SAGE Working Group on Pertussis Vaccines

Summary of Evidence: Resurgence Potential and Vaccine Impacts

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and Chair until February 2014

WHO SAGE Meeting

April 1-3, 2014

Evidence Reviewed

- Country data
- Review of randomized trials (from 1980s and 90s)
- Animal model of pertussis (baboon study)
- Modelling studies

COUNTRY DATA

Country Data

- Methods
  - 21 countries approached for detailed data collection
    - High vaccine coverage with history of good disease control
    - Able to provide high quality data (coverage & disease trends)
    - Representative of:
      - Countries with and without apparent pertussis resurgence
      - wP or aP based programs
      - Developing and industrialized countries
      - Differing world regions

Country Data

- Methods
  - Standardized questionnaire developed by WG
    - Captured pertussis incidence, vaccination coverage/schedule, surveillance methods, case definitions, and type of vaccine used
    - Relevant publications also used to complete questionnaire
  - Resurgence definition
    - Larger burden of disease than expected when compared to previous cycles in same setting
      - Given periodic variability of naturally recurring pertussis disease

Country Data

- Results
  - Questionnaire completed for 19 countries
    - 15 countries were high income countries
    - 4 were upper middle income countries
    - 2 countries (Argentina and Colombia) did not return completed questionnaires
      - Insufficient published information for inclusion

Country Data: Australia (aP using)

Large epidemic 1996-7 with infant deaths - related to low whole cell vaccine coverage.

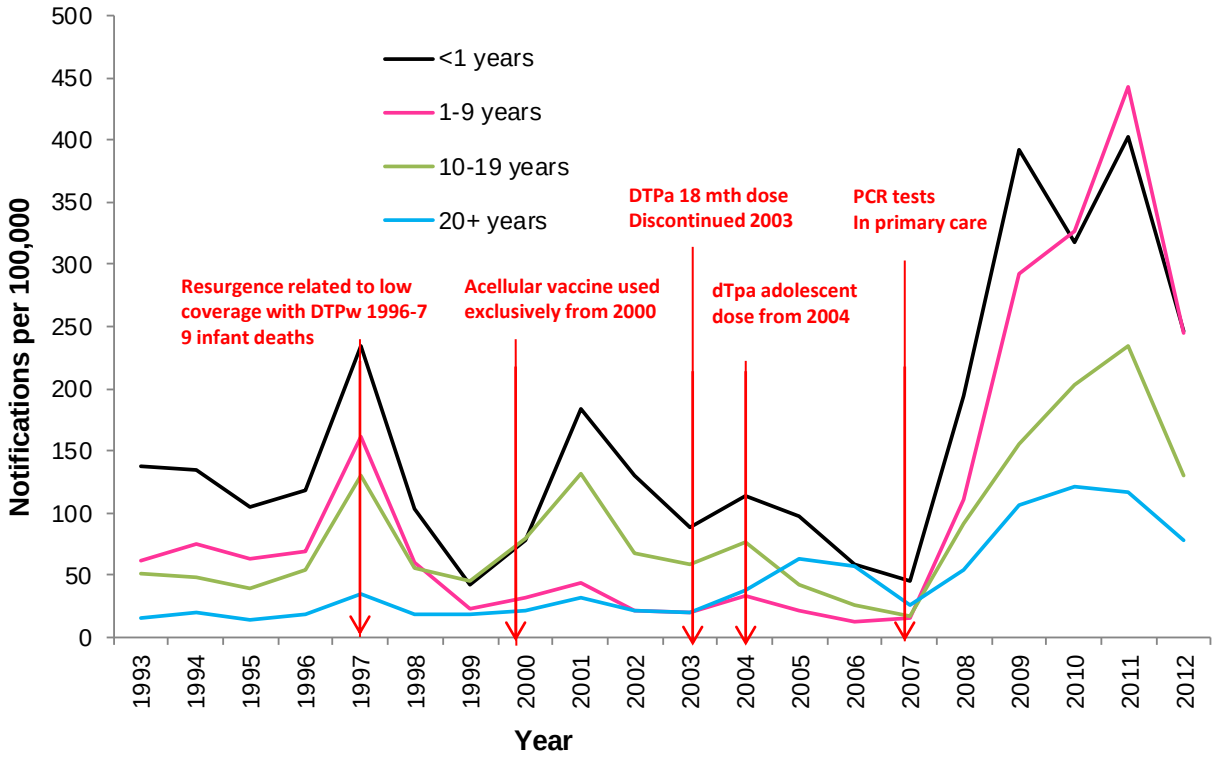
Increasing incidence in adults from 1990s related to availability of serologic tests.

Resurgence of pertussis - all ages from 2008-2012; disproportionate in children < 10 years.

Epidemic from 2008 in younger children consistent with waning immunity and widespread availability of PCR for outpatients.

