Supplementary material

S1 Analysis of WHO data, 1980–2012

Yearly case counts and pertussis vaccine coverage estimates were extracted from the WHO database for all years between 1980 and 2012[1]. Yearly population data, available from the World Bank's development indicator[2], were used to calculate yearly country-specific incidences. Estimated segmented regression models and yearly trends in the 63 countries that met our inclusion criteria are presented in Figures S1 and S2. Incidence data for the 43 countries that did not switch to aP are presented in Figure S3; vaccination characteristics for countries that switched to aP are shown in Table S1.

[1] `http://www.who.int/immunization/monitoring_surveillance/data/en/`, accessed 23 June 2014
[2] `http://data.worldbank.org/data-catalog/world-development-indicators`, accessed 23 June 2014

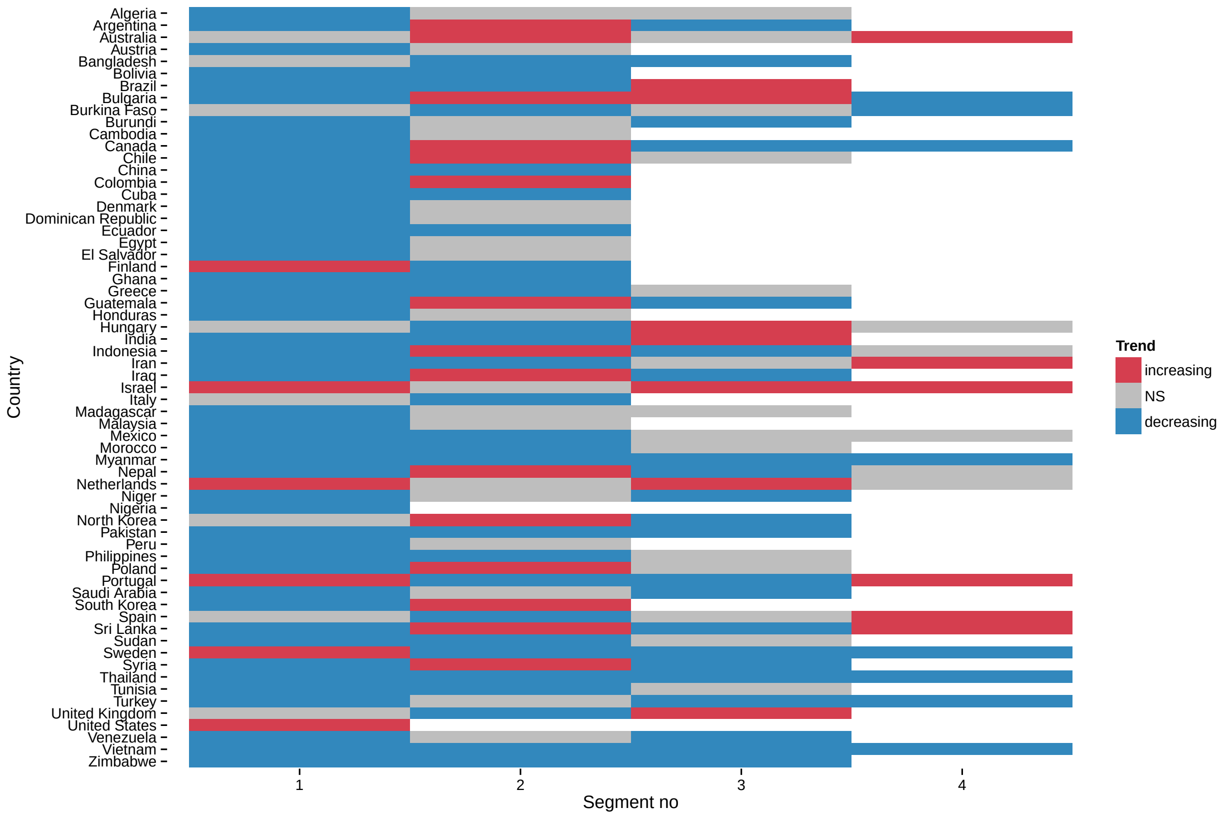

Figure S1: Summary of segmented regression models in 63 countries that met our inclusion criteria (population size >5 million and >80% complete case count). Number of slopes estimated in each model, and sign of each estimated slope (red: significantly >0, blue: significantly < 0; grey: not significantly different from 0) are indicated for each country. White rectangles indicates slopes that were not estimated because the best model had fewer breakpoints.

