Resurgence of pertussis – and a search for solution

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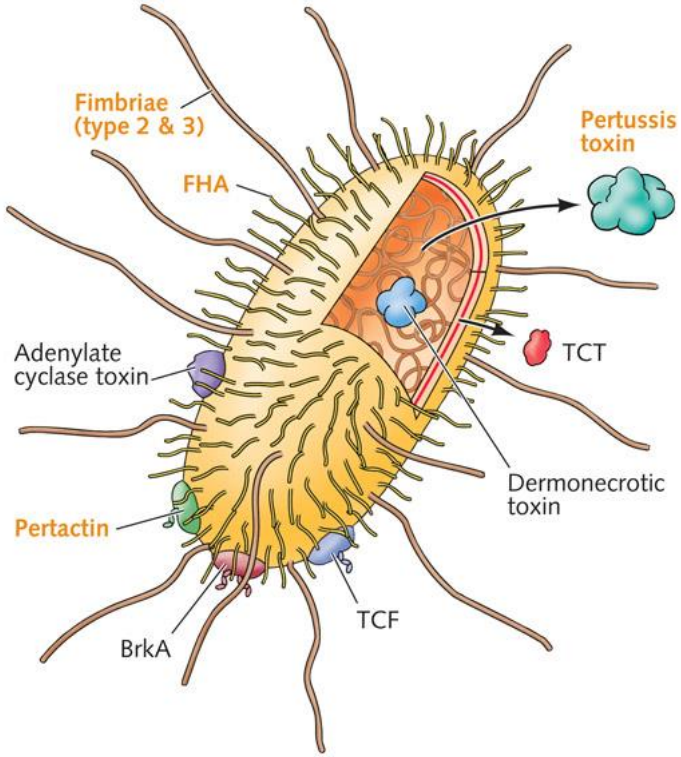
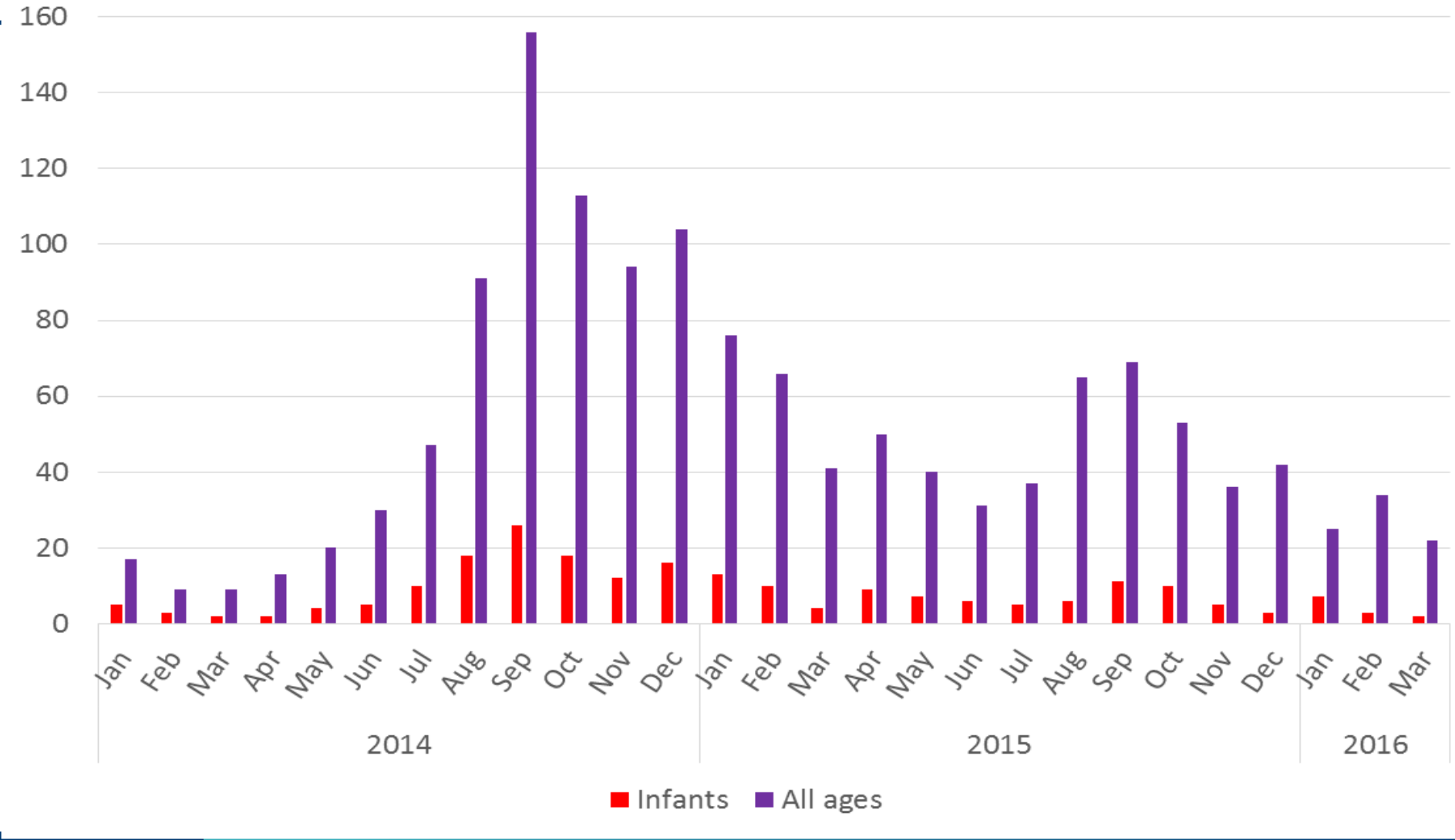
B. Pertussis


