# Pertussis Epidemiology and Vaccine Impact in the United States

**Stacey Martin, MSc**
Epidemiology Team Lead
Meningitis and Vaccine Preventable Diseases Branch
Centers for Disease Control and Prevention

**Presented at Fondation Mérieux Conference - Pertussis: biology, epidemiology and prevention**

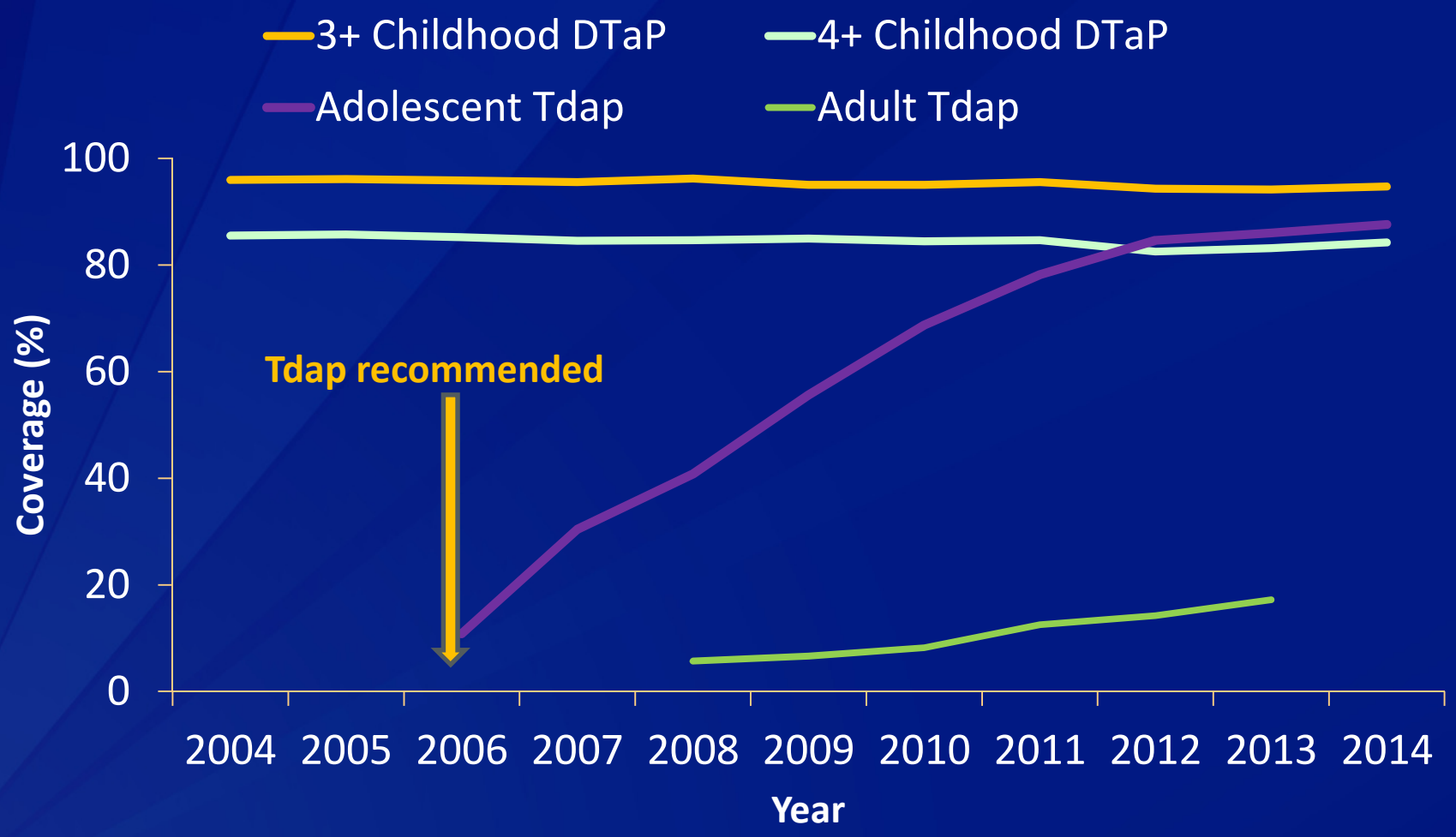
**11-13 November 2015**

National Center for Immunization & Respiratory Diseases
Division of Bacterial Diseases