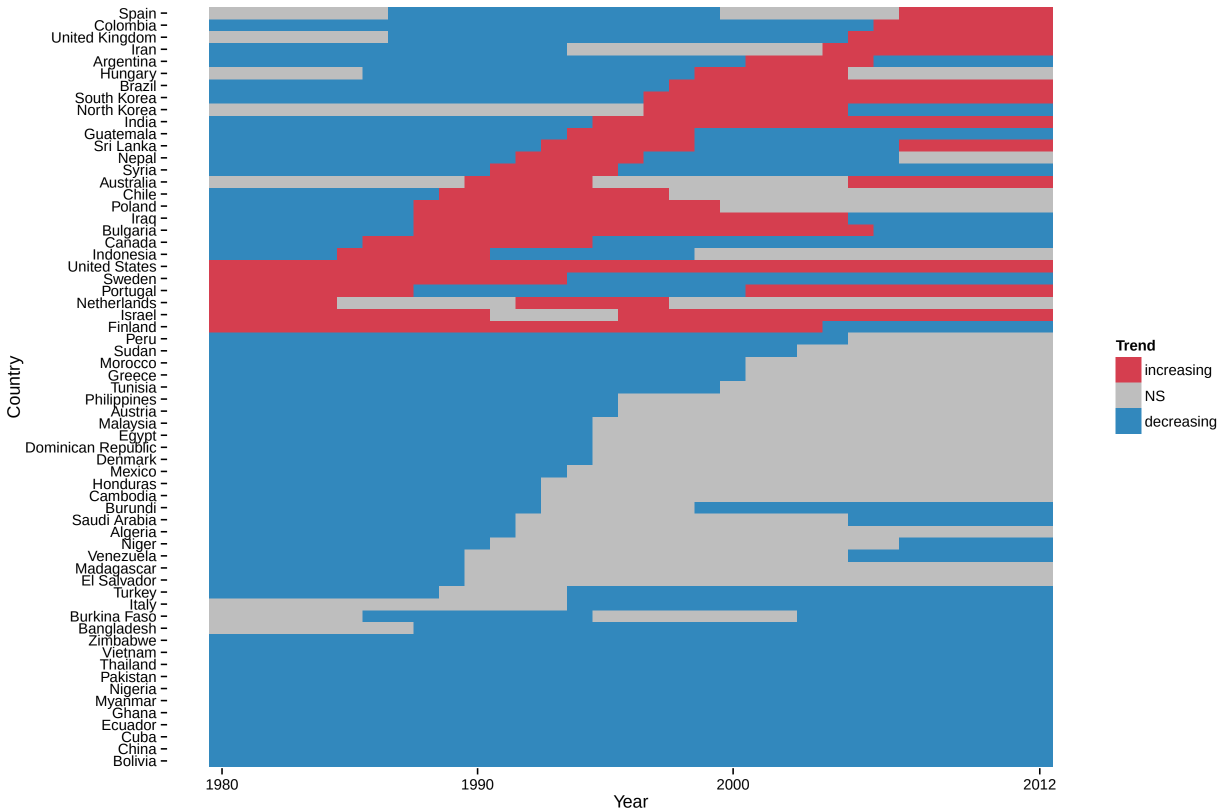

Figure S2: Summary of incidence trends in 63 countries that met our inclusion criteria (population size >5 million and >80% complete case count). Yearly trends (red: significantly >0, blue: significantly < 0; grey: not significantly different from 0) are indicated for each country. For bottom to top, countries are ranked by increasing year of first change in trend, if any.

