The dynamics of pertussis transmission: evaluating the impact of control measures through mathematical modeling.

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INIFTA CONICET UNLP

Projects

→ Control of pertussis transmission

→ Risk of measles introduction in BsAs

→ Stochastic fluctuations in *simple models* of disease transmission (endemic & epidemic)

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Interdisciplinary project

Liliana Lazo
Paula Bergero
Gabriel Fabricius | physicists

Alberto Maltz (mathematician)

Laboratory: VacSal
Molecular Biology and Biotechnology Institute (UNLP)

- → basic research on pertussis
- → vaccine developing
- → diagnosis (National Reference Laboratory)

Daniela Hozbor (biochemistry)

Outline of the talk

- Pertussis or whooping cough: Disease characteristics.
  Epidemiological problem.

- Mathematical model for pertussis transmission.

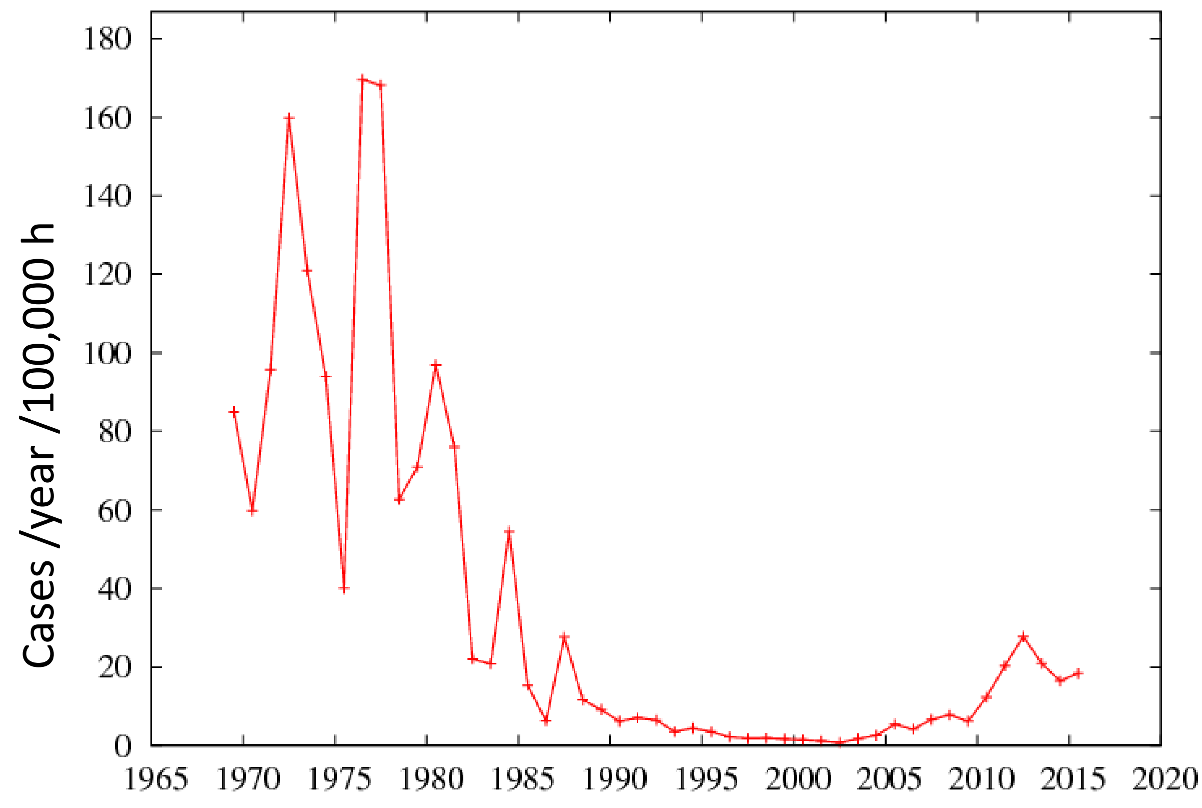
  Evaluation of vaccination strategies:

  → adolecent booster
  → improve administration (reduction of delays & increase in coverages)
  →pregnant women booster

Pertussis or whooping cough

- highly contagious respiratory disease
- caused by bacteria *Bordetella pertussis*
- very serious illness for infants
  (several complications, even death)
- Vaccination reduced drastically the incidence
  and mortality of the disease

Incidence from reported cases in Argentina

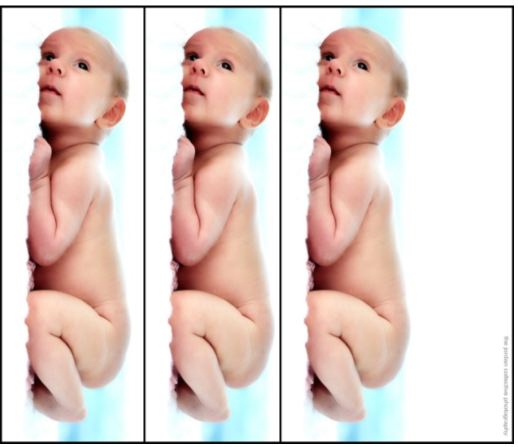


2011: 76 deaths (74 < 1 year)

- The immunity conferred by pertussis vaccines is lost with time:

Adolescents and adults get ill

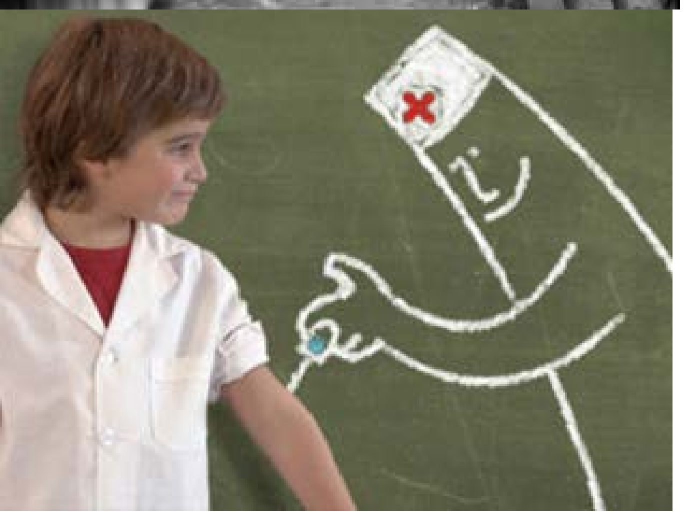
Pertussis vaccination schedule in Argentina



≈ 80% of vaccinated babies
are protected against
mild or severe pertussis

2m **4m** **6m** **18m**

School entry



- frequent and careless contacts
- probably… sibling infants

6 years

Pertussis vaccination schedule in Argentina

(similar for all countries)

2 - 4 - 6 m

18m

6 y

risk age-group

Pertussis incidence increase for teenagers

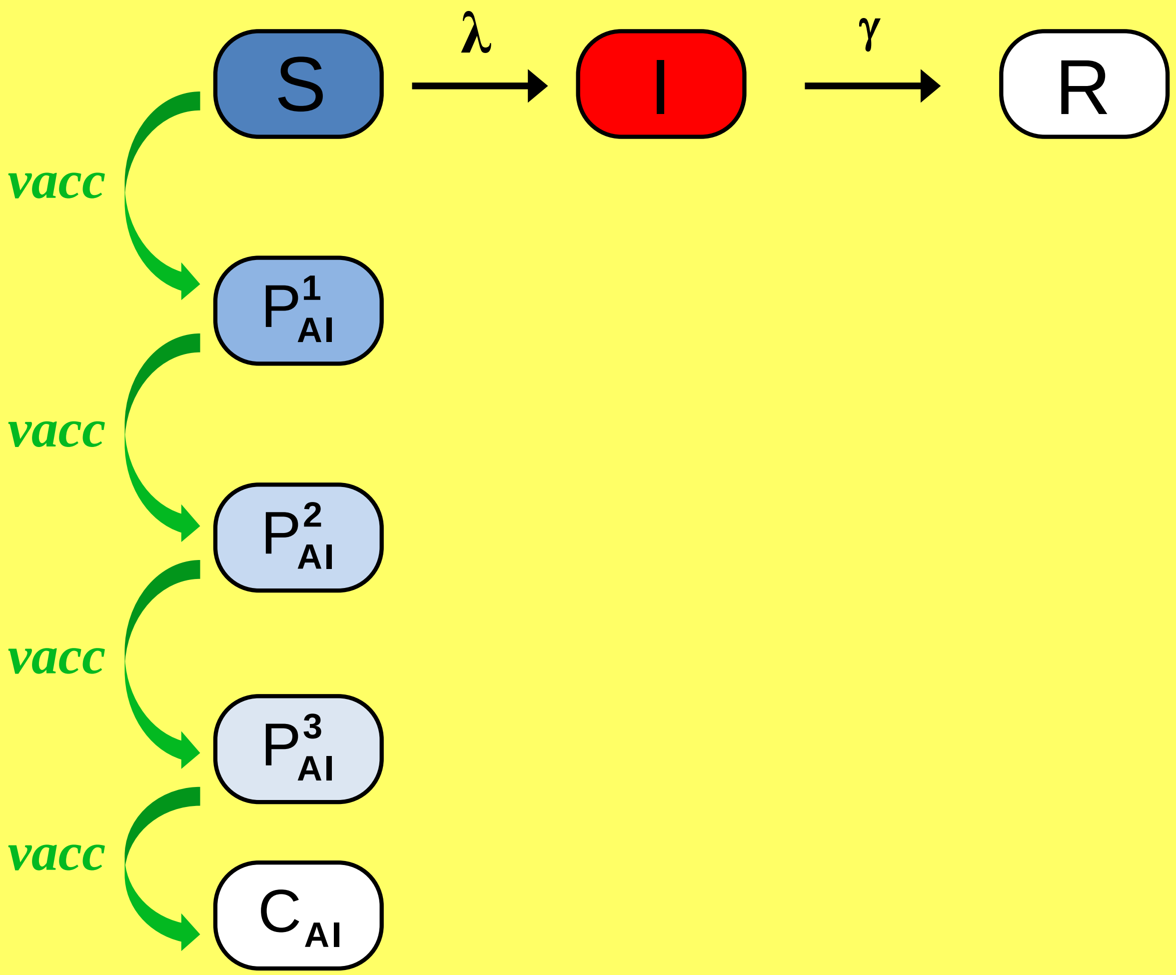
?

Tdap GPI 2002
CDC 2006

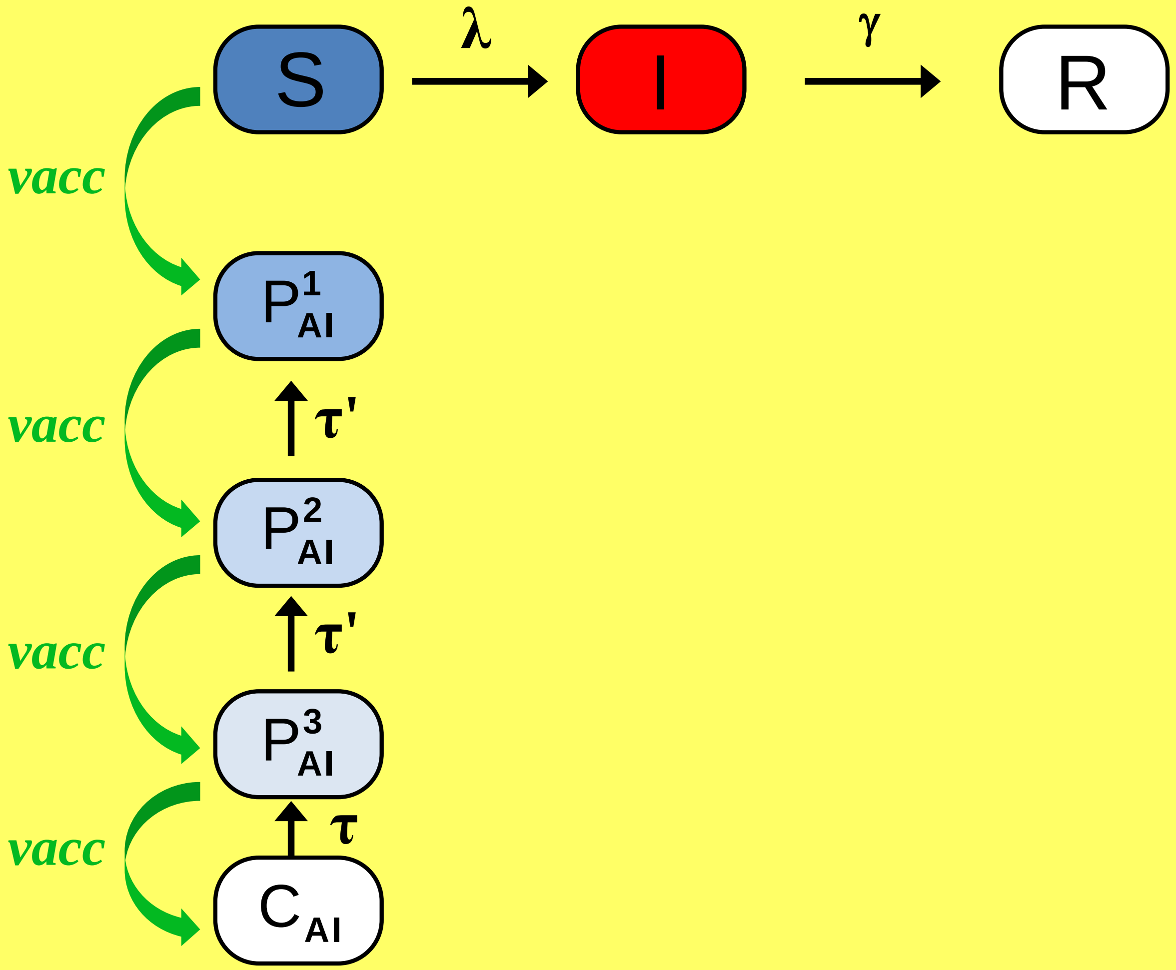
The WHO recommend **not to apply** more than 5 doses of the whole cell vaccine (DTP)

