PERTUSSIS

Response to comment on "The impact of past vaccination coverage and immunity on pertussis resurgence"

Matthieu Domenech de Cellès[1], Aaron A. King[2,3,4], Pejman Rohani[5,6,7]*

We present new evidence that the immunity conferred against pertussis by the DTaP acellular vaccine wanes more slowly than widely believed.

We thank Winter *et al.* for their Technical Comment and their interest in our paper (*1*). They correctly point out that our study comprised a limited time period following the switch to the DTaP acellular vaccine for routine immunization against pertussis in the United States. As we explained in our *Science Translational Medicine* paper (*2*), we deliberately restricted our analyses to data spanning the time period 1990–2005 because of consistent surveillance in Massachusetts before the introduction of polymerase chain reaction as a diagnostic method in January 2005 (*2*). Thus, the study period embraced 9 years during the DTaP vaccine era, including several years after the first birth cohorts vaccinated with the DTaP vaccine entered school (with an associated increase in contacts). We reasoned that, if the duration of DTaP-derived immunity is as short as a few years as estimated in a recent meta-analysis (*3*) and alluded to in the discussion of a 2012 study (*4*), the effect of the switch to the DTaP vaccine from the whole-cell DTwP vaccine would be manifest in incidence data, particularly in the 5- to 9-year-old demographic. To check this reasoning, we performed counterfactual simulations to examine two different scenarios: (i) no switch to DTaP from DTwP and (ii) a switch to DTaP from DTwP, assuming a very short average duration of DTaP immunity (*3*). As shown in Fig. 1, the incidence of pertussis in children aged 5 to 9 years was predicted to be many-fold higher under the second scenario, even before the school entry of the first cohorts of children vaccinated with DTaP (as a result of the lower protection conferred by the booster dose in that age group). However, such a strong effect was not discernible in the Massachusetts data that we analyzed in our study (*2*), despite a slight increase from 2001 to 2005 [figure S5 in (*2*)]. Furthermore, contrary to Winter *et al.*'s claim in their Technical Comment (*1*), our paper does report the results of tests of a model with different rates of waning immunity between DTaP and DTwP/natural infection [table S9 in (*2*)]; the average duration of protection conferred by DTwP/natural infection was fixed to 75 years in that model. Despite higher estimation uncertainty due to the shorter time period, our main results have held up under this scenario, with an average waning rate for DTaP-mediated immunity

of 0.017 [95% confidence interval (CI), 0.002 to 0.039] per year (*2*). In response to Winter *et al.*'s concerns, we performed new simulations to examine the impact of including a booster dose in teenagers with the Tdap vaccine on our model-based predictions of the odds ratio, that is, the yearly relative change in the odds of acquiring pertussis in children aged 5 to 9 years (*3, 4*). As shown in Fig. 2, our results are robust to the inclusion of the Tdap booster dose and to the study period considered. Aggregating all scenarios, the median model-based odds ratio was 1.49 (95% CI, 1.28 to 1.76), a range of values slightly higher than those we initially predicted [figure 3F in (*2*)] but closer to those of empirical studies in the United States (*3, 4*). The mechanism underlying high vaccine effectiveness and high odds ratios is explained in our follow-up paper (www.biorxiv.org/content/early/2018/07/25/376947). Hence, we stand by the results of our original study (*2*) and question the odds ratios estimated in recent empirical studies as evidence for rapid loss of DTaP-mediated immunity (*3, 4*). A recent meta-analysis has also exposed this error (*5*).

We have also made out-of-fit forecasts of age-stratified pertussis incidence in 2010 and 2014 (Fig. 3). This model, which assumes a mean DTaP-mediated immunity duration of 40 years and a corresponding annual increase in odds of acquiring pertussis of ~38%, was able to capture the observed increase in pertussis incidence in teenagers (*6*), which was driven by a cohort effect in the first DTaP-vaccinated birth cohorts reaching teenagehood. This is explained by the fact that, although DTaP immunity wanes slowly on average, the large variability in the duration of protection provides enough susceptible individuals to sustain increased pertussis incidence (*2*). The consistency of this finding with the empirical observations discussed by Winter *et al.* further supports that DTaP immunity wanes (possibly at a higher rate than that of DTwP), but not nearly as rapidly as has been claimed. We note that our model-predicted incidence of pertussis in infants does not agree with the data presented in (*6*). This disagreement is likely explained by the impact of prenatal Tdap vaccination in California, a control measure not currently incorporated into our model.