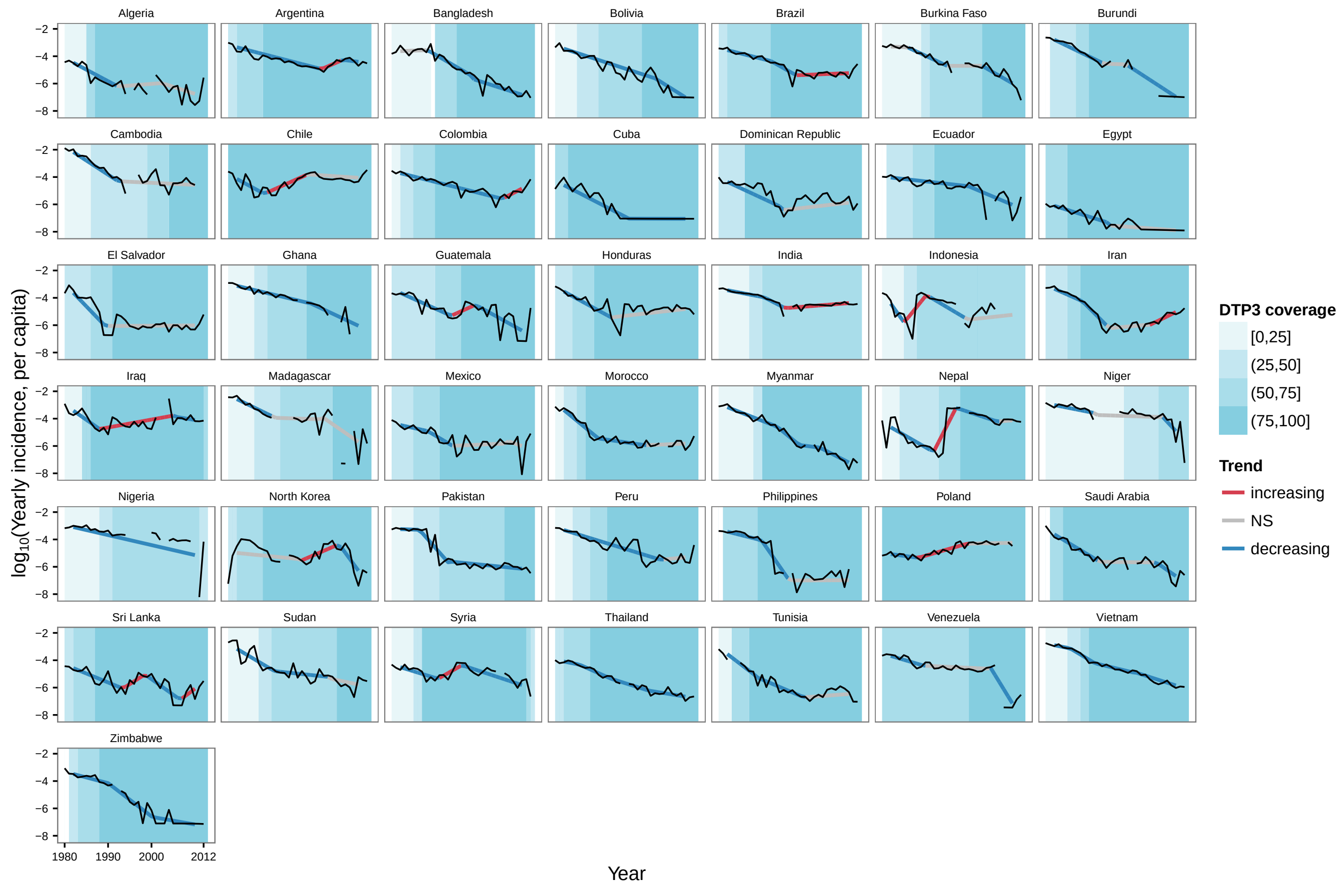

Figure S3: Segmented regression on incidence data in 43 countries that use wP vaccines for primary immunization and that met our inclusion criteria (population size >5 million and >80% case count). For each country, we represent the annual incidence (black solid lines) and the fitted values from segmented regression, colored according to the trend (red lines: significantly increasing; grey lines: no significant trend; blue lines: significantly decreasing). Colored blue areas indicate the vaccine coverage for the third dose of DTwP vaccine. From left to right and top to bottom, countries are sorted by alphabetical order.

Country	Primary Series	Pediatric booster		Adolescent/Adult booster	Switch wP to aP	Source
		Second year	Preschool			
Australia	2, 4, 6 mo	NA	4 yo	10–15 yo	March 1999	[1]
Austria	3 doses 0–1 yo	1–2 yo	NA	NA	1998	[2]
Bulgaria	2, 3, 4 mo	16 mo	6 yo	NA	2010	`http://tinyurl.com/qfuqyzo`
Canada	2, 4, 6 mo	18 mo	4–6 yo	14–16 yo	1997	`http://tinyurl.com/ksljyc5`
China	3, 4, 5 mo	18 mo	NA	NA	2007	[3]
Denmark	3, 5, 12 mo	NA	5 yo	NA	1997	[4]
Finland	3, 5, 12 mo	NA	4 yo	14–15 yo	2005	[5]
Greece	2, 4, 6 mo	15–18 mo	4–6 yo	11–12 yo	1997	[6]
Hungary	2, 3, 4 mo	18 mo	NA	11 yo	2006	`http://tinyurl.com/qfuqyzo`
Israel	2, 4, 6 mo	12 mo	NA	14 yo	2002	[7]
Italy	3, 5–6, 11–13 mo	11–13 mo	5–6 yo	11–18 yo	1994	[8]
Malaysia	2, 3, 5 mo	18 mo	NA	NA	2008	`http://tinyurl.com/q4anyy9`
Netherlands	2, 3, 4 mo	11 mo	4 yo	NA	2005	[9]
Portugal	2, 4, 6 mo	18 mo	5–6 yo	NA	2006	`http://tinyurl.com/qz6nanw`
South Korea	2, 4, 6 mo	15–18 mo	4–6 yo	11–12 yo	1989	[10]
Spain	2, 4, 6 mo	15–18 mo	NA	6 yo	2002	[11]
Sweden	3, 5, 12 mo	NA	5–6 yo	14–16 yo	1996	[12]
Turkey	2, 4, 6 mo	18 mo	6 yo	NA	2008	[13]
United Kingdom	2, 3, 4 mo	NA	3–5 yo	NA	October 2004	[14]
United States	2, 4, 6 mo	15–18 mo	4–6 yo	11–12 yo	1996	[15]

Table S1: Pertussis vaccination characteristics in 20 countries that switched to aP and that met our inclusion criteria (population size >5 million and >80% complete case count). The date of switch corresponds to the switch to aP for primary immunization (that is, for the primary course in unvaccinated infants).

S2 Pertussis in adults

S2.1 Review of incidence estimates in adults

We reviewed estimates of symptomatic cases incidence in adults presented in ref. [16] (for a review of incidence estimates specific to U.S. adults, please see ref. [17]). For all these studies, the estimates represent the yearly number of symptomatic cases per adult population, a quantity that can be linked to outputs of standard epidemic models (cf text below). From Table S2, reported estimates were in the range (5–500) cases per 100,000 adult population per year.