Pertussis transmission model

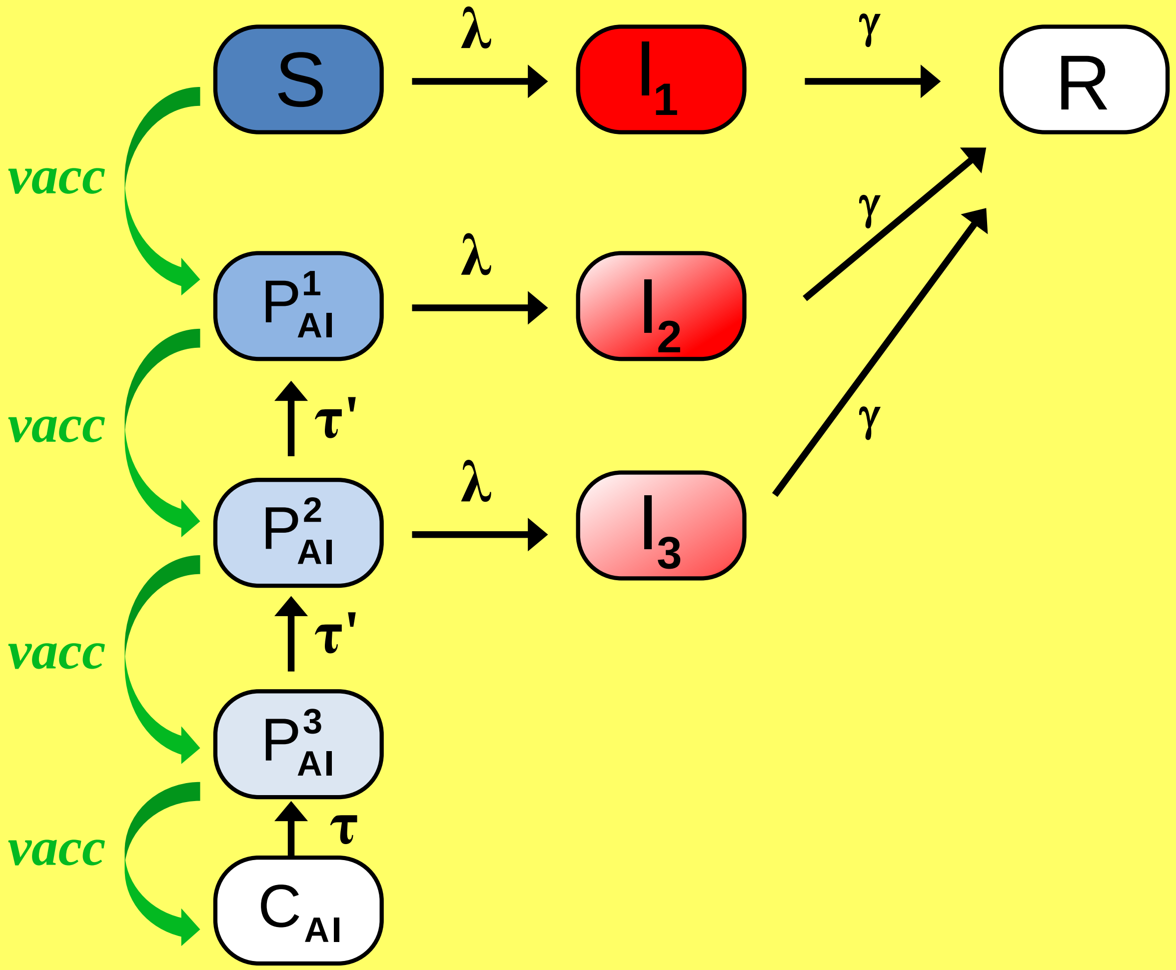
Pertussis transmission model



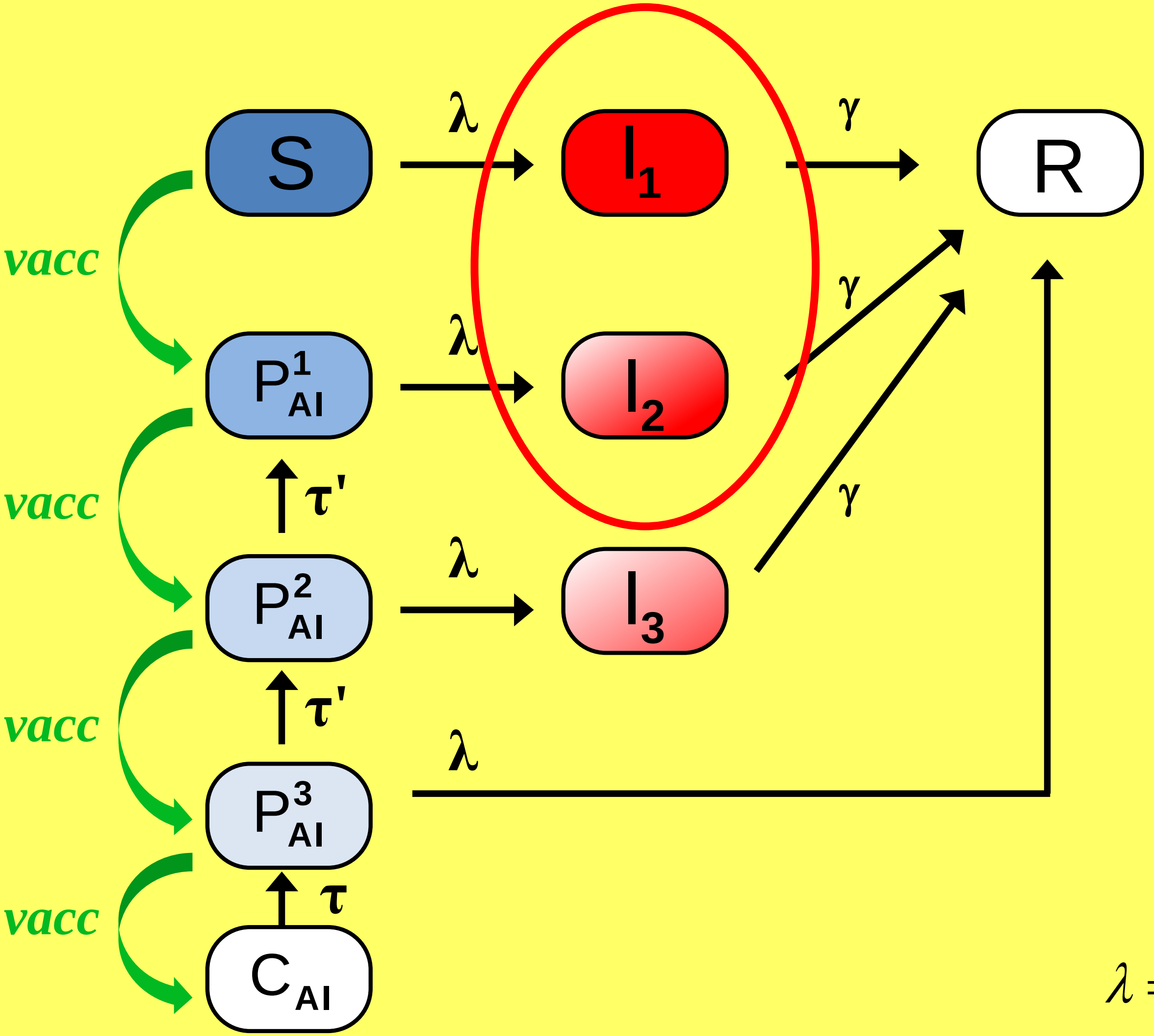
Pertussis transmission model

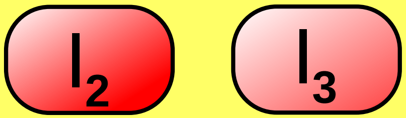


Pertussis transmission model



Pertussis transmission model





Infected with fewer symptoms

↓

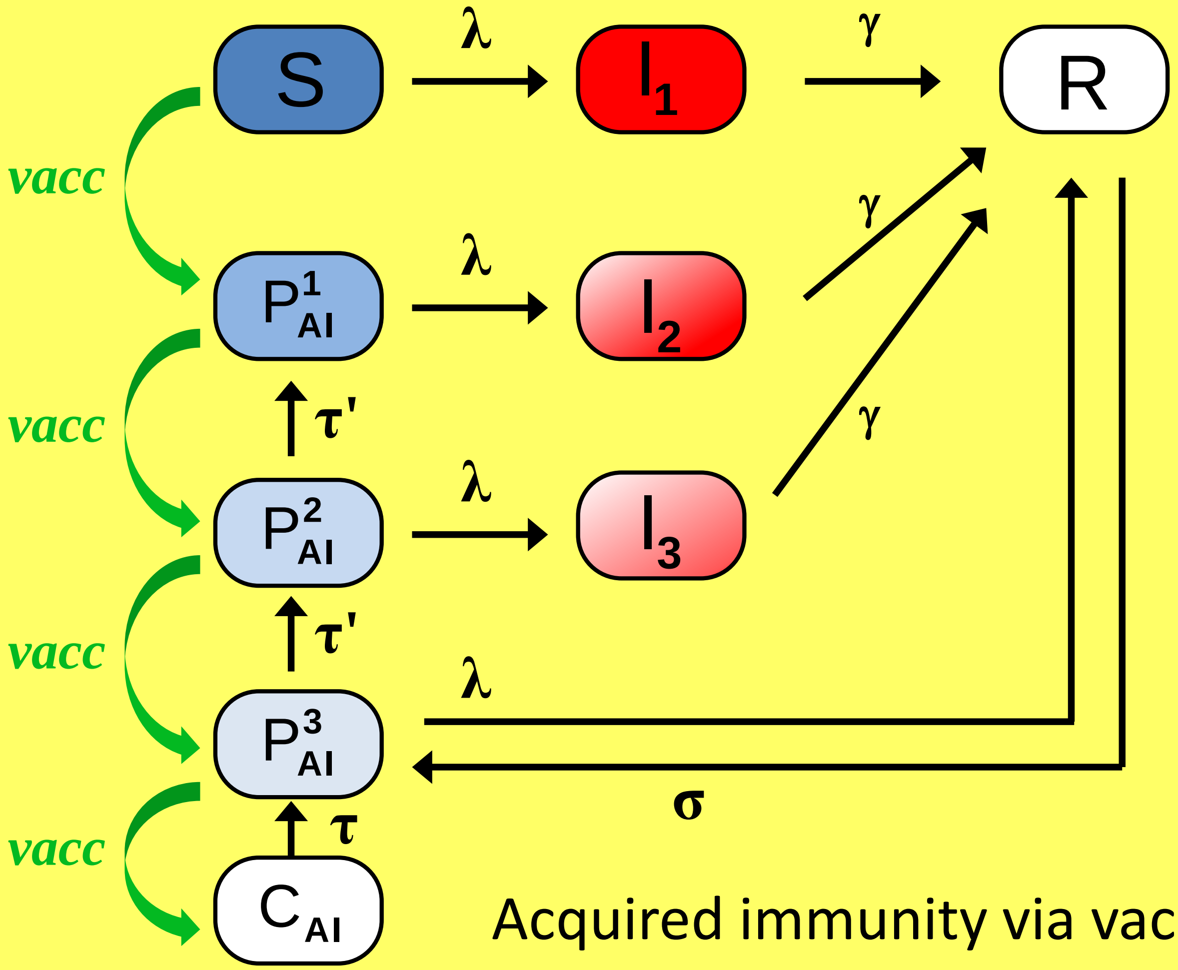
less contagious

$$\lambda = \beta \, I^*$$

$$I^* = I_1 + \rho I_2 + \rho' I_3$$

$$\rho < \rho' < 1$$

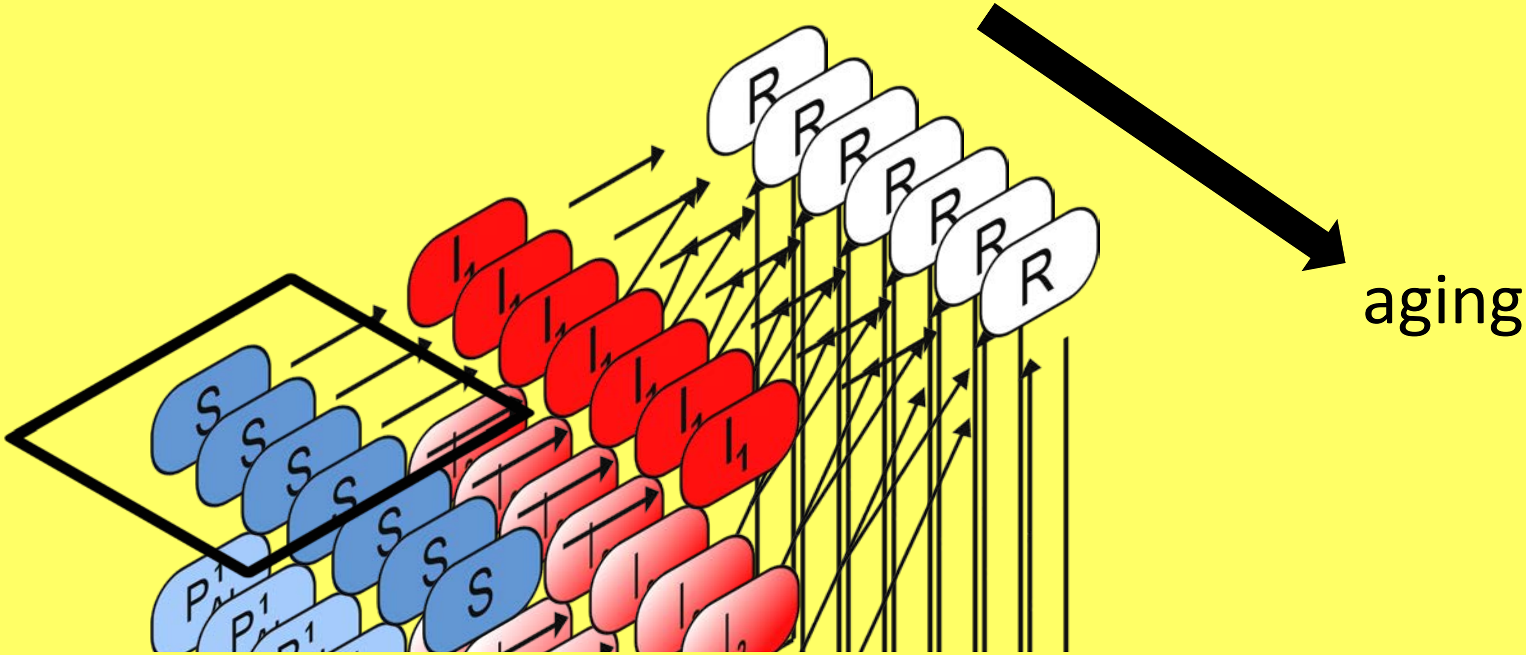
Pertussis transmission model



$\sigma >> \tau \approx \tau'$

Acquired immunity via vacc. is lost at rates τ, τ'

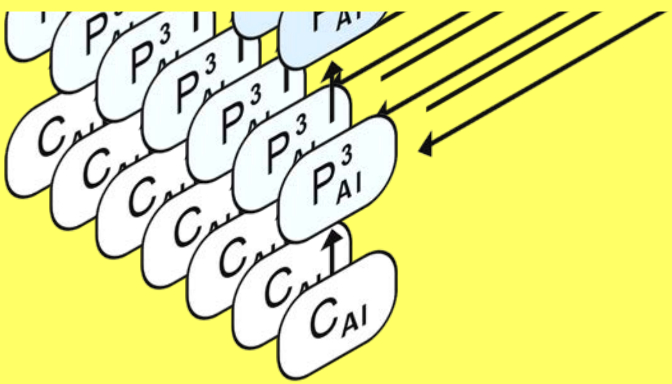
Natural acquired immunity is lost at rate σ

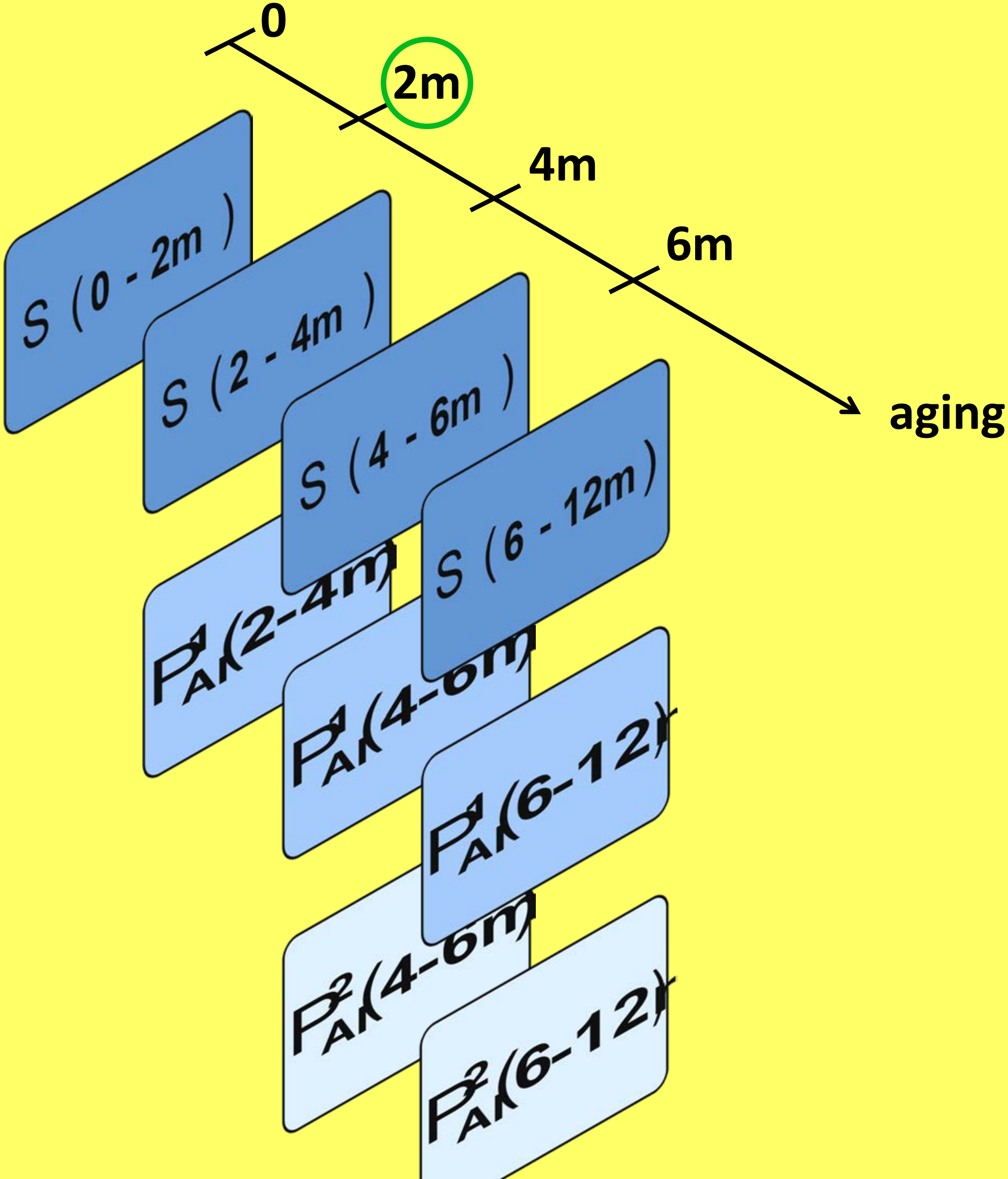


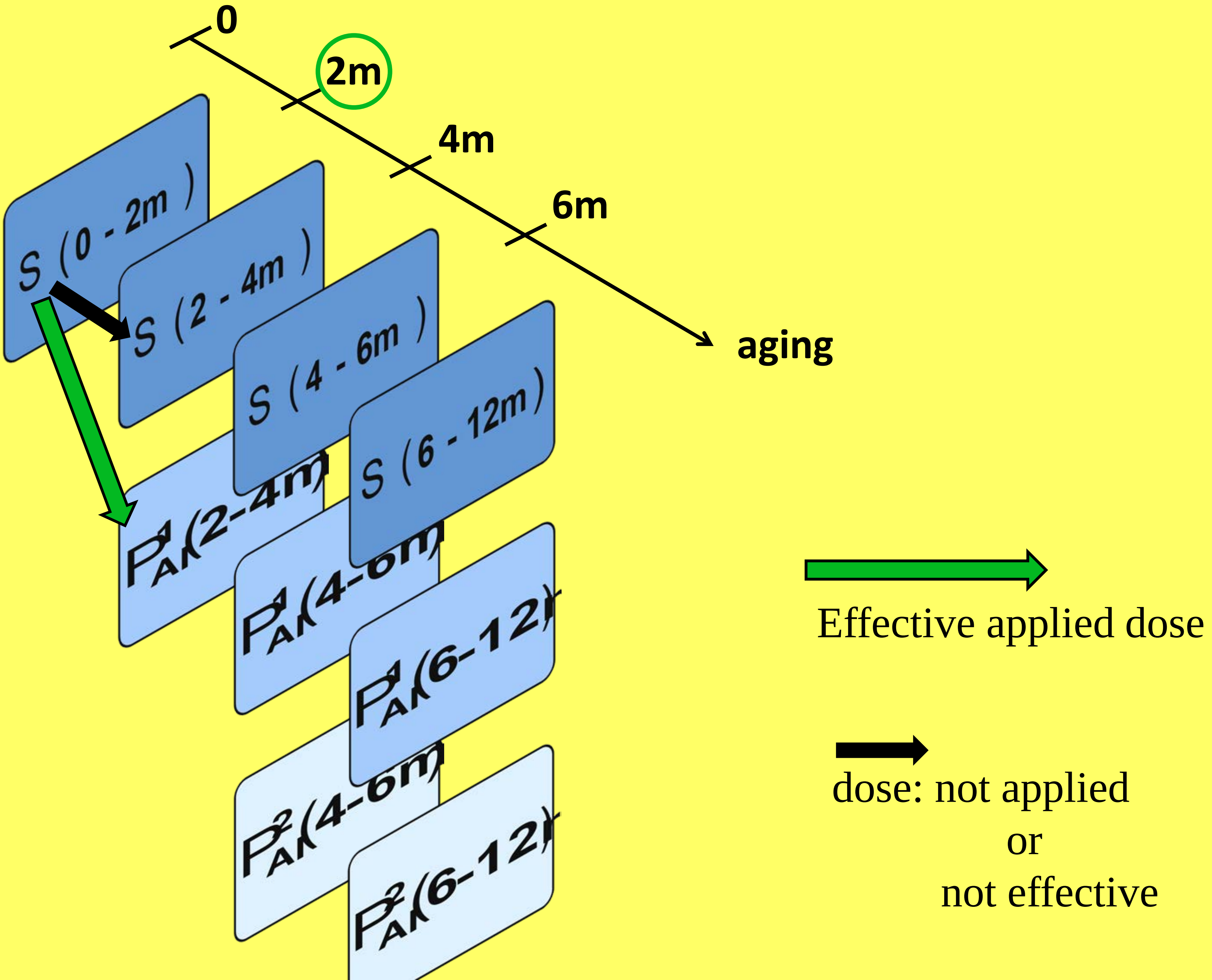
Age groups:

(0-2m) (2m-4m) (4m-6m) (6m-12m) (12m-18m) (18m-2y) (2y-3y) (3y-4y) (4y-5y) (5y-6y) (6y-7y)…

2m dose **4m dose** **6m dose** **18m dose** **6y dose**




0
2m
4m
6m
aging
S (0 - 2m)
S (2 - 4m)
S (4 - 6m)
S (6 - 12m)