Fimbriae
(type 2 & 3)
FHA
Pertussis
toxin
TCT
Adenylate
cyclase toxin
Dermonecrotic
toxin
Pertactin
TCF
BrkA

Is there universal resurgence?

- *”steep rise in infants – significant mortality”*
  - *England*
  - *Spain*
  - *Netherlands*
  - *Bulgaria*
  - *Israel*
  - *USA*
  - *Australia*
    - *De Cellès …. Rohani P. Proc R Soc B 2015; 283: 20152309*

Reported cases of pertussis in Sweden, January 2014 - March 2016



Recent epidemiology in infant pertussis (crude numbers)

- **Sweden**: 121 in 2014; 89 in 2015 (range 39-121)
- **Norway**: Range 34-81, average 60
- **Denmark**: 71 in 2014
- **Finland**: 22-32 in 2013 and 2014 (under 5 years of age)

Swedish review, 2015

- Systematic literature review to get the best available knowledge for defined questions.
- GRADE methodology
- PICO-format
- Population - infants up to 6 months of age
- Intervention - variable
- Control group - variable
- Outcome - pertussis incidence, hospitalisation due to pertussis and death due to pertussis

Swedish review, 2015

- 7500 studies were assessed by the team.

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Peter McIntyre, Sydney

Prevention strategy, PICO 1
Timelier compliance with the first dose

- A small number of studies from Denmark, Sweden, Netherlands, Australia and New Zealand.
- Conclusion incidence: The confidence for this strategy is limited (++)
- Conclusion mortality: The confidence for this strategy is moderately strong (+++)

  – Nilsson L et al. Vaccine 2012; 30: 3239-47
  – Tiwari TSP et al. Pediatrics 2015; 135: 990-9

Prevention strategy, PICO 2
Neonatal vaccination, 0-28 days

- Three old studies from England, USA and Nigeria using whole cell pertussis vaccines (wP), no longer on the market
- Conclusion: The confidence for this strategy is limited (++)

  – Butler NR et al. Lancet 1962; 280: 112-4

Prevention strategy, PICO 3 Cocooning

- Three studies from USA and Australia using acellular pertussis vaccine (aP)
- Two USA studies were from Texas depicting the same population. These studies have been widely misinterpreted.
- The confidence for this strategy is limited (++)

  – Quinn HE. Pediatrics 2014; 134: 713-20.