# Reported NNDSS pertussis cases: 1922-2014

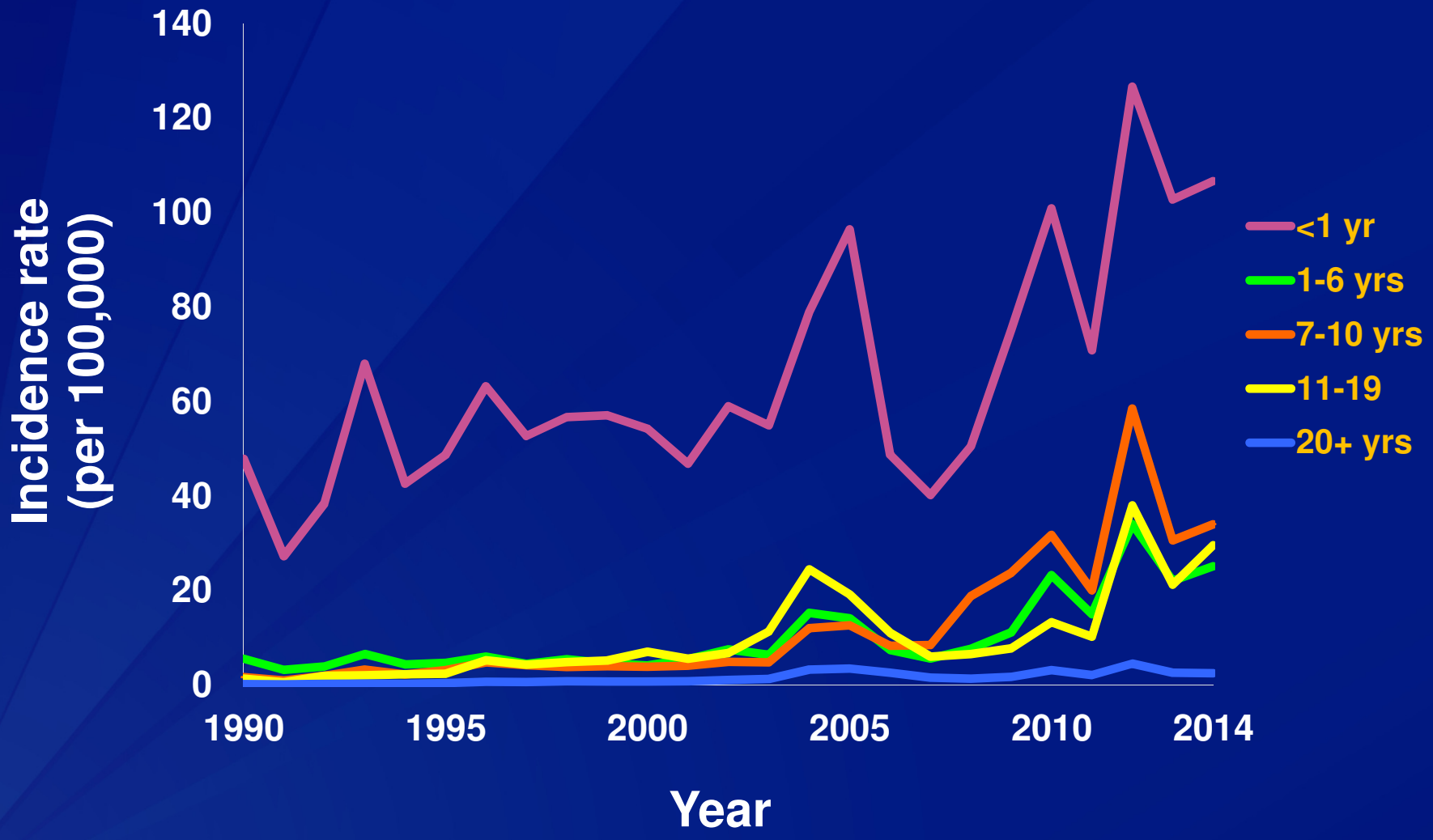

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

# DTaP Coverage Among Children and Tdap Coverage Among Adolescents and Adults




*CDC National Immunization Survey: DTaP among children aged 19 through 35 months , Tdap coverage among adolescents aged 13 through 17 years . Coverage among adults aged 19 through 64 years from National Health Information Survey .

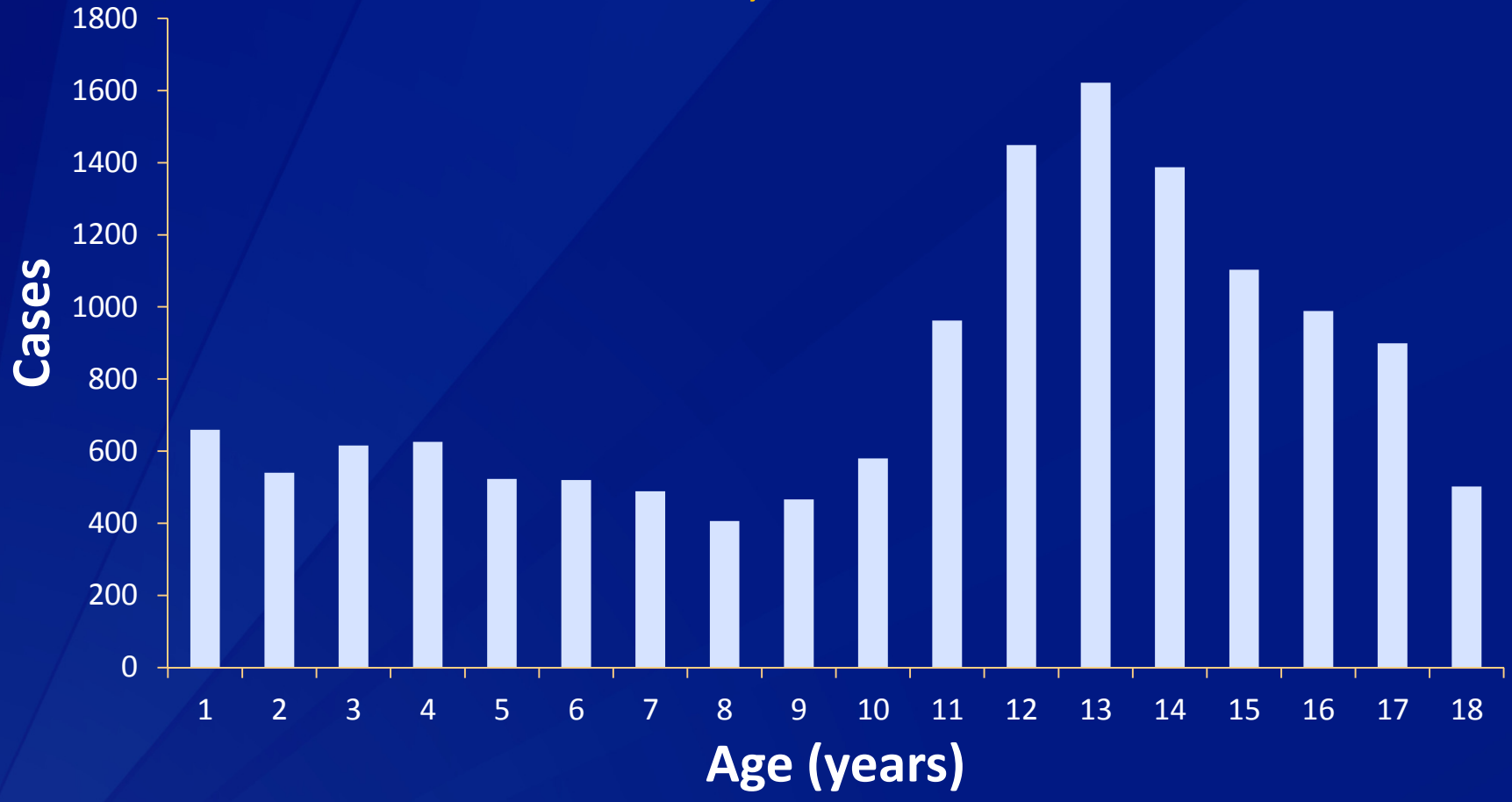
# Reported pertussis incidence by age group: 1990-2014




SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

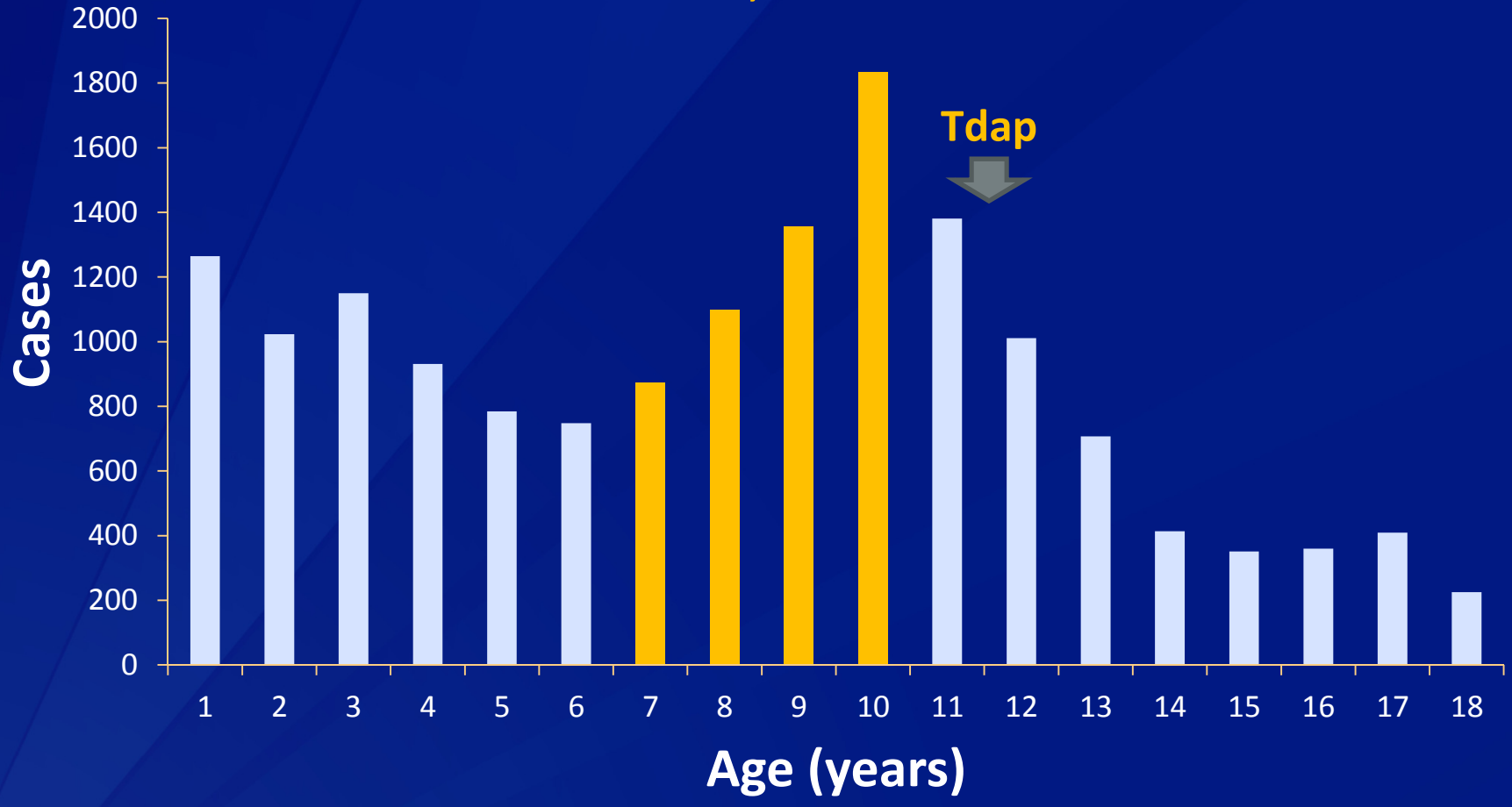
# Pertussis cases by age — United States, 2004

n=25,827




# Pertussis cases by age — United States, 2010

n=27,550




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

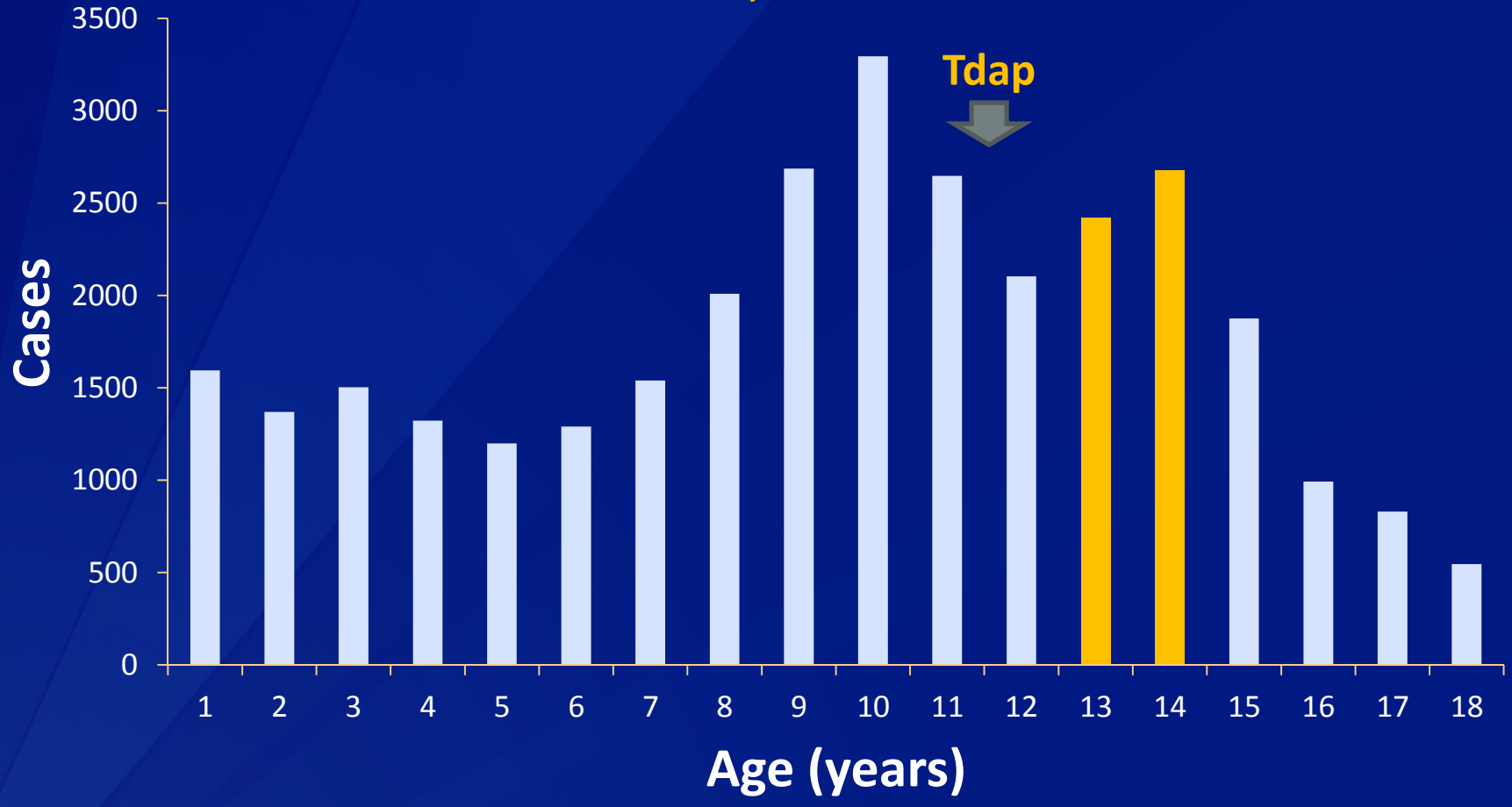
| Model * | Case (n) | Control (n) | VE, % | 95% CI |
|---|---|---|---|---|
| Overall VE, All Ages | | | | |
| 0 dose | 53 | 19 | Ref | -- |
| 5 doses | 629 | 1,997 | 88.7 | 79.4 – 93.8 |
| Time since 5th dose | | | | |
| 0 doses | 53 | 19 | Ref | -- |
| < 12 months | 19 | 354 | 98.1 | 96.1 – 99.1 |
| 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 |