0
2m
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S (0 - 2m)
S (2 - 4m)
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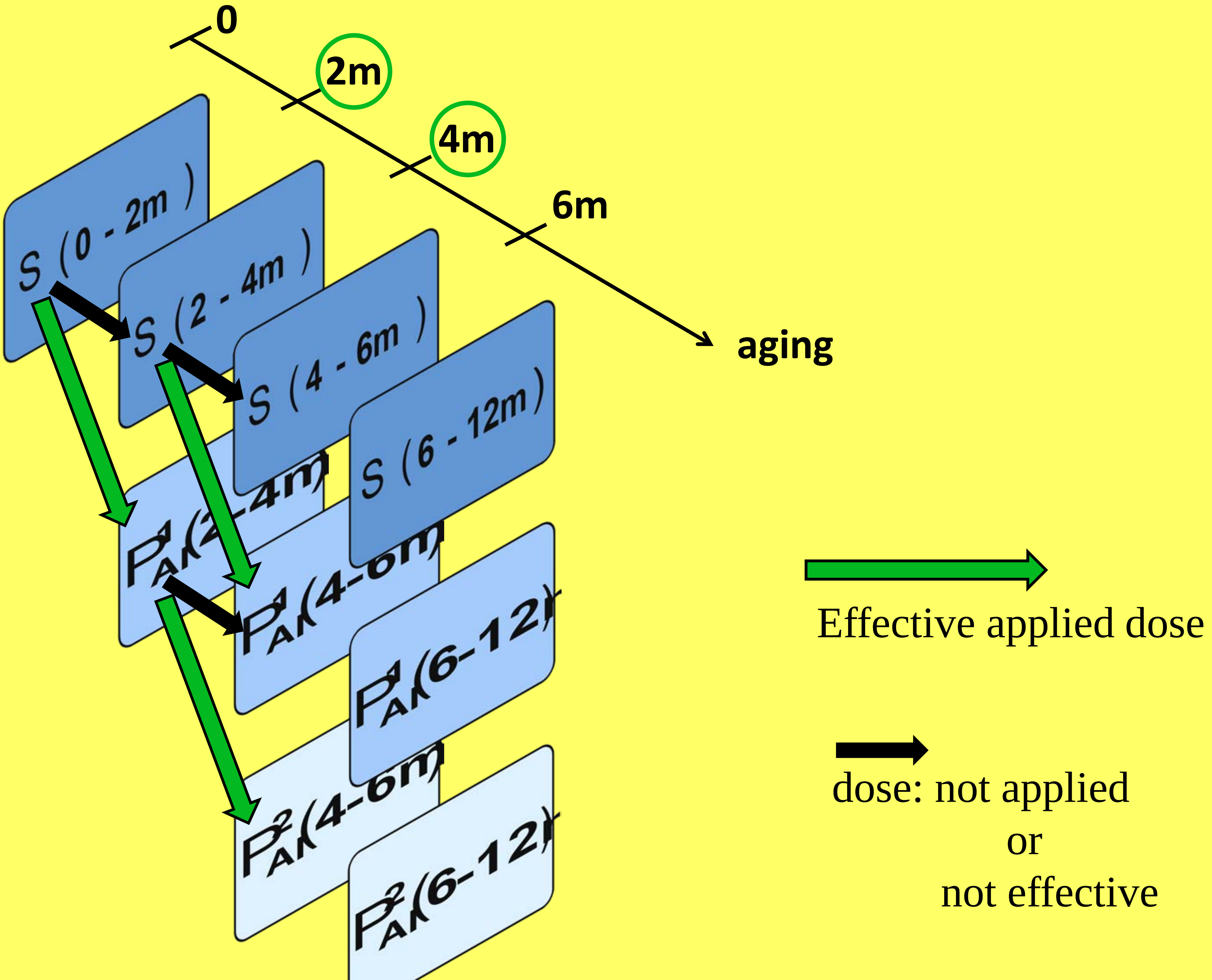
S (6 - 12m)
P1AI(2-4m)
P1AI(4-6m)
P1AI(6-12
P2AI(4-6m)
P2AI(6-12
Effective applied dose
dose: not applied
or
not effective



0
2m
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6m
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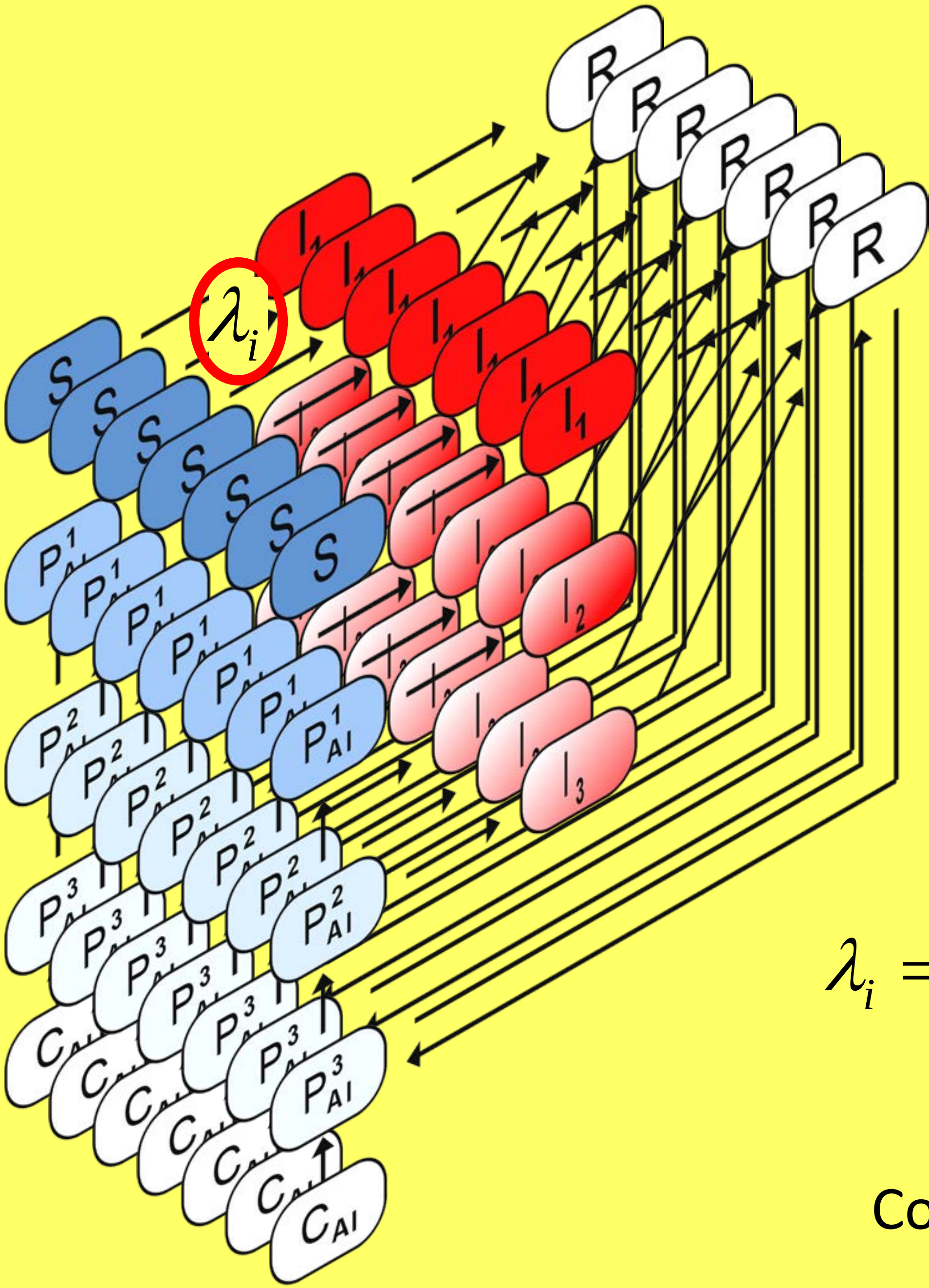
S (0 - 2m)
S (2 - 4m)
S (4 - 6m)
S (6 - 12m)
Effective applied dose
dose: not applied
or
not effective

This way of introducing vaccination in compartmental models was used by Hethcote

H.W. Hethcote (1997) *Math.Biosc.* **145**, 89-136

“An Age-Structured Model for pertussis transmission”



Force of infection: λ_i

is the rate at which individuals in clases S, P^1_{AI} and P^2_{AI} , age-group ***i***, acquire infection.

$$\lambda_i = \sum_{j=1}^{N} \beta_{ij} \left(I_1^j + \rho I_2^j + \rho' I_3^j \right)$$

Contact parameter matrix

$$\frac{dS_i}{dt} = -\lambda_i S_i + \sigma_0 P^1_{\mathrm{AI}i} - \mu_i S_i + c_{i-1}(1 - vacc_i) S_{i-1} - c_i S_i + \delta_{i0} B$$

$$\frac{dP^1_{\mathrm{AI}i}}{dt} = -\lambda_i P^1_{\mathrm{AI}i} - \sigma_0 P^1_{\mathrm{AI}i} + \tau' P^2_{\mathrm{AI}i} - \mu_i P^1_{\mathrm{AI}i} + c_{i-1}(1 - vacc_i) P^1_{\mathrm{AI}i-1} - c_i P^1_{\mathrm{AI}i} + c_{i-1} vacc_i S_{i-1}$$

$$\frac{dP^2_{\mathrm{AI}i}}{dt} = -\lambda_i P^2_{\mathrm{AI}i} - \tau' P^2_{\mathrm{AI}i} + \tau' P^3_{\mathrm{AI}i} - \mu_i P^2_{\mathrm{AI}i} + c_{i-1}(1 - vacc_i) P^2_{\mathrm{AI}i-1} - c_i P^2_{\mathrm{AI}i} + c_{i-1} vacc_i P^1_{\mathrm{AI}i-1}$$

$$\frac{dP^3_{\mathrm{AI}i}}{dt} = -\lambda_i P^3_{\mathrm{AI}i} - \tau' P^3_{\mathrm{AI}i} + \tau C_{\mathrm{AI}i} - \mu_i P^3_{\mathrm{AI}i} + \sigma R + c_{i-1}(1 - vacc_i) P^3_{\mathrm{AI}i-1} - c_i P^3_{\mathrm{AI}i} + c_{i-1} vacc_i P^2_{\mathrm{AI}i-1}$$

$$\frac{dC_{\mathrm{AI}i}}{dt} = -\tau C_{\mathrm{AI}i} - \mu_i C_{\mathrm{AI}i} + c_{i-1} C_{\mathrm{AI}i-1} - c_i C_{\mathrm{AI}i} + c_{i-1} vacc_i P^3_{\mathrm{AI}i-1}$$

$$\frac{dI_{1i}}{dt} = \lambda_i S_i - \gamma I_{1i} - \mu_i I_{1i} + c_{i-1} I_{1i-1} - c_i I_{1i}$$

$$\frac{dI_{2i}}{dt} = \lambda_i P^1_{\mathrm{AI}i} - \gamma I_{2i} - \mu_i I_{2i} + c_{i-1} I_{2i-1} - c_i I_{2i}$$

$$\frac{dI_{3i}}{dt} = \lambda_i P^2_{\mathrm{AI}i} - \gamma I_{3i} - \mu_i I_{3i} + c_{i-1} I_{3i-1} - c_i I_{3i}$$

$$\frac{dR_i}{dt} = \lambda_i P^3_{\mathrm{AI}i} + \gamma (I_{1i} + I_{2i} + I_{3i}) - \sigma R - \mu_i R + c_{i-1} R_{i-1} - c_i R_i$$

$i=1, \ldots 30$

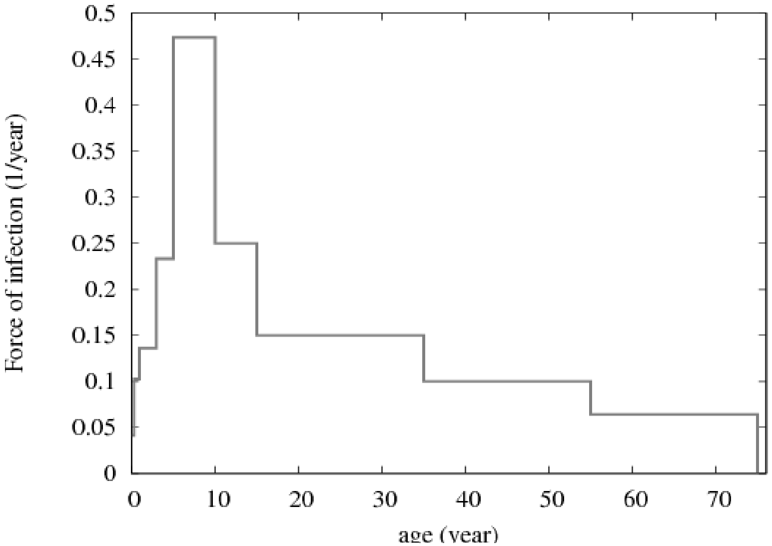
Model Parameters

Diferent methods

Diferentes sources of data

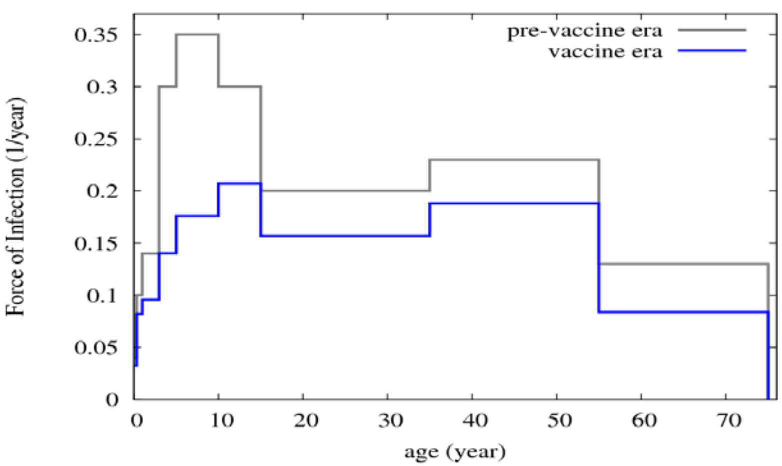
$\beta_{i\,j}$: WAIFW matrixes +

Forces of infection from:



Pre-vaccine era

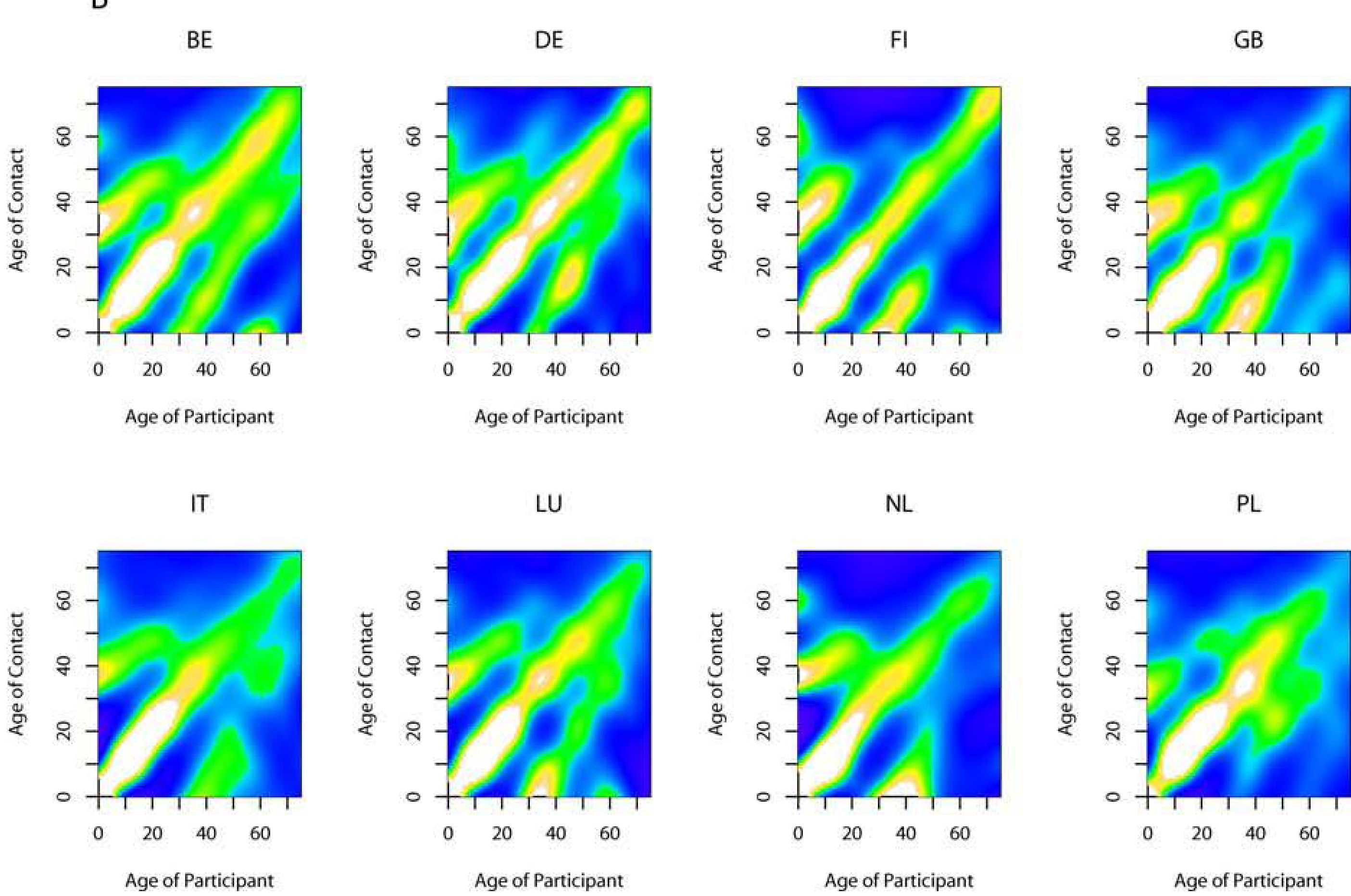
H.Hethcote, Math. Biosc. (1997)
based on reported cases in England & Wales



Vaccine era

M.Kretzschmar *et al.*
Plos Medicine **7** issue 6, 1-10 (2010)
Using data for 8 european countries

Direct estimation of contact matrixes



J. Mossong et al. Plos Medicine **5** (3) 0381-0391 (2008)

"Social contacts and mixing paterns relevant to the spread of infectious diseases"

Modeling pertussis transmission to evaluate the effectiveness of an adolescent booster in Argentina.

G.Fabricius, P.Bergero, M.Ormazabal, A.Maltz and D. Hozbor.

Epidemiology and Infection **141**, 718-734 (2013).

