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

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Projects

→ Control of pertussis transmission

→ Risk of measles introduction in BsAs

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

- Control of pertussis transmission
- Risk of measles introduction in BsAs
- Stochastic fluctuations in *simple models of disease transmission* (endemic & epidemic)
Interdisciplinary project

Liliana Lazo     |     Alberto Maltz (mathematician)
Paula Bergero   |     physicists
Gabriel Fabricius

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:
  → adolescent 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
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

Pertussis incidence increase for teenagers

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

The model represents the disease progression from susceptible (S) to infected (I) to removed (R) states. The transitions are governed by parameters $\lambda$ and $\gamma$. The susceptibility to infection is denoted by $vacc$. The disease dynamics are influenced by parameters $P_{AI}^1$, $P_{AI}^2$, $P_{AI}^3$, and $C_{AI}$.
Pertussis transmission model

\[ S \xrightarrow{\lambda} I \xrightarrow{\gamma} R \]

\[ \tau' \]

\[ \tau \]

\[ C_{AI} \]

\[ P^1_{AI} \]

\[ P^2_{AI} \]

\[ P^3_{AI} \]
Pertussis transmission model

\[ S \xrightarrow{\lambda} I_1 \xrightarrow{\gamma} R \]

\[ P^1_{Al} \xrightarrow{\lambda} I_2 \]

\[ P^2_{Al} \xrightarrow{\lambda} I_3 \]

\[ P^3_{Al} \xrightarrow{\tau'} \]

\[ C_{Al} \xrightarrow{\tau} \]

\[ \text{vacc} \]

\[ \text{vacc} \]

\[ \text{vacc} \]

\[ \text{vacc} \]
Pertussis transmission model

\[ \lambda = \beta I^* \]

\[ I^* = I_1 + \rho I_2 + \rho' I_3 \]

\[ \rho < \rho' < 1 \]
Pertussis transmission model

\[ S \xrightarrow{\lambda} I_1 \xrightarrow{\gamma} R \]

\[ P_{Ai}^1 \xrightarrow{\lambda} I_2 \xrightarrow{\gamma} I_3 \]

\[ P_{Ai}^2 \xrightarrow{\lambda} I_2 \]

\[ P_{Ai}^3 \xrightarrow{\lambda} I_3 \]

\[ C_{Ai} \xrightarrow{\tau} P_{Ai}^3 \]

\[ \sigma \gg \tau \approx \tau' \]

Acquired immunity via vacc. is lost at rates \( \tau, \tau' \)

Natural acquired immunity is lost at rate \( \sigma \)
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
Effective applied dose

- dose: not applied
- or
- not effective
Effective applied dose

dose: not applied
or
not effective
This way of introducing vaccination in compartmental models was used by Hethcote


“An Age-Structured Model for pertussis transmission”
Force of infection: \( \lambda_i \)

is the rate at which individuals in classes \( S, P_{A1}^1 \) and \( P_{A1}^2 \), age-group \( i \), acquire infection.

\[
\lambda_i = \sum_{j=1}^{N} \beta_{i,j} \left( I_1^j + \rho I_2^j + \rho' I_3^j \right)
\]

Contact parameter matrix
\[
\begin{align*}
\frac{dS_i}{dt} &= -\lambda_i S_i + \sigma_0 P^1_{Al_i} - \mu_i S_i + c_{i-1}(1 - vacc_i)S_{i-1} - c_i S_i + \delta_{i0} B \\
\frac{dP^1_{Al_i}}{dt} &= -\lambda_i P^1_{Al_i} - \sigma_0 P^1_{Al_i} + \tau' P^2_{Al_i} - \mu_i P^1_{Al_i} + c_{i-1}(1 - vacc_i)P^1_{Al_{i-1}} - c_i P^1_{Al_i} + c_{i-1}vacc_i S_{i-1} \\
\frac{dP^2_{Al_i}}{dt} &= -\lambda_i P^2_{Al_i} - \tau' P^2_{Al_i} + \tau' P^3_{Al_i} - \mu_i P^2_{Al_i} + c_{i-1}(1 - vacc_i)P^2_{Al_{i-1}} - c_i P^2_{Al_i} + c_{i-1}vacc_i P^1_{Al_{i-1}} \\
\frac{dP^3_{Al_i}}{dt} &= -\lambda_i P^3_{Al_i} - \tau' P^3_{Al_i} + \tau C_{Al_i} - \mu_i P^3_{Al_i} + \sigma R + c_{i-1}(1 - vacc_i)P^3_{Al_{i-1}} - c_i P^3_{Al_i} + c_{i-1}vacc_i P^2_{Al_{i-1}} \\
\frac{dC_{Al_i}}{dt} &= -\tau C_{Al_i} - \mu_i C_{Al_i} + c_{i-1} C_{Al_{i-1}} - c_i C_{Al_i} + c_{i-1}vacc_i P^3_{Al_{i-1}} \\
\frac{dI^1_{1i}}{dt} &= \lambda_i S_i - \gamma I^1_{1i} - \mu_i I^1_{1i} + c_{i-1} I^1_{1i-1} - c_i I^1_{1i} \\
\frac{dI^2_{2i}}{dt} &= \lambda_i P^1_{Al_i} - \gamma I^2_{2i} - \mu_i I^2_{2i} + c_{i-1} I^2_{2i-1} - c_i I^2_{2i} \\
\frac{dI^3_{3i}}{dt} &= \lambda_i P^2_{Al_i} - \gamma I^3_{3i} - \mu_i I^3_{3i} + c_{i-1} I^3_{3i-1} - c_i I^3_{3i} \\
\frac{dR_i}{dt} &= \lambda_i P^3_{Al_i} + \gamma (I^1_{1i} + I^2_{2i} + I^3_{3i}) - \sigma R - \mu_i R + c_{i-1} R_{i-1} - c_i R_i \\
\end{align*}
\]