Regarding the duration of infection-derived immunity, we first point out that the studies cited by Winter *et al.* do not support their claim. In the cross-sectional seroprevalence study in young American and German adults (*7*), the vaccination status of participants was not documented, such that the statement that antibodies "persist at higher concentrations among DTP [DTwP]-vaccinated adults compared to vaccine-naïve adults with exposure to natural disease" is not supported by the evidence. Even were this not the case, the absence of definite serological correlates of protection makes it impossible to interpret antibody titers as indicators of protection. Regarding

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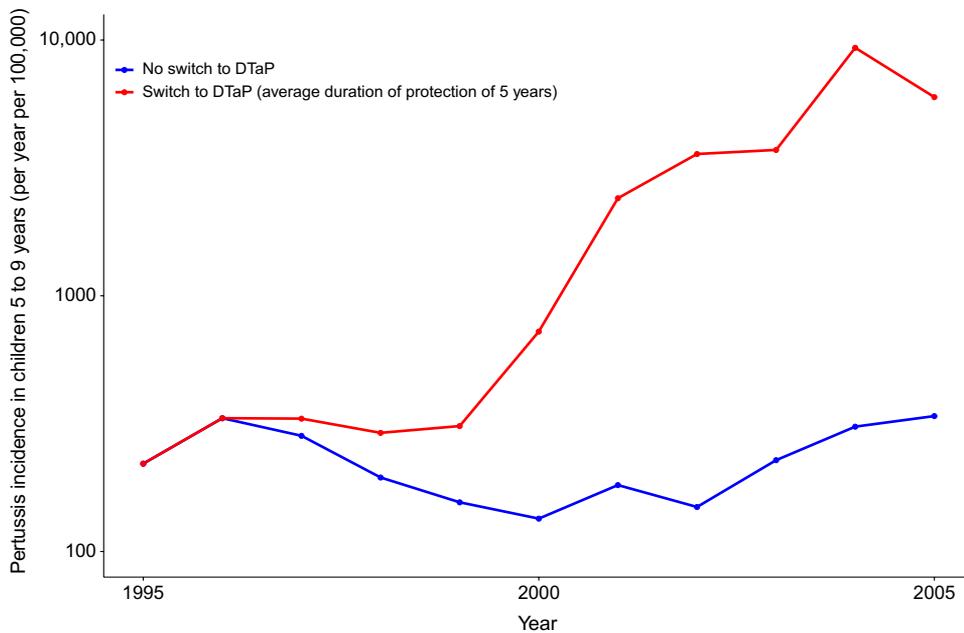*Corresponding author. Email: rohani@uga.edu

Fig. 1. Simulated incidence of pertussis in children aged 5 to 9 years. The simulated incidence of pertussis (not corrected for under-reporting) under two different scenarios is shown. In the first scenario (blue), there was no switch to the DTaP acellular vaccine from the DTwP whole-cell vaccine (waning rate of DTwP immunity fixed to 0.011 per year) (*2*); in the second scenario (red), there was a switch to DTaP from DTwP in 1997 for both the primary vaccine course and the pre-school booster (waning rate of DTaP immunity fixed to 0.2 per year, giving an average duration of protection of 5 years). For clarity, the *y* axis is $\log_{10}$-transformed.
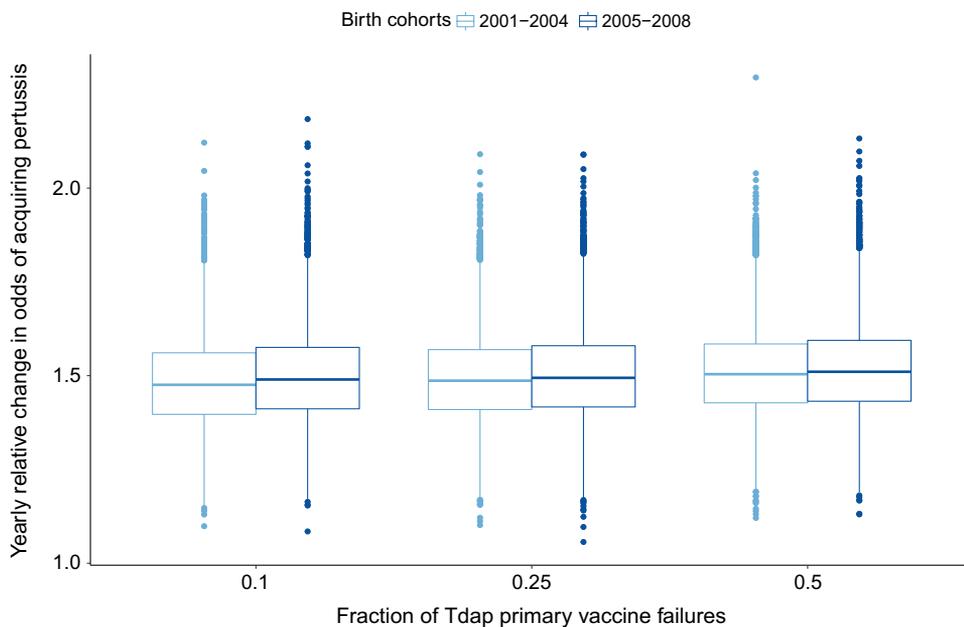

