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Use of CHIMs for Demonstration of Effectiveness of New Pertussis Vaccines

Vaccines and Related Biological Products Advisory Committee Meeting

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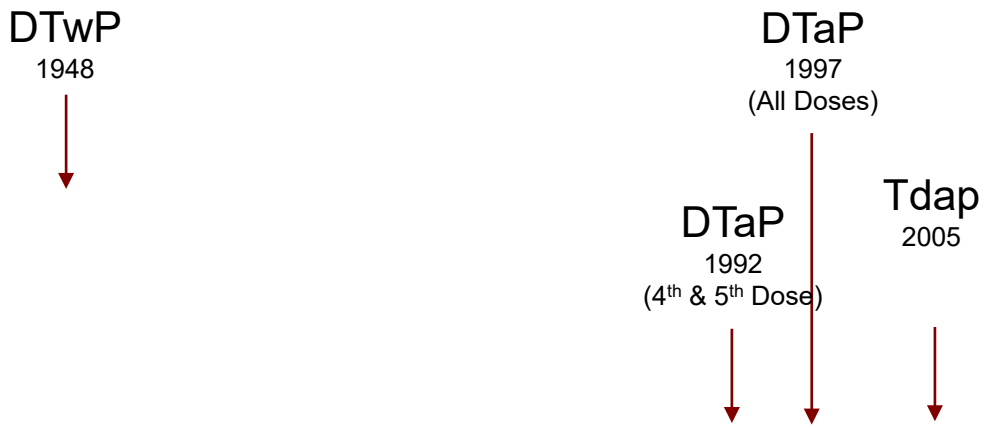
Pertussis Disease

- Pertussis is an acute respiratory disease caused by the Gram-negative bacterium *Bordetella pertussis.*
- The severity of the disease manifestations depends on age, prior infection, and vaccination status.
- Unvaccinated infants present with the most severe disease.
- Severe cases can occur in any age group, but most hospitalizations and deaths occur in infants under two months of age.

Pertussis Epidemiology

- Reservoir of *B. pertussis* is exclusively human.
- Pertussis disease is transmitted via airborne droplets, and persistence in the population requires an unbroken chain of transmission.
- The pertussis attack rate varies among studies. Studies are confounded by:
  - Age of the population being studied.
  - Immune status due to vaccination or previous exposure.
  - Environment in which study is conducted.
- Attack rates in household contact studies in the pre-vaccine era varied between 64–86%.
- Attack rates in school classroom contact studies in the pre-vaccine era varied from 0–36%.
- Close or prolonged contact is required for efficient transmission.

Pertussis Vaccine History



Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service.

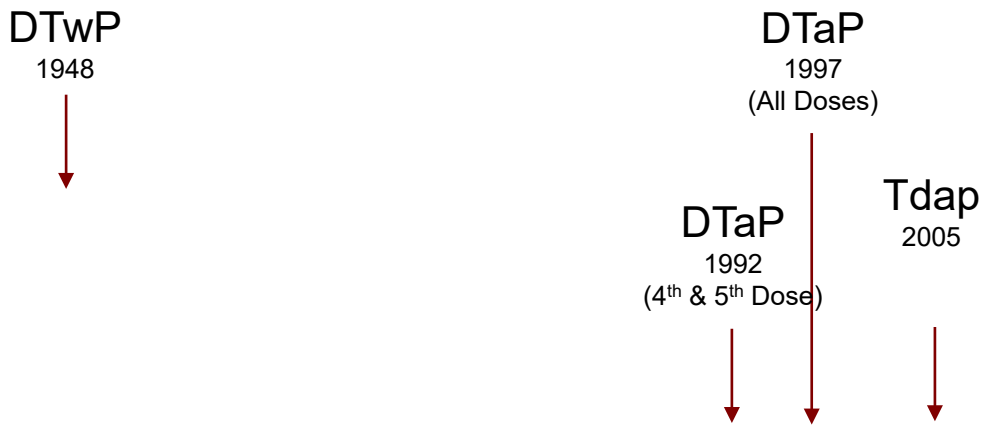
Reactogenicity of wP Vaccines

Common:	**Less Common:**	**Uncommon:**
Injection site reactions (redness, swelling, pain)	Vomiting	Convulsions
Fever (≥ 38˚C)	Anorexia	Hypotonic-hyporesponsive episodes
Fretfulness	Persistent crying	
Drowsiness		

- Widespread publicity about safety concerns of whole-cell pertussis vaccines led to decreased acceptance of these vaccines and efforts to develop acellular pertussis vaccines.

Cody et al., Pediatrics. 68(5):650-660, Nov. 1981.
Decker et al., Pediatrics 1995;96;557.
Cherry and Doustmohammadi, Current Opinion in Pediatrics. 34(2):126-131, Apr. 2022.