\(i = 1, \ldots, 30\)
Model Parameters

Diferent methods

Diferentes sources of data
$\beta_{ij}$ : WAIFW matrixes +

Forces of infection from:

**Pre-vaccine era**


**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


“Social contacts and mixing patterns 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.

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

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

<5% drop in the severe+moderate cases
DTP3-coverage, Argentina

Number of vaccinated individuals per dose by age

Ideal situation: no delay
Number of vaccinated 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

\[ \text{S} \xrightarrow{\lambda} \text{I}_1 \xrightarrow{\gamma} \text{R} \]

\[ \text{P}^1_{AI} \xrightarrow{\lambda} \text{I}_2 \]

\[ \text{P}^2_{AI} \xrightarrow{\lambda} \text{I}_3 \]

\[ \text{P}^3_{AI} \]

\[ \text{C}_{AI} \]

\[ \text{vacc} \]

\[ \tau' \]

\[ \lambda \]

\[ \gamma \]

\[ \sigma \]
Previous model

\[ S \]

\[ P^1_{AI} \]

\[ P^2_{AI} \]

\[ P^3_{AI} \]
Previous model

Present model: Extra classes to account for delayed vaccination

Effective dose

Ineffective dose
Mathematical modeling of delayed pertussis vaccination in infants.


Vaccine 33, 5475-5480 (2015).
Impact of delay reduction on infants (0-1y)

1) Urban region $\rightarrow$ not-delayed vaccination.
   \[DTP3\text{-cov}=95\%\] $\rightarrow$ [DTP3\text{-cov}=95\%]
Impact of delay reduction on infants (0-1y)

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

**Diagram 1:**
- Horizontal axis: Age (Días)
- Vertical axis: Number of vaccinated

**Diagram 2:**
- Horizontal axis: Age (Días)
- Vertical axis: Number of vaccinated

- 1st dose
- 2nd dose
- 3rd dose
Impact of delay reduction on infants (0-1y)

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

   20% drop in the severe+moderate cases
   (15% drop in the severe cases)
Impact of delay reduction on infants (0-1y)

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

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

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

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

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

2) Suburban region  →  Urban region
   [DTP3-cov=87%]                                     [DTP3-cov=95%]
Impact of delay reduction on infants (0-1y)

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Not Delayed (ND)</th>
<th>Delayed Urban (U)</th>
<th>Delayed Suburban (S)</th>
<th>Percentage improvement 100*(U-ND)/U</th>
<th>Percentage improvement 100*(S-U)/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP1A-SDI</td>
<td>15.1</td>
<td>18.9</td>
<td>26.5</td>
<td>19.9</td>
<td>28.7</td>
</tr>
<tr>
<td>CP1A-MDI</td>
<td>16.2</td>
<td>19.7</td>
<td>27.0</td>
<td>17.8</td>
<td>27.0</td>
</tr>
<tr>
<td>CP1A-LDI</td>
<td>15.5</td>
<td>18.5</td>
<td>25.2</td>
<td>16.4</td>
<td>26.5</td>
</tr>
<tr>
<td>CP1B-SDI</td>
<td>18.8</td>
<td>24.2</td>
<td>34.2</td>
<td>22.3</td>
<td>29.3</td>
</tr>
<tr>
<td>CP1B-MDI</td>
<td>21.0</td>
<td>26.0</td>
<td>35.2</td>
<td>19.2</td>
<td>26.2</td>
</tr>
<tr>
<td>CP1B-LDI</td>
<td>21.5</td>
<td>26.2</td>
<td>34.0</td>
<td>17.9</td>
<td>23.0</td>
</tr>
<tr>
<td>CP2-SDI</td>
<td>25.1</td>
<td>28.2</td>
<td>35.0</td>
<td>10.9</td>
<td>19.5</td>
</tr>
<tr>
<td>CP2-MDI</td>
<td>18.6</td>
<td>20.8</td>
<td>26.3</td>
<td>11.0</td>
<td>20.9</td>
</tr>
<tr>
<td>CP2-LDI</td>
<td>14.1</td>
<td>15.8</td>
<td>20.3</td>
<td>11.0</td>
<td>22.1</td>
</tr>
</tbody>
</table>
Our results *suggest* that for Argentina (at least) efforts should be directed to achieve \textbf{vaccination on time} \textbf{an with high coverages} for the risk age-group.
Communication strategy in Flandres (Belgium)

Change of the vacc. Schedule:

2–3–4 months $\rightarrow$ 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.