Vaccine effectiveness estimates support waning protection from 2 years without 18 month booster (Quinn et al, Pediatrics 2014).

The 2008-12 resurgence not associated with increase in infant mortality.



Resurgence 9 years after aP introduction

World Health Organization

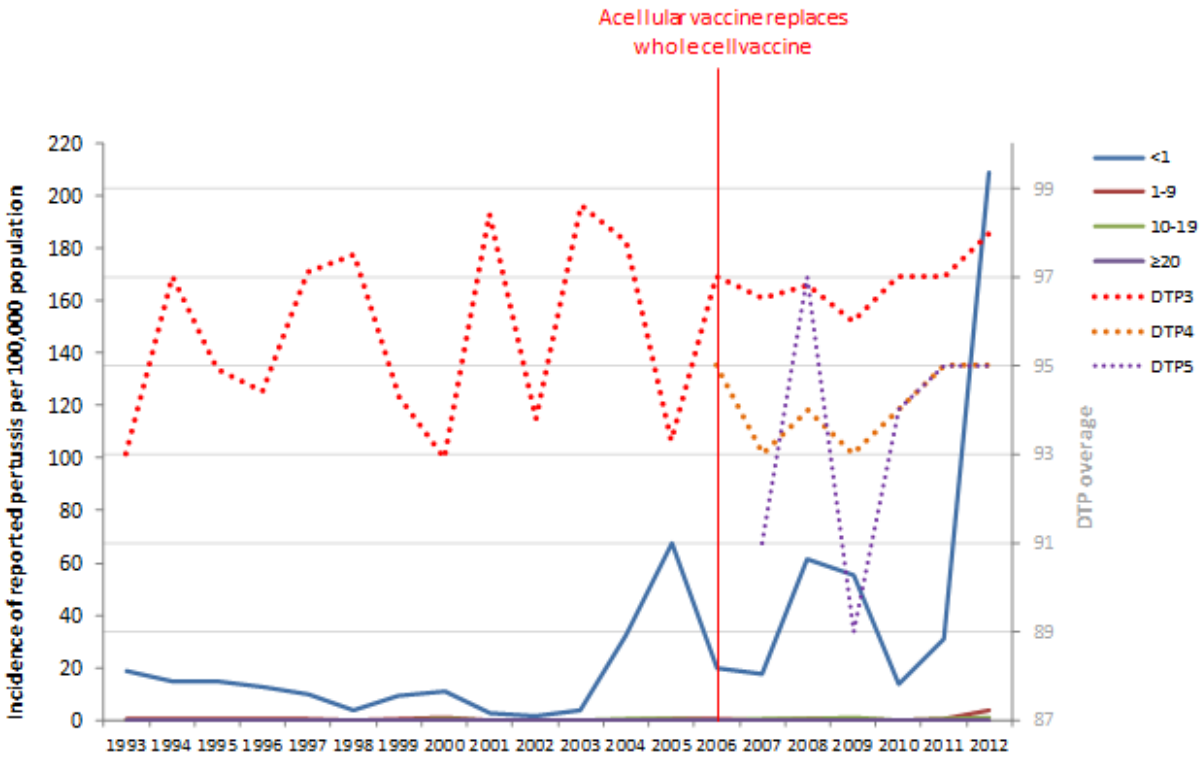
Country Data: Portugal (aP using)

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

In 2012, large rise in infants <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.

Data for older age groups unreliable due to under ascertainment (increase from 1 reported case in 10+ yr olds in 2011 to 17 in 2012).



Resurgence 6 years after aP introduction

World Health Organization

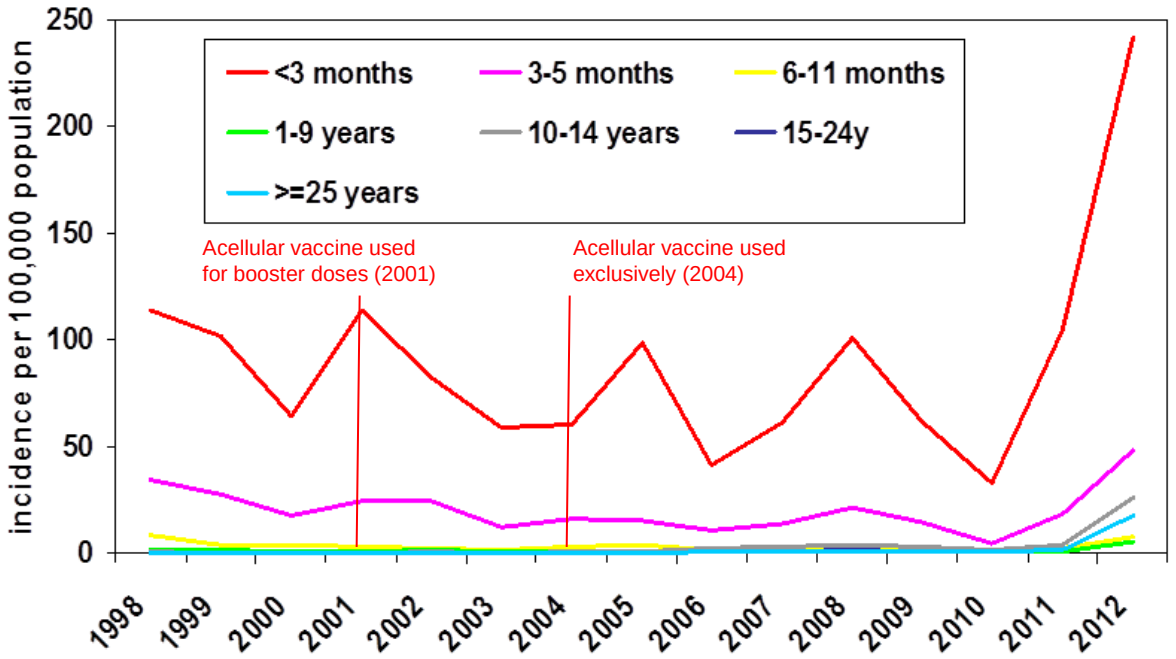
Country Data: England and Wales(aP using)