Study	Location	Age group	Yearly incidence in age group, $10^5 \times \Lambda_A$
[18]	USA	10–49 yr	507 (C+PCR+S)
			150 (C)
[19]	USA	$\geq$18 yr	176 (S)
[20]	France	$\geq$18 yr	508 (C+PCR+S)
[21]	USA	11–19 yr	71 (C+PCR+S)
		$\geq$ 20 yr	5 (C+PCR+S+E)

Table S2: Review of incidence estimates in adults. C: culture; S: serology; E: epidemiological link.

S2.2 Model of pertussis in adults

To allow comparison with empirical estimates of incidence in adults and to assess the role of waning immunity in shaping pertussis epidemiology, we formulated a simple age-structured SIR model with two age classes (Figure S4), children (subscript C) and adults (subscript A). Assuming a symmetric transmission matrix, $\Gamma = \begin{pmatrix} \beta & \chi\beta \\ \chi\beta & \xi\beta \end{pmatrix}$ and no mortality in children, the model equations for the proportions of vaccinated, susceptibles, infected, and recovered are:

$$
\begin{aligned}
\frac{dV_C}{dt} &= \mu p - (\alpha_V + \mu_C)V_C \\
\frac{dS_C}{dt} &= \mu(1-p) + \alpha_V V_C - S_C(\beta I_C + \chi\beta I_A) - \mu_C S_C + \alpha_I R_C \\
\frac{dI_C}{dt} &= S_C(\beta I_C + \chi\beta I_A) - (\gamma + \mu_C)I_C \\
\frac{dR_C}{dt} &= \gamma I_C - (\alpha_I + \mu_C)R_C \\
\frac{dV_A}{dt} &= \mu_C V_C - (\alpha_V + \mu_A)V_A \\
\frac{dS_A}{dt} &= \mu_C S_C + \alpha_V V_A - S_A(\chi\beta I_C + \xi\beta I_A) - \mu_A S_A + \alpha_I R_A \\
\frac{dI_A}{dt} &= \mu_C I_C + S_A(\chi\beta I_C + \xi\beta I_A) - (\gamma + \mu_A)I_A \\
\frac{dR_A}{dt} &= \mu_C R_C + \gamma I_C - (\alpha_I + \mu_A)R_A
\end{aligned}
$$

Here μ represents the birth rate, p the effective vaccine coverage, μ_C the aging rate, γ the recovery rate, μ_A the death rate in adults, α_I the rate of loss of infection-derived immunity, and α_V the rate of loss of vaccine-derived immunity (Table S3). Assuming that $\frac{1}{\mu} = \frac{1}{\mu_C} + \frac{1}{\mu_A}$, the proportions in each age group remain constant, $N_C = \frac{\mu}{\mu_C}$ and $N_A = 1 - N_C = \frac{\mu}{\mu_A}$, leading to a reduced system of equations:

$$
\begin{aligned}
\frac{dV_C}{dt} &= \mu p - (\alpha_V + \mu_C)V_C \\
\frac{dS_C}{dt} &= \mu(1-p) + \alpha_V V_C - S_C(\beta I_C + \chi\beta I_A) - \mu_C S_C + \alpha_I(N_C - V_C - S_C - I_C) \\
\frac{dI_C}{dt} &= S_C(\beta I_C + \chi\beta I_A) - (\gamma + \mu_C)I_C \\
R_C &= N_C - V_C - S_C - I_C \\
\frac{dV_A}{dt} &= \mu_C V_C - (\alpha_V + \mu_A)V_A \\
\frac{dS_A}{dt} &= \mu_C S_C + \alpha_V V_A - S_A(\chi\beta I_C + \xi\beta I_A) - \mu_A S_A + \alpha_I(N_A - V_A - S_A - I_A) \\
\frac{dI_A}{dt} &= \mu_C I_C + S_A(\chi\beta I_C + \xi\beta I_A) - (\gamma + \mu_A)I_A \\
R_A &= N_A - V_A - S_A - I_A
\end{aligned}
$$

The parameters χ (ratio of contact rate between children and adults to that between children) and ξ (ratio of contact rate between adults to that between children) were fixed from self-reported contacts from the POLYMOD study (Table S3). In numerical applications, we assumed a vaccine coverage of 90% and a vaccine efficacy of 85%, leading to an effective vaccine coverage of ca. 0.75. Following the results of Wearing and Rohani [22], we considered three possible values for the duration of infection-derived immunity, in the range 30–80 years (Table S3).