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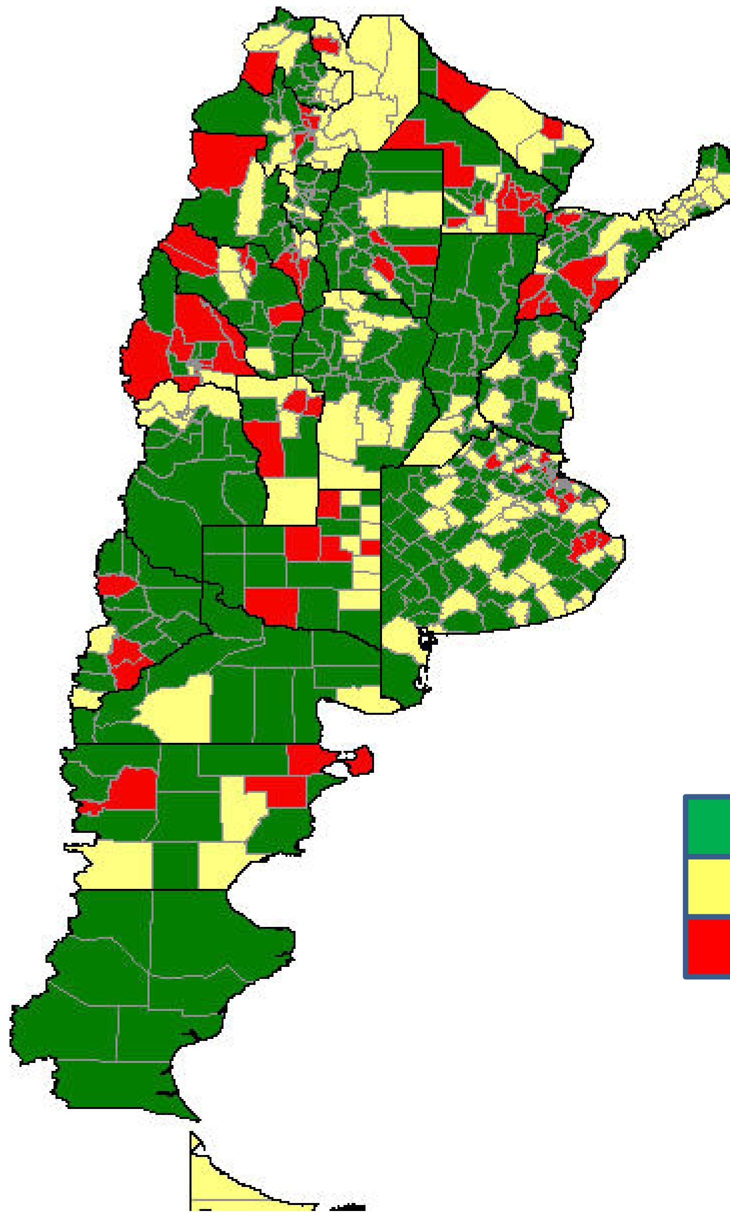
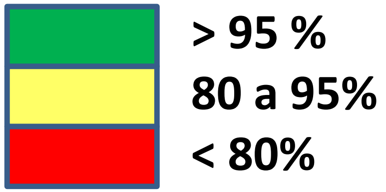
Impact in risk age group (0-1y):

<5% drop in the severe+moderate cases

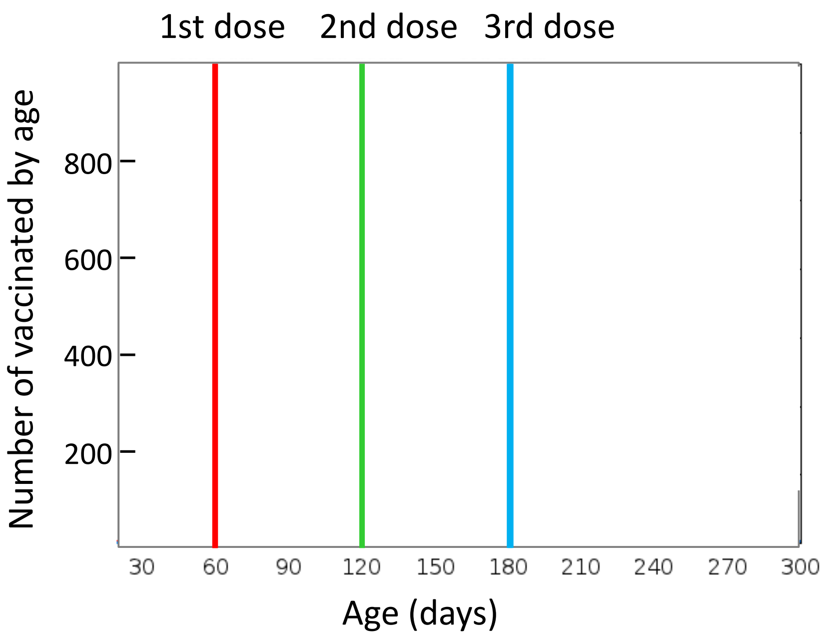
DTP3-coverage, Argentina





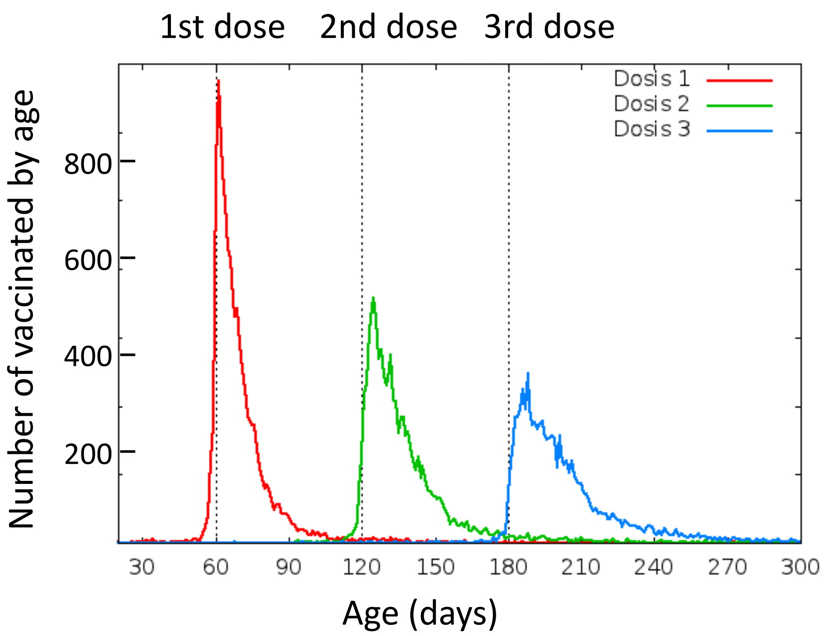
http://www.msal.gov.ar/htm/site/sala_situacion/PANELES/boletines/BEP2008/1-Inmunoprevenibles.pdf

Number of vacinated individuals per dose by age



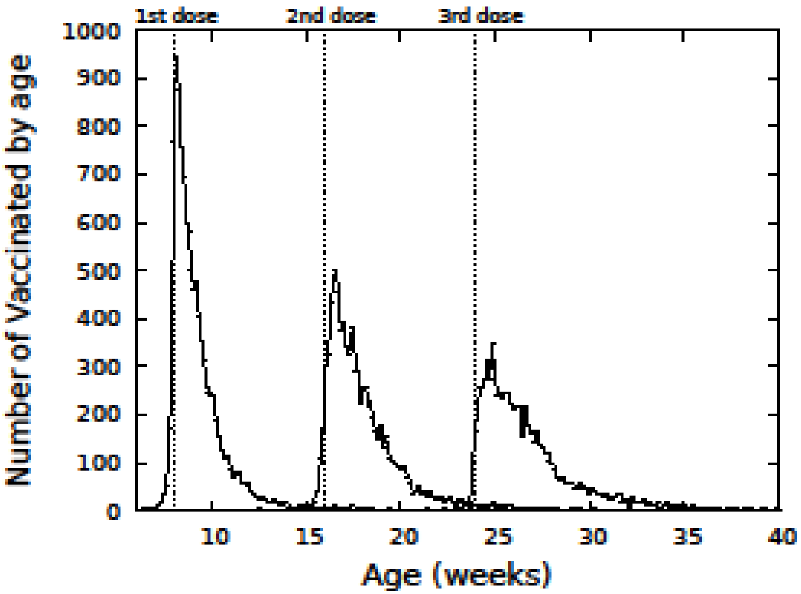
Ideal situation: no delay

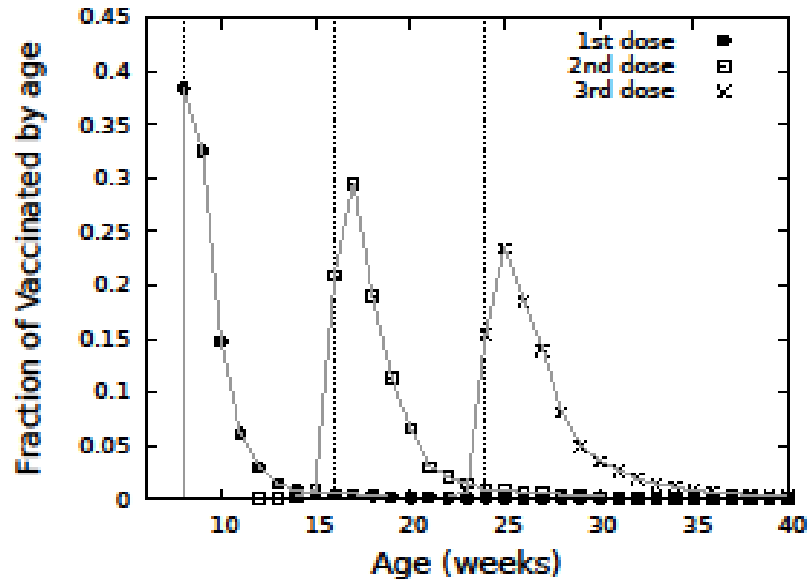
Number of vacinated individuals per dose by age



Data from an urban vaccination center in La Plata city (Argentina).

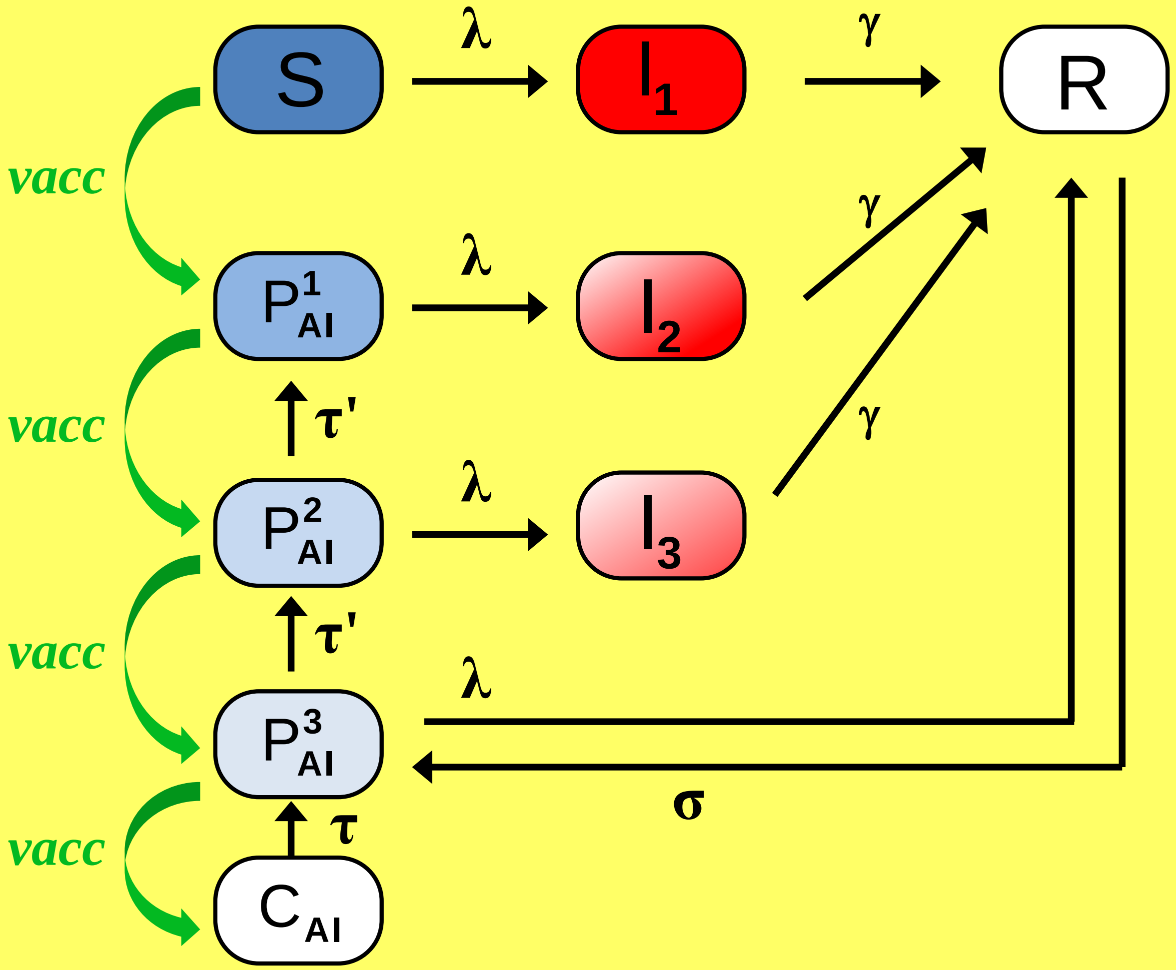
Age groups: weekly for age (2m,1y)



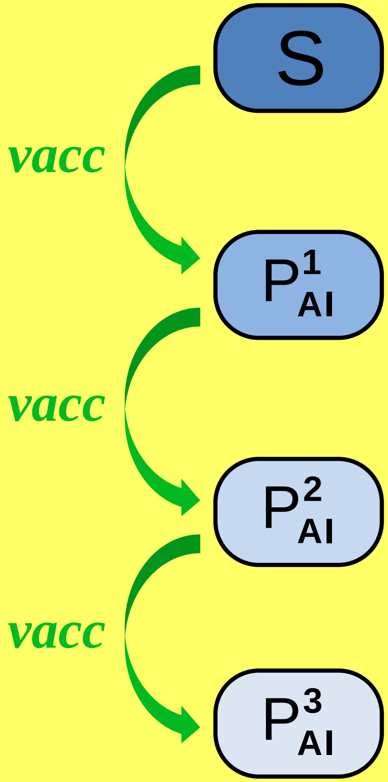


Weekly discretization of the data

Pertussis transmission model

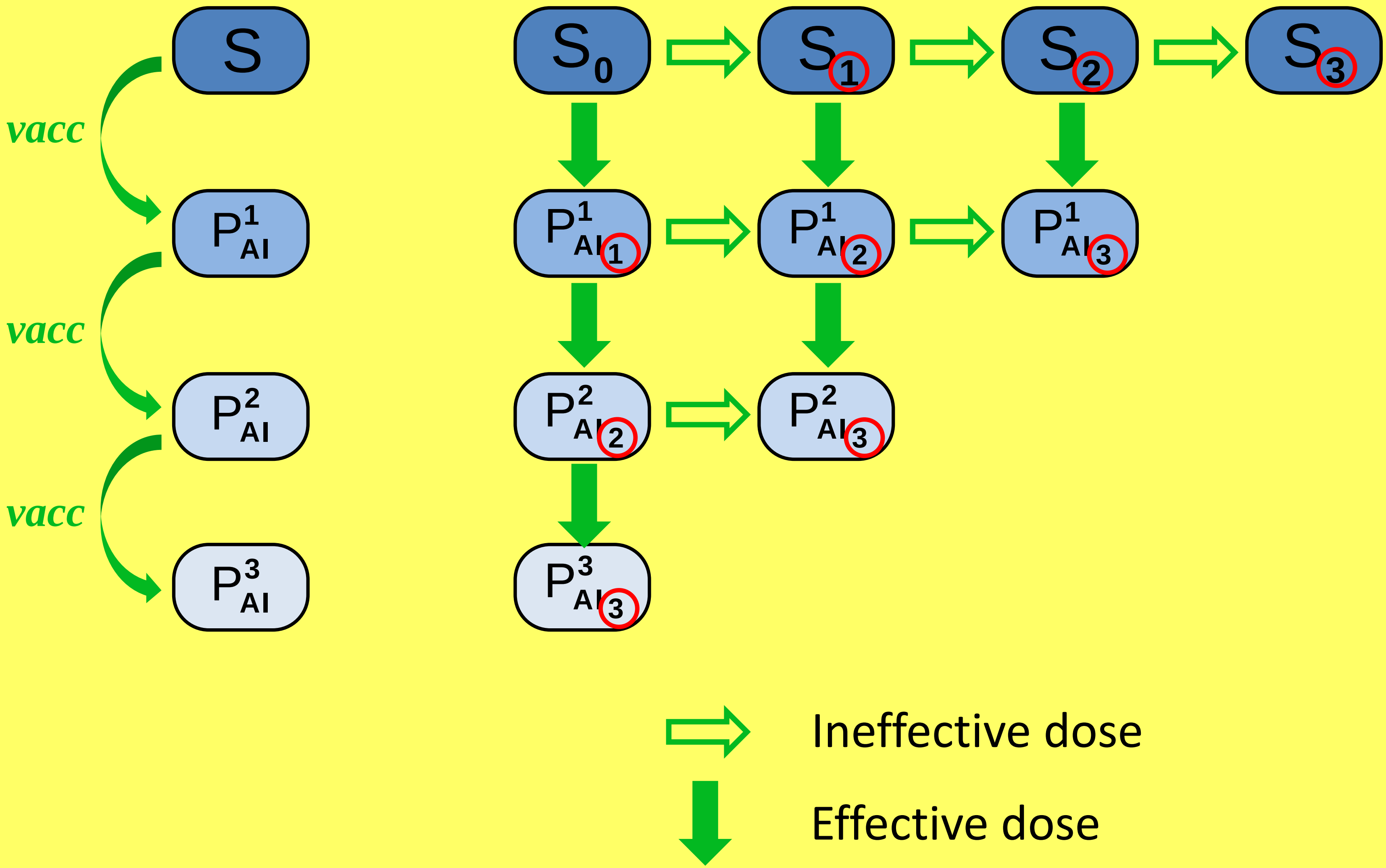


Previous model



Previous model

Present model: Extra classes to account for delayed vaccination



Mathematical modeling of delayed pertussis vaccination in infants.

P. Pesco, P.Bergero, G. Fabricius and D. Hozbor.

Vaccine **33**, 5475-5480 (2015).