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

Study using screening method suggests no waning with aP5 up to pre-school booster (Campbell et al, EID 2012).



Resurgence 8 years after aP introduction

World Health Organization

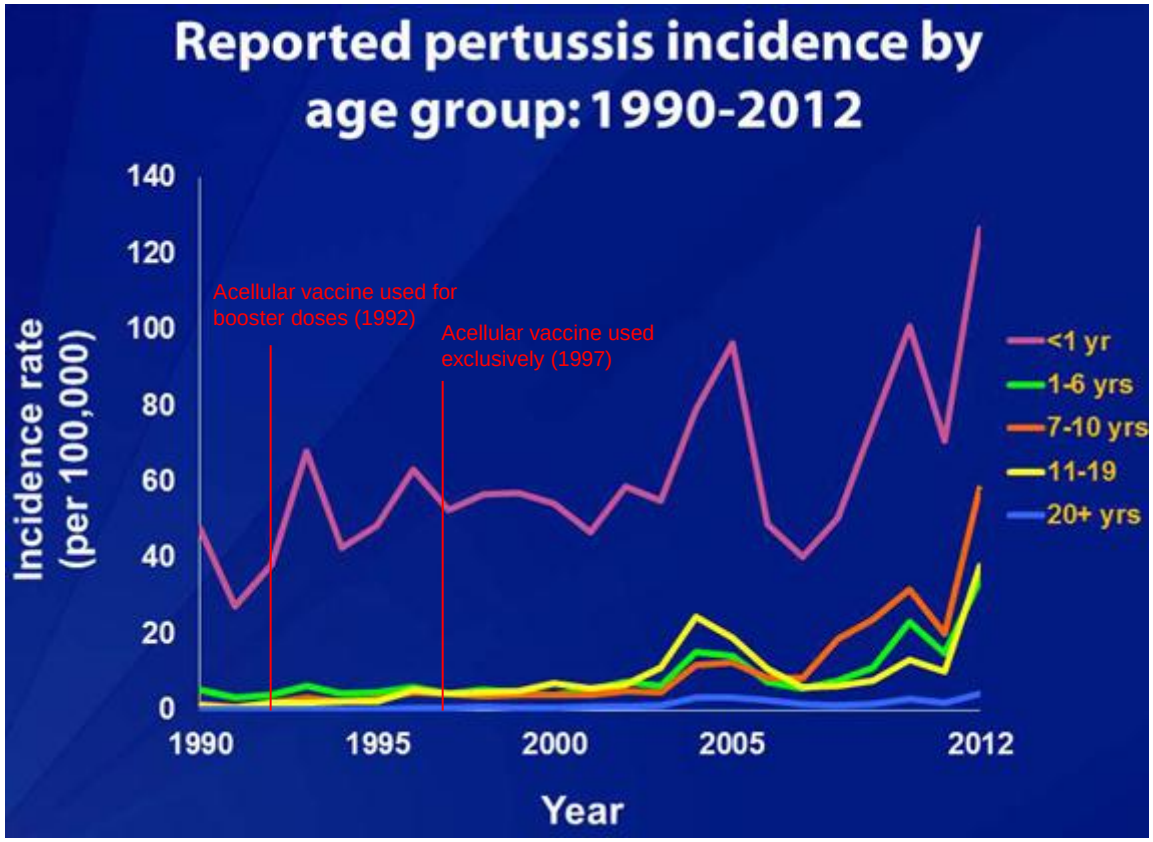
Country Data: USA (aP using)

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

In increase in all age groups in 2011-2012.

Mortality in under one year olds not increased.