Because waning immunity results in higher prevalences at equilibrium, it is often necessary to rescale the basic reproduction number [22]. To do this, we back-calculated the transmission rate β to keep the age at first infection at equilibrium constant in the pre-vaccine era ($p = 0$). For the system of equations above in the pre-vaccine era, this quantity equals:

$$\text{mean age at first infection} = \frac{\overbrace{\left(\frac{1}{\lambda_C + \mu_C}\right)}^{\text{mean age to exit susceptible children class}} \overbrace{\left(\frac{\lambda_C}{\lambda_C + \mu_C}\right)}^{\text{probability of getting infected as a child}} + \overbrace{\left(\frac{1}{\lambda_C + \mu_C} + \frac{1}{\lambda_A + \mu_A}\right)}^{\text{mean age to exit susceptible adult class}} \overbrace{\left(\frac{\mu_C}{\lambda_C + \mu_C}\right)}^{\text{probability of not getting infected as a child}} \overbrace{\left(\frac{\lambda_A}{\lambda_A + \mu_A}\right)}^{\text{probability of getting infected as an adult}}}{\underbrace{\left(\frac{\lambda_C}{\lambda_C + \mu_C}\right)}_{\text{probability of getting infected as a child}} + \underbrace{\left(\frac{\mu_C}{\lambda_C + \mu_C}\right)}_{\text{probability of not getting infected as a child}} \underbrace{\left(\frac{\lambda_A}{\lambda_A + \mu_A}\right)}_{\text{probability of getting infected as an adult}}}$$

$$= \frac{1}{\lambda_C + \mu_C} + \frac{\mu_C \lambda_A}{(\lambda_A + \mu_A)(\lambda_C(\lambda_A + \mu_A) + \lambda_A \mu_C)}$$

where $\lambda_C = \beta I_C + \chi \beta I_A$ and $\lambda_A = \chi \beta I_C + \xi \beta I_A$ are the per-susceptible force of infection at equilibrium in children and adults, respectively. With this value of β, we then solved the system of equations to find the equilibrium values $(V_C, S_C, I_C, V_A, S_A, I_A)$ and calculated the per-susceptible force of infection in adults at equilibrium, λ_A. To allow comparison with empirical estimates of pertussis incidence in adults, we calculated the per-adult force of infection (that is, the number of cases in adults divided by the total number of adults) from the model: $\Lambda_A = \lambda_A \times \frac{S_A}{N_A}$. The results are presented in Fig. S5.

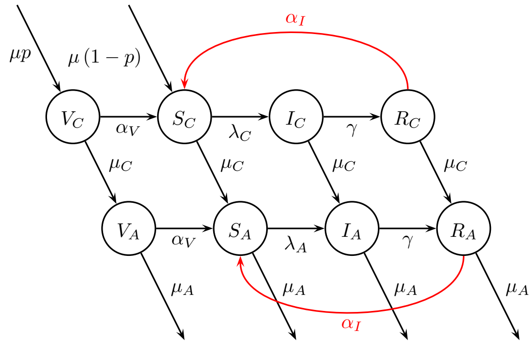

Figure S4: Model schematic.

Parameter	Meaning	Value	Reference
p	Effective vaccine coverage	0.75	Assumed
μ	Birth rate	$\frac{1}{75}$ yr^{-1}	Assumed
μ_C	Aging rate in children	$\frac{1}{18}$ yr^{-1}	Assumed
μ_A	Death rate in adults	$\frac{1}{57}$ yr^{-1}	Assumed
β	Transmission rate	varied	Fixed to keep age at first infection constant in the pre-vaccine era
χ	Ratio of contact rate between children and adults to that between children	0.31	[23]
ξ	Ratio of contact rate between adults to that between children	0.21	[23]
A	Mean age at first infection in the pre-vaccine era	4 years	[22]
$1/\gamma$	Average infectious period	21 days	[24]
$1/\alpha_I$	Duration of infection-derived immunity	30, 50, or 80 years	[22]
$1/\alpha_V$	Duration of vaccine-derived immunity	varied in [10, ∞) years	[25]

Table S3: Parameters used in the model.