Impact of delay reduction on infants (0-1y)

1) Urban region → not-delayed vaccination.
   [DTP3-cov=95%] [DTP3-cov=95%]

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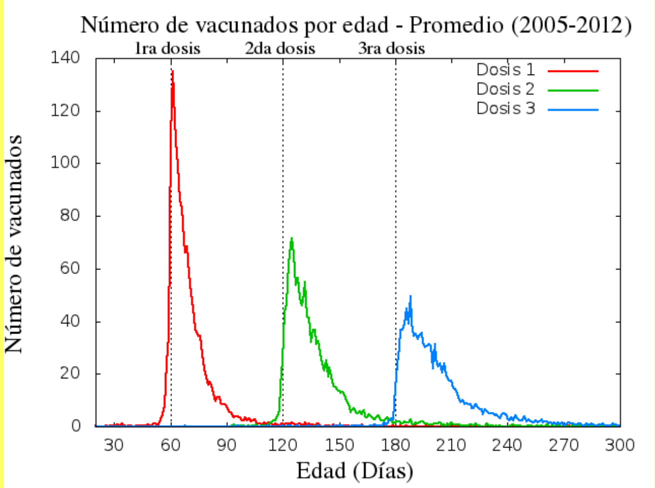

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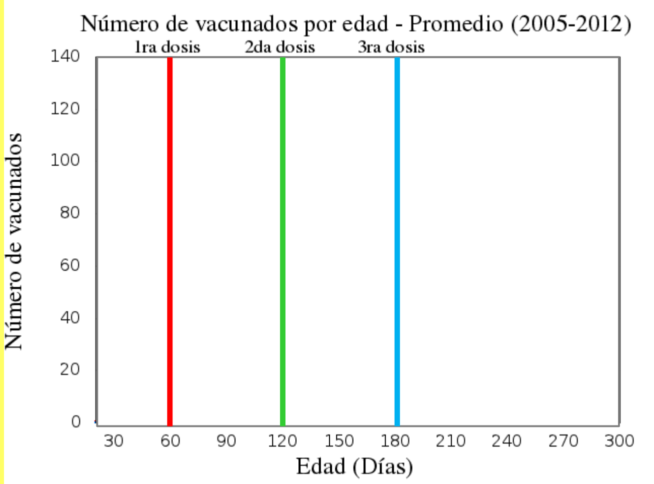

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20% drop in the severe+moderate cases
(15% drop in the severe cases)

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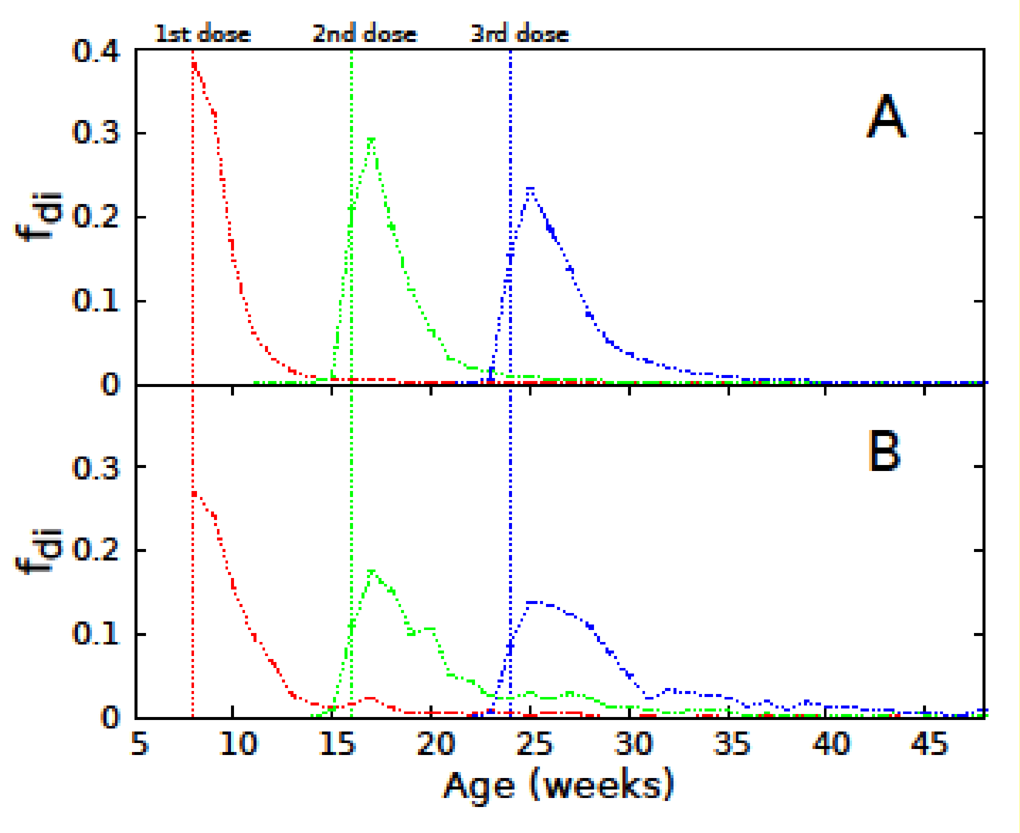
2) Suburban region → Urban region
   [DTP3-cov=87%] [DTP3-cov=95%]

Vaccination profiles for Urban and Suburban areas of La Plata city (800,000 inhabitants)

Urban

Suburban



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20% drop in the severe+moderate cases

(15% drop in the severe cases)

2) Suburban region → Urban region

[DTP3-cov=87%] [DTP3-cov=95%]

25% drop in the severe+moderate cases

(35% drop in the severe cases)

Incidences in the 0-1y age group (Inc1+Inc2=severe+mild) for delayed and not-delayed vaccination profiles for diferent epidemiological scenarios.

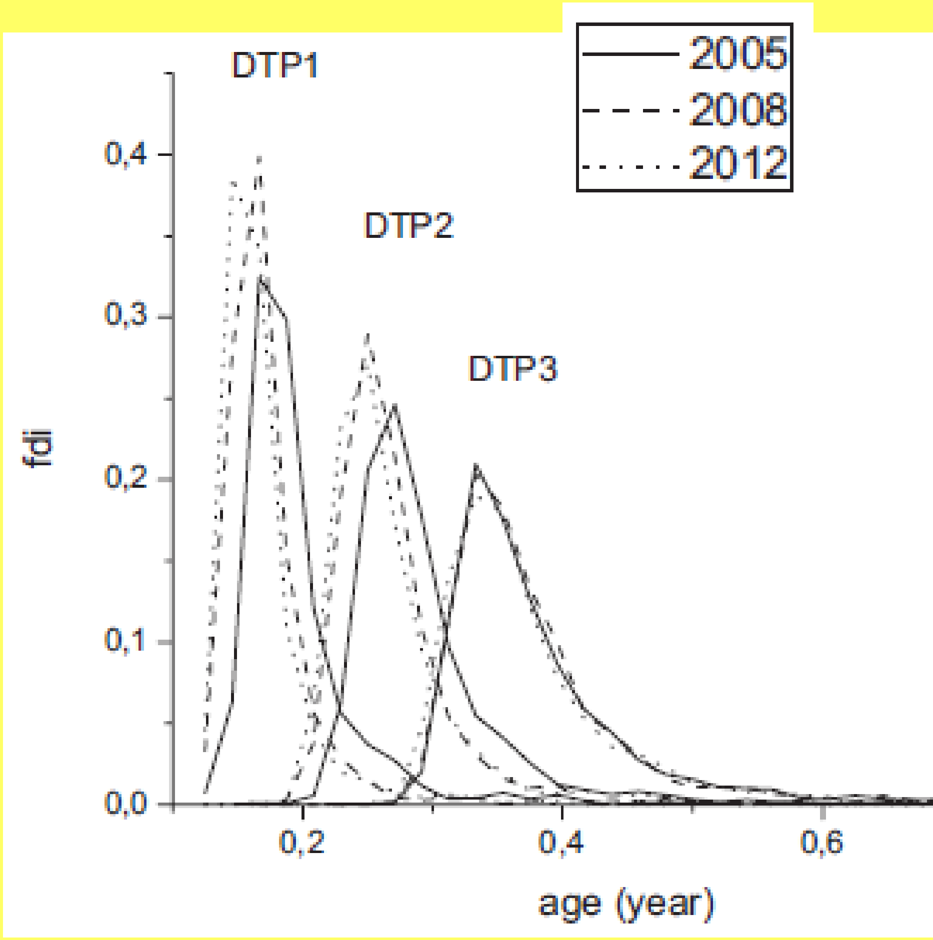
Scenario	Not Delayed (ND)	Delayed Urban (U)	Delayed Suburban (S)	Percentage improvement 100*(U-ND)/U	Percentage improvement 100*(S-U)/S
CP1A-SDI	15.1	18.9	26.5	19.9	28.7
CP1A-MDI	16.2	19.7	27.0	17.8	27.0
CP1A-LDI	15.5	18.5	25.2	16.4	26.5
CP1B-SDI	18.8	24.2	34.2	22.3	29.3
CP1B-MDI	21.0	26.0	35.2	19.2	26.2
CP1B-LDI	21.5	26.2	34.0	17.9	23.0
CP2-SDI	25.1	28.2	35.0	10.9	19.5
CP2-MDI	18.6	20.8	26.3	11.0	20.9
CP2-LDI	14.1	15.8	20.3	11.0	22.1

Our results *suggest* that for Argentina (at least) efforts should be directed to achieve **vaccination on time** an with **high coverages** for the risk age-group.

Communication strategy in Flanders (Belgium)

Change of the vacc. Schedule:

2–3–4 months → 8–12–16 weeks



Communication strategy in Flanders (Belgium)

The model predicts 15%-20% reduction of severe cases

Potential impact of changes in the schedule for primary DTP immunization as control strategy for pertussis.

P. Bergero, G. Fabricius, D. Hozbor, H. Theeten and N. Hens.

The Pediatric Infectious Disease Journal **37**, p e36-e42 (2018)

Evaluation of the introduction

of the booster to pregnant women

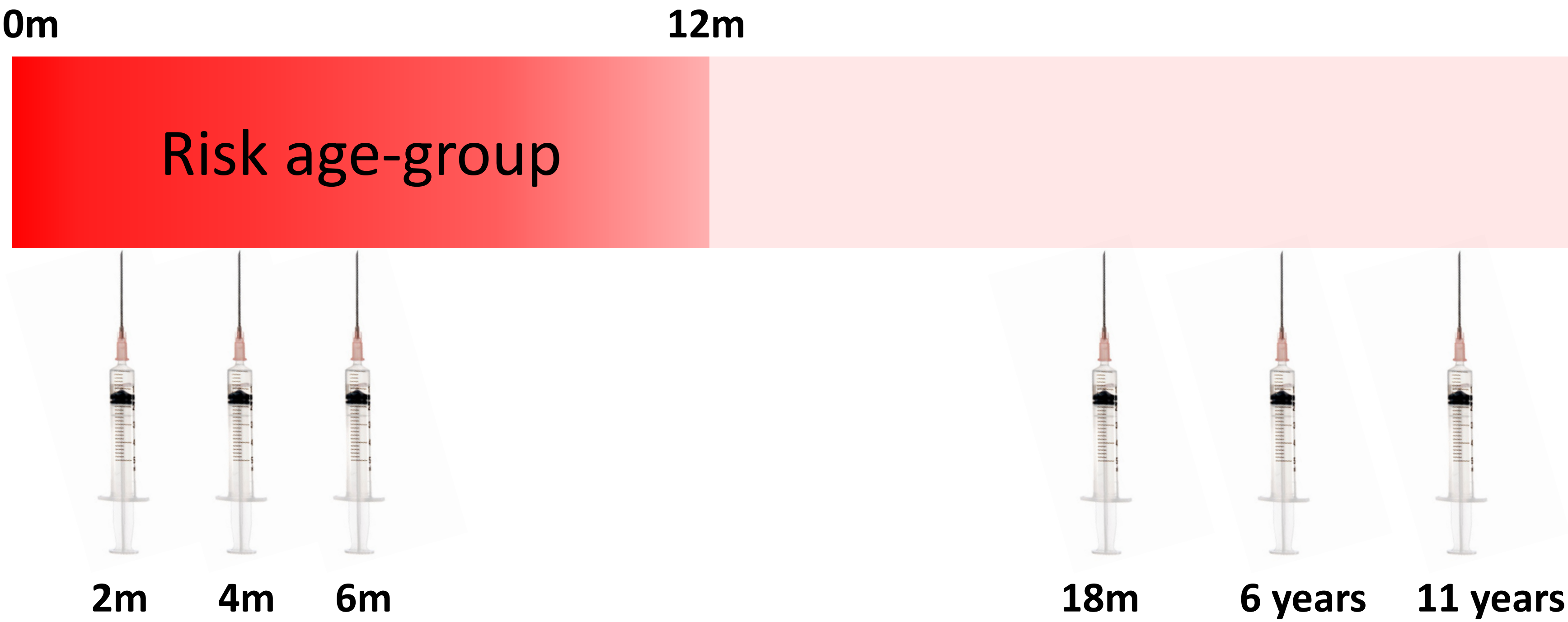
Several studies indicate that:

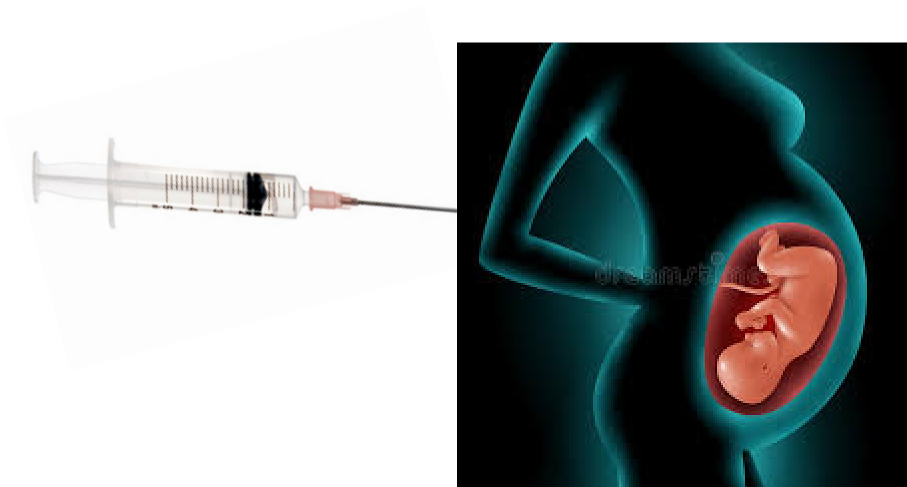
- Vaccination during pregnancy with a-celular vaccine (aP) is safe.
- aP induces high concentrations of antibodies during pregnancy that are transferred via the placenta to the fetus.
- 90% effectiveness in protecting neonates for 2 months from contracting *severe* pertussis

In 2011 the Advisory Committee on Immunization Practices (ACIP) from USA recommended vaccinating women during pregnancy with an acellular vaccine (aP).

In 2012 the booster was introduced in Argentina.

Anti-pertussis Argentinian vaccination Schedule 2012





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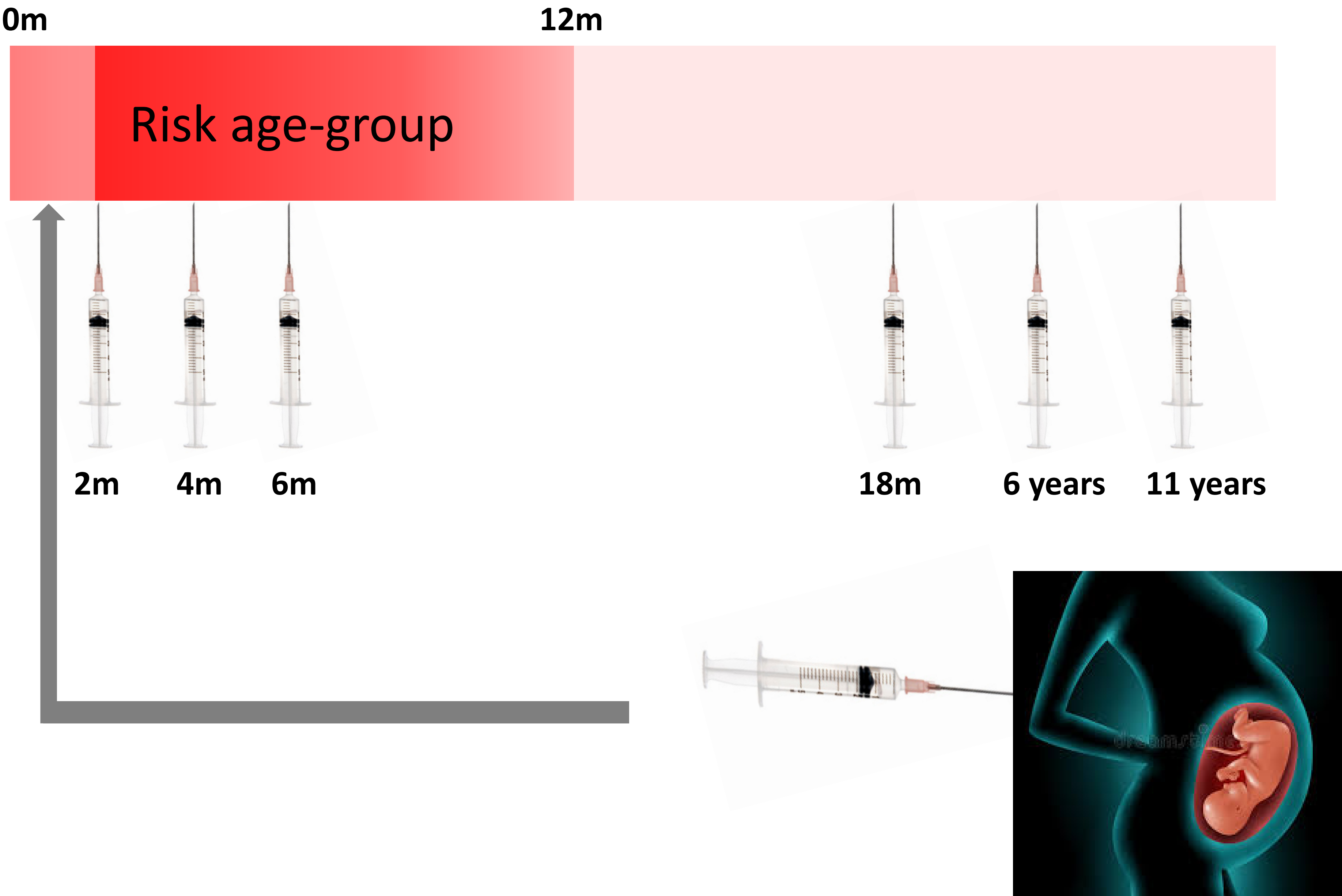
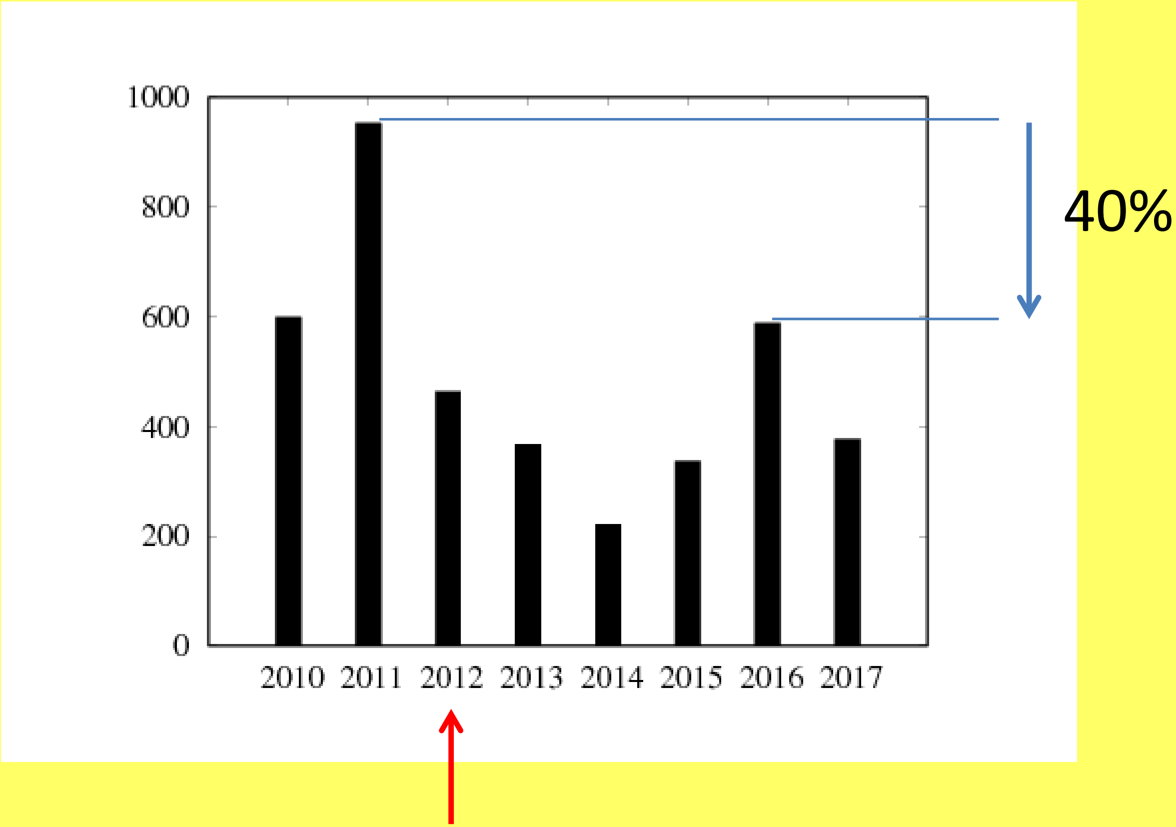