Pertussis Vaccine History

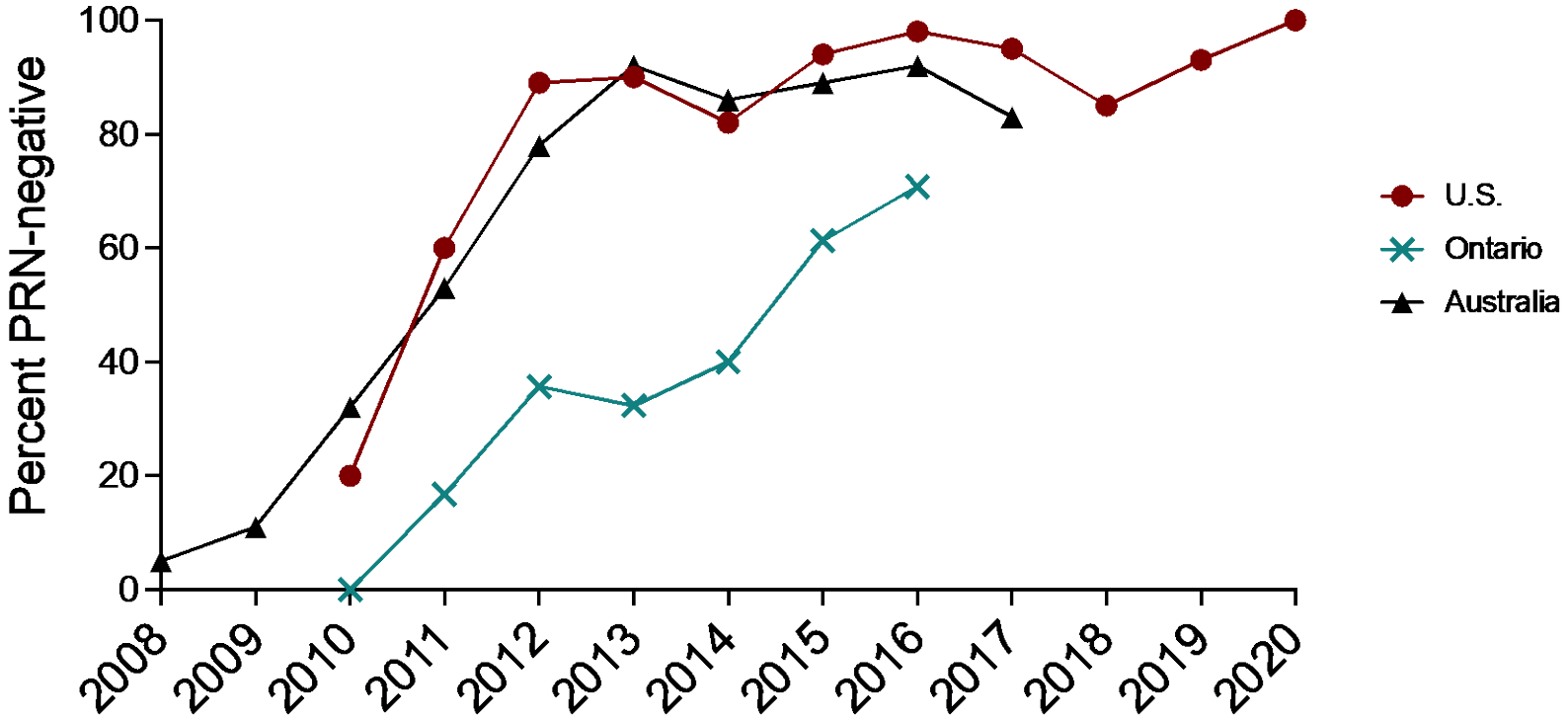


Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service.