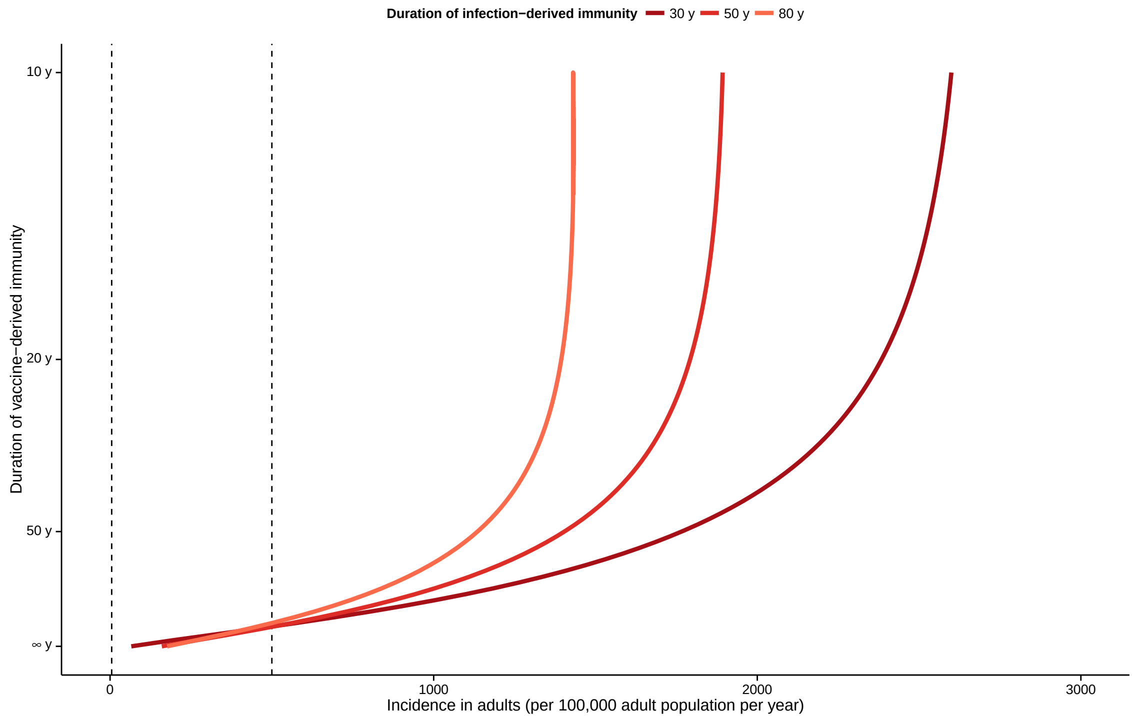

Figure S5: Incidence in adults predicted from a simple age-structured model.

S3 Figure S6 and Table S4

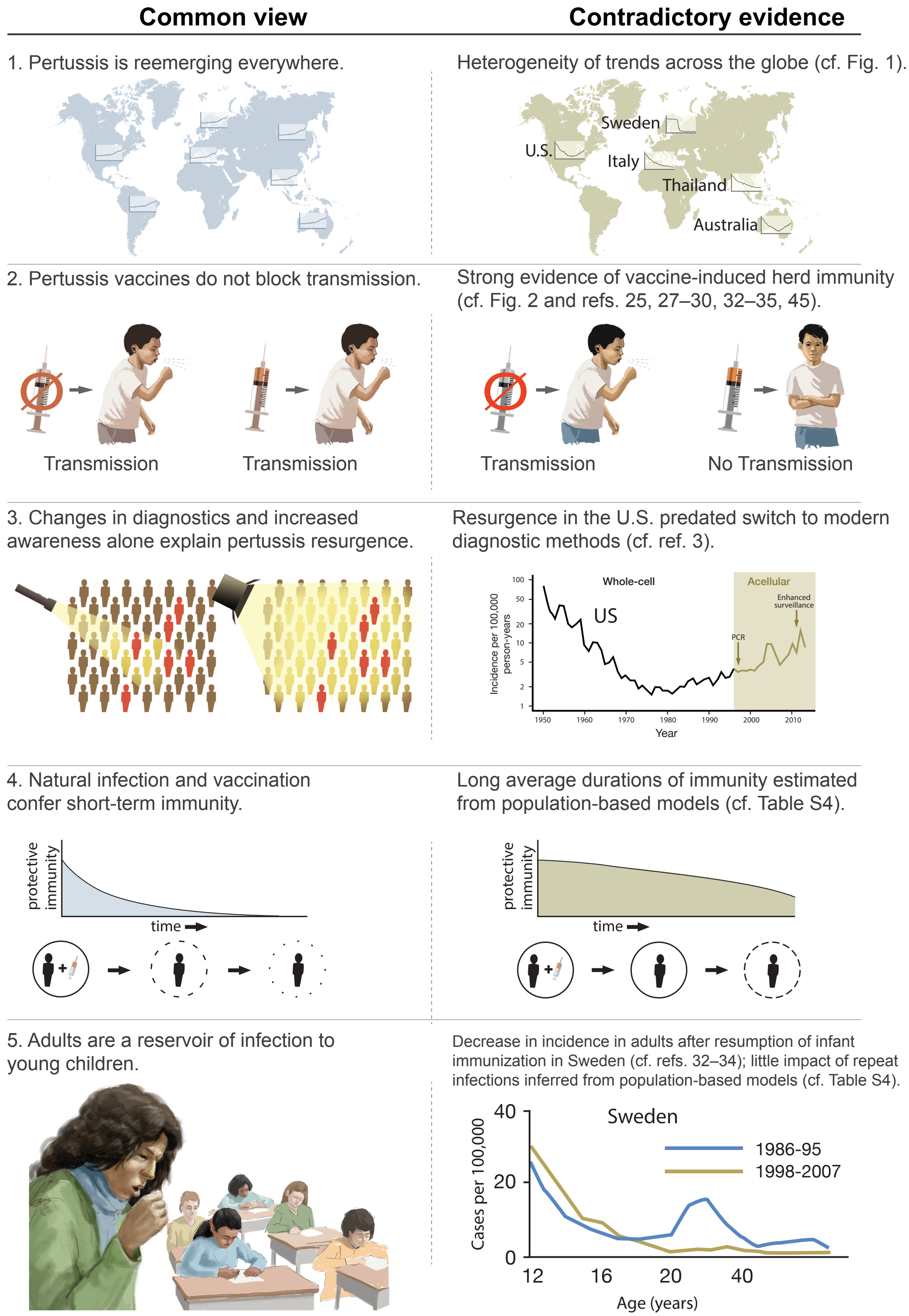

Figure S6: Illustration of widespread views on pertussis. Common views on pertussis epidemiology are represented in the left column; corresponding empirical evidence is represented in the right column. Citation numbers refer to references in the main text. Illustration by John Megahan.

