Report on the work of the WHO Strategic Advisory Group of Experts (SAGE) Working Group on Pertussis Vaccines

Liz Miller

Annecy meeting November 2015

Working Group members

- Claire-Anne Siegrist, Switzerland (Chair after February 2014)
- Elizabeth Miller, UK (Chair to February 2014)
- Thomas Clark, USA
- Kathryn Edwards, USA
- Nicole Guiso, France
- Scott Halperin, Canada
- Teeranart Jivapaisarnpong, Thailand
- Daniel Levy-Bruhl, France
- Peter McIntyre, Australia
- Gabriela Moreno, Chile
- Piyanit Tharmaphornpilas, Thailand
- Carl Heinz Wirsing von König, Germany
- Philippe Duclosp SAGE secretariat

Terms of Reference of Pertussis WG

1. Review epidemiological data from selected countries using aP and/or wP vaccines
   - Evaluate evidence for pertussis resurgence
   - Evaluate evidence for hypothesis that resurgence is due to shorter lived protection from aP vaccines
2. Review evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants
3. Review evidence on effectiveness of cocooning, neonatal vaccination and maternal vaccination on severe disease and death from pertussis in very young infants
4. Review evidence for optimal primary vaccination scheduling and timing of booster dose(s)
5. Review evidence that changes in circulating pertussis strains had an adverse impact on the effectiveness of aP or wP vaccines
6. Propose updated recommendations for SAGE consideration on use of pertussis vaccines (published WER August 2015)

Generation of concerns about aP vaccine efficacy

- **Klein et al. N Eng J Med 2012: Waning protection after fifth dose of acellular pertussis vaccine in children**
  - …"each year after the fifth dose of DTaP was associated with a 42% increased odds of acquiring pertussis"
- **Witt et al. Clin Infect Dis 2012: Unexpectedly Limited Durability of Immunity Following Acellular Pertussis Vaccination in Preadolescents in a North American Outbreak**
  - "Our data suggests that the current schedule of acellular pertussis vaccine doses is insufficient to prevent outbreaks of pertussis"
- **Sheridan et al JAMA 2014**
  - "Infant priming with DTwP was associated with a lower risk of subsequent pertussis than DTaP only primed children in this cohort. This difference persisted for more than a decade"

Assessing factors contributing to resurgences

- Epidemiological data from countries with and without a resurgence using aP or wP vaccines
- Mathematic models simulating pertussis transmission
- Animal model of pertussis (baboon study)
- Review of randomized trials (from 1980s and 90s)

http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pdf

Review of Randomized Trials

2015 Pertussis position paper

“aP vaccines are more effective than low-efficacy wP vaccines (wP vaccines shown to be suboptimal are no longer in use), but may be less effective than the highest-efficacy wP vaccines”

Epidemiological Data

- Methods
  - 21 countries approached for detailed data collection (19 complied)
    - High vaccine coverage with history of good disease control
    - Could provide high quality data (coverage & disease trends)
    - Representative of:
      - Countries with and without apparent pertussis resurgence
      - wP or aP based programs
      - Upper middle income (4) and high income countries (15)
      - Differing world regions

Methods cont.

- Standardized questionnaire developed by WG
  - Captured pertussis incidence, vaccination coverage/schedule, surveillance methods, case definitions, and type of vaccine used
  - Published papers also reviewed
- Resurgence definition
  - Larger burden of disease than expected when compared to previous cycles in same setting
    - Given periodic variability of naturally recurring pertussis disease
    - Not explained by changes in surveillance or diagnostic methods

Country Data: results

- Assessment of pertussis trends complex!
- Between country variance on multiple factors
  - Vaccine (type, composition/production, schedules, coverage, boosters)
  - Population (age distribution, mixing, transmission patterns)
  - Surveillance systems and diagnostic methods
- No evidence of global resurgence of pertussis
  - Majority of increased incidence likely associated with natural cyclic patterns exacerbated by increased awareness and more sensitive diagnostic testing
  - No evidence of that emergence of new strains (eg PRN negative) was causally associated with the resurgence

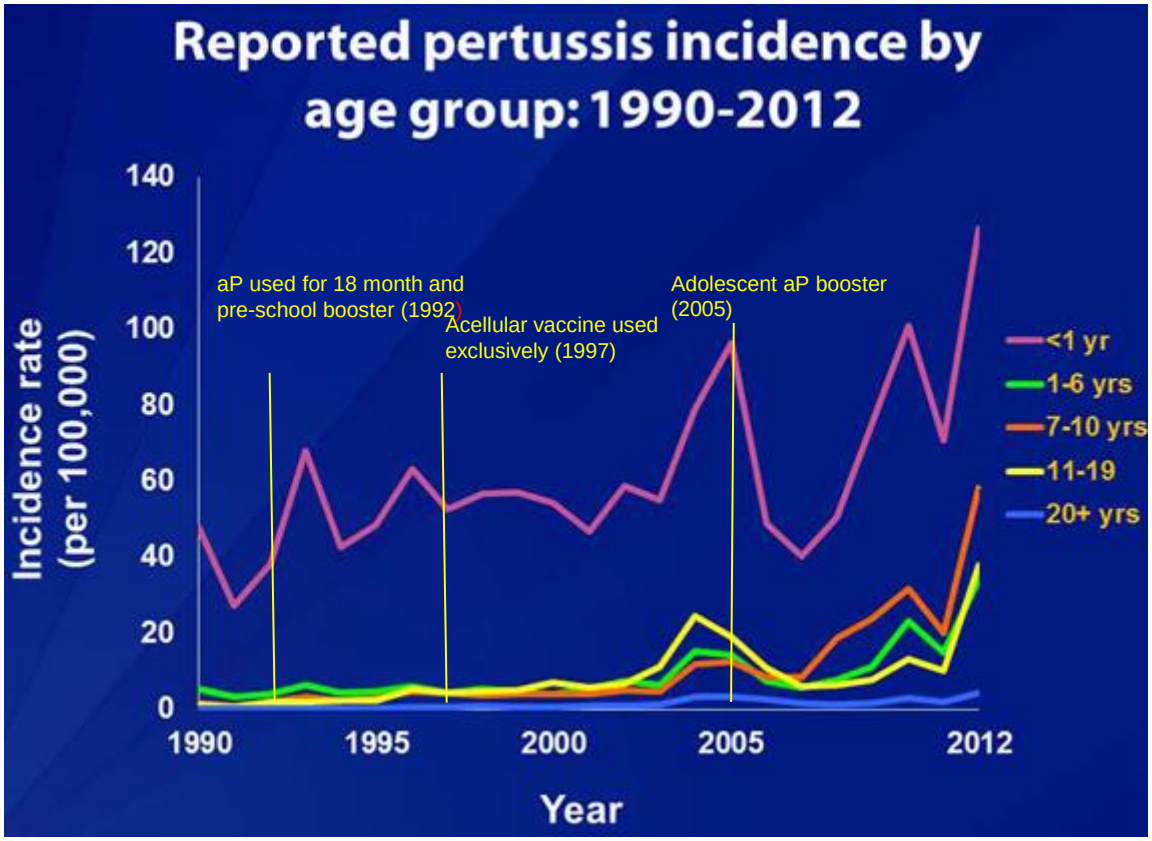
– 5 countries with convincing evidence of a true resurgence.

Country Data: USA (aP using)

Despite sustained high coverage, increase in incidence observed in 2004, 2005, and 2012, mostly affecting infants <6 months and adolescents,

Increase in all age groups in 2011-2012

Mortality in under one year olds not increased.



<u>Resurgence 8 years after aP introduction</u>

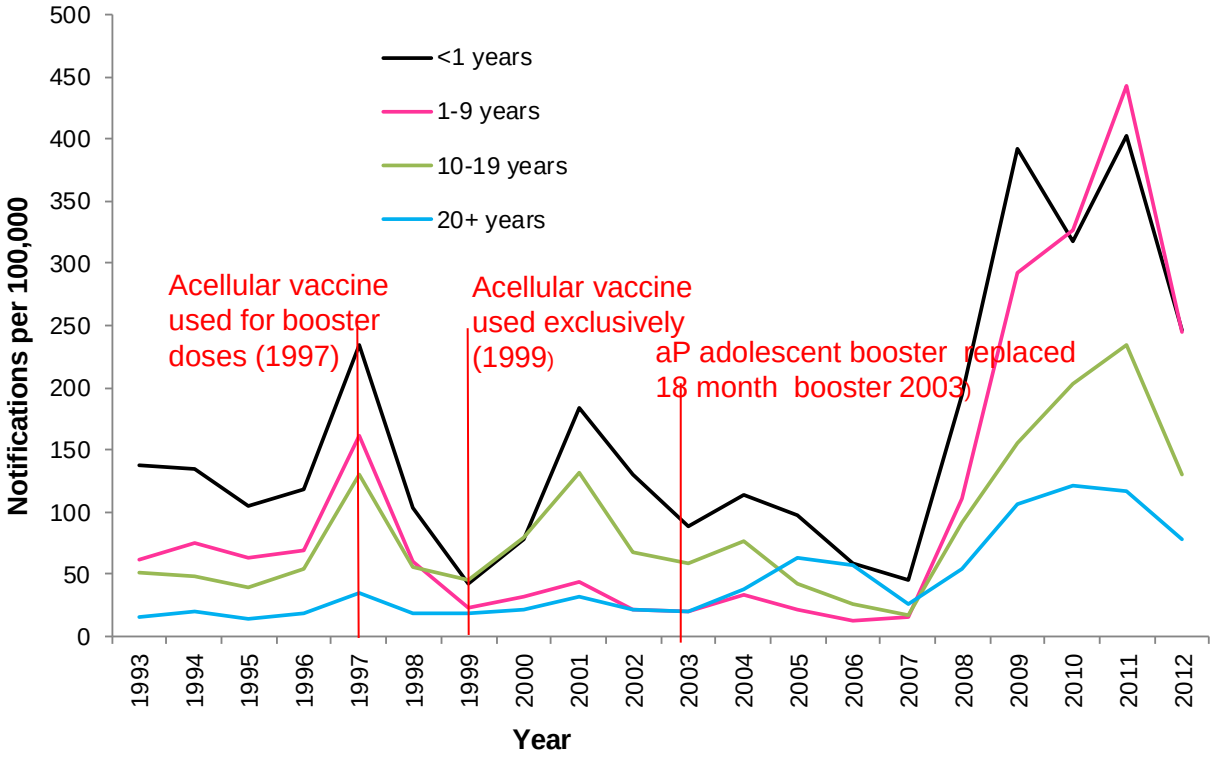
Country Data: Australia (aP using)

Resurgence from 2008-2012 in all age groups

Increase seen in 20+ yr olds before resurgence probably related to availability of serologic tests

Evidence of rapid waning of immunity after the primary 2/4/6 month aP schedule in the absence of a 18 month booster.

Resurgence not associated with any increase in infant pertussis deaths



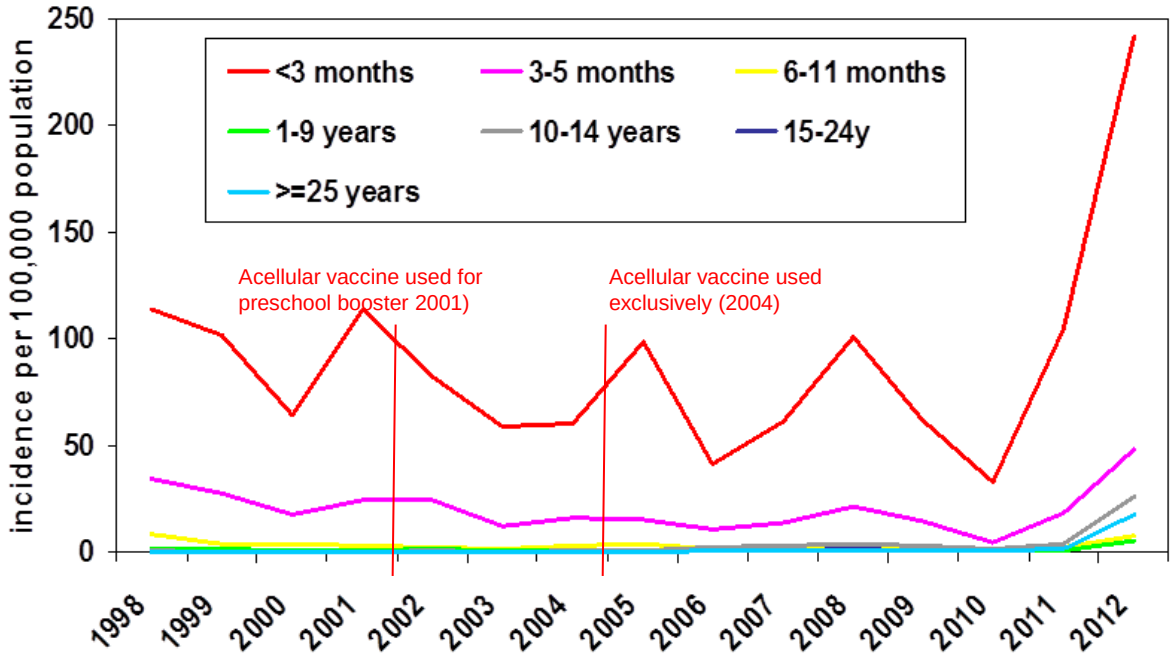
<u>Resurgence 9 years after aP introduction</u>.

Country Data: England and Wales(aP using)

Incidence declined over last 20 years as coverage improved but no interruption of natural 3-4year epidemic cycle

In 2012, increase in all age groups (expected peak of next 4 year cycle) but greater than in previous peak years

Increase in infants <3 months seen in notified cases, hospitalizations and infant deaths.



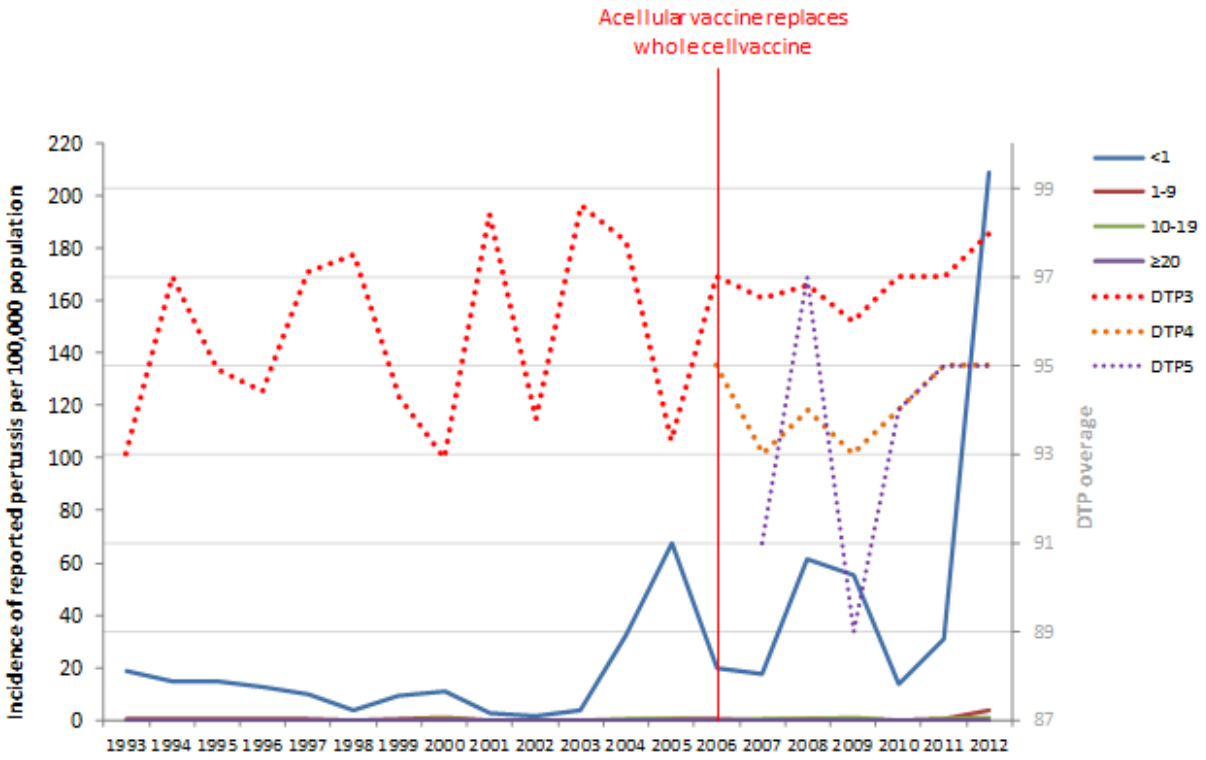
<u>Resurgence 8 years after aP introduction</u>

Country Data: Portugal (aP using)

Vaccine coverage for DTP3 and DTP4 (at 18 months) continuously high

In 2012, large rise in cases <1 year suggesting true resurgence, though changes potentially magnified by increased PCR testing.

Increase in infant mortality in 2012, though similar to other countries from 2000-2011



<u>Resurgence 6 years after aP introduction</u>

Country Data: Chile (wP using)

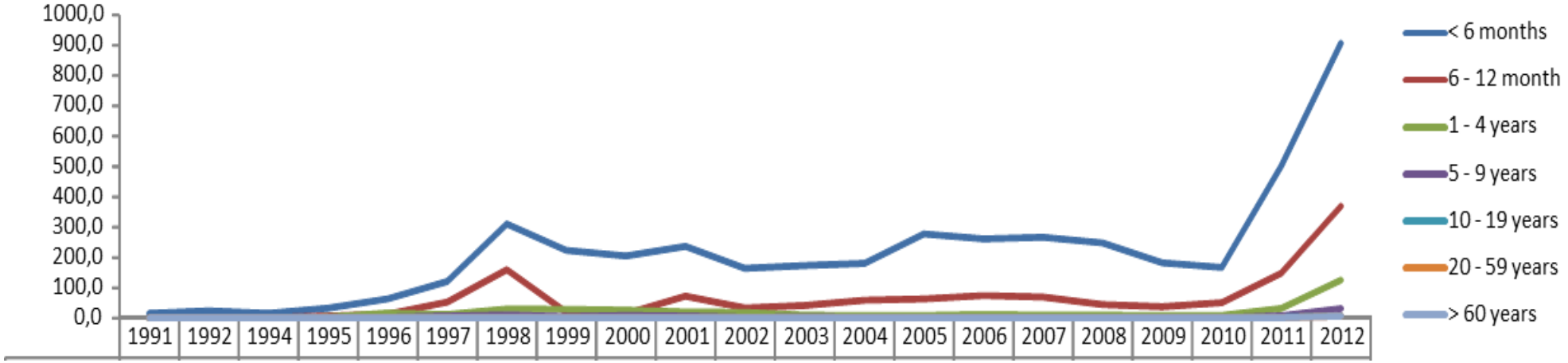
Data quality greatly improved in 2012

Specificity of laboratory methods may have changed as direct immunofluoresence method now widely used and can give rise to false positives

The resurgence of pertussis observed in 2011 and 2012 was preceded by a drop in vaccine coverage in under 4 yr olds (from 91.3% in 2005 to 77.0% in 2011) which may be linked with this drop in coverage.

No evidence that resurgence is linked to use of wP vaccine with low efficacy.

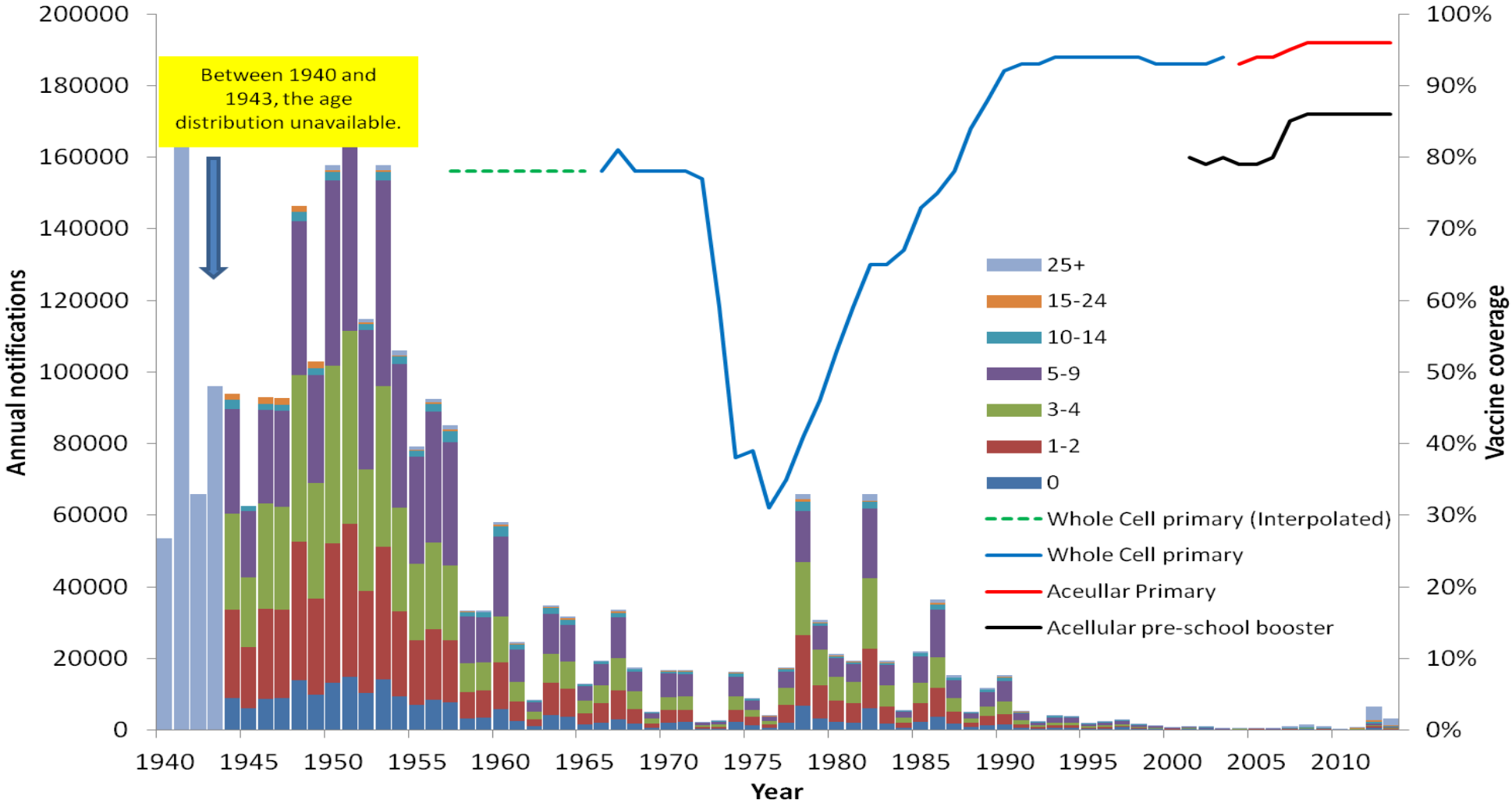
Exclusive use of whole cell vaccines (Sanofi Pasteur, SII,GSK, Biosano, Novartis)



But: examples of aP using countries with no resurgences

- Norway: changed to aP in 1998 using 3/5/10 month schedule
- Sweden: no vaccination prior to 1996 then aP at 3,5 12 months
- Finland: changed to aP in 2005 using 3,5,12 month schedule
- Denmark: changed to aP in 1997 using 3,5 12 month schedule

But:even where resurgence documented morbidity and mortality still low compared with pre-vaccine era



Overall WG conclusions on resurgence

- Both wP and aP vaccines effective in reducing disease incidence and infant mortality
- No evidence of broad resurgence at global level
- Role of aP vaccine
  - Lower initial efficacy and faster waning of immunity
  - Reduced impact on infection and transmission
  - Modelling and baboon data support hypothesis from surveillance data that wP to aP transition is associated with disease resurgence in some settings
  - Probably many factors determining when/if resurgence occurs in aP using countries
  - Whereas only insufficient coverage or poor vaccine leads to resurgence with wP.

Modelling studies

- WG reviewed age stratified, dynamic transmission models developed by Australia, US and UK

- Each country used its national data for model fitting and to estimate key parameters eg duration and degree of natural and vaccine induced immunity against infection

- Model structures varied between countries in complexity and assumptions eg about transmission potential and clinical expression of re-infections

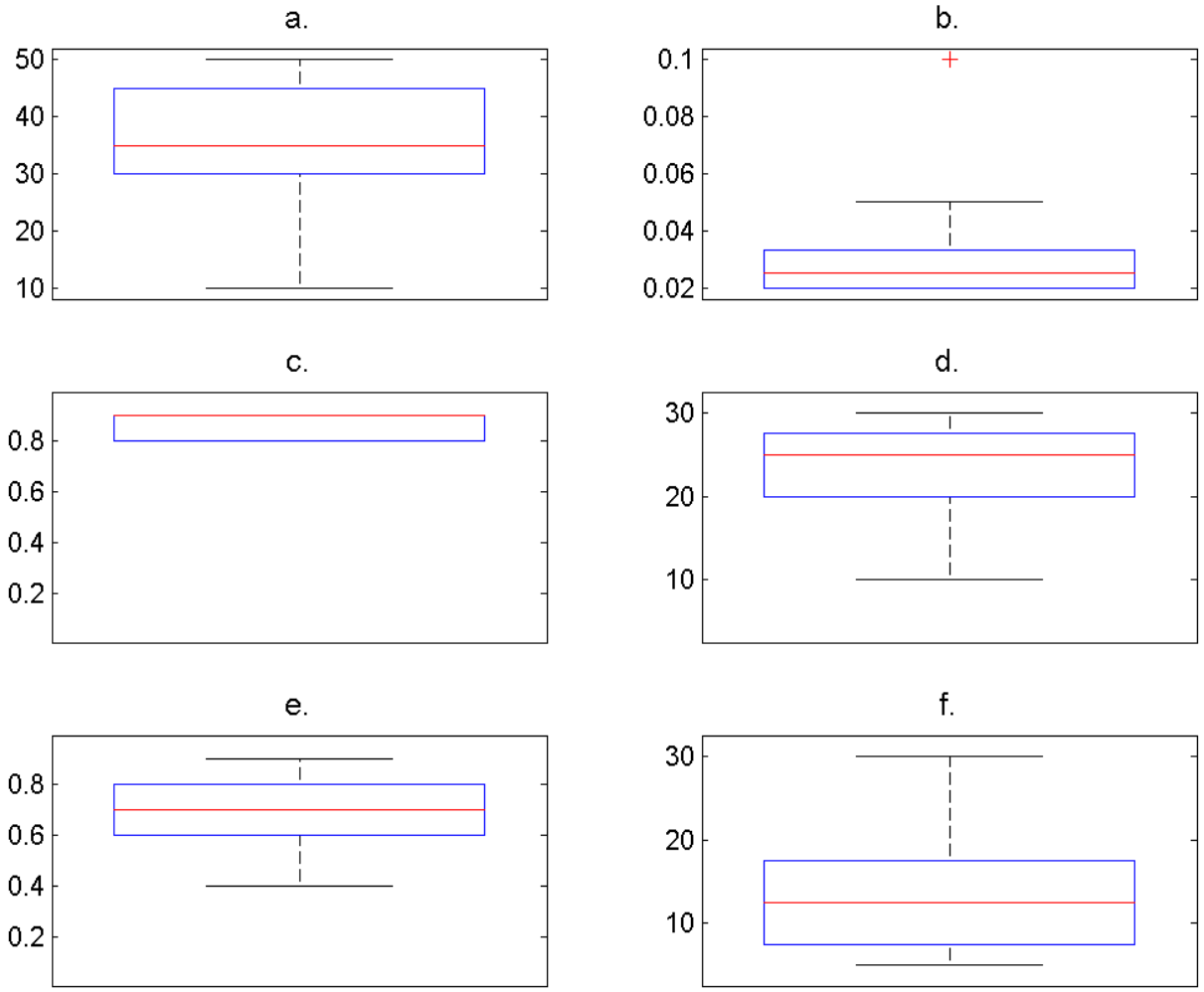
Results

- While precise aims of each modelling exercise differed between countries some key conclusions were broadly similar
  - Duration of immunity following natural infection longest
  - UK and US models suggest shorter duration of aP than wP immunity
  - UK model run to explore whether resurgence would have occurred if wP had been retained

Key features of UK model

- Model fitted to UK notification data from 1956 to 2013
- Protection induced by vaccination against disease and infection can be different whereas natural infection protects against disease and infection equally (as per baboon model)
- Vaccine-induced and natural immunity wanes allowing re-infection which can transmit but is less likely to produce notifiable (clinically typical symptoms)
- Duration of aP, wP and natural immunity, and degree of aP and wP protection against infection, estimated from the model fitting

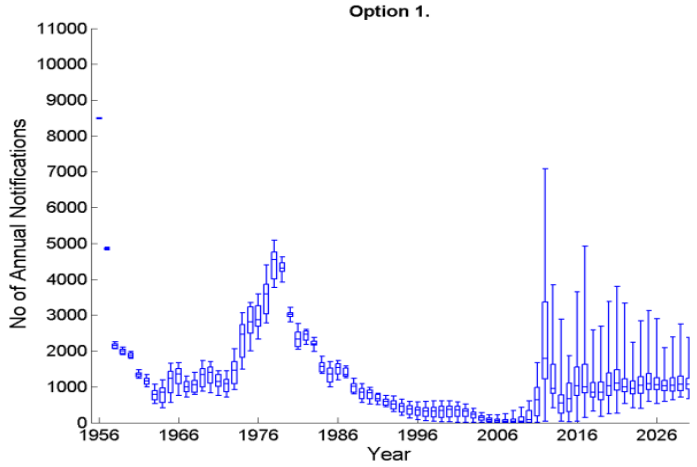
Key parameters estimated from the UK model (Choi et al submitted)



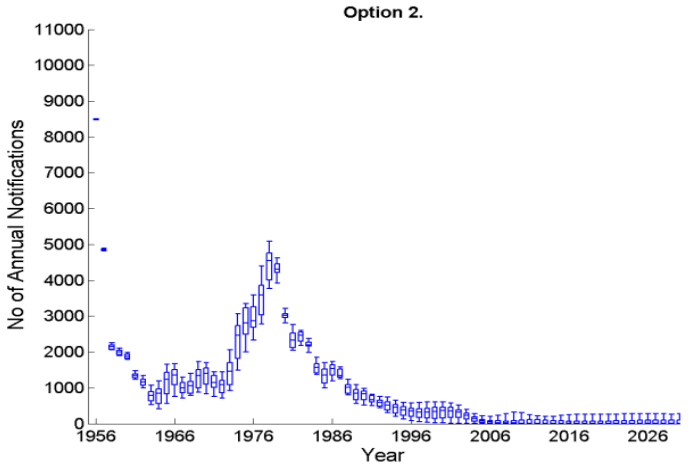
a. Duration (yrs) natural immunity
b. Proportion of secondary VS primary infections with clinically typical pertussis
c. Degree of wP protection against infection
d. Duration of wP protection
e. Degree of aP protection against infection
f. Duration of aP protection

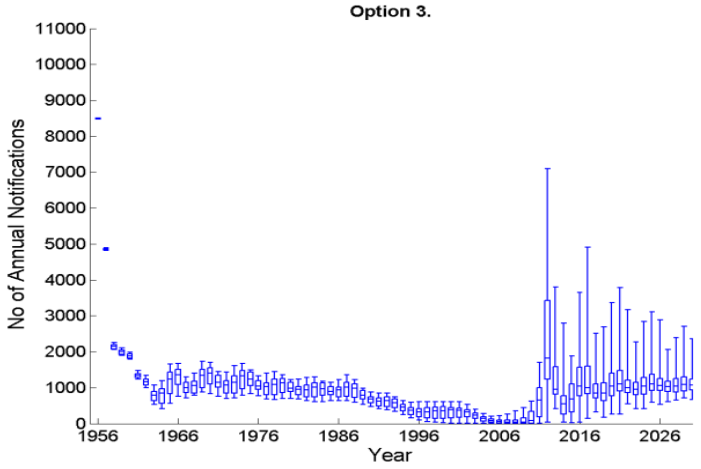
Comparison of different vaccination options on disease in infants under 1 yr (Choi et al. submitted)

UK programme without maternal vaccination

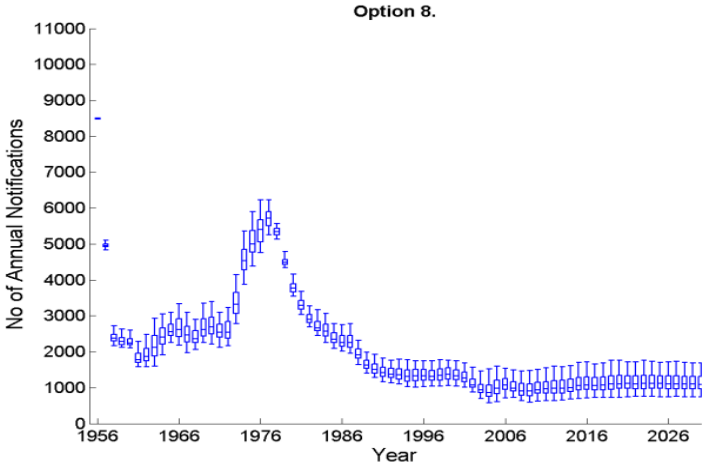


Without change to aP in 2004



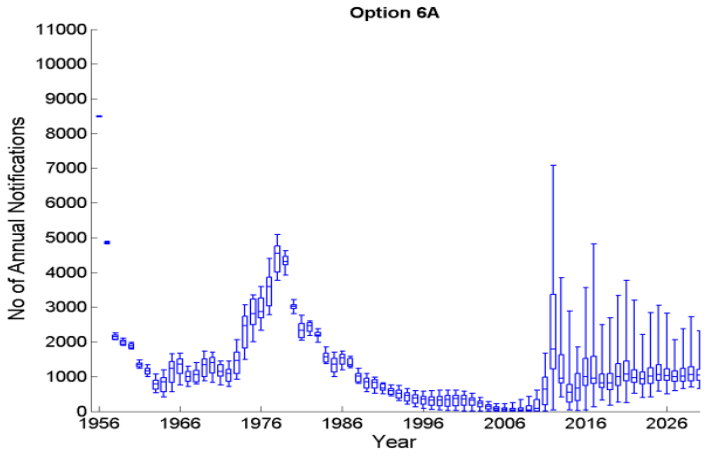


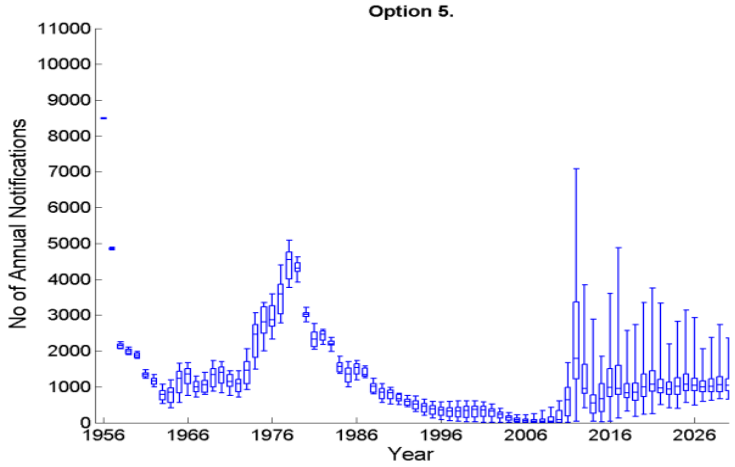
Without drop in coverage in 1970s and 80s

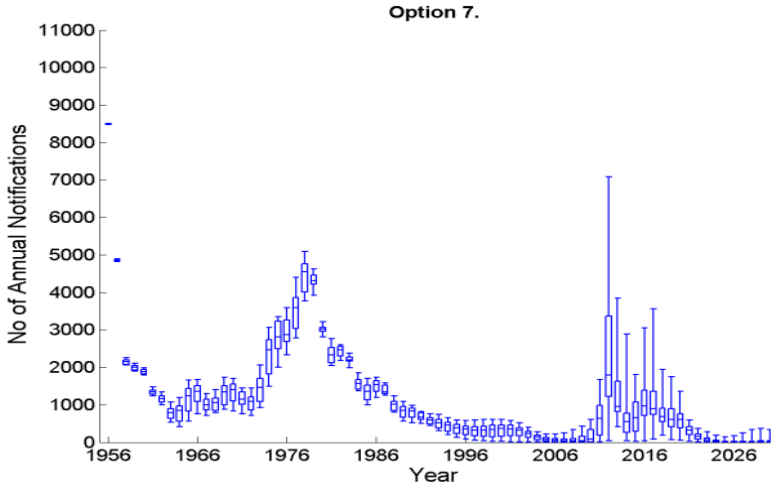


Using aP since 1956

Addition of 12 month booster







Return to wP-like vaccine in 2015

Addition of adolescent booster

SAGE recommendation: WER July 2014

- *"The shorter duration of protection and likely reduced impact on infection and transmission conferred by aP vaccines play a critical role in the resurgence of pertussis"*

- *"Thus, the switch from wP to aP vaccines for primary infant immunization should only be considered if the inclusion in the national immunization schedules of large numbers of doses (including several boosters) can be assured"*