Fig. 2. Model-based estimates of odds ratios in children aged 5 to 9 years. The waning model presented in (*2*) was extended to incorporate the introduction of the Tdap vaccine booster in teenagers in 2006 in the United States (assuming a Tdap vaccine coverage of 10% in 2006, linearly increasing to 85% in 2012, and plateauing thereafter). Linear regression was used to estimate the yearly relative change in the odds of acquiring pertussis in children aged 5 to 9 years. The analysis was repeated for different assumptions regarding the value of Tdap primary vaccine failure (i.e., 1 minus efficacy on the *x* axis). The analysis was also repeated for two cohorts of children born during 2001 to 2004 (tracked until ages 5 to 9; resulting study period 2006–2013) and during 2005 to 2008 (study period 2010–2017). Each boxplot is based on 10^4 model simulations, accounting for parametric uncertainty by sampling from the bootstrap distribution [as was the case for figure 3F in (*2*)].

correct because it was calculated on the basis of anecdotal evidence of reinfection from studies that were not designed to assess the duration of immunity. In contrast, model-based analyses of incidence data have indicated far longer durations of protection in many locations (*9–11*). A recent population-based study in California (where an extended pertussis disease case definition is in use) also found that repeat infections were rare, occurring in 0.1% of children within 4 years of follow-up (*12*). Hence, our assumption of lifelong infection-derived immunity is reasonable. Last, we report in our follow-up paper (www.biorxiv.org/content/early/2018/07/25/376947) that assumptions of transient infection-derived immunity do not substantially affect model-based estimates of annual changes in the odds of acquiring pertussis after the fifth vaccine dose.

In conclusion, we suggest that many of the persistent controversies in pertussis epidemiology have resulted from a reliance on received wisdom (i.e., expert opinion) and on misinterpretation of data. We submit that the path to resolving these issues lies in rigorous, reproducible, transparent approaches that reconcile all available data. In our studies, we have striven for such an approach and, while we recognize that our conclusions run counter to the prevailing narrative on pertussis, we propose that the robustness of our findings should lead to a re-examination of basic assumptions.

another study cited by Winter *et al.* (*8*), we have previously highlighted the shortcomings of its methodology (*9*). Briefly, the reported estimate of 4 to 20 years of protective immunity after natural infection is in-

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Fig. 3. Out-of-fit model forecasts of age-stratified pertussis incidence. Out-of-fit model forecasts of age-stratified pertussis incidence (not corrected for under-reporting) in 2010 and 2014 are shown. The model consists of data for routine immunization with the DTwP whole-cell vaccine until 1996 (waning rate of 0.011 per year) and subsequently with the DTaP acellular vaccine (waning rate 0.025 per year, corresponding to an odds ratio of 1.38). The model introduced the DTaP vaccine in teenagers in 2006, assuming a primary failure probability of 25% and a vaccine coverage of 10% in 2006, increasing to 85% in 2012, and plateauing thereafter.
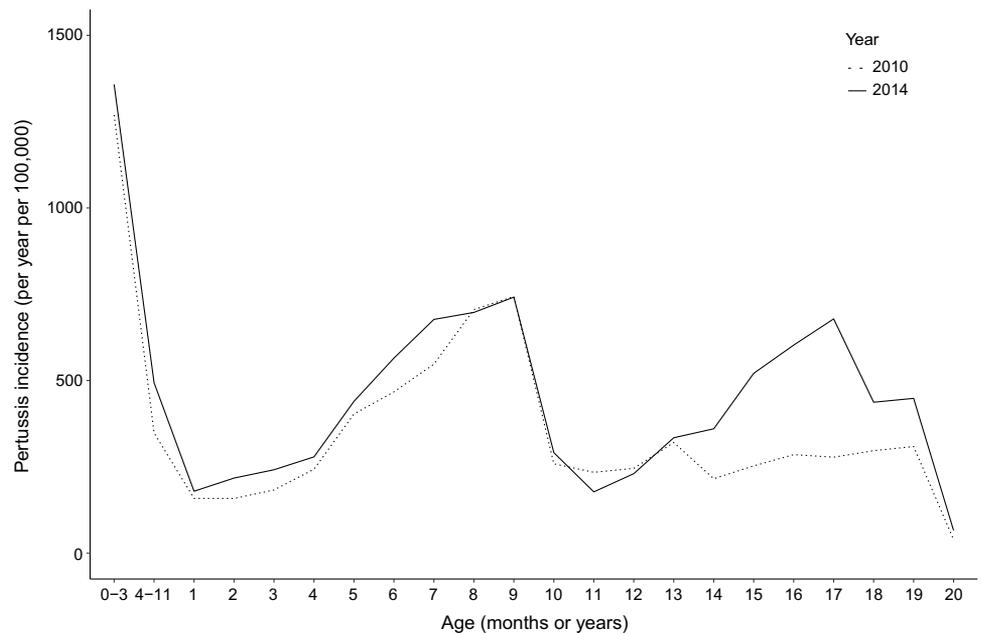
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