Potential Explanations for Increase of Pertussis in the aP Era

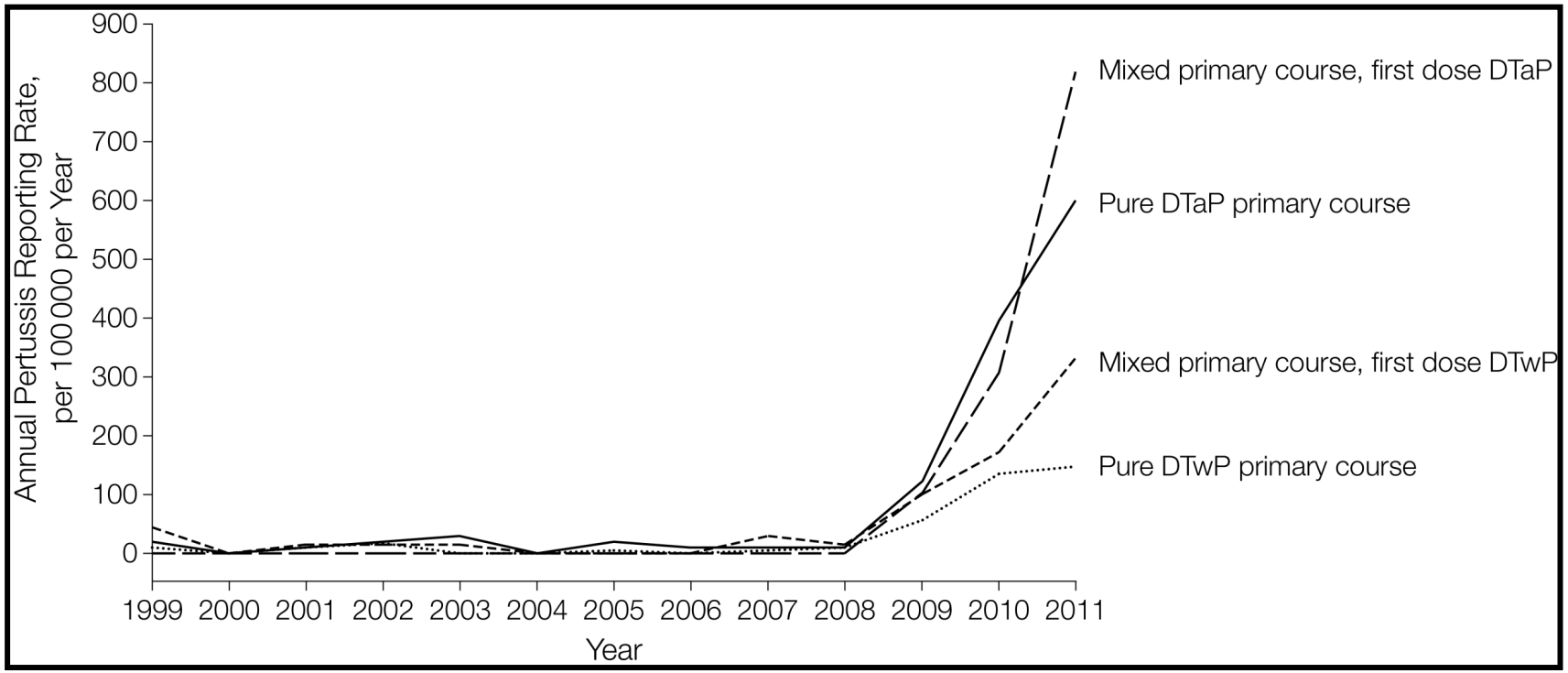
- Increased awareness of pertussis in adolescents and adults.
- Improved diagnostics.
- Genetic adaptation of circulating strains to escape vaccine pressure.
- Rapid waning of aP vaccine-induced immunity relative to wP.
- Failure of aP-containing vaccines to prevent *B. pertussis* colonization, carriage, and transmission.

aP-driven Selection for Vaccine Escape Mutations: Pertactin-negative Strains



Tsang et al., Can J Microbiol. 2019;65(11):823-830.
Xu et al., Emerg Infect Dis. 2019 Jun;25(6):1196-1199.
Lam et al., Emerg Infect Dis. 2014 Apr;20(4):626-33.
CDC, unpublished data.