Case control study showed each year after 5th dose of DTaP associated with a 1.42 (95% CI 1.21 to 1.66) increase in odds of pertussis (Klein et al, JAMA 2012).



Resurgence 8 years after aP introduction

World Health Organization

DTaP VE and Duration of Protection Estimates—California, 2010[1]

Model *	Case (n)	Control (n)	VE, %	95% CI
Overall VE, All Ages				
0 dose	53	19	Ref	--
5 doses	629	1,997	88.7	79.4 – 93.8
Time since 5th dose				
0 doses	53	19	Ref	--
< 12 months	19	354	98.1	96.1 – 99.1
12 – 23 months	51	391	95.3	91.2 – 97.5
24 – 35 months	79	366	92.3	86.6 – 95.5
36 – 47 months	108	304	87.3	76.2 – 93.2
48 – 59 months	141	294	82.8	68.7 – 90.6
60+ months	231	288	71.2	45.8 – 84.8

[1]JAMA. 2012;308:2126-2132.

Thomas Clark
CDC, USA

*Accounting for clustering by county and provider

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

Country Data: Chile (wP using)

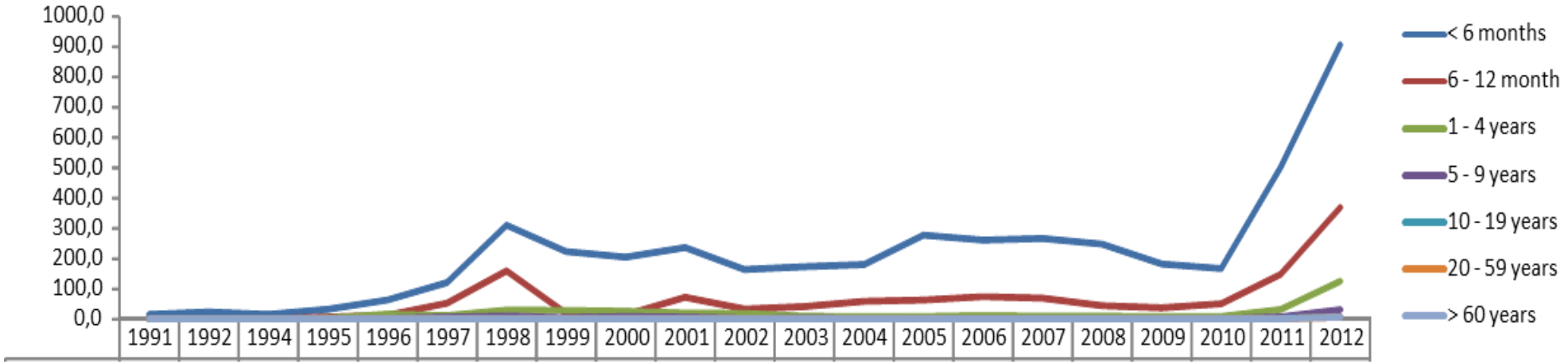
Data quality greatly improved in 2012

Specificity of laboratory methods may have changed as direct immunofluorescence 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)



World Health Organization

Country Data

- Conclusions
  - 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 associated with natural cyclic patterns
    - Increased awareness and more (sensitive) diagnostic testing

