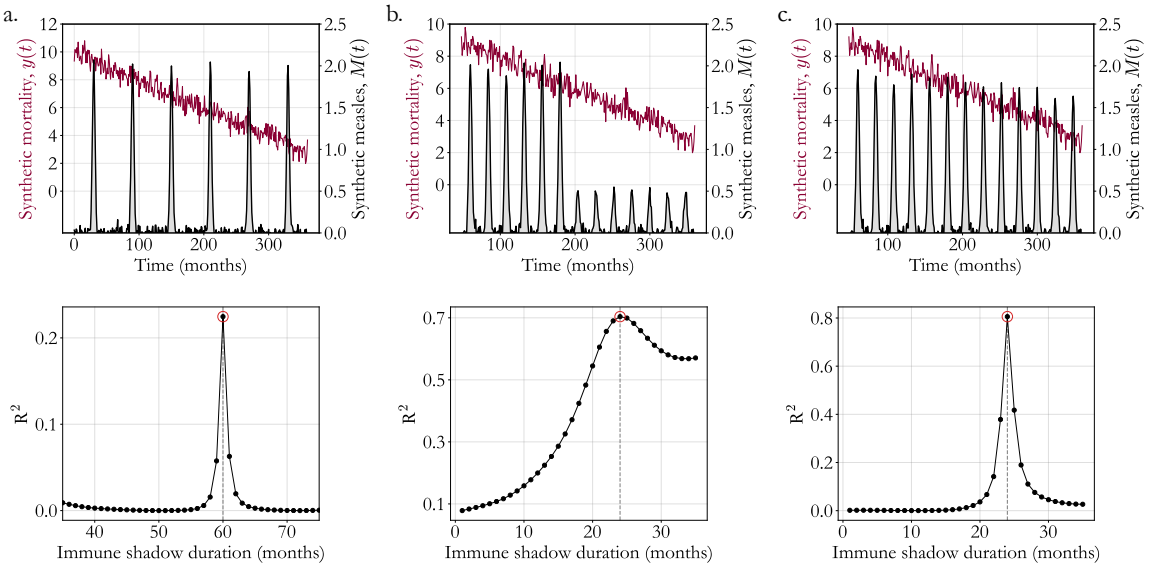

Figure 2: Simulation study. (a) Synthetic measles trace $M(t)$ (black) is created by summing Gaussian functions with standard deviation of 2 months and means separated by $P = 60$ months. Simultaneously, $y(t)$ (red) is a line with $m = -0.1$ per month and $b = 10$. Both traces are distorted by white noise with standard deviation 0.05 and 0.5 respectively. Applying the regression procedure yields an optimal duration $d^* = P = 60$, in agreement with our theoretical analysis. (b) On data created to mimic the UK MCV roll-out, R^2 reaches 0.7 while maintaining the periodicity dependence of d^*. (c) The effect persists when a $\sim 1\%$ decline is applied to the outbreak amplitudes, demonstrating that a large R^2 is possible with no causal connection between $y(t)$ and $M(t)$.

Under these fairly strict assumptions, $S(t)$ can be calculated analytically for arbitrary d, and the optimization problem defining the inferred immunomodulation duration, d^*,

$$d^* = \min_d \int_0^T dt\,(y(t) - \hat{\beta}_1 S(t) - \hat{\beta}_0)^2 \tag{1}$$

where $\hat{\beta}_1$ and $\hat{\beta}_0$ are the d-dependent slope and intercept from the least-squares regression of $y(t)$ against $S(t)$ over time period T, can be solved directly. Differentiating the right-hand-side yields

$$\int_0^T dt\, M(t - d^*) \left[y(t) - \hat{\beta}_1 S(t) - \hat{\beta}_0 \right] = 0, \tag{2}$$

which is satisfied at $d^* = P$ if T contains complete periods (i.e., records contain complete outbreaks) since $M(t)$ is even and the term in brackets is odd.

This suggests the possibility that Ref. [1]'s regression approach is constrained to return multiples of $M(t)$'s period. For our purposes, we see that in Iceland R^2 peaks at ~ 4 years in reasonable agreement with the observed average time between importations post-1945, and in the U.K., U.S., and Denmark, R^2 peaks at ~ 2.3 years in agreement with the observed biennial outbreak cycle [1].

We can verify that this idealized result is robust to noise by creating synthetic data and applying the method. This is done in Fig. 2(a) by approximating $M(t)$ as a set of Gaussians with means separated by $P = 60$ months (black) and then distorting both $M(t)$ and $y(t)$ (red) by white-noise. Carrying out the analysis, we find R^2 is optimized at $d^* = P = 60$, in agreement with the theory.

Simulation study can be used to further test the effect's robustness when assumptions are explicitly broken. In Fig. 2(b), we adjust the synthetic data by setting $P = 24$ months (to model biennial outbreaks) and by introducing a large-scale decrease in outbreak amplitude halfway through the model period (to mimic vaccine introduction). Despite the lack of causal connection between $M(t)$ and $y(t)$, we see that this change increases the optimal R^2 value to 0.7 while maintaining the relationship between P and d^*. Similarly, in Fig. 2(c), we test smaller deviations from our assumptions by forcing a $\sim 1\%$ decline in outbreak amplitude over time (modeling the persistent decrease in U.K. outbreak amplitude pre- and post-vaccine introduction), and we find $R^2 = 0.81$ at $d^* = P = 24$ months. Taken together, these tests indicate that the optimal immune shadow duration may still be constrained to the period even if R^2 is large due to potential spurious correlations.

Our work suggests that Mina *et al.*'s results should be interpreted carefully. While they perform some sensitivity tests, none of them probe the relationship between the inferred immunomodulation duration and the incidence periodicity, and they instead demonstrate that d^* vanishes if $M(t)$ is aperiodic (as is the case for pertussis in the U.K.). Moreover, our analysis of data from Iceland shows that measles importation does not significantly effect child mortality in a developed world context. This indicates that while measles vaccine remains an extremely cost-effective health intervention, more work is needed to explain its protective effects against non-measles diseases.

References

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