aP Vaccine Exhibits Reduced Duration of Immunity; Queensland, Australia

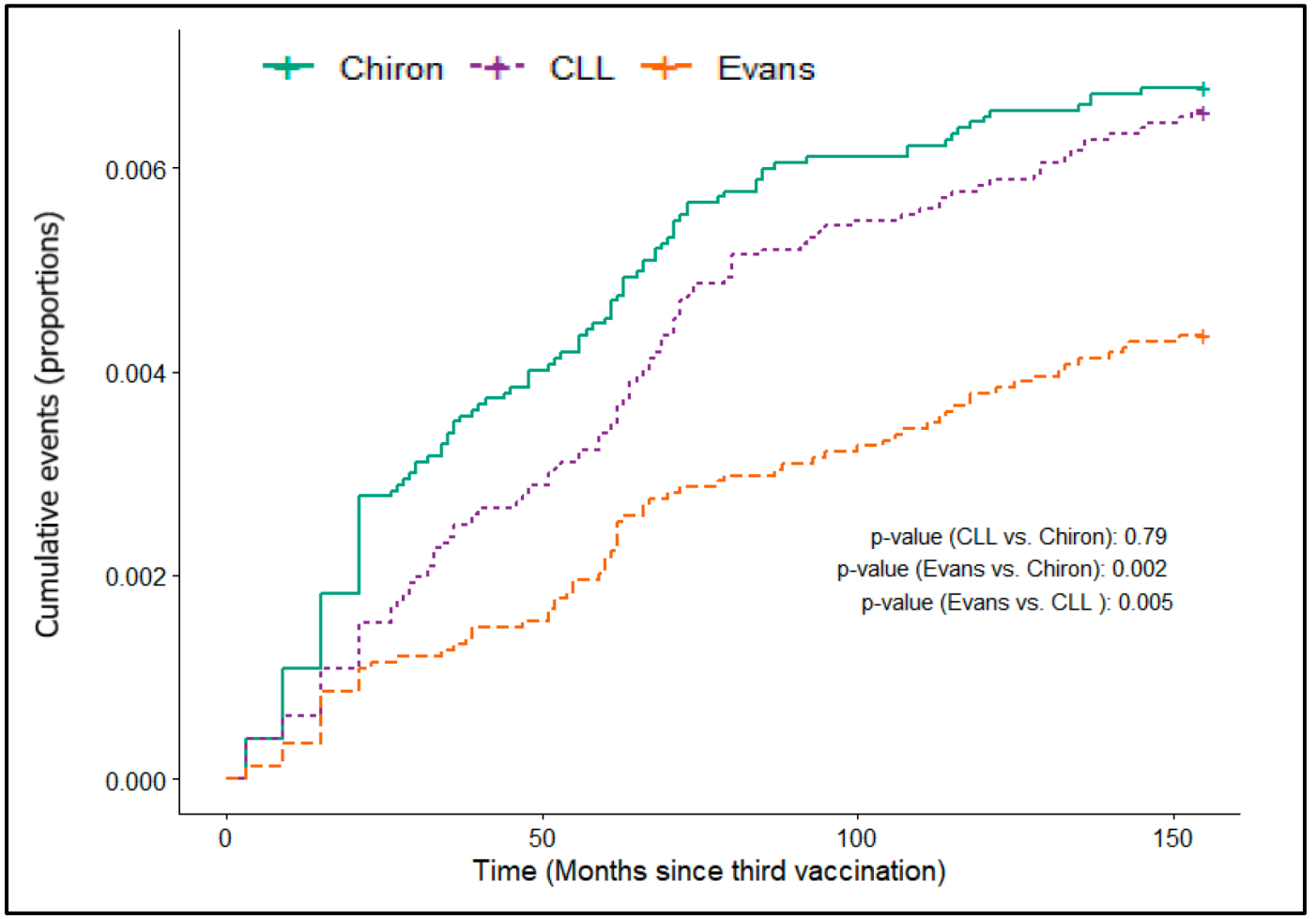


- DTaP replaced DTwP for publicly-funded primary immunizations in March 1999. This meant children born in 1998 could receive a primary course consisting of only DTwP, only DTaP, or a mixed schedule.
- Australia experienced a sustained pertussis epidemic, with the highest incidence rates in Queensland in 2011 in children aged 6 to 11 years. The authors compared pertussis reporting rates by primary course vaccination in the 1998 birth cohort.

Sheridan et al., JAMA. 2012;308(5):454-456.

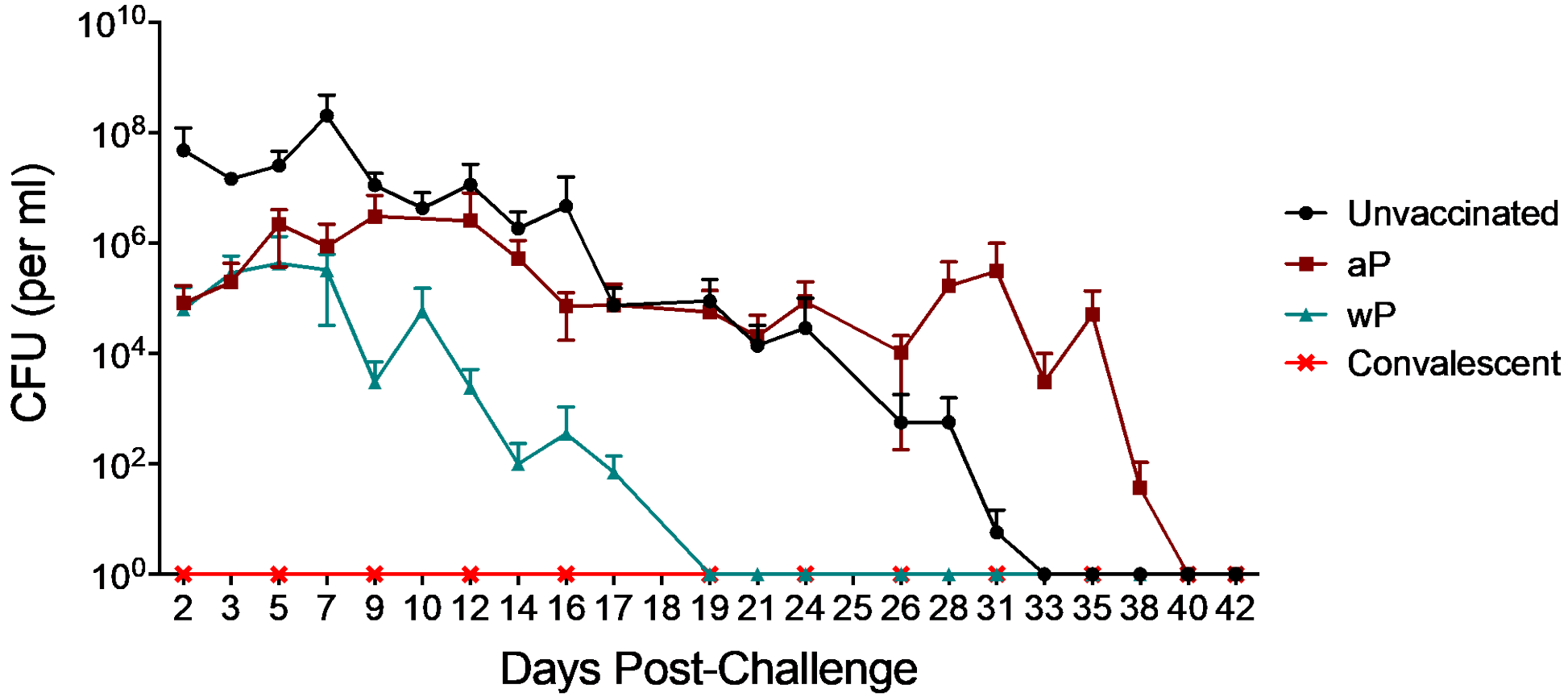
aP Vaccine Exhibits Reduced Duration of Immunity Sweden Efficacy Study: 12-year follow-up