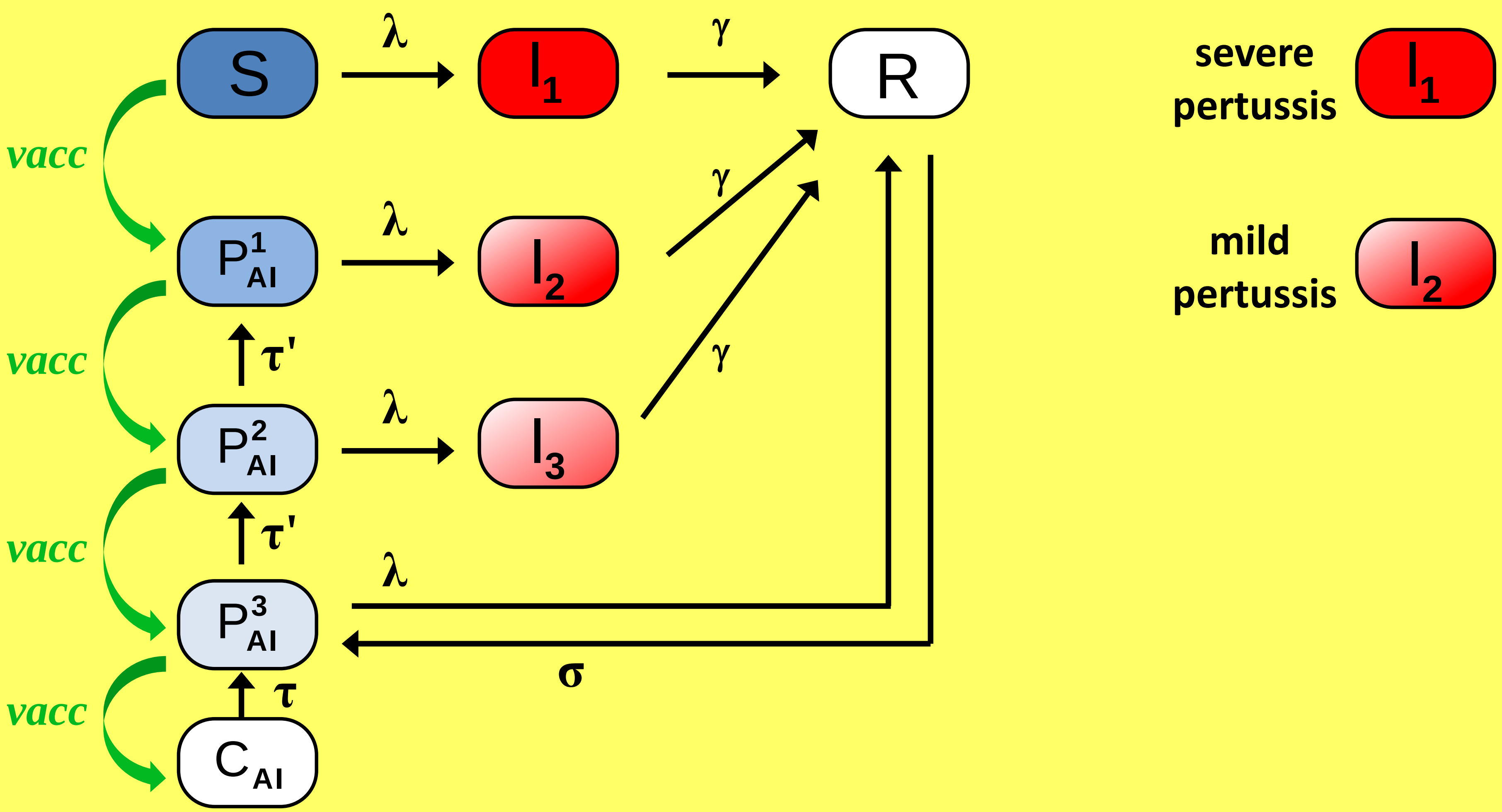
Confirmed pertussis cases in 0-12m age group

(VacSal- Prov.BsAs)



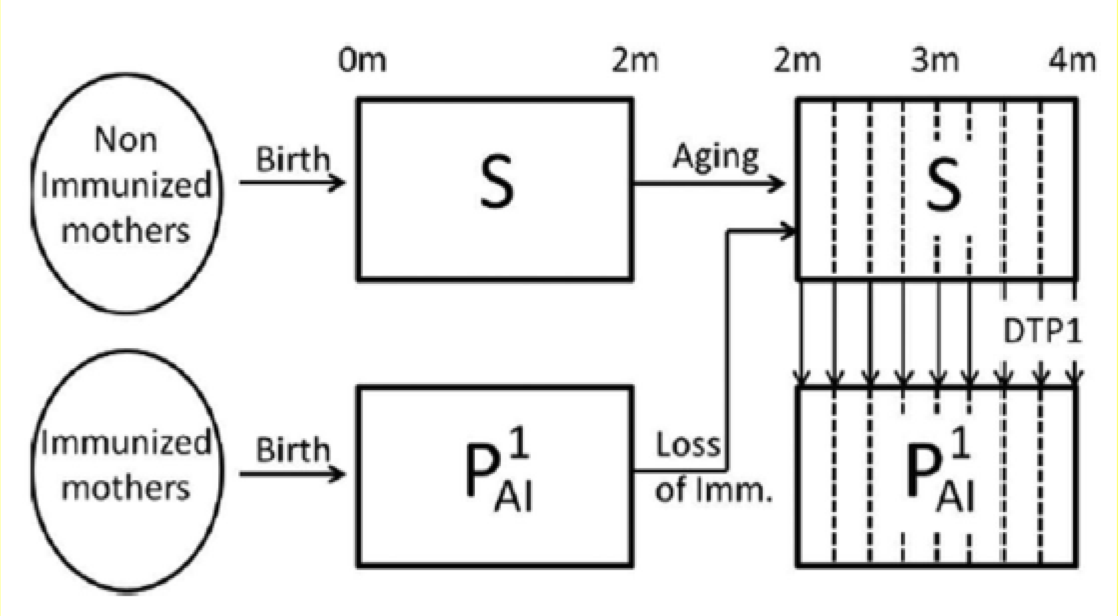
Introduction of maternal immunization

Previous pertussis transmission model



Hypothesis for the model:

Infants born from immunized mothers
get a *mild* form of the disease if they are infected
in the first two months of life.



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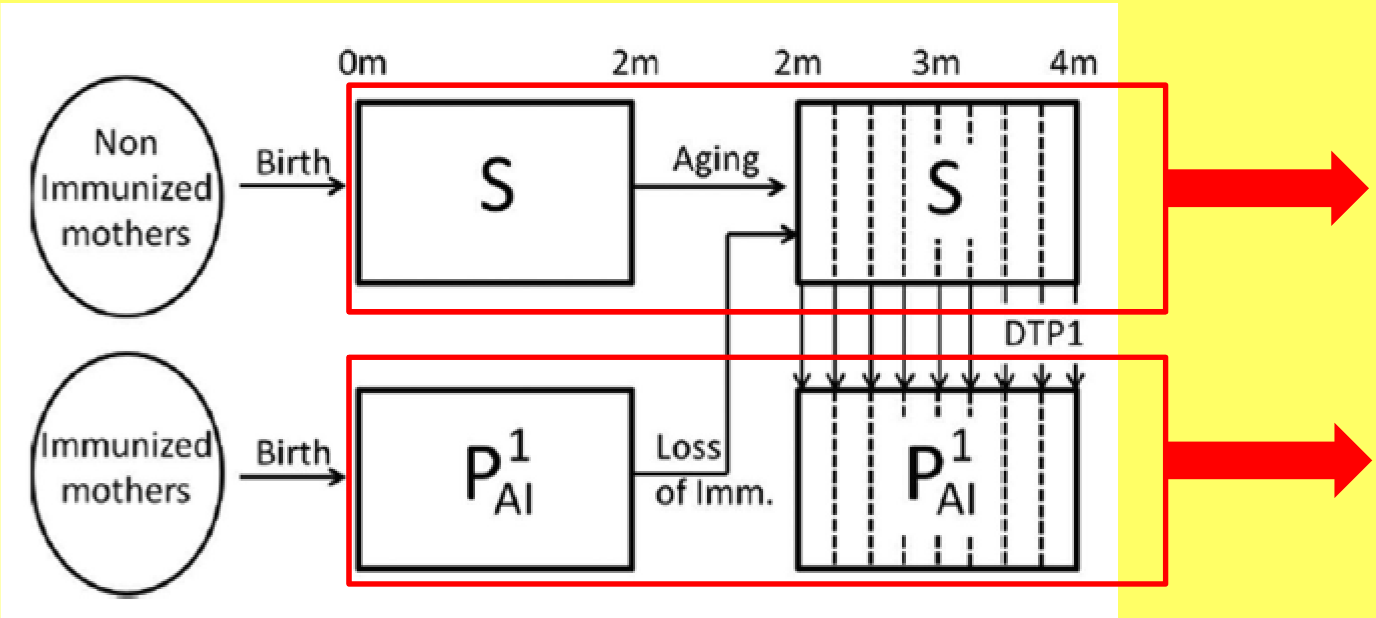
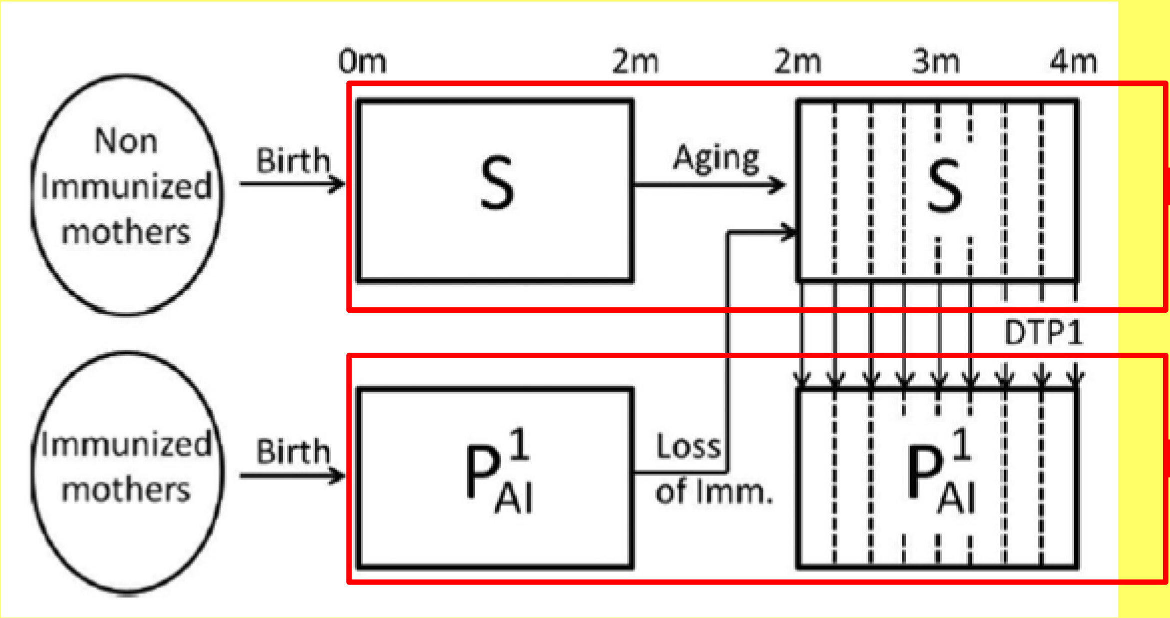


In contact with the pathogen:

Severe pertussis (I_1)

Mild pertussis (I_2)

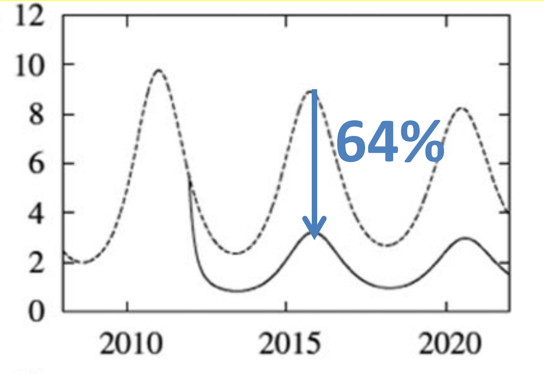


In contact with the pathogen:

Severe pertussis (I_1)

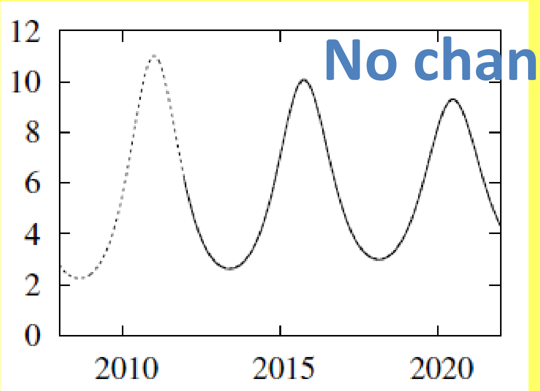
Mild pertussis (I_2)

Severe incidence:



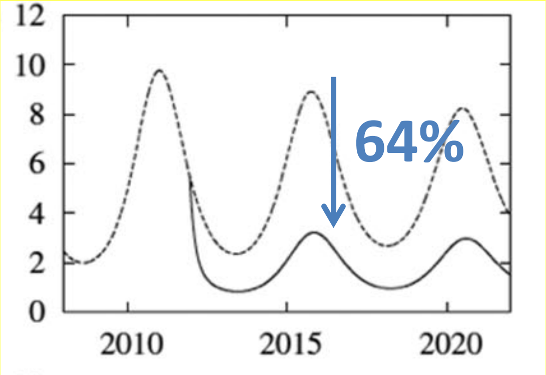
Model predictions for the 0-2months age group

Severe + mild incidences:



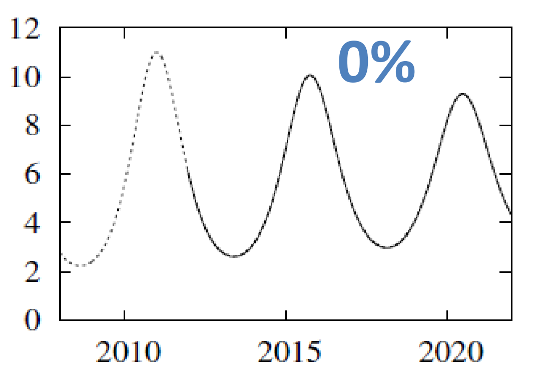
Model predictions:

Severe incidence:



0-2months

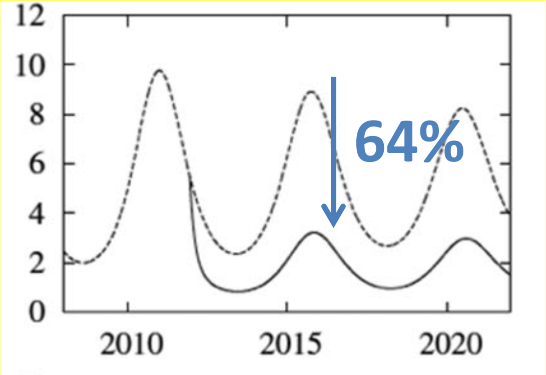
Severe + mild incidences:



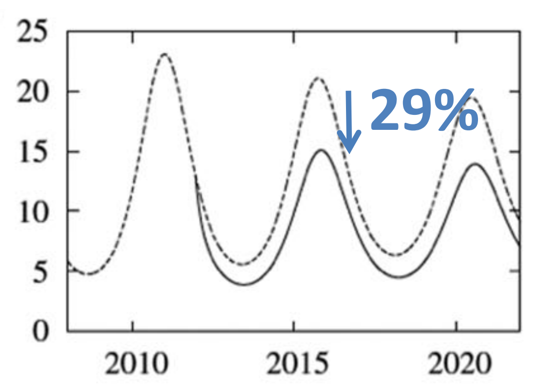
0-2months

Model predictions:

Severe incidence:

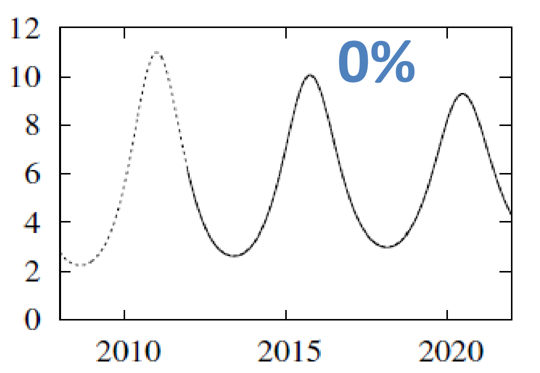


0-2months

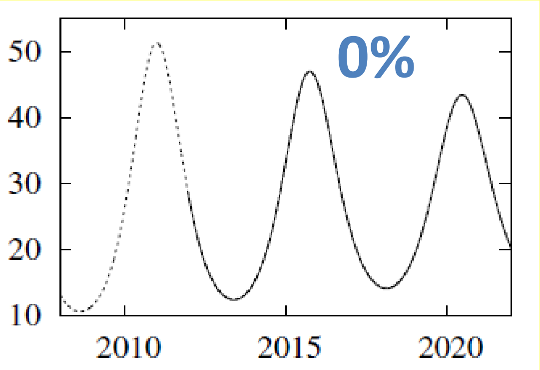


0-12months

Severe + mild incidences:

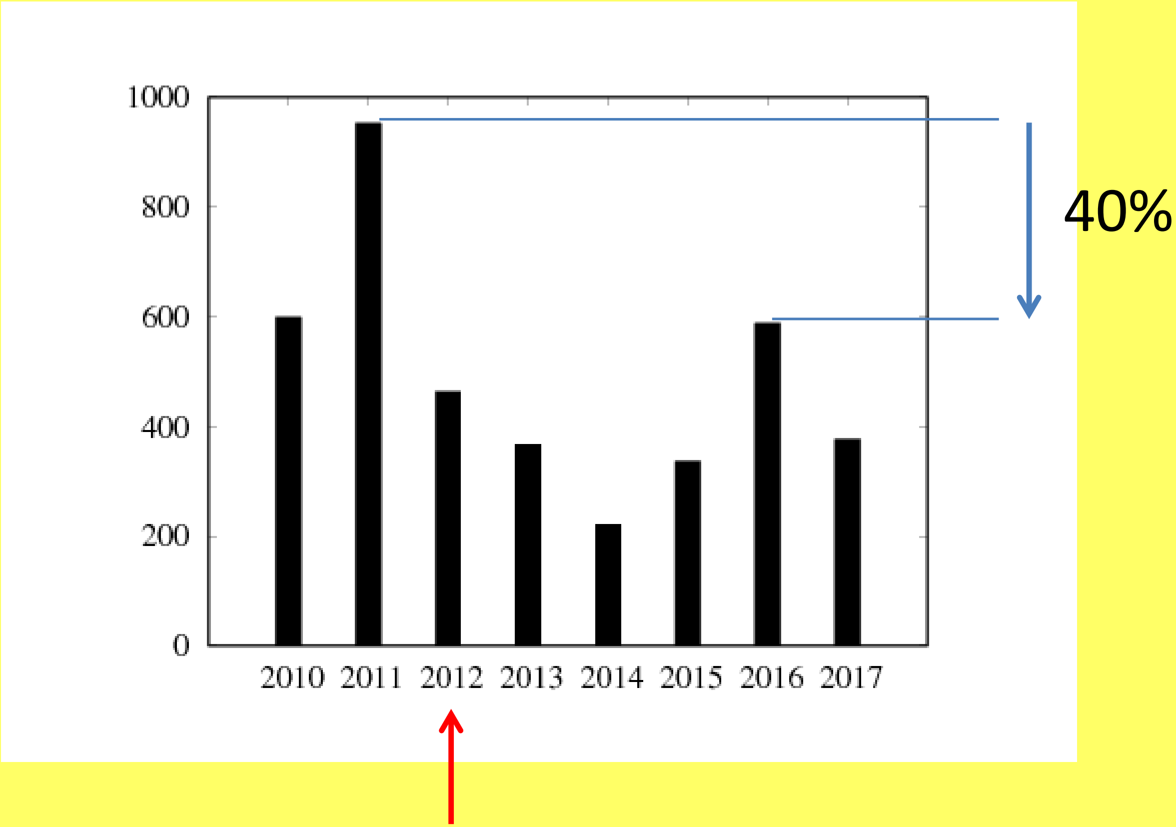


0-2months



0-12months

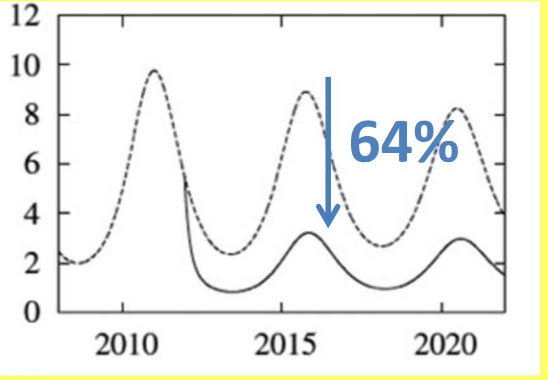
Confirmed pertussis cases in 0-12m age group
(VacSal- Prov.BsAs)



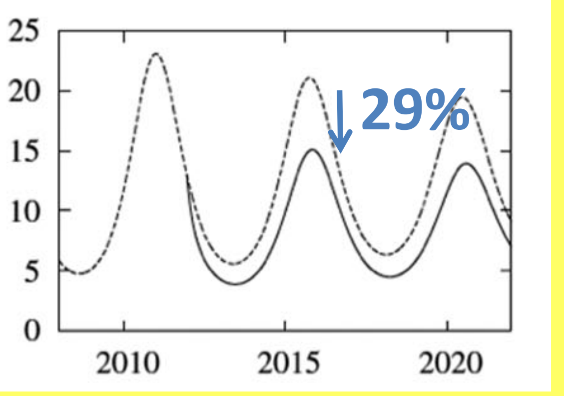
Introduction of maternal immunization

Model predictions:

Severe incidence:

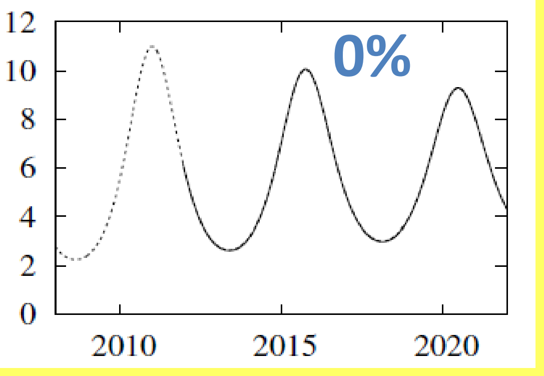


0-2months

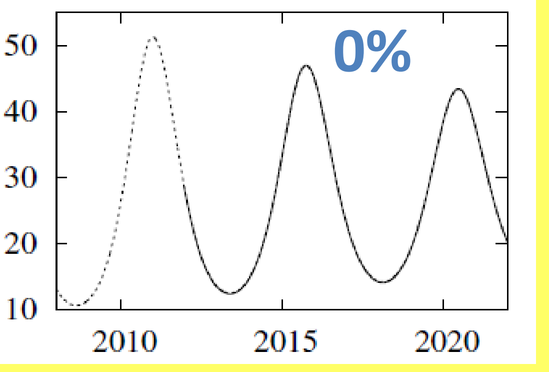


0-12months

Severe + mild incidences:



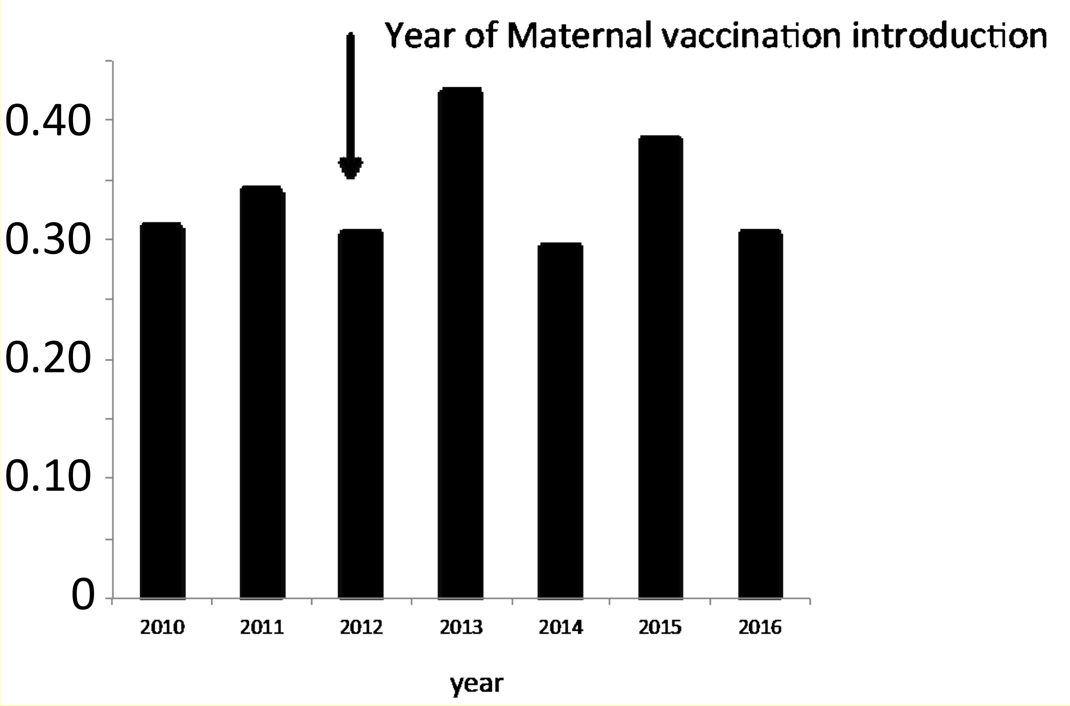
0-2months



0-12months

Confirmed pertussis cases (VacSal- Prov.BsAs)

Cases (0-2m)
/
Cases (0-12m)



Comparison of model results with epidemiological data

- There is under-reporting
- Under-reporting probably depends on many features
- For example, under-reporting is lower at the peaks, because surveillance increases at outbreaks

Then: → we compare data at the 2011 and 2016 peaks (outbreaks)

→ we consider that under-reporting

for 0-2m age group may be ≠ than for 0-12m age group

for severe cases may be ≠ than for mild cases

Reporting factor of a population group *g*

$$f_g^R = \frac{Inc_g^R}{Inc_g^A}$$

Reported incidence

Actual incidence

Calculated incidence

We consider 4 population groups:

Population group	Age	symptomatology
s,0-2	0-2 months	severe
m,0-2	0-2 months	mild
s,2-12	2-12 months	severe
m,2-12	2-12 months	mild

Then, the reported incidence in the 0-12m age group:

$$Inc^{R}_{0-12m} = Inc^{R}_{s,0-2} + Inc^{R}_{m,0-2} + Inc^{R}_{s,2-12} + Inc^{R}_{m,2-12}$$

Could be expressed in terms of the calculated incidences in each group and 4 independent reporting factors

Reporting factors

Reported incidences

Calculated incidences

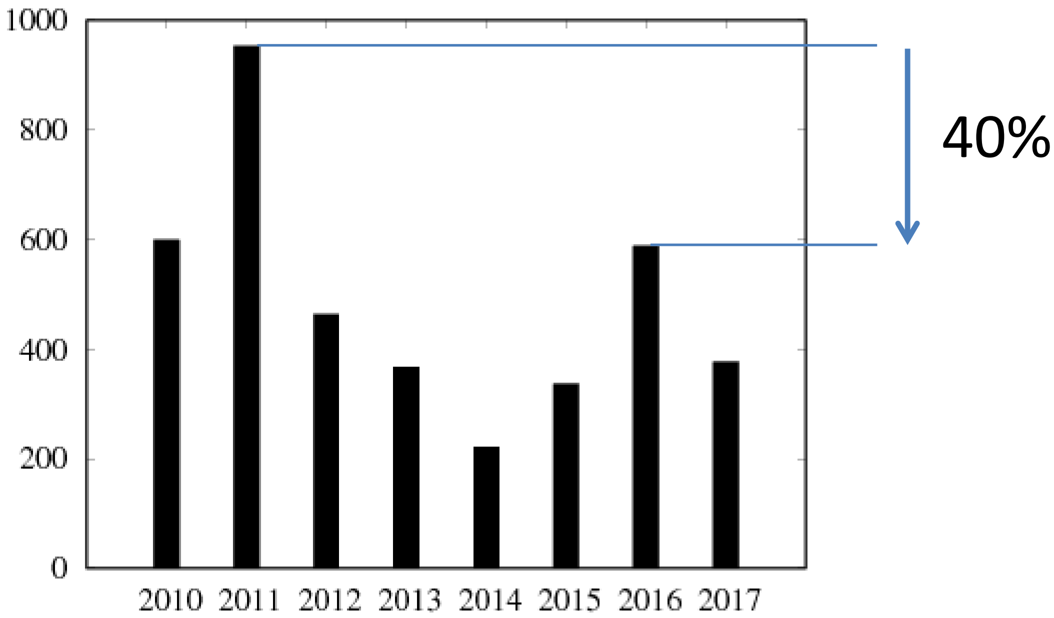
$$Inc^{R}_{s,0-2} = f_{s,0-2}\, Inc^{C}_{s,0-2}$$

$$Inc^{R}_{m,0-2} = f_{m,0-2}\, Inc^{C}_{m,0-2}$$

$$Inc^{R}_{s,0-12} = f_{s,0-12}\, Inc^{C}_{s,0-12}$$

$$Inc^{R}_{m,0-12} = f_{m,0-12}\, Inc^{C}_{m,0-12}$$

Confirmed pertussis cases in 0-12m age group
(VacSal- Prov.BsAs)



$$A = \frac{Inc^{R}_{0-12m}(2016)}{Inc^{R}_{0-12m}(2011)}$$

$$A = \frac{Inc^{C}_{s,0-2}(2016) + f_{symt}\ Inc^{C}_{m,0-2}(2016) + f_{age}\ Inc^{C}_{s,2-12}(2016) + \ f'_{symt}\ f_{age}\ Inc^{C}_{m,2-12}(2016)}{Inc^{C}_{s,0-2}(2011) + f_{symt}\ Inc^{C}_{m,0-2}(2011) + f_{age}\ Inc^{C}_{s,2-12}(2011) + \ f'_{symt}\ f_{age}\ Inc^{C}_{m,2-12}(2011)}$$

$$f_{age} = {f^{R}_{s,2-12}}\big/{f^{R}_{s,0-2}} \qquad f_{symp} = {f^{R}_{m,0-2}}\big/{f^{R}_{s,0-2}} \qquad f'_{symp} = {f^{R}_{m,2-12}}\big/{f^{R}_{s,2-12}}$$

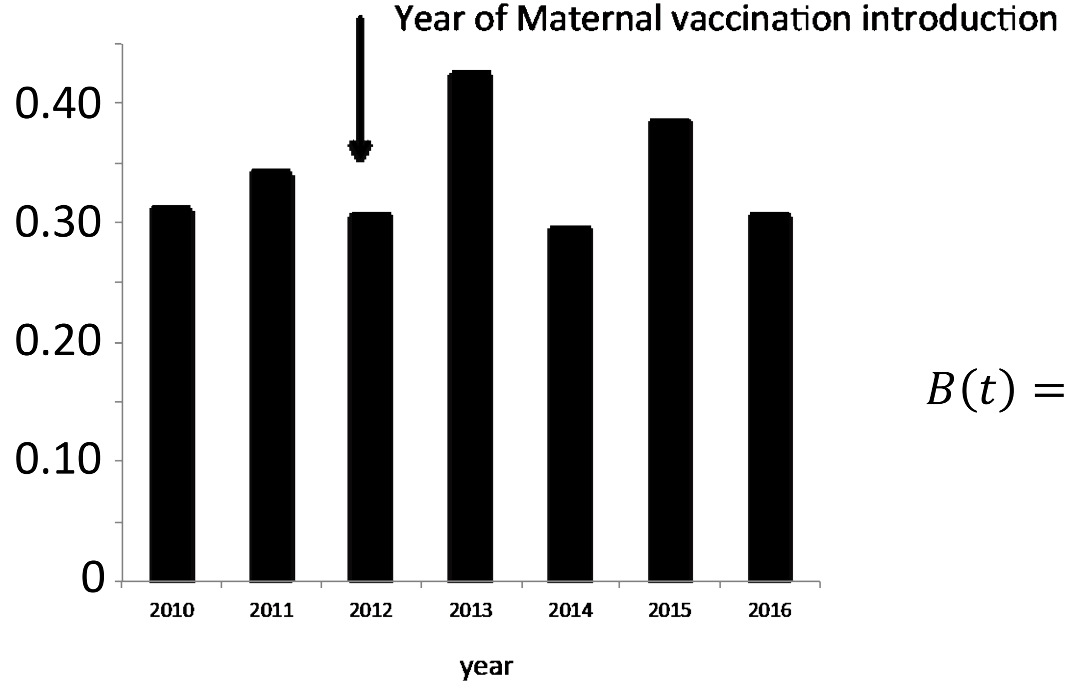
$$f_{age} = f^R_{s,2-12} / f^R_{s,0-2} \qquad f_{symp} = f^R_{m,0-2} / f^R_{s,0-2} \qquad f'_{symp} = f^R_{m,2-12} / f^R_{s,2-12}$$

$$0 \leq \; f_{age}, f_{symp}, f'_{symp} \; \leq 1$$

We search for the region: $\left(f_{age}, f_{symp}, f'_{symp} \right)$

that satisfies: $0.55 \leq A\left(f_{age}, f_{symp}, f'_{symp} \right) \leq 0.65$

$$\frac{\text{Cases (0-2m)}}{\text{Cases (0-12m)}}$$



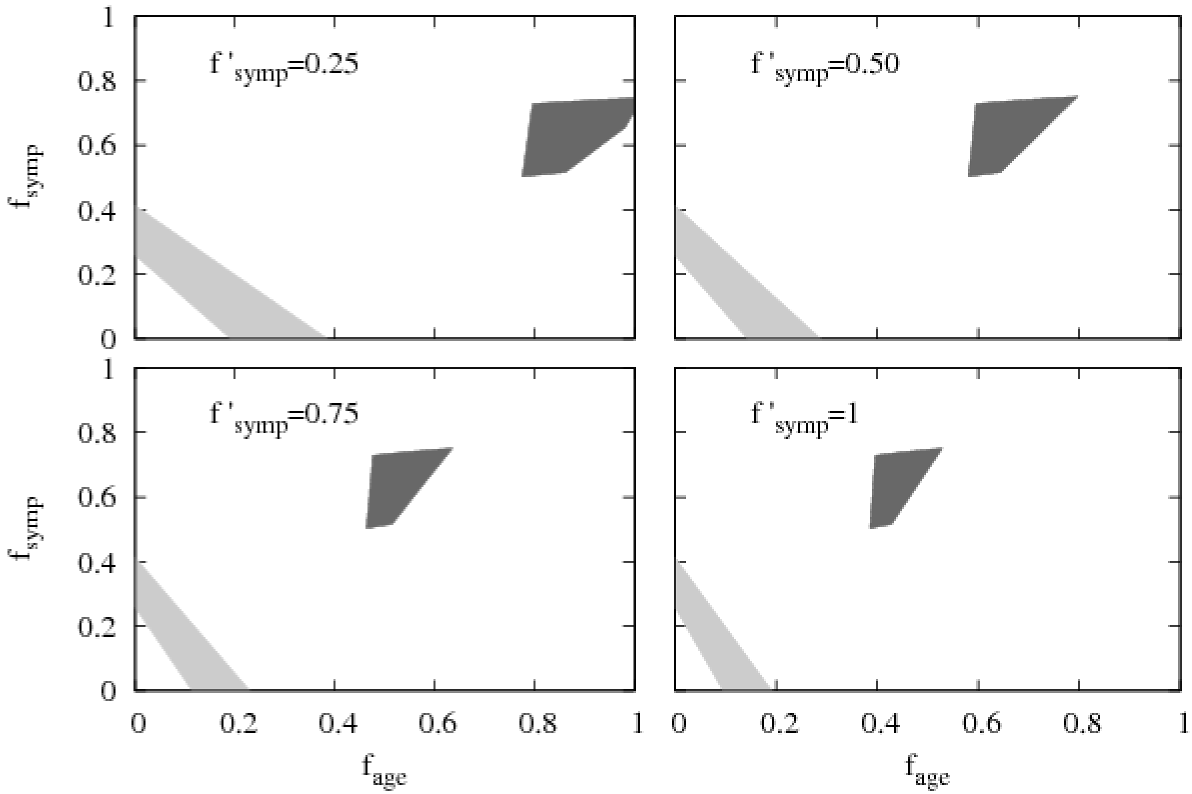
$$B(t) = \frac{Inc^{R}_{0-2m}(t)}{Inc^{R}_{0-12m}(t)}$$