Cont. Prevention strategy, PICO 3 Cocooning

- Cocooning is a very expensive strategy.
- Number of parents needed to vaccinate (NNV) to prevent one death is more than one million
- NNV to prevent one hospitalisation is more than ten thousand in a population with low to medium pertussis incidence.

- Skowronski DM et al. Clin Infect Dis 2012; 54: 318-27

Prevention strategy, PICO 4
Maternal vaccination in last trimester of pregnancy

- Conclusion: The confidence for this strategy is limited (++) and mainly based on Dabrera G et al CID 2015; 60: 333-7
- Comment: Case control study with 58 cases and 55 controls. Vaccine Efficacy 91%. Ten of 58 cases were vaccinated compared to 39 of 55 controls.
  Only median four days at hospital for infants with pertussis.

Prevention strategy, PICO 5
Booster vaccine at 4 - 7 years of age

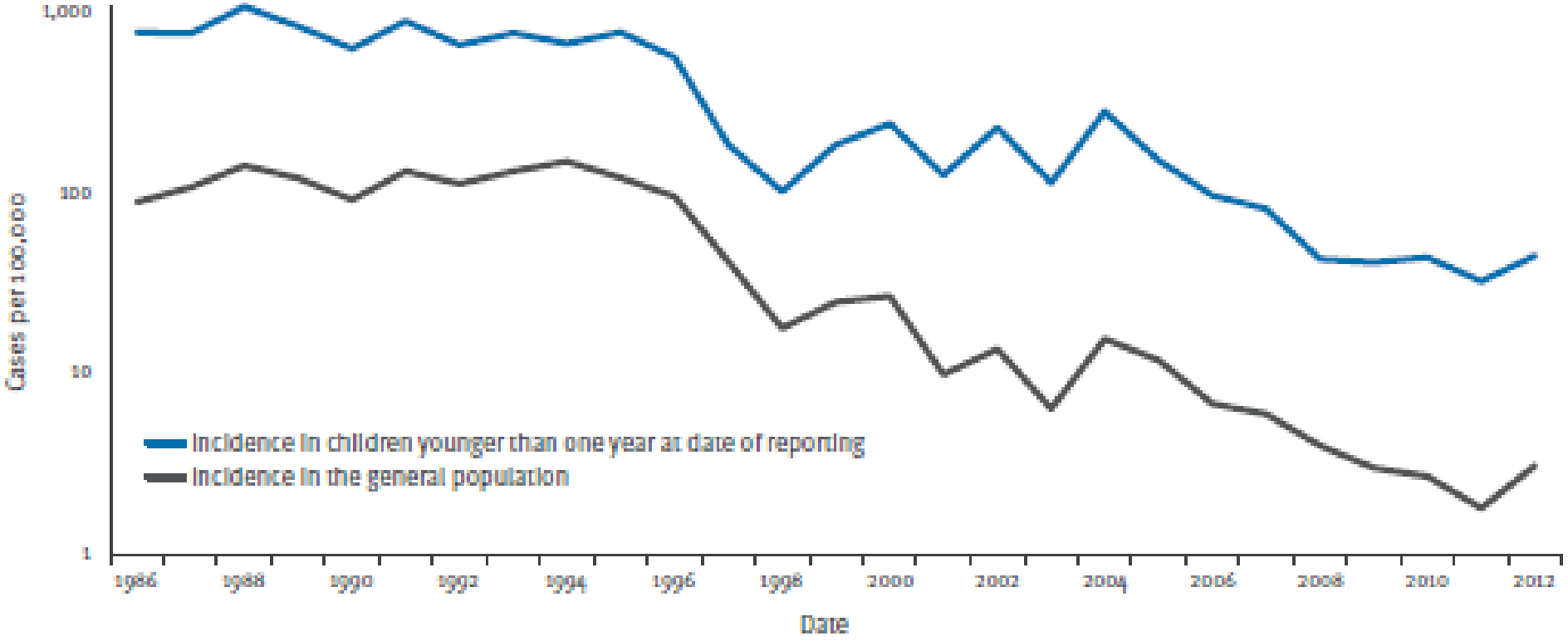
- A small number of studies from Sweden, Netherlands, England, Israel and Australia.
- Conclusion: The confidence for this strategy is moderately strong (+++)

Carlsson RM et al. Eurosurveillance 2015; 20: pii=21032

Comment: Median 7 days at hospital for unvaccinated children. Nine infant deaths during 11 years of surveillance, 4/9 in preterm infants.