- Sweden discontinued routine childhood vaccination against pertussis between 1979 and 1995, resulting in high incidence of disease.
- 52,818 children born between 1 June 1993, and 30 June 1994, were vaccinated with either:
  - 5-component aP (CLL)
  - 3-component aP vaccine (Chiron)
  - British licensed wP vaccine (Evans)
- The children did not receive booster doses against pertussis.



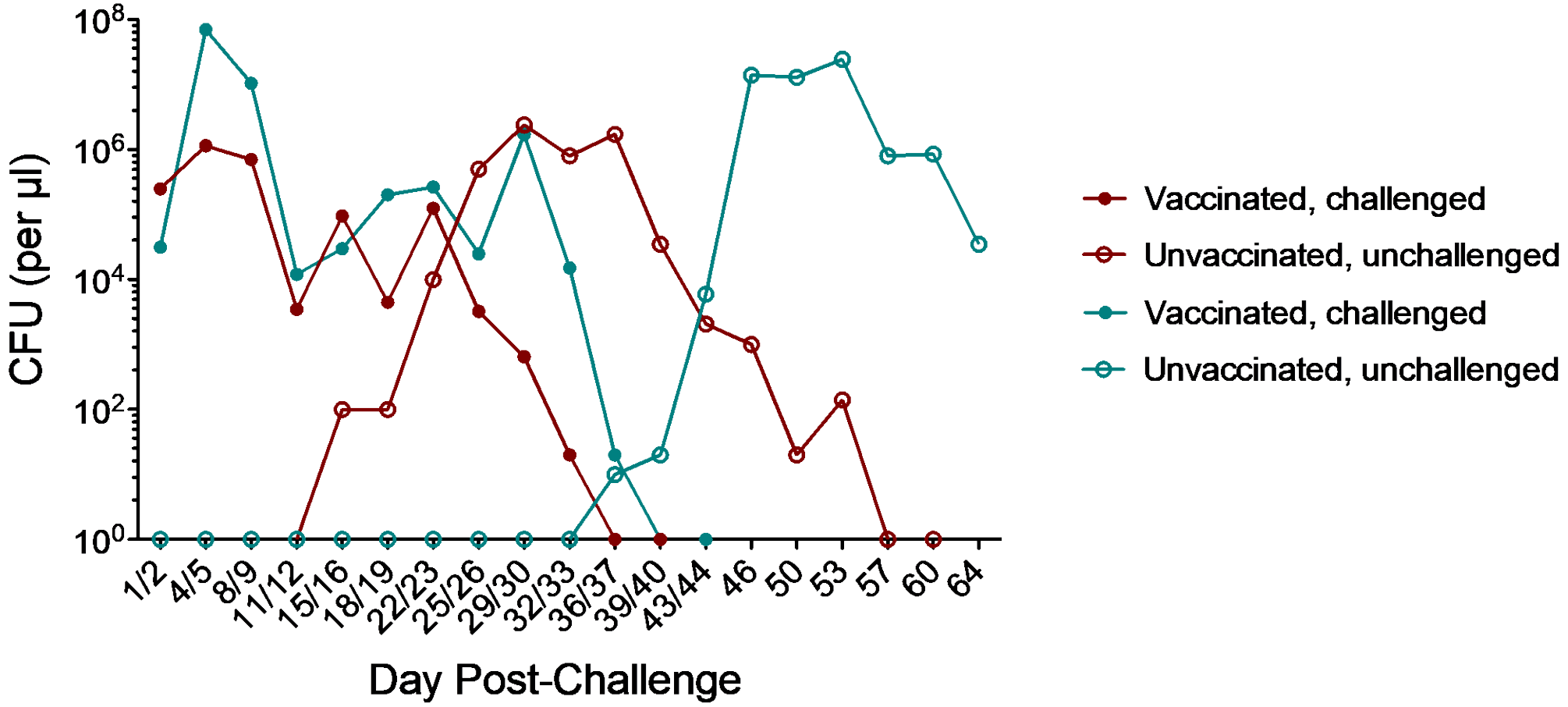
Aronsson et al., Acta Paediatr. 2021.