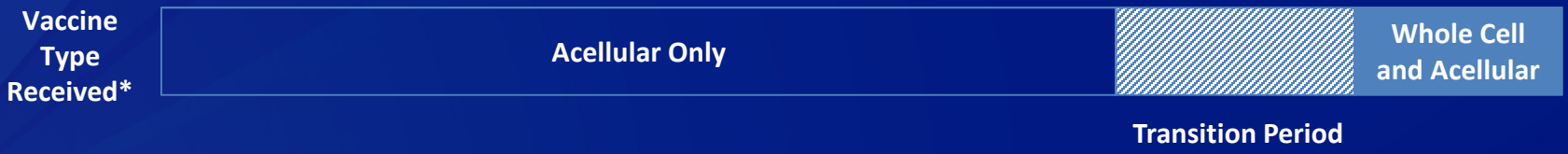
[1]JAMA. 2012;308:2126-2132.

*Accounting for clustering by county and provider

# Pertussis cases by age — United States, 2012

n=48,277



# Tdap duration of protection among populations born during 1998-2000, that only received acellular vaccines, Washington and Wisconsin, 2012

**Vaccine Effectiveness (VE)**

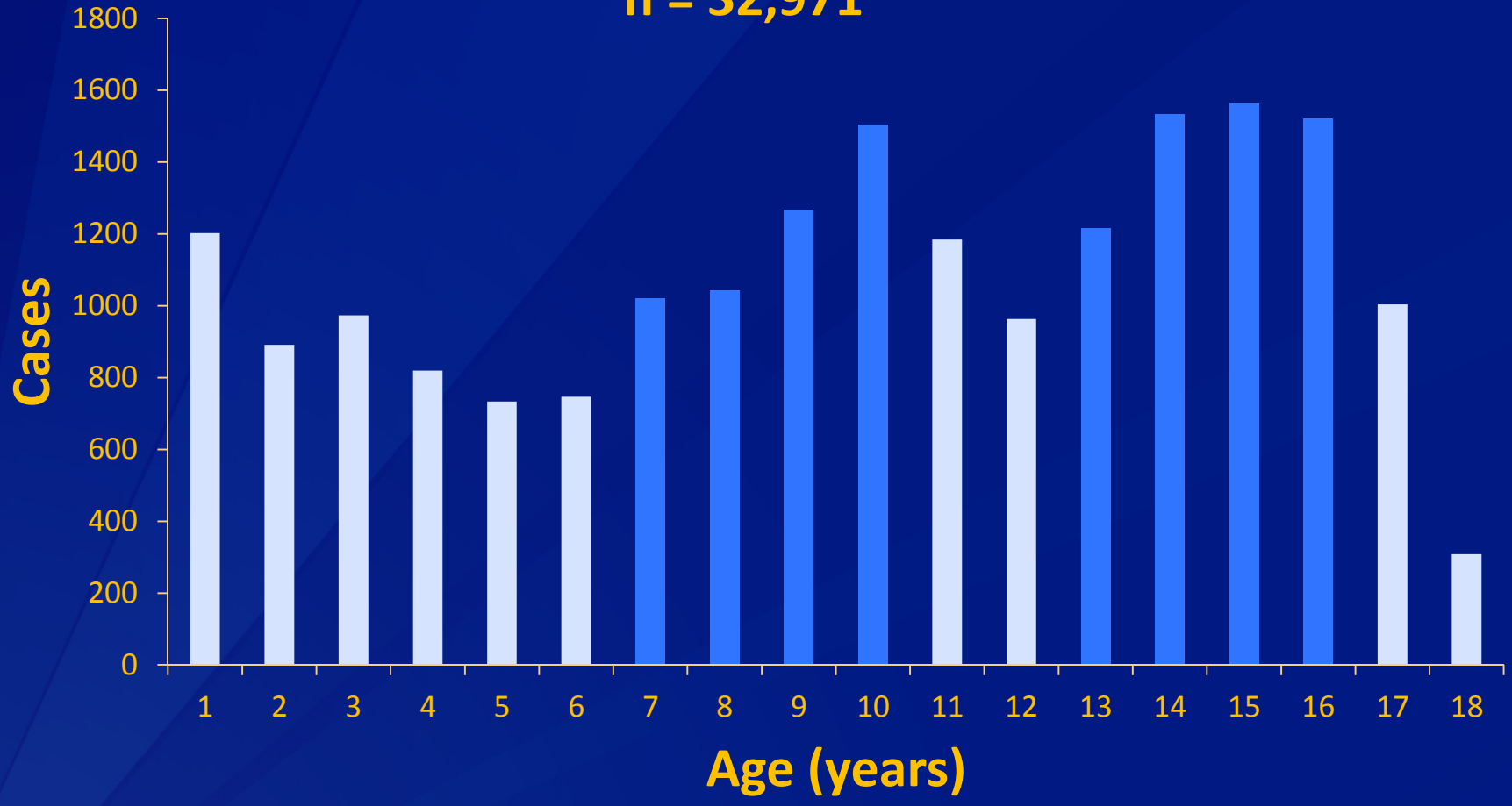
| Washington[1] | | Wisconsin[2] | |
|---|---|---|---|
| **Time since Tdap** | **VE, % (95% CI)** | **Year of Tdap Receipt** | **VE, % (95% CI)** |
| No Tdap | Reference | No Tdap | Reference |
| < 1 year | 73.1 (60.3-81.8) | 2012 | 75.3 (55.2-86.5) |
| 1 - < 2 years | 54.9 (32.4-70.0) | 2011 | 68.2 (60.9-74.1) |
| 2 - < 4 years | 34.2 (-0.03-58.0) | 2010 | 34.5 (19.9-46.4) |
| | | 2009/2008 | 11.9 (-11.1-30.1) |

[1]Acosta et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics 2015, 135(6):981-989.

[2]Koepke et al. Estimating the Effectiveness of Tdap Vaccine for Preventing Pertussis: Evidence of Rapidly Waning Immunity and Differences in Effectiveness by Tdap Brand. The Journal of Infectious Diseases 2014.