$$B(t) = \frac{Inc^{C}_{s,0-2}(t) + f_{symp}\, Inc^{C}_{m,0-2}(t)}{Inc^{C}_{s,0-2}(t) + f_{symp}\, Inc^{C}_{m,0-2}(t) + f_{age}\, Inc^{C}_{s,2-12}(t) + f'_{symp}\, f_{age}\, Inc^{C}_{m,2-12}(t)}$$

$$0.30 \leq B(f_{age}, f_{symp}, f'_{symp}, 2011) \leq 0.40$$

$$0.30 \leq B(f_{age}, f_{symp}, f'_{symp}, 2016) \leq 0.40$$

Compatibility of epidemiological data with the results of the calculations



$$f_{age} = f^R_{s,2-12} \Big/ f^R_{s,0-2}$$

$$f_{symp} = f^R_{m,0-2} \Big/ f^R_{s,0-2}$$

$$f'_{symp} = f^R_{m,2-12} \Big/ f^R_{s,2-12}$$

$$0.55 \leq A\,(f_{age}, f_{symp}, f'_{symp}) \leq 0.65$$

$$A = \frac{Inc^R_{0-12m}(2016)}{Inc^R_{0-12m}(2011)}$$

$$0.30 \leq B(f_{age}, f_{symp}, f'_{symp}, 2011) \leq 0.40$$

$$0.30 \leq B(f_{age}, f_{symp}, f'_{symp}, 2016) \leq 0.40$$

$$B(t) = \frac{Inc^R_{0-2m}(t)}{Inc^R_{0-12m}(t)}$$

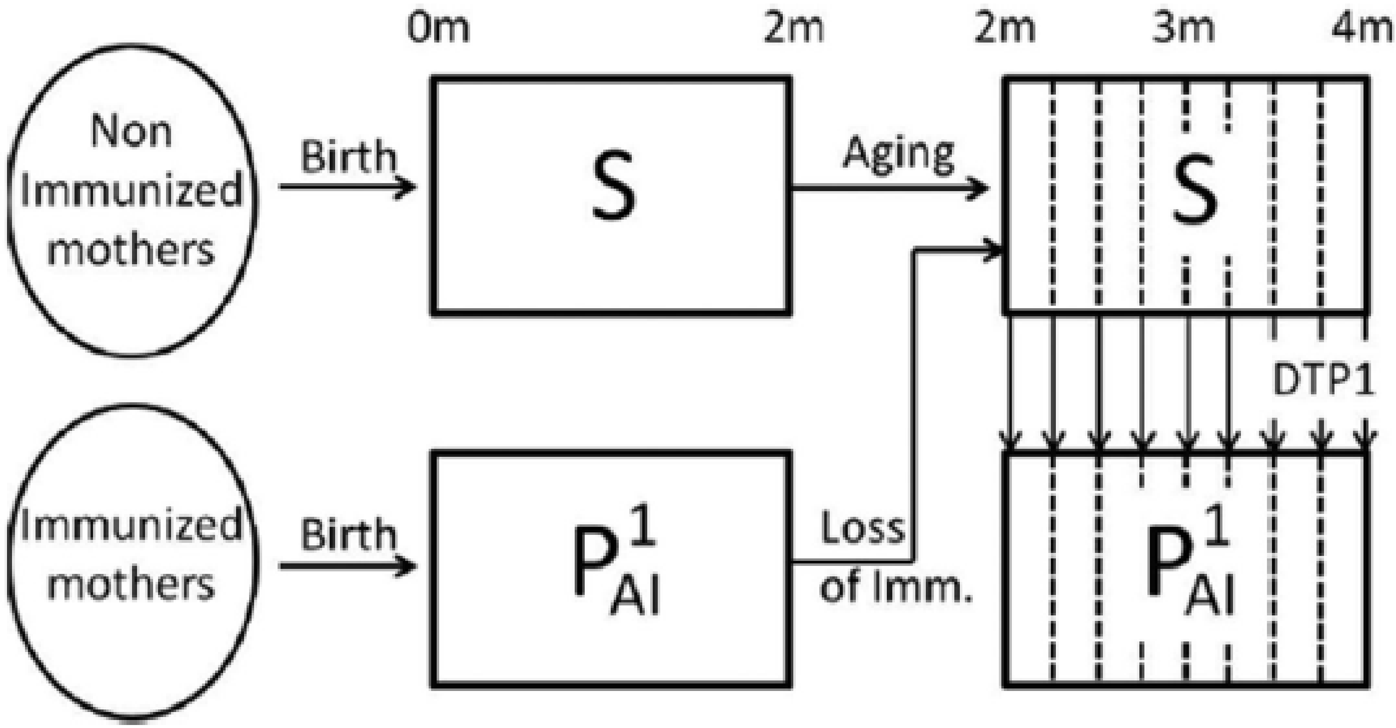
We review the hypotheses of the model

Baxter R, et al. (2017) Pediatrics **139**, e20164091

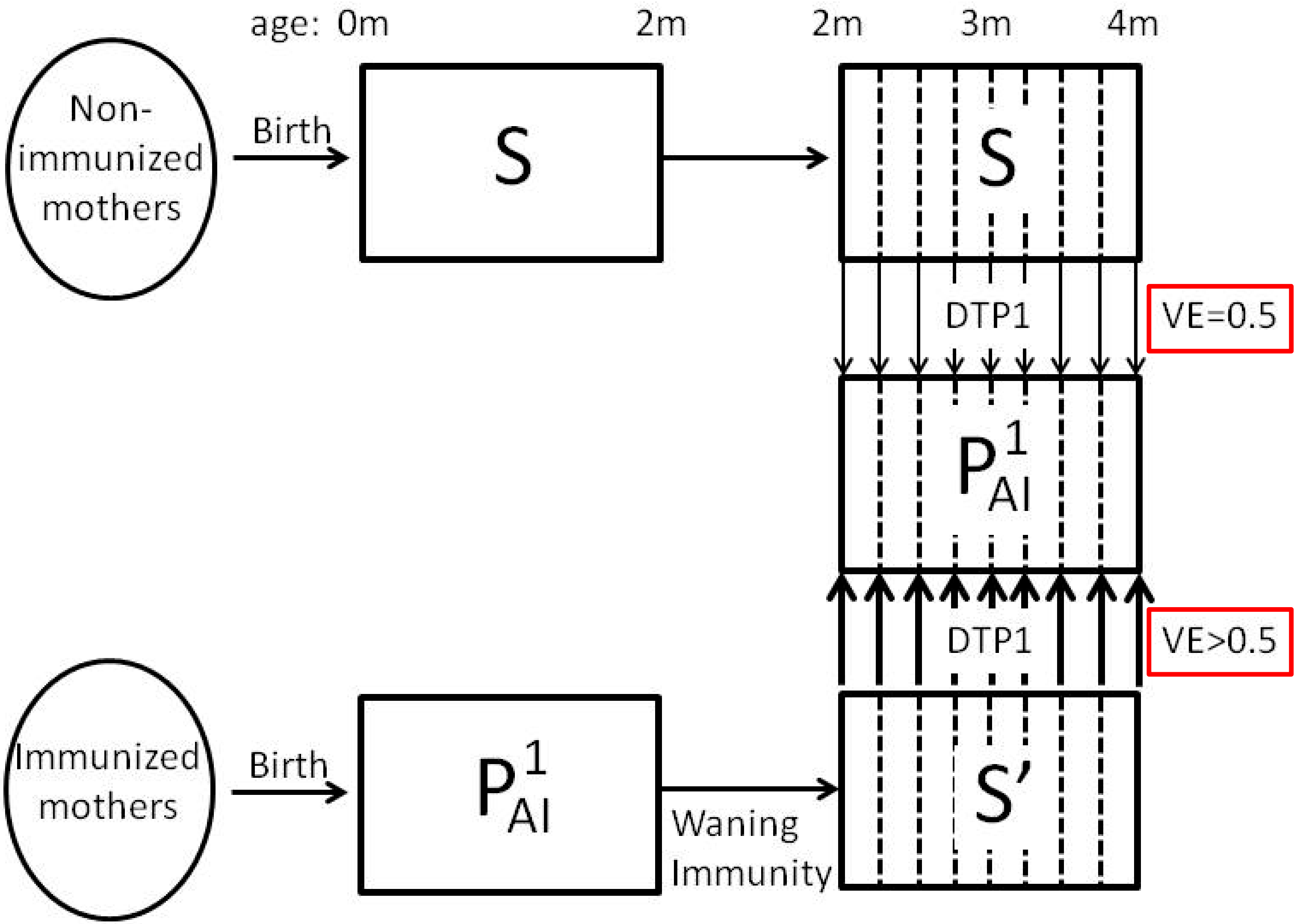
“Effectiveness of vaccination during pregnancy to prevent infant pertussis."

- They studied the effect of Tdap in 0-12m infants (California).
- They found that Tdap effects go beyond 2months, in particular, in infants that have received the 1st DTP dose.

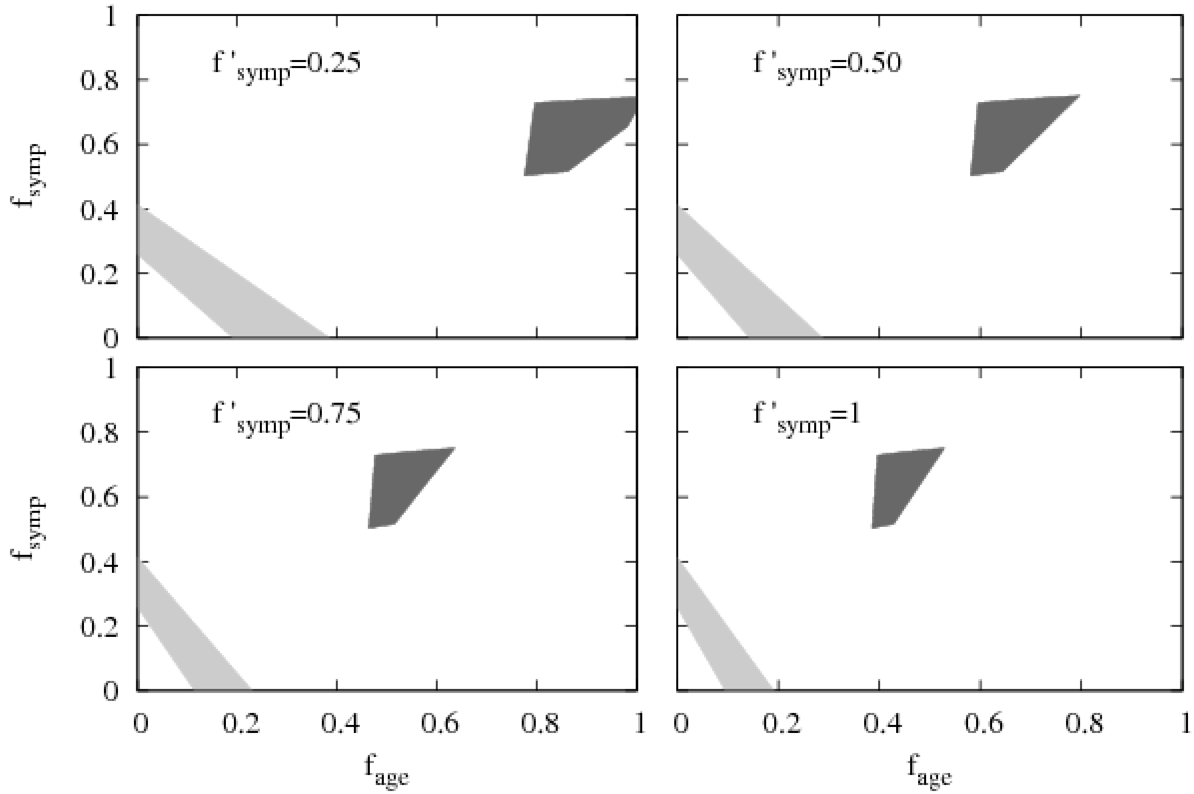
Original model: protective effects of Tdap up to 2 months



Modified model: DTP1 is more effective for chidren of immun.mothers

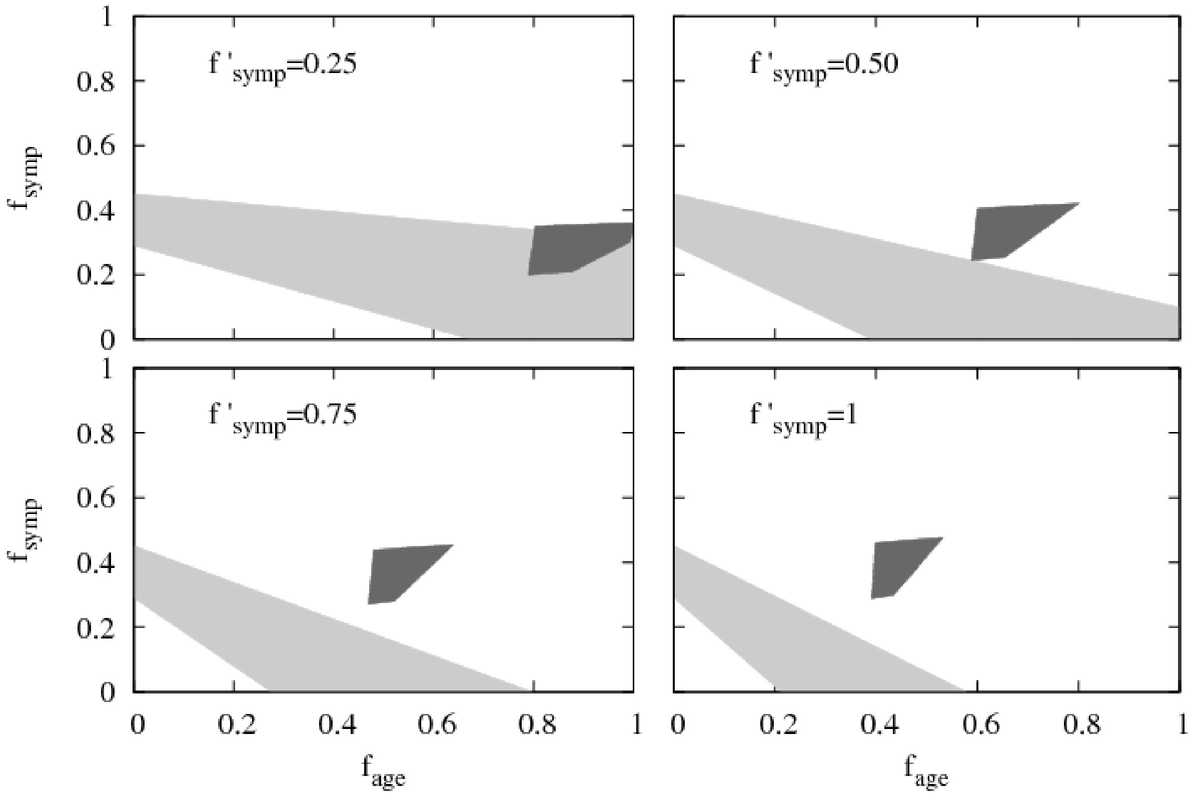


Compatibility of epidemiological data with the results of the calculations



Maternal immunization → protection to 0-2m infants (only)

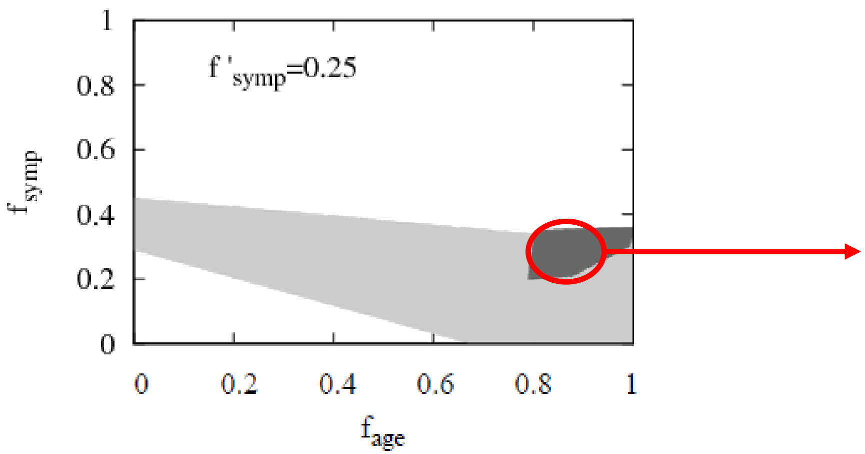
Compatibility of epidemiological data with the results of the calculations



Maternal immunization → protection to 0-2m infants

→ + increased effectiveness of DTP1 (>2m)

Compatibility of epidemiological data with the results of the calculations



$$f_{age} = {f^R_{s,2-12}}\Big/{f^R_{s,0-2}} \approx 0.85$$

$$f_{symp} = {f^R_{m,0-2}}\Big/{f^R_{s,0-2}} \approx 0.35$$

$$f'_{symp} = {f^R_{m,2-12}}\Big/{f^R_{s,2-12}} \approx 0.25$$

$$f_{age} = {f^R_{s,2-12}}\Big/{f^R_{s,0-2}} \approx 0.85$$

$$f_{symp} = {f^R_{m,0-2}}\Big/{f^R_{s,0-2}} \approx 0.35$$

$$f'_{symp} = {f^R_{m,2-12}}\Big/{f^R_{s,2-12}} \approx 0.25$$

CONCLUSION:

Comparison of the **model results** with **epidemiological data** suggests that maternal immunization would have a protective effect in infants born from immunized mothers *beyond 2 months*.

G. Fabricius, PM Aispuro P, P. Bergero, M. Gabrielli, D. Bottero, and D.Hozbor. "Pertussis epidemiology in Argentina: trends after the introduction of maternal immunization."
Epidemiology and Infection **146**, 858-866 (2018).

Thank you !

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