aP Vaccine Fails to Prevent Colonization and Carriage Baboon Vaccine Studies



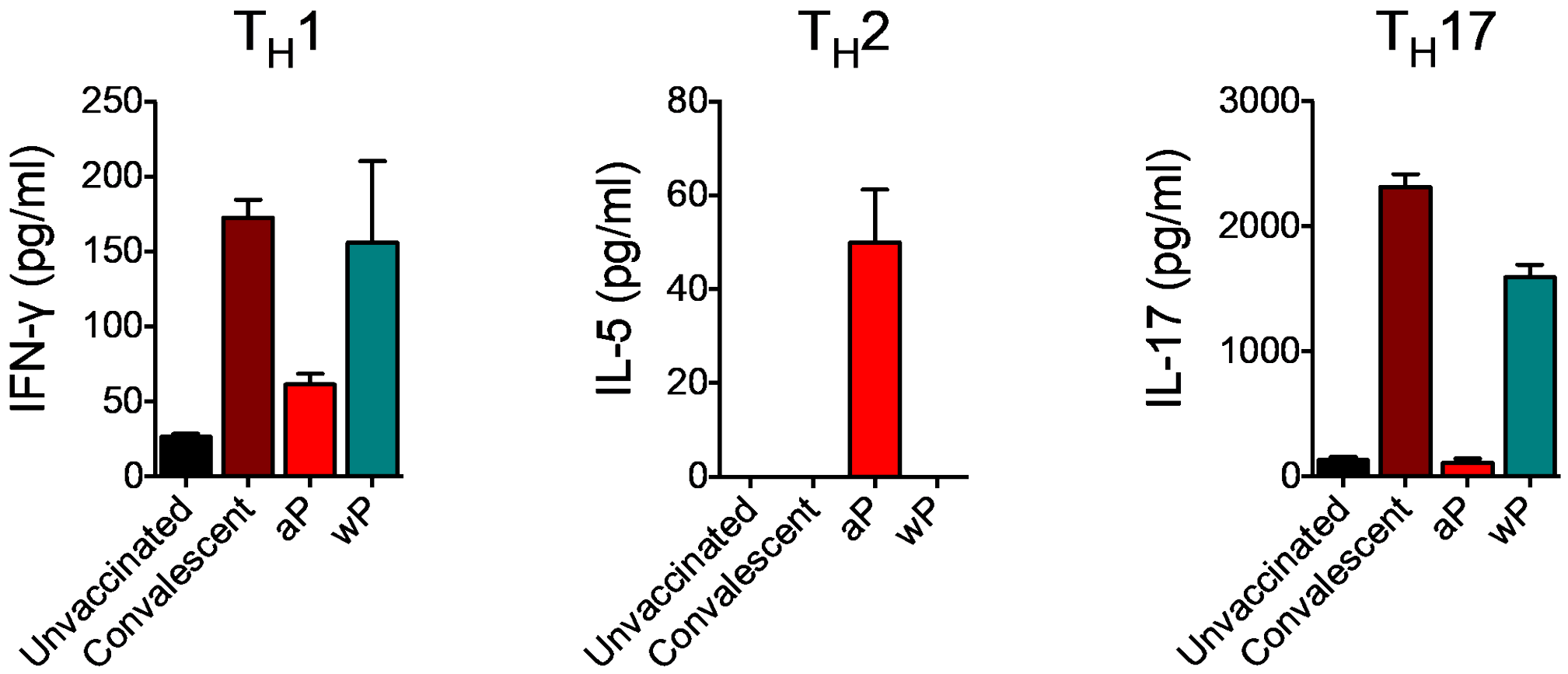
Merkel, TJ, unpublished compiled data

aP-vaccinated Animals Transmit Disease



Warfel et al Proc Natl Acad Sci USA 2014 111(2): 787-782

Exposure Determines Skewing of T-cell Responses in Baboons



Merkel, TJ, unpublished compiled data

Strategies for New Pertussis Vaccines

- Improved subunit (aP) vaccines:
  - New adjuvants to drive more balanced T_H1, T_H2, and T_H17 responses
  - New antigens to target the bacterial cell
- mRNA vaccines
- Whole-cell vaccines engineered to have reduced reactogenicity
- Outer membrane vesicle-based vaccines
- Live attenuated vaccines
- Alternative routes of vaccination to enhance mucosal immune responses

Licensing of aP Vaccines

- Vaccine licensure requires **substantial evidence of effectiveness**
- **Effectiveness**
  - Primarily based on demonstration of **efficacy in preventing clinical disease** in a clinical endpoint efficacy study
  - Can be based on immunologic response when there is a scientifically **well-established immunologic marker that predicts protection** that can be reliably measured in a validated assay
- There is no scientifically well-established immunologic marker of protection for pertussis.

Licensing of DTaP Vaccines

There are two DTaP vaccines licensed in the U.S. for pediatric primary and booster immunizations:

Daptacel

Infanrix

Licensing was based on a demonstration of efficacy in preventing pertussis in clinical endpoint efficacy studies.