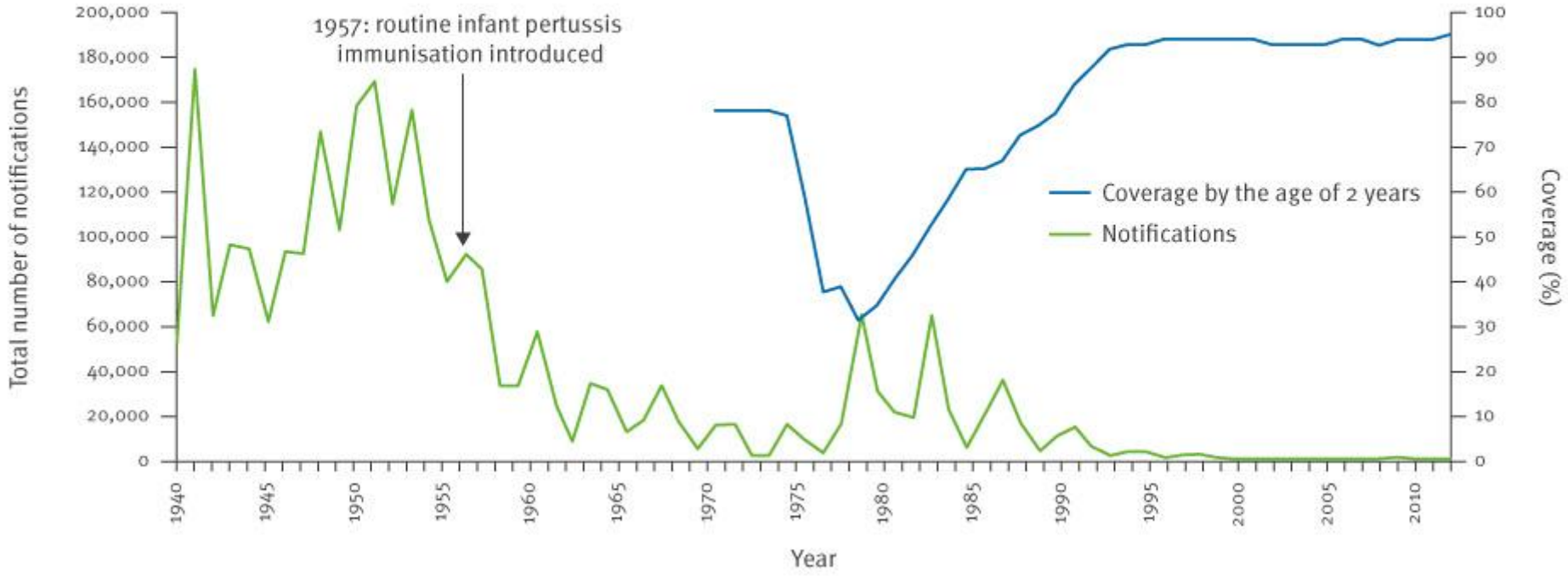
Country Data

- Conclusions
  - Pertussis vaccination provides effective disease protection
    - Long term substantial reductions in incidence and infant mortality compared with pre-vaccine era with both wP and aP vaccines
    - But evidence of earlier waning of immunity with aP vaccines
  - Resurgence seen in 5 of 19 countries
    - Australia, Portugal, USA, UK (aP)
    - Chile (wP)
      - Likely due vaccine coverage drop and changes in surveillance

Even where resurgence documented rates morbidity and mortality still low compared with pre-vaccine era

FIGURE 1

Annual notifications of pertussis (1940–2012, England and Wales) and vaccine coverage by the age of 2 years (1970–2012, England only)



Source: [3], updated with data up to 2012.