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

Introduction of maternal immunization
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.
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.

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:

Severe + mild incidences:
Model predictions:

Severe incidence:

- 0-2 months: 64% decrease
- 0-12 months: 29% decrease

Severe + mild incidences:

- 0-2 months: 0%
- 0-12 months: 0%
Confirmed pertussis cases in 0-12m age group (VacSal- Prov.BsAs)

Introduction of maternal immunization

40%
Model predictions:

Severe incidence:

- 0-2months: 64%
- 0-12months: 29%

Severe + mild incidences:

- 0-2months: 0%
- 0-12months: 0%
Confirmed pertussis cases (VacSal - Prov.BsAs)

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

Year of Maternal vaccination introduction
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: \[\rightarrow\text{we compare data at the 2011 and 2016 peaks (outbreaks)}\]

\[\rightarrow\text{we consider that under-reporting for 0-2m age group may be }\neq\text{ than for 0-12m age group for severe cases may be }\neq\text{ than for mild cases}\]
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:

<table>
<thead>
<tr>
<th>Population group</th>
<th>Age</th>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s,0-2$</td>
<td>0-2 months</td>
<td>severe</td>
</tr>
<tr>
<td>$m,0-2$</td>
<td>0-2 months</td>
<td>mild</td>
</tr>
<tr>
<td>$s,2-12$</td>
<td>2-12 months</td>
<td>severe</td>
</tr>
<tr>
<td>$m,2-12$</td>
<td>2-12 months</td>
<td>mild</td>
</tr>
</tbody>
</table>
Then, the reported incidence in the 0-12m age group:

\[ Inc_{0-12m}^R = Inc_{s,0-2}^R + Inc_{m,0-2}^R + Inc_{s,2-12}^R + Inc_{m,2-12}^R \]

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

- \( Inc_{s,0-2}^R = f_{s,0-2} Inc_{s,0-2}^C \)
- \( Inc_{m,0-2}^R = f_{m,0-2} Inc_{m,0-2}^C \)
- \( Inc_{s,0-12}^R = f_{s,0-12} Inc_{s,0-12}^C \)
- \( Inc_{m,0-12}^R = f_{m,0-12} Inc_{m,0-12}^C \)
Confirmed pertussis cases in 0-12m age group
(VacSal- Prov.BsAs)

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

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

\[ f_{\text{age}} = \frac{f_{s,2-12}}{f_{s,0-2}} \quad f_{\text{sympt}} = \frac{f_{m,0-2}}{f_{s,0-2}} \quad f'_{\text{sympt}} = \frac{f_{m,2-12}}{f_{s,2-12}} \]
\[ f_{age} = \frac{f_{s,2-12}}{f_{s,0-2}} \quad f_{symp} = \frac{f_{m,0-2}}{f_{s,0-2}} \quad f'_{symp} = \frac{f_{m,2-12}}{f_{s,2-12}} \]

\[ 0 \leq f_{age}, f_{symp}, f'_{symp} \leq 1 \]

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

that satisfies: \( 0.55 \leq A(f_{age}, f_{symp}, f'_{symp}) \leq 0.65 \)
\[ B(t) = \frac{Inc_{0-2m}^C(t)}{Inc_{0-12m}^R(t)} \]

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

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

\[ 0.30 \leq B(f_{\text{age}}, f_{\text{symp}}, f'_{\text{symp}}, 2016) \leq 0.40 \]
Compatibility of epidemiological data with the results of the calculations

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

\[ A = \frac{Inc_{0-12m}^R(2016)}{Inc_{0-12m}^R(2011)} \]

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

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

\[ B(t) = \frac{Inc_{0-2m}^R(t)}{Inc_{0-12m}^R(t)} \]
We review the hypotheses of the model


"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 children of immunized mothers.
Compatibility of epidemiological data with the results of the calculations

Maternal immunization $\rightarrow$ protection to 0-2m infants (only)
Compatibility of epidemiological data with the results of the calculations

Maternal immunization $\rightarrow$ protection to 0-2m infants

$\rightarrow$ + increased effectiveness of DTP1 (>2m)
Compatibility of epidemiological data with the results of the calculations

\[ f_{\text{age}} = \frac{f_{s,2-12}^R}{f_{s,0-2}^R} \approx 0.85 \]

\[ f_{\text{symp}} = \frac{f_{m,0-2}^R}{f_{s,0-2}^R} \approx 0.35 \]

\[ f_{\text{symp}}' = \frac{f_{m,2-12}^R}{f_{s,2-12}^R} \approx 0.25 \]
\[
\begin{align*}
    f_{age} &= f_{a,2-12}^R / f_{a,0-2}^R \approx 0.85 \\
    f_{symp} &= f_{m,0-2}^R / f_{a,0-2}^R \approx 0.35 \\
    f'_{symp} &= f_{m,2-12}^R / f_{a,2-12}^R \approx 0.25
\end{align*}
\]
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.

Thank you!

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