Licensing of DTaP-based Combination Vaccines and Tdap Boosters

- Licensed **DTaP-based combination vaccines** contain the same DTaP component as Daptacel or Infanrix plus additional antigens.
  - Effectiveness of the pertussis component was supported by comparative immunogenicity analyses evaluating immune responses relative to separately administered control vaccines, including the relevant DTaP vaccine for which efficacy was demonstrated.
- Licensed **Tdap vaccines** for adolescents and adults contain the same aP components as Daptacel or Infanrix.
  - Effectiveness of the Tdap pertussis component was supported by comparison of pertussis immune responses in Tdap-vaccinated adolescents and adults relative to infants in whom efficacy was demonstrated.

Licensing of DTaP-based Combination Vaccines and Tdap Boosters

Immunobridging was possible due to the DTaP-based combination vaccines and Tdap vaccines having the same aP component as the DTaP-only vaccines for which efficacy was demonstrated.

- ✓ Same pertussis antigens
- ✓ Same manufacturer
- ✓ Same manufacturing process

Licensing of aP Vaccines:
Challenges for new pertussis vaccines

- Prospective clinical endpoint efficacy studies for pertussis are not feasible.
  - Unpredictable and sporadic occurrence of pertussis disease
  - Need for large sample sizes
- New pertussis vaccines cannot be immunobridged to the licensed vaccines.
  - ✘ Different pertussis antigens
  - ✘ New adjuvants driving different immune responses
  - ✘ Different manufacturers and manufacturing processes
  - ✘ No established immunologic marker that predicts protection for pertussis

Pertussis Controlled Human Infection Models (CHIMs)

- May enable the generation of effectiveness data to support licensure of new pertussis vaccines.
- Models in which colonization is established rapidly with a high dose of culture-grown bacteria, in contrast to natural infection with a small dose of bacteria in respiratory droplets.
- Provide data for outcomes only in primed healthy adults.

Discussion Topics

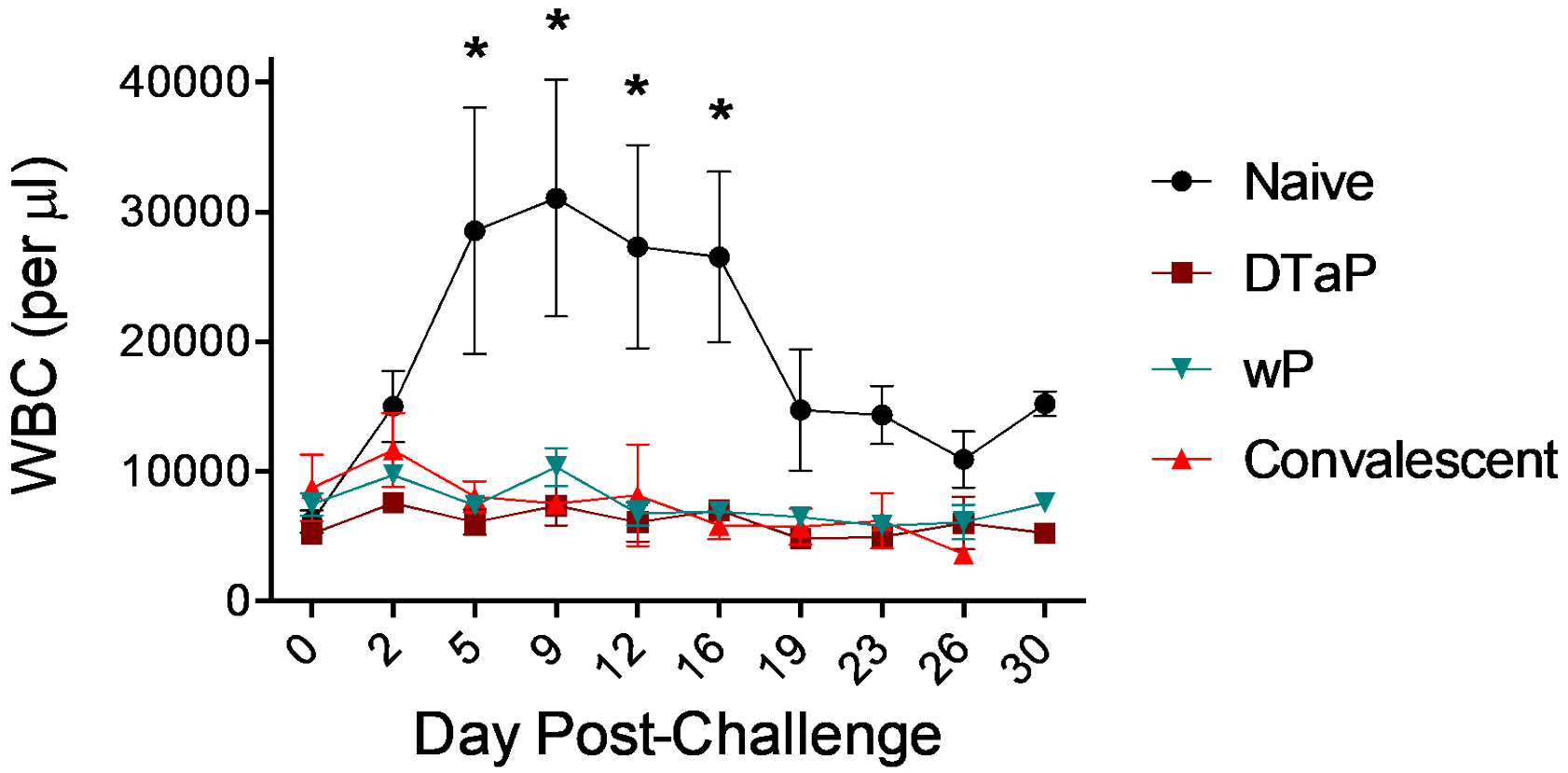
1. **Controlled Human Infection Model—*Disease Endpoint***
    a. Do *B. pertussis* controlled human infection models, in their current stage of development, produce signs and symptoms of disease that accurately and reliably reflect human disease caused by natural infection with *B. pertussis*?
    b. If yes, are *B. pertussis* controlled human infection models, in their current stage of development, sufficiently robust models of natural infection and disease to provide the primary human data to support effectiveness of new pertussis vaccines for booster vaccination of adults?
2. **Controlled Human Infection Model—*Colonization Endpoint***
    a. Can prevention of *B. pertussis* colonization be considered a surrogate endpoint that is reasonably likely to predict clinical benefit, specifically prevention of pertussis disease?
    b. If yes, do *B. pertussis* controlled human infection models of colonization, in their current stage of development, accurately and reliably reflect colonization following natural *B. pertussis* exposure?