Study	Data	Model(s) used	Inference method	Duration of infection-derived immunity	Duration of vaccine-derived immunity	Impact of repeat infections
[22]	Weekly cases, England and Wales	Base model: VSEIRS2E2I2; Immune-boosting model: VSEIRS2BE2I2 (stochastic, process noise and observation noise)	Model-data agreement on epidemiological signatures	>30 y (E)	Not well identified, but likely shorter than duration of infection- derived immunity	Small contribution to transmission cycle
[26]	Age-stratified annual cases, Sweden 1986–2007	Base model: Age-structured SEIR; Extended model: age-structured SEIRS (stochastic, process noise and observation noise)	Likelihood-based (assuming steady state)	SEIR: ∞ (F); SEIRS: 25, 10, 5 y (F)	Assumed equal to duration of infection-derived immunity	SEIR: no impact SEIRS: minimal contribution to transmission cycle
[24]	Monthly cases, Thailand 1981–2000	Model comparison, based on AIC; Best model: VSIR; Other models tested: VSIRS, VSIRS2I2, VSIRS2BI2 (stochastic, process noise and observation noise)	Likelihood-based (MIF)	VSIR: ∞ (F); VSIRS: 69 y (E); VSIRS2I2: 70 y (E); VSIRS2BI2: not identified (E)	Assumed equal to duration of infection-derived immunity	VSIR: no impact VSIRS2BI2: repeat infections account for 4–6% of primary infections
[27]	Weekly cases, Copenhagen 1900–1937	Model comparison, based on AIC; Best model: SIRWS; Other models tested: SIR, SIRS (stochastic, process noise and observation noise)	Likelihood-based (MIF)	SIRWS: 34 (17–66) y (E); SIR: ∞ (F); SIRS: 192 (178–192) y (F)	Not applicable (prevaccine-era data)	Not applicable
[28]	Annual cases, U.S 1950–1989; age-stratified annual cases, U.S. 1990–2009	VSIRS2I2, with leaky infection-derived immunity (stochastic, no process noise but observation noise)	Markov Chain Monte Carlo (MCMC), assuming no process noise	Waning rate: 3×10^{-5} $(2\times10^{-6}, 2\times10^{-4})$ yr^{-1}; Leakiness: 0.32	Waning rate: Whole-cell: 3×10^{-5} $(2 \times 10^{-6}, 2 \times 10^{-4})$ yr^{-1}; Acellular: 0.018 (0.015, 0.02) yr^{-1}	Unstated

Table S4: Summary findings of population-based models that used statistical inference on pertussis incidence data. MIF: maximum iterated filtering algorithm [29]. E: estimated parameter; F: fixed parameter. Models signification. S(E)IR, Susceptible (Exposed) Infected Recovered: basic epidemic model, assuming perfect infection- and vaccine-derived immunity (i.e., no repeat infections). VS(E)IR: S(E)IR model extension allowing to track vaccinated individuals, assuming perfect infection- and vaccine-derived immunity (no repeat infections). (V)S(E)IRS: extension of the (V)S(E)IR model allowing for waning infection- or vaccine-derived immunity; repeat infections are allowed and assumed identical (i.e., as infectious and as observable) to primary infections. S(E)IRWS: extension of the S(E)IRS model, allowing for waning infection- or vaccine-derived immunity and immune boosting (2 recovered classes: R, recently recovered and highly immune individuals; W, individuals still immune, but whose immunity can be boosted upon reexposure). VS(E)IRS2(E2)I2: extension of the VS(E)IRS model, in which repeat infections are explicitly modeled and, therefore, may differ from primary infections. VS(E)IRS2B(E2)I2: extension of the VS(E)IRS2(E2)I2 model, with immune boosting. References for this table were identified through searches of PubMed by use of the terms "pertussis" or "whooping cough", "mathematical" or "dynamical", and "modeling". We restricted to papers that used statistical inference on longitudinal incidence data to estimate the duration of infection- or vaccine-derived immunity.

References

[1] Sheridan, S. L., Ware, R. S., Grimwood, K. & Lambert, S. B. Number and order of whole cell pertussis vaccines in infancy and disease protection. *JAMA* **308**, 454–6 (2012).

[2] Rendi-Wagner, P., Paulke-Korinek, M., Stanek, G., Khanakah, G. & Kollaritsch, H. Impact of a pertussis booster vaccination program in adolescents and adults on the epidemiology of pertussis in Austria. *Pediatr Infect Dis J* **26**, 806–10 (2007).

[3] Wu, Y. *et al.* Antitoxins for diphtheria and tetanus decline more slowly after vaccination with DTwP than with DTaP: a study in a Chinese population. *Vaccine* **32**, 2570–3 (2014).