World Health Organization

REVIEW OF RANDOMIZED TRIALS

Review of Randomized Trials

- aP vaccines effective in preventing confirmed pertussis
  - Marginally less effective than the best wP vaccines
  - 1,2,3, and 5 component vaccines all effective
    - Notably, no resurgence in Denmark despite use of monocomponent vaccine
- No simple relationship between immunogenicity and efficacy
- Large variation in efficacy between wP vaccines used in trials
- Batch release tests for pertussis vaccines not predictors of effectiveness

Baboon Study

ANIMAL MODEL

Attribution: Tod J. Merkel et al Laboratory of Respiratory and Special Pathogens CBER/FDA

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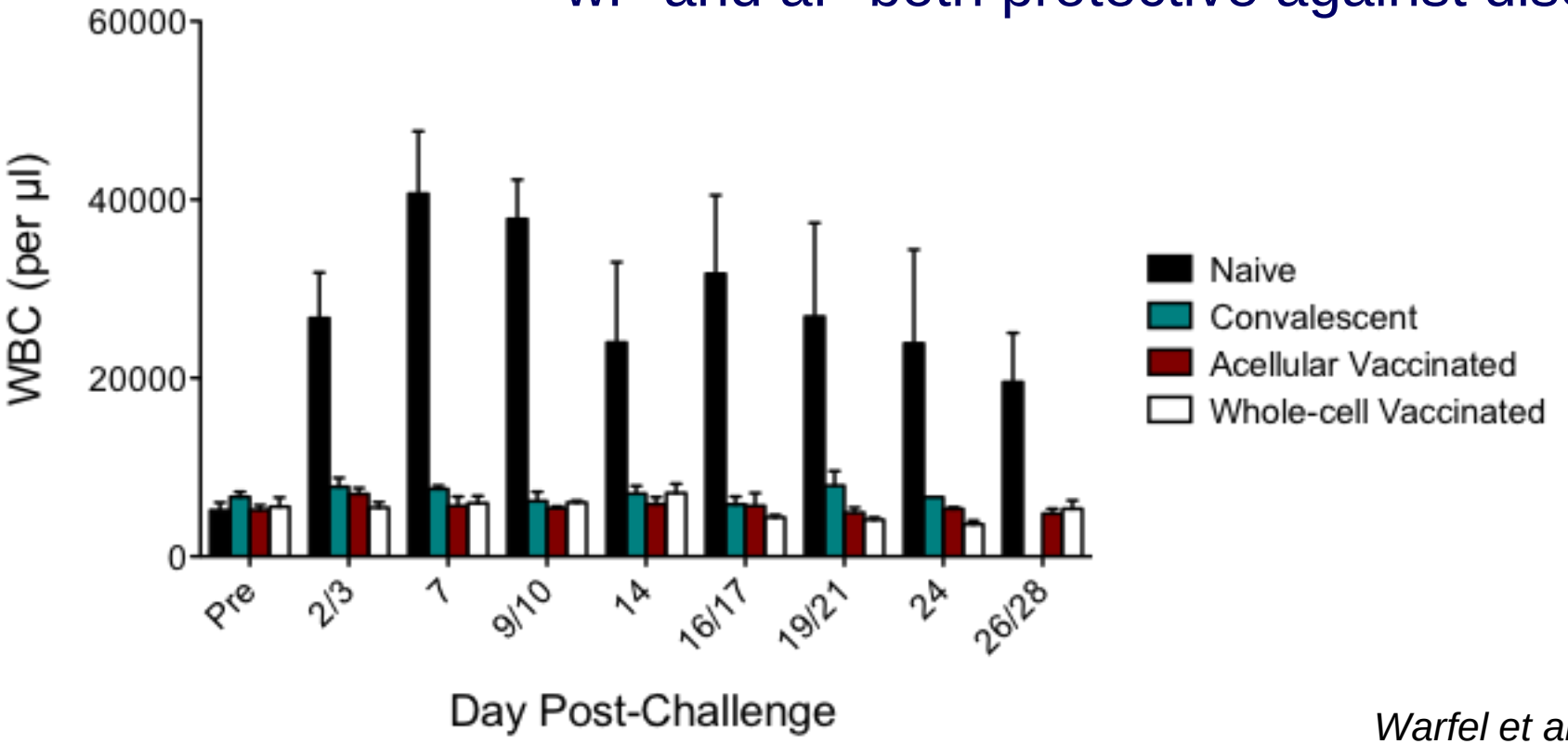
Animal Model (Baboon Study)