Cont. Prevention strategy, PICO 5

Pertussis incidence according to regular notifications of laboratory-confirmed pertussis, Sweden, 1986-2012



Prevention strategy, PICO 6
Booster vaccine at 13 - 19 years of age

- Three studies from USA, Australia and Canada.
- Conclusion: The confidence for this strategy is low (+)

Prevention strategy, PICO 7
Post exposure treatment with antibiotics

- Conclusion: The confidence for this strategy is moderately strong (+++)
  - Granström G et al. JID 1987; 155: 1210-4
  - Comment: 32/35 pregnant women and 28 of their offspring were treated with erythromycin 1975-1985. No cases of infant pertussis.

Does widespread use of aP reduce transmission?

- The answer is no according to Benjamin M. Althouse and Samuel V Shapiro *"Asymptomatic transmission and the resurgence of Bordetella pertussis."* BMC Medicine 2015; 13: 146.
- The answer is yes according to de Cellès and Rohani in *Proc R Soc B 2015; 283: 20152309*
- The answer is yes according to Rose-Marie Carlsson et al. Eurosurveillance 2015; 20: pii=21032

Does use of aP reduce transmission in animal models?

- An important publication: Jason M Warfel, Lindsey I Zimmerman and Tod J Merkel *"Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model."* PNAS 2014; 111: 787-92.
- In challenge experiments aP-vaccinated baboons were colonized for 35 days and wP-vaccinated baboons for 18 days
- aP-vaccinated baboons were capable of transmitting disease to naive contacts.

Sustained transmission in vaccinated 1 - 5 year old children

- A pre-school outbreak in Florida
- 33 cases among 117 exposed children, all with more than two weeks of cough, four hospitalised 1-5 days
- Vaccine efficacy after 3 or 4 doses aP: 45%.
- Average number of days from last aP until first symptoms: 22 months

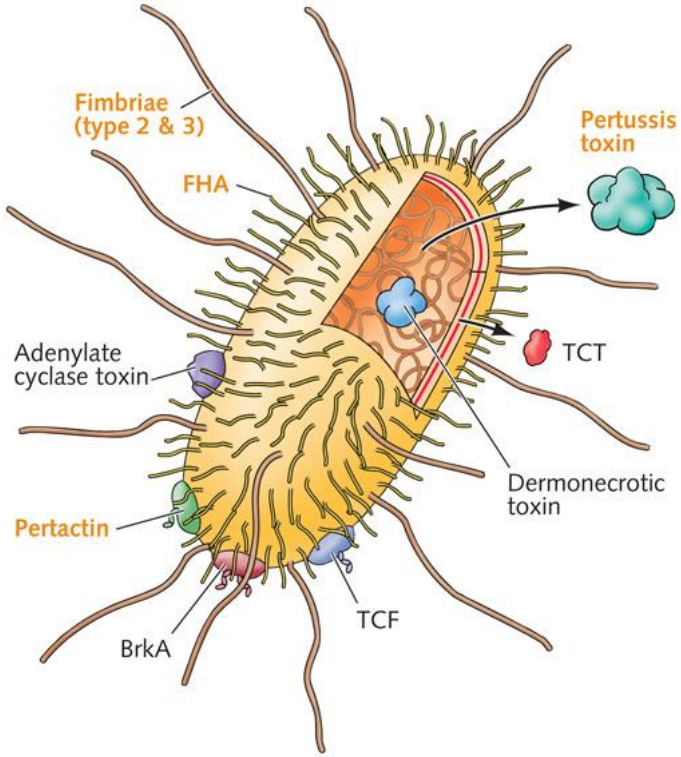
– Matthias J et al. Emerg Inf Dis 2016; 22: 242-36

Immunology and memory

- Problems with aP: Narrow specificity, IgG1 subclass. Th2-skew
- High antigen doses → vigorous short-term immunity but impaired long-term immunity
- aP-primed CD4+ memory T-cells may be more end-stage differentiated than those induced by wP.