# U.S. Pertussis Cases by Age — 2014

## n = 32,971

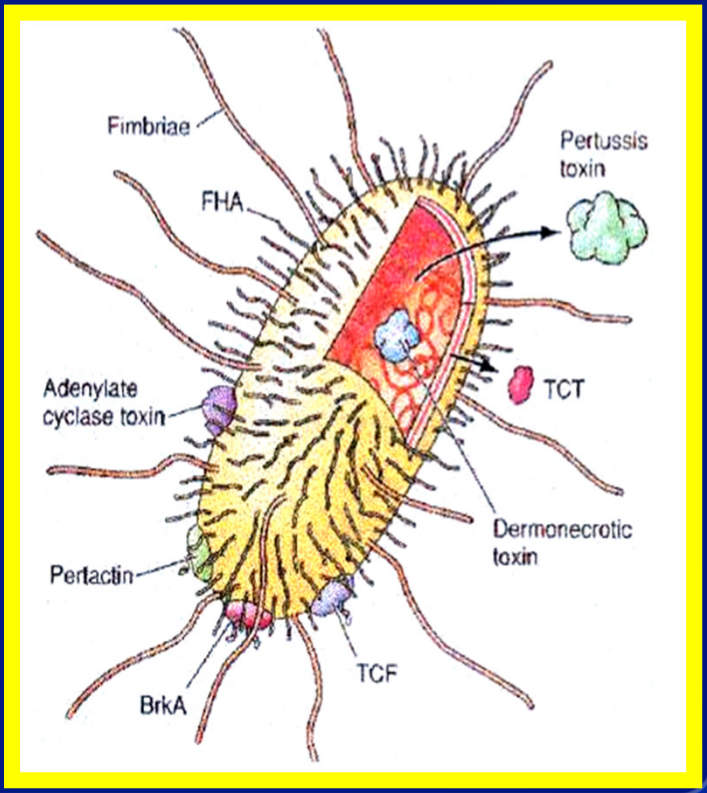



| Vaccine Type Received* | Acellular Only | Whole Cell and Acellular |
|---|---|---|

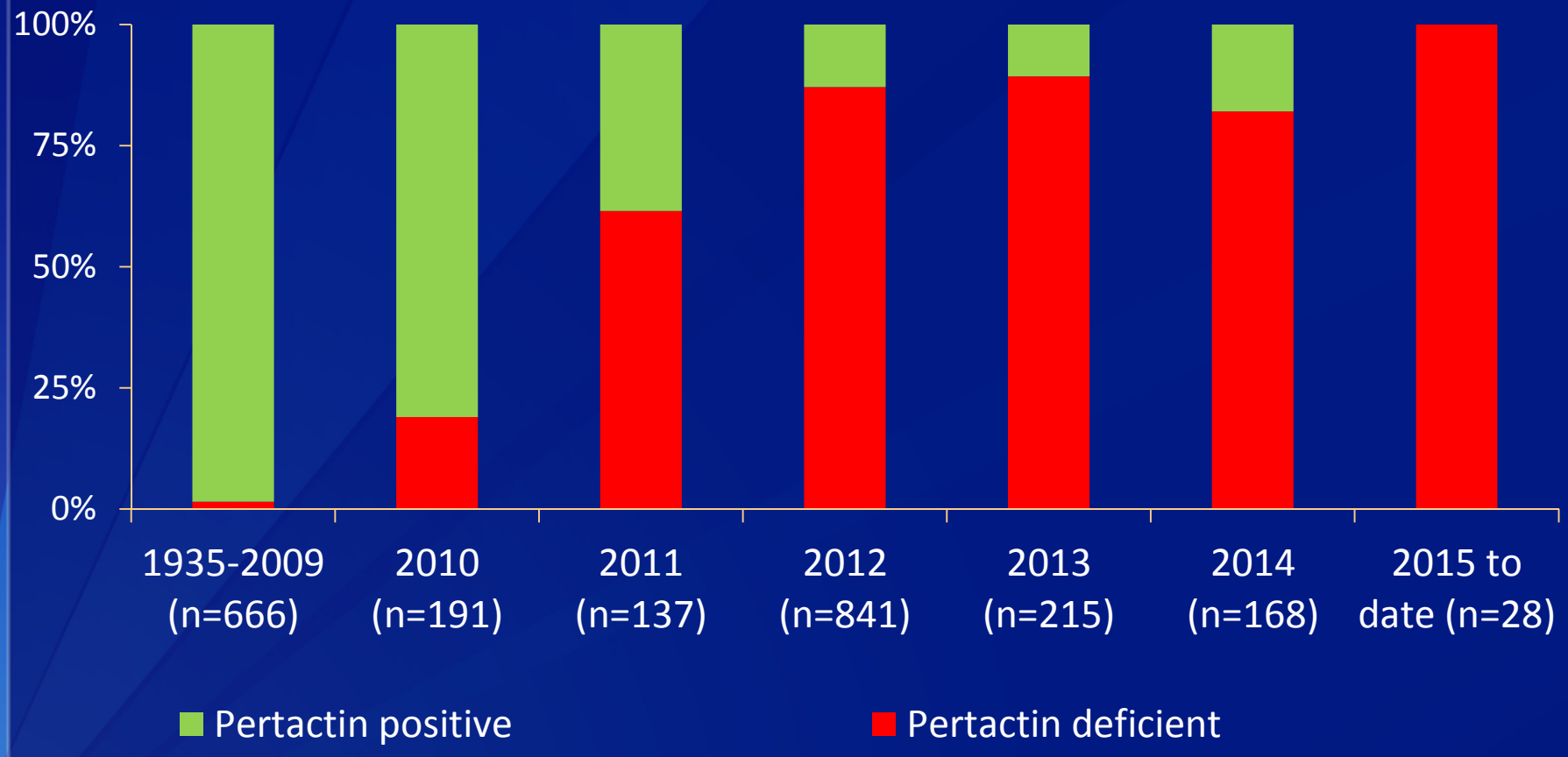
Source : CDC National Notifiable Disease Surveillance System, 2014

# Antigenic and Biologically Active Components

- pertussis toxin (PT)
- filamentous hemagglutinin (FHA)
- pertactin
- fimbriae
- agglutinogens
- adenylate cyclase
- tracheal cytotoxin