- wP and aP both protective against disease

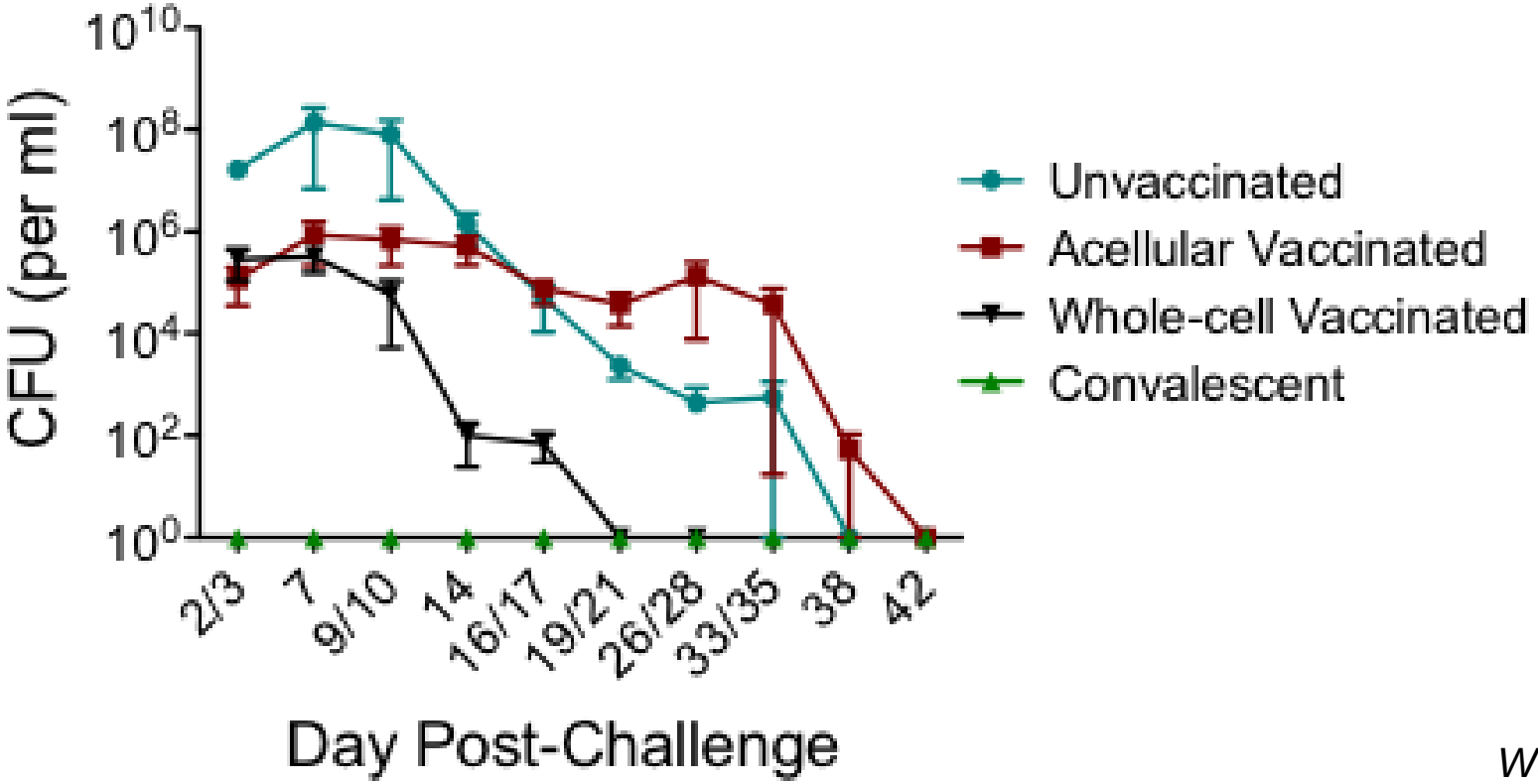


Warfel et al. PNAS January 2014

World Health Organization

Animal Model (Baboon Study)

- wP better than aP in clearing infection



Warfel et al. PNAS January 2014

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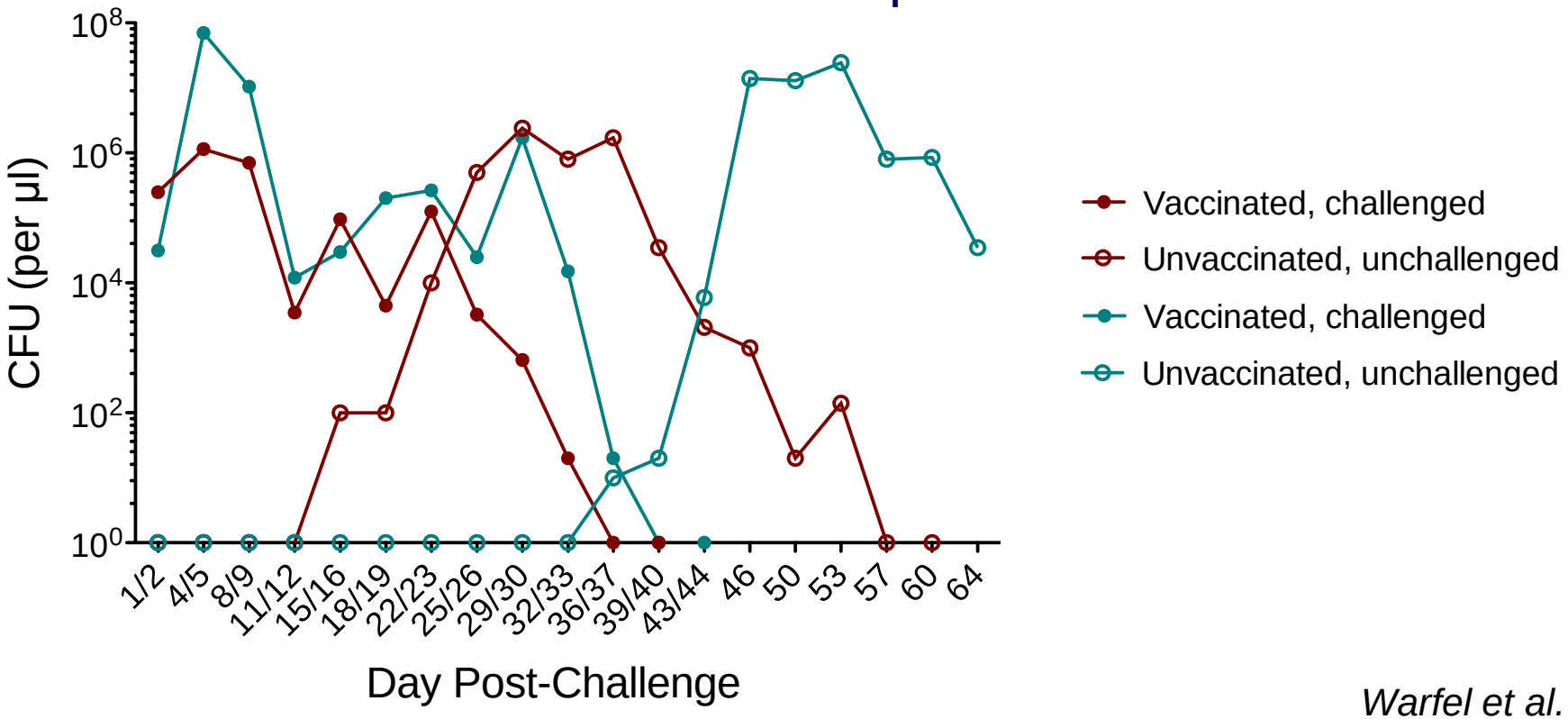
Colonisation data from two aP vaccinated baboons, challenged with *B. Pertussis* and each caged with unvaccinated, unchallenged baboon

- aP did not prevent transmission



Warfel et al. PNAS January 2014

World Health Organization

Animal Model (Baboon Study)