Back-up Slides

B. pertussis Causes Disease in the Baboon Model

Merkel, TJ, unpublished compiled data

Baboon Challenges Result in Characteristic Disease



Merkel, TJ, unpublished compiled data

Accelerated approval:

- Qualifying criteria:
  - Serious condition [21 CFR 312.300(b)(1)]
  - Meaningful advantage over available therapies, and
  - Demonstrates effect on surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (i.e., an intermediate clinical endpoint)
- Condition of approval:
  - Postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit. These trials must be completed with due diligence

* https://www .ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-E/section-601.41
** https://www.fda.gov/drugs/accelerated-approval-program/ongoing-infectious-disease-accelerated-approvals-vaccines

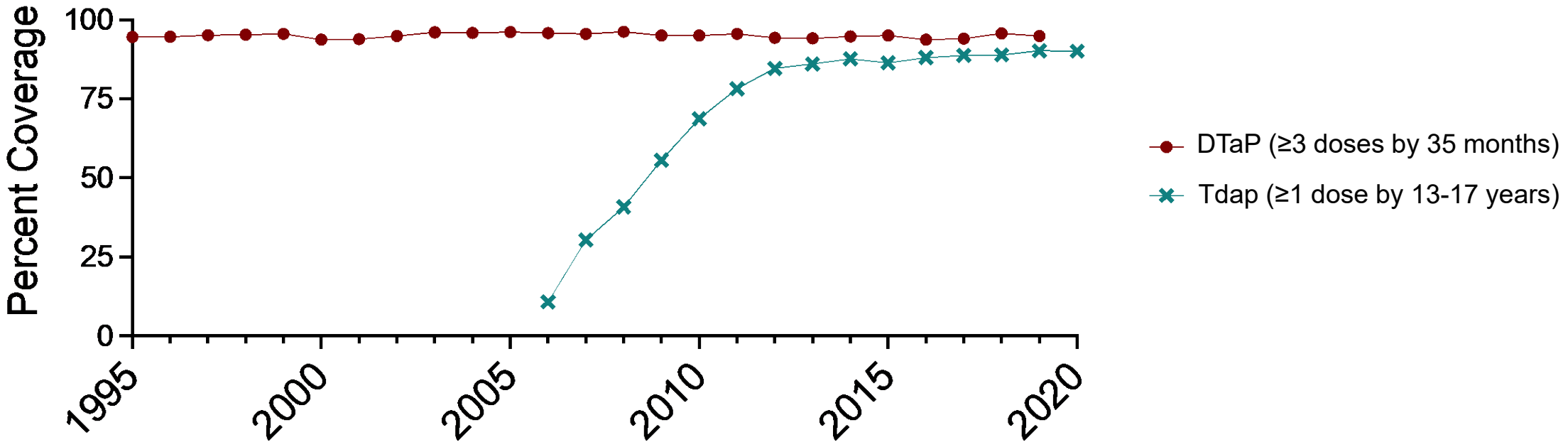
aP Vaccines are Less Reactogenic than wP Vaccines

- A study was conducted that evaluated reaction data following 6375 vaccinations in 2189 infants. The groups included 2 whole-cell (WCL) and 13 acellular pertussis vaccines that differed in the source, manufacture, and quantity of included antigens.

- For every acellular vaccine, every monitored reaction except vomiting occurred at a significantly lower frequency and severity than was seen with WCL.

Decker et. al., Pediatrics 1995;96;557.

DTaP and Tdap Coverage



Source: CDC National Immunization Survey.