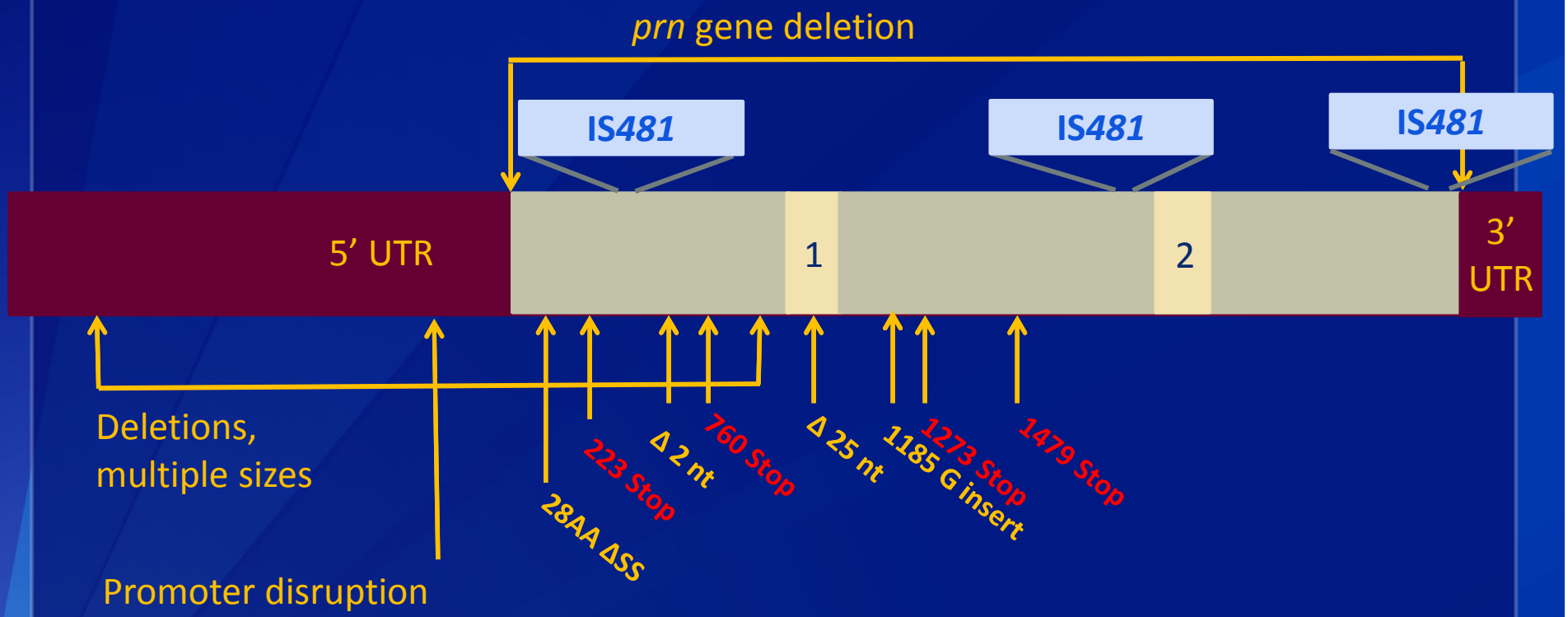
# Proportion of *B. pertussis* Isolates from the United States Lacking Prn




Pawloski LC et al. Clin. Vaccine Immunol. 2014; 21:119-25

Martin SW et al. Clin Infect Dis. 2015; 60:223-7

# Mutations Causing Lack of Prn



# Clinical and Epidemiological Significance of Pertactin-Deficient *B. pertussis*

- **Epi-Analysis of 753 isolates and corresponding case data**
  - Isolates from 2012
    - 6 Enhanced Pertussis Surveillance (EPS) sites plus epidemics in WA and VT
  - Pertactin-deficiency (PRN-) fully assessed
  - 85% were PRN-
    - All states had a high proportion of PRN- isolates
  - Proportion of patients reporting pertussis symptoms similar by pertactin status
    - Except more without the deficiency reported apnea (p-value=0.005)
  - Vaccinated patients had a higher odds of having PRN- *B. pertussis* as compared to unvaccinated (OR=3.2; 95% CI= 1.9-5.3)
    - When vaccinated patients were restricted to those up-to-date with vaccinations the OR increased to 3.7 (95% CI=1.9-7.0).

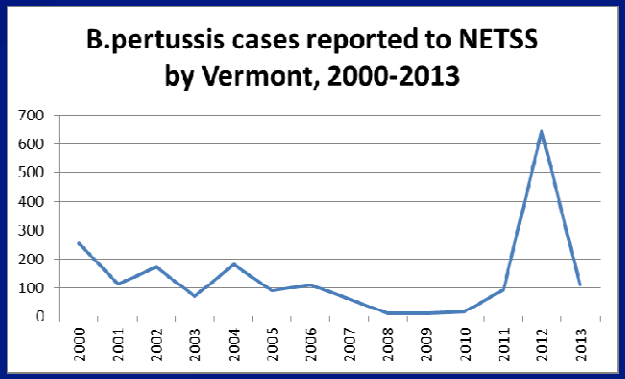
Martin SW et al. Pertactin-negative Bordetella pertussis strains: evidence for a possible selective advantage. CID 2015, 60(2):223-227.

## Summary: Pertactin-Deficient *B. pertussis*

- **The ~3-fold greater odds of having PRN- *B. pertussis* when up-to-date with vaccinations compared to unvaccinated**
  - First evidence for a possible selective advantage of PRN- strains
- **The large number of mutations (>16)**
  - Vaccine pressure may have played a significant role in the emergence of PRN- strains
- **Next step: vaccine effectiveness in pertactin-deficient strains**
  - Case-control evaluation in Vermont

# Impact of Pertactin-deficiency on Vaccine Effectiveness: Vermont VE Evaluation

- **Vermont reported 645 cases in 2012**
  - (103/100,000 population)
- **Centralized testing at the VT SPHL**
  - All PCR+ specimens are cultured
  - 94% of tested isolate are Prn-deficient




**Objective:**

- **Estimate VE and duration of protection**
  - 5-dose DTaP series among 4-10 year olds
  - Tdap dose among 11-19 year olds

*slide provided by Anna Acosta, MD (MVPDB/CDC)

# DTaP Duration of Protection

**Do not distribute – pending publication**

| Vaccine Status | Case (n) | Control (n) | VE % (95% CI) |
|---|---|---|---|
| No DTaP doses | 19 | 11 | 84 (58-94) |
| 5 on-schedule DTaP doses | 244 | 715 | |

**Duration of Protection**

| Time since 5th DTaP (years) | Case (n) | Control (n) | VE % | (95% CI) |
|---|---|---|---|---|
| No DTaP doses | 19 | 11 | | Ref |
| <1 | 19 | 95 | 90 | (71-97) |
| 1 – 2 | 21 | 144 | 93 | (79-98) |
| 2 – 3 | 28 | 119 | 89 | (69-96) |
| 3 – 4 | 33 | 120 | 87 | (63-95) |
| 4 – 5 | 60 | 113 | 76 | (33-91) |
| 5 – 7 | 83 | 124 | 68 | (10-88) |

*slide provided by Anna Acosta, MD (MVPDB/CDC)

# Tdap Duration of Protection

**Do not distribute – pending publication**

| Vaccine status | Case | Control | VE % (95% CI) |
|---|---|---|---|
| No Tdap dose | 103 | 163 | 70 (54-81) |
| 1 on-schedule Tdap | 141 | 551 | |

**Duration of Protection**

| Time since Tdap (years) | Case | Control | VE % (95% CI) |
|---|---|---|---|
| No Tdap dose | 103 | 163 | Ref |
| <1 | 35 | 202 | 76 (60-85) |
| 1 – 2 | 51 | 180 | 63 (37-78) |
| 2 – 4 | 55 | 169 | 56 (16-77) |