  – Brummelman J. Mills KHG. FEMS Pathogens and Disease 2015; 73: ftv067 (Minireview)

B. Pertussis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BrkA

Fritz Mooi, Bilthoven, Netherlands

B. Pertussis evolution

- Since 1953 variation in the genes for Pertussis Toksin (pt), Pertactin (prn), Fimbriae (fim), and promotor for pt (ptx) – in *»clonal sweeps»*
- ptxP1 / ptxA4 / prn1 / fim 3-1 are replaced by ptxP3 / ptxA1 / prn 2/3 / fim 3-2
- Recently in many countries pertactin-negative *B. Pertussis* strains appear, typically 12-15 years after aP introduction

Ref. F.R.Mooi et al. Epidemiol Infect 2014;142:685-94

B. Pertussis evolution

- Strong relationship over time with use of aP
- After the English pertussis epidemic 2012 it was noticed that «vaccine ag genes are unusually fast evolving»
- Signal in **unbiased genome wide approach**: «*Ever increasing vaccine escape in clonal sweeps*»

Ref: T. Belcher et al. Pathogens and Disease, 21 Aug 2015

Lack of durable immunity, US

- ”Immunity wanes each year following the 5th dose such that, after 5 years, DTaP-vaccinated children are 4-fold to 15-fold more likely to acquire pertussis relative to the initial protection.”
- ”Adolescents who received all DTaP doses were 3.3-fold more likely to be diagnosed with pertussis compared to children vaccinated with only DTwP.”

  – Warfel JM and Edwards KM. Current Opinion in Immunology 2015; 35: 48-54.

Meta-analysis, duration of efficacy, aP and wP

- ”…receipt of even a single dose of whole-cell pertussis (wP) vaccine as part of the childhood series confers more durable protection against pertussis” - compared to aP only

  – Fulton TR et al. Clin Infect Dis 2016; 62: 1100-10.

Meta-analysis, duration of efficacy, aP

- ”The average duration of vaccine protection from DTaP is ~3 years, assuming 85% vaccine efficacy.”
- ”Ten % of children vaccinated with DTaP will be immune to pertussis 8.5 years after the last dose.”

  – McGirr et al. Pediatrics 2015; 2: 331-343

Duration of cellular immunity, 9 - 12 year-old children

- ”Cytokine responses were broader after wP vaccination.”
- ”The frequency of children responding with both proliferation and cytokine production was twice as high for wP - compared to aP-vaccinated children.”

  – Smits K et al. Vaccine 2014; 32: 111-8

dTaP vaccination during pregnancy

- A number of recent studies show a trend of blunting of infant immune responses later in life when the mother is vaccinated during pregnancy.
- Transplacental transport of IgG antibody is effective

  – Maertens K et al. Vaccine 2016; 34: 142-50
  – Hoang HTT et al. Vaccine 2016; 34: 151-9
  – Munoz FM et al. JAMA 2014; 311: 1760-9

Possible options for new vaccines - Revise or replace

1. aP single vaccine
2. Modification of antigens (more PT, genetic detoxified PT, new variants antigens)
3. Additional antigens (Adenylate Cyclase Toxin, BrkA, IRP-3)
4. Modification of adjuvant / new adjuvants
5. Change in delivery systems (live bacteria, live vectors, vesicles, other)

- Ref: Meade BD, Plotkin SA, Locht C. JID 2014; 209 (suppl 1): S24-7

Primate studies

- Chimpanzees were studied in the 1930´s
- Macaques and cebus monkeys – *Bordetella pertussis* causes only mild infection. Inconsistent results re. sympt.
- Baby baboon model set up in Oklahoma

- In 1933 a small human challenge study was performed (JID 1933; 53: 328-30)
- A standardised human challenge model is now called for

  – Merkel TJ, Halperin SA. JID 2014; 209 (suppl 1): S20-3