[4] Hviid, A. & Melbye, M. Impact of routine vaccination with a conjugate *Haemophilus influenzae* type b vaccine. *Vaccine* **22**, 378–82 (2004).

[5] Elomaa, A., He, Q., Minh, N. N. T. & Mertsola, J. Pertussis before and after the introduction of acellular pertussis vaccines in Finland. *Vaccine* **27**, 5443–9 (2009).

[6] Theodoridou, M. *et al.* Pertussis Epidemiology in Greece and Emerging Risk Groups during the Vaccination Era (1980-2008). *Adv Prev Med* **2012**, 303846 (2012).

[7] Moerman, L. *et al.* The re-emergence of pertussis in Israel. *Isr Med Assoc J* **8**, 308–11 (2006).

[8] Gabutti, G. & Rota, M. C. Pertussis: a review of disease epidemiology worldwide and in Italy. *Int J Environ Res Public Health* **9**, 4626–38 (2012).

[9] van der Maas, N. A. T. *et al.* Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? *Vaccine* **31**, 4541–7 (2013).

[10] Choe, Y. J., Park, Y.-J., Jung, C., Bae, G.-R. & Lee, D.-h. National pertussis surveillance in South Korea 1955-2011: epidemiological and clinical trends. *Int J Infect Dis* **16**, e850–4 (2012).

[11] Crespo, I. *et al.* Geographical differences in whooping cough in Catalonia, Spain, from 1990 to 2010. *BMC Public Health* **14**, 268 (2014).

[12] Carlsson, R.-M. & Trollfors, B. Control of pertussis–lessons learnt from a 10-year surveillance programme in sweden. *Vaccine* **27**, 5709–18 (2009).

[13] Beyazova, U., Yüksel, N., Aksakal, F. N. & Camurdan, A. D. Comparison of the reactogenicity of three different immunization schedules including diphtheria, tetanus, pertussis, *Haemophilus influenza* b and polio vaccine in Turkey. *Trans R Soc Trop Med Hyg* **107**, 438–43 (2013).

[14] Litt, D. J., Neal, S. E. & Fry, N. K. Changes in genetic diversity of the *Bordetella pertussis* population in the United Kingdom between 1920 and 2006 reflect vaccination coverage and emergence of a single dominant clonal type. *J Clin Microbiol* **47**, 680–8 (2009).

[15] Rohani, P. & Drake, J. M. The decline and resurgence of pertussis in the us. *Epidemics* **3**, 183–8 (2011).

[16] von König, C. H. W., Halperin, S., Riffelmann, M. & Guiso, N. Pertussis of adults and infants. *Lancet Infect Dis* **2**, 744–50 (2002).

[17] Cortese, M. M., Baughman, A. L., Brown, K. & Srivastava, P. A "new age" in pertussis prevention new opportunities through adult vaccination. *Am J Prev Med* **32**, 177–185 (2007).

[18] Strebel, P. *et al.* Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis* **183**, 1353–9 (2001).

[19] Nennig, M. E., Shinefield, H. R., Edwards, K. M., Black, S. B. & Fireman, B. H. Prevalence and incidence of adult pertussis in an urban population. *JAMA* **275**, 1672–4 (1996).

[20] Gilberg, S. *et al.* Evidence of *Bordetella pertussis* infection in adults presenting with persistent cough in a French area with very high whole-cell vaccine coverage. *J Infect Dis* **186**, 415–8 (2002).

[21] Yih, W. K. *et al.* The increasing incidence of pertussis in Massachusetts adolescents and adults, 1989-1998. *J Infect Dis* **182**, 1409–16 (2000).

[22] Wearing, H. J. & Rohani, P. Estimating the duration of pertussis immunity using epidemiological signatures. *PLoS Pathog* **5**, e1000647 (2009).

[23] Mossong, J. *et al.* Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* **5**, e74 (2008).

[24] Blackwood, J. C., Cummings, D. A. T., Broutin, H., Iamsirithaworn, S. & Rohani, P. Deciphering the impacts of vaccination and immunity on pertussis epidemiology in Thailand. *Proc Natl Acad Sci U S A* **110**, 9595–600 (2013).

[25] Wendelboe, A. M., Van Rie, A., Salmaso, S. & Englund, J. A. Duration of immunity against pertussis after natural infection or vaccination. *Pediatr Infect Dis J* **24**, S58–61 (2005).

[26] Rohani, P., Zhong, X. & King, A. A. Contact network structure explains the changing epidemiology of pertussis. *Science* **330**, 982–5 (2010).

[27] Lavine, J. S., King, A. A., Andreasen, V. & Bjørnstad, O. N. Immune boosting explains regime-shifts in prevaccine-era pertussis dynamics. *PLoS One* **8**, e72086 (2013).

[28] Gambhir, M. *et al.* A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. *PLoS Comput Biol* **11**, e1004138 (2015).

[29] Ionides, E. L., Bretó, C. & King, A. A. Inference for nonlinear dynamical systems. *Proc Natl Acad Sci U S A* **103**, 18438–43 (2006).