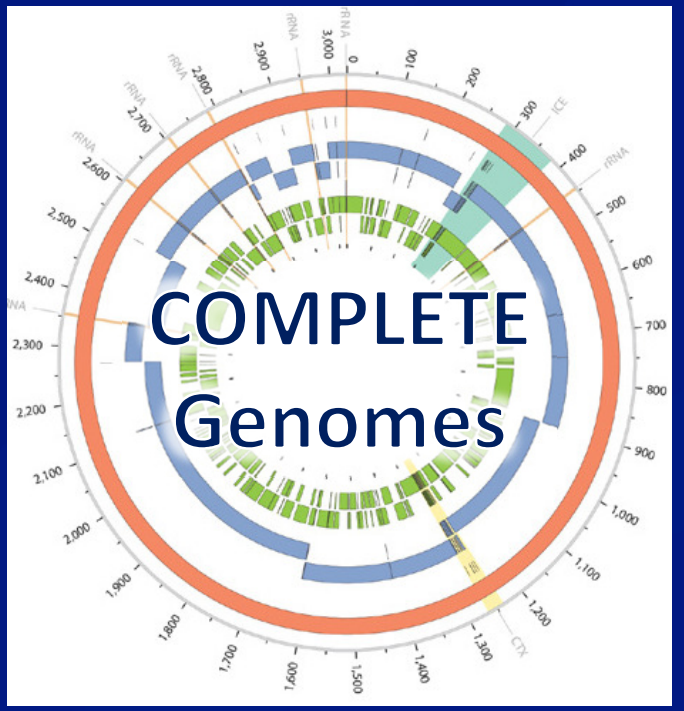
*slide provided by Anna Acosta, MD (MVPDB/CDC)

# Vaccine Effectiveness among Pertactin-Deficient Strains – Tdap

**Do not distribute – pending publication**

| Tdap | No. of doses | Case | Control | VE % (95% CI) |
|---|---|---|---|---|
| All | 0 | 103 | 163 | 70 (54-81) |
| | 1 | 141 | 551 | |
| | Total | 244 | 714 | |
| Pertactin-deficient strains only | 0 | 33 | 62 | 51 (5-75) |
| | 1 | 71 | 246 | |
| | Total | 104 | 308 | |

*slide provided by Anna Acosta, MD (MVPDB/CDC)




# CDC'S ADVANCED MOLECULAR DETECTION INITIATIVE

# *B. pertussis* Genome Sequencing

| | Year | Selected | Sequenced | CLOSED Assembly |
|---|---|---|---|---|
| Geographic Diversity | 2000 – 2013 | 175 | 101 | 81 |
| Enhanced Pertussis Surveillance | 2011 – 2014 | 117 | 92 | 82 |
| California Epidemic | 2010 | 13 | 13 | 13 |
| Vermont Epidemic | 2012 | 20 | 20 | 20 |
| Prospective, Non-EPS | 2014 | 88 | 48 | 9 |
| Other* | | 20 | 14 | 10 |
| | **Total** | **433** | **288** | **215** |

* Other
Vaccine strains (Tohama I, CS, Sanofi-Pastuer)
Pertussis toxin-negative (2)
Filamentous hemagglutinin-negative (2)

All assemblies yield closed genomes that will be publically-available via NCBI.

*slide provided by Michael Weigand, PhD (MVPDB/CDC)

# *B. pertussis* Comparative Genomics, mid-2014

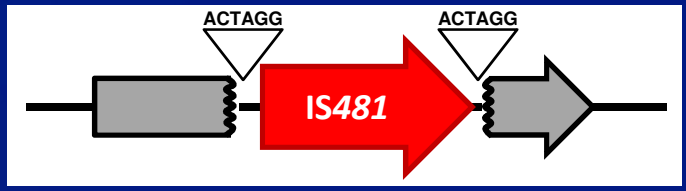
- Limited ability to detect variation with short-read technologies, challenged by:
  - High G+C content
  - Repeat regions
  - High copy number of insertion sequence elements (IS*481*)
- Genomics based on reference sequence of Tohama I through resequencing efforts

**Sequence (SNPs)**

Very few nucleotide differences in most genes


**IS*481***

Occasional gene disruption (e.g. *prn*)




RESULT: Global population appeared

**CLONAL and MONOMORPHIC**

**(despite unexplained variation in PFGE)**

*slide provided by Michael Weigand, PhD (MVPDB/CDC)

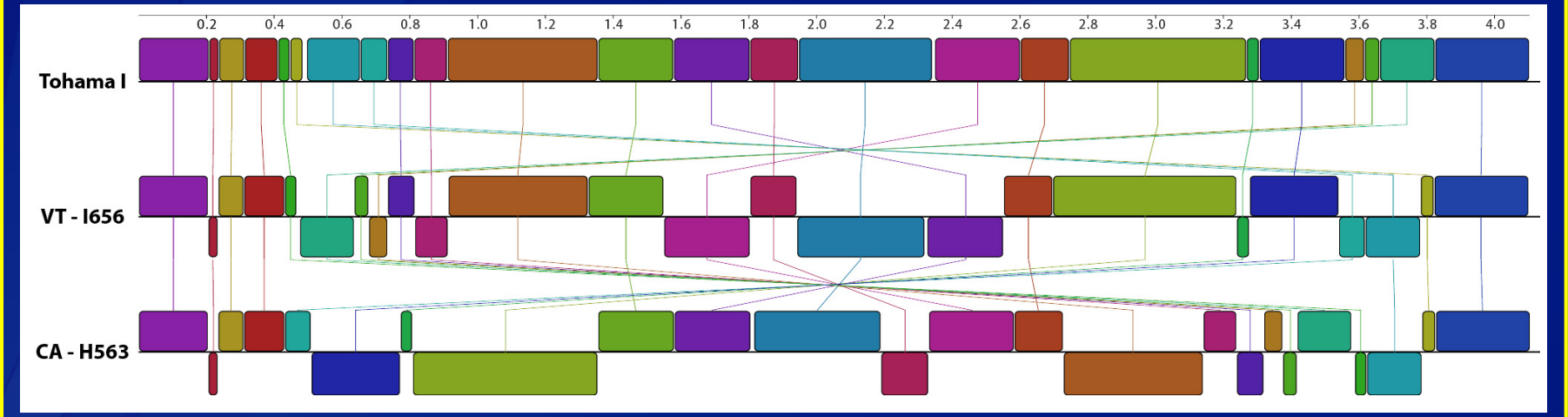
# Complete Genome View of *B. pertussis*

Reference-free, comprehensive detection of all variation:

- **Sequence**
  - SNPs, insertions/deletions
- **Structural/Organization**
  - IS-element stability
  - Genome architecture

## Rearrangements

Genome structure varies between *B. pertussis* strains:

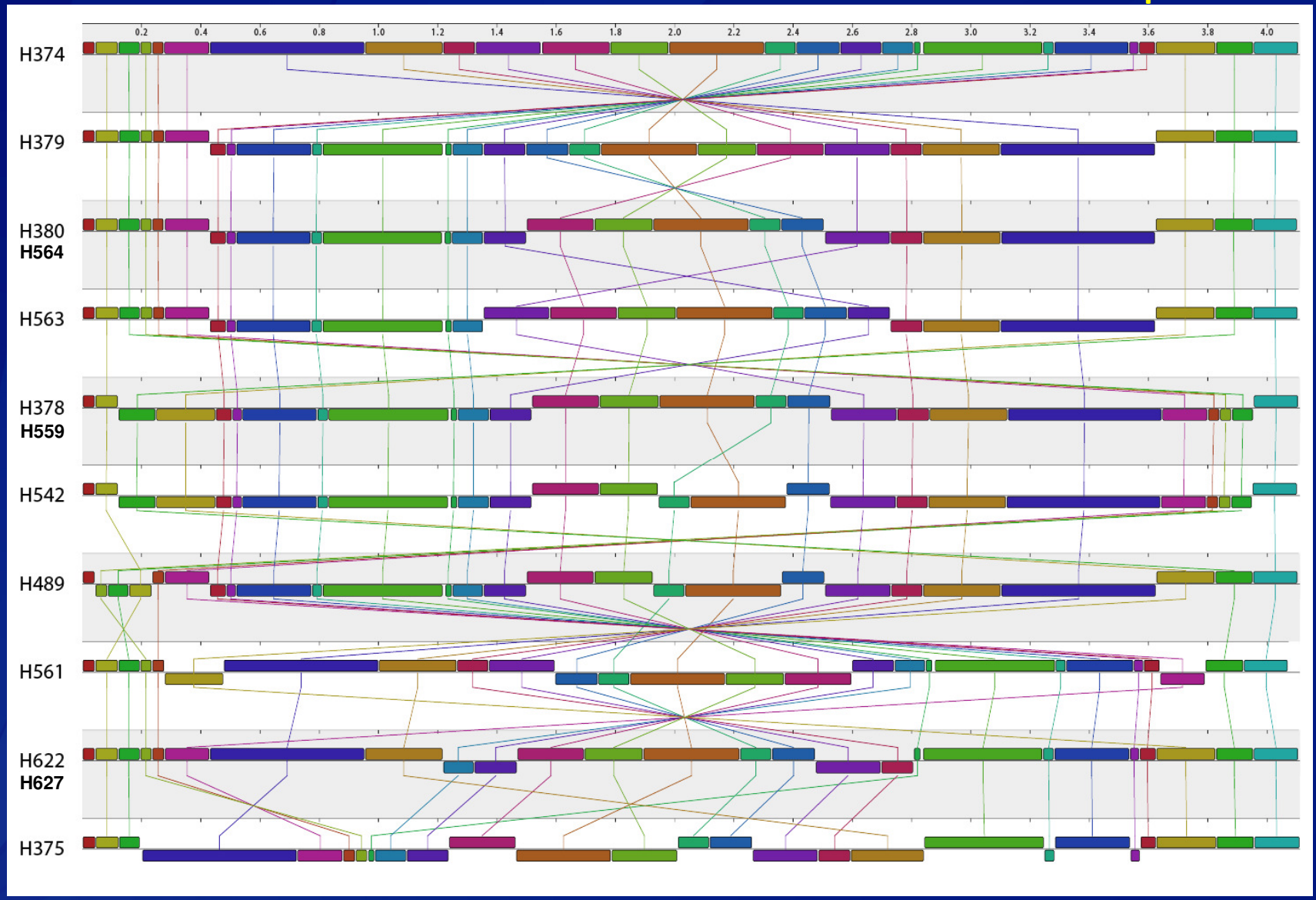



**Only resolvable with CLOSED (complete) assemblies**

*slide provided by Michael Weigand, PhD (MVPDB/CDC)

# Genome Structural Diversity Within an Epidemic

**Example: CA 2010**




*slide provided by Michael Weigand, PhD (MVPDB/CDC)

Progressive Mauve (Darling et al. 2010, PLoS ONE )

# VACCINATION STRATEGIES TO PROTECT INFANTS

# Changing pertussis epidemiology – shift in source of transmission to infants

- **Previously, parents commonly identified as source**
  - Mothers most often
- **More recently, siblings identified as most common source**
  - Having a sibling was a risk factor for infant pertussis
  - Source of infection study
    - 2006-2013 a source of infection for 44% of identified infant pertussis cases
    - 85% of identified sources were classified as family members
      - Siblings most commonly identified (35.5%)

Wendelboe AM, et al. PIDJ 2004; 23(11):985-989;
de Greeff SC, et al. CID 2010 May 15;50(10):1339-45;
Jardine A, et al. Commun Dis Intell, 2010. 34(2):116-21;
Wiley KE, et al. Vaccine. 2013 Jan 11;31(4):618-25;
Bertilone C, et al. Commun Dis Intell Q Rep. 2014 Sep 30;38(3):E195-200;

Skoff, et al. Sources of Infant Pertussis Infection in the United States. Pediatrics. 2015 Oct;136(4):635-41.

# Tdap coverage among pregnant women from various sources, United States

- **Vaccine Safety Datalink sites**
  - 13.7% (2012)
- **Michigan Medicaid**
  - 14.3% (2011-2013)
- **2014-2015 Internet Panel Survey of pregnant women, during flu season**
  - 23.5% (2014-2015 flu season)

Kharbanda EO, et al. Receipt of pertussis vaccine during pregnancy across 7 Vaccine Safety Datalink Sites. Prev Med. 2014 Oct;67:316-9.

Housey M et al. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid--Michigan, 2011-2013 MMWR Morb Mortal Wkly Rep. 2014 Sep 26;63(38):839-42.

CDC. Internet Panel Survey. Women aged 18–49 years pregnant at any time since August of prior year (e.g. 2014 for the April 2015 survey) were recruited in a general population internet panel operated by Survey Sampling International.

# Effectiveness of Maternal Tdap Vaccination Strategies at Preventing Infant Pertussis

- **Objective:** Measure effectiveness of vaccination during pregnancy at preventing pertussis among infants <6 months of age ( <2 months, 2-<6 months groups)
- **CA, CT, MN, NM, NY, OR**
- **Case-control evaluation; 1:3**
  - Cases: Confirmed and probable pertussis cases, also PCR+ cases with cough of any duration; cough onset 1/1/11 – 12/31/14
  - Controls: birth certificates; selected by age group & birth hospital
- **Provider-verified vaccination status:**
  - Case/control infants and mothers

*slide provided by Tami Skoff, MS (MVPDB/CDC)

# Effectiveness of Maternal Tdap Vaccination Strategies at Preventing Infant Pertussis

- **Exclude cases and controls <2 weeks**
  - Disproportionate number of controls <2 weeks
- **Multivariate models control for:**
  - Infant age in weeks
  - More than 2 family members in the household
  - Hispanic ethnicity
  - Income less than $75,000/year
  - Mother did not attend any college