- Conclusions
  - Prior infection, wP, aP all protected against symptomatic disease
  - wP provided some sterilizing immunity
    - aP not different from unvaccinated
    - wP better than aP but less than natural infection
    - Infection and wP induced Th1 and Th17 memory
  - aP did not prevent infection and transmission
    - Higher Th2 but lower Th1 and Th17 responses
    - Lack of mucosal immunity induction likely has role in pertussis resurgence

Attribution: Tod J. Merkel et al
Laboratory of Respiratory and Special Pathogens CBER/FDA

MODELLING STUDIES

Modelling Studies

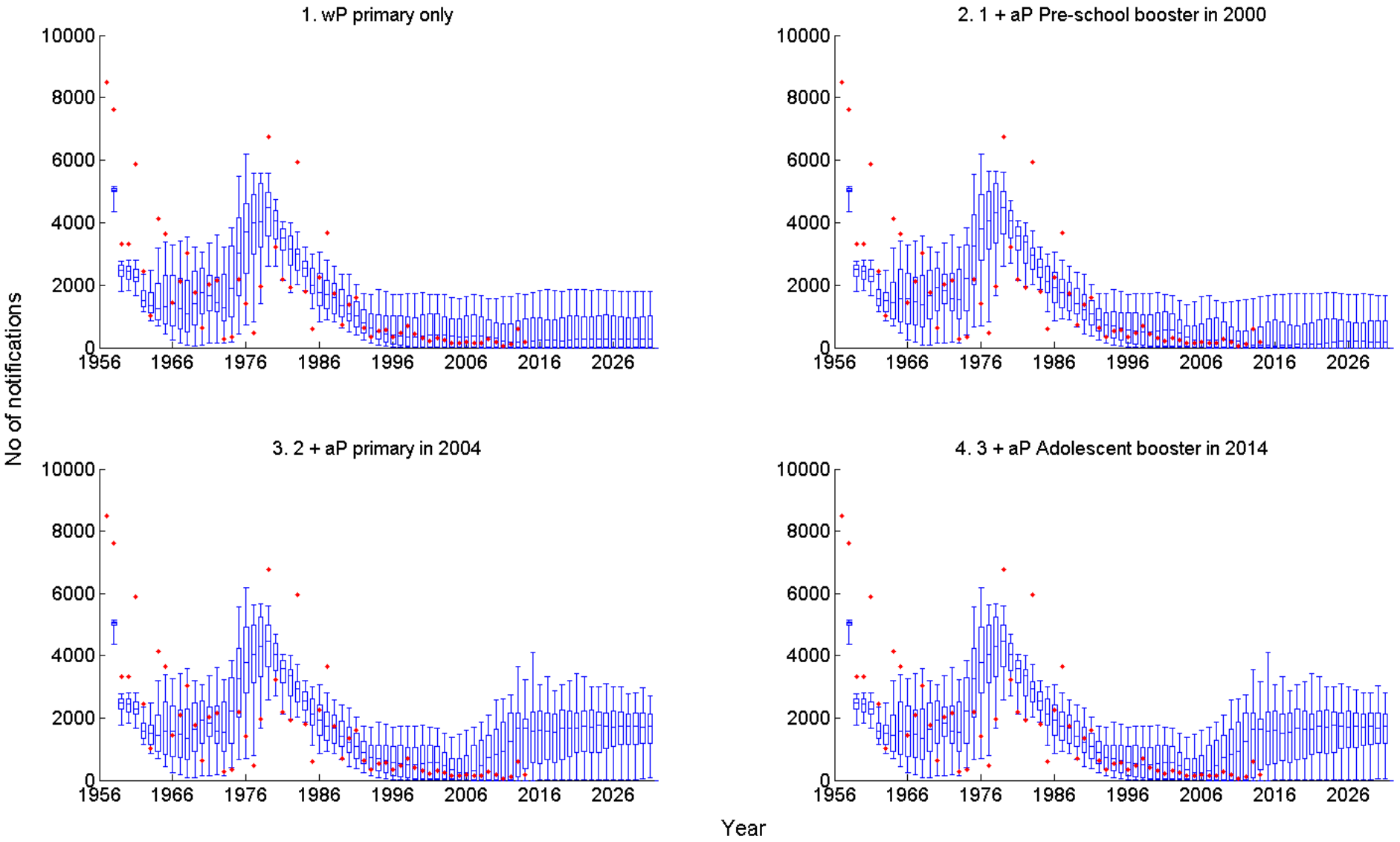
- WG reviewed age stratified, dynamic transmission models developed by Australia, US and UK
- Each country used its national surveillance and coverage data for model fitting and to estimate key parameters (e.g. duration of natural and vaccine induced immunity)
- Model structures varied between countries in complexity and assumptions about relationship between susceptibility to re-infection, and transmission potential and disease expression associated with re-infection

Modelling Results

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

Public Health England

Comparison of Vaccination Programme Scenarios - 0 year olds



Overall WG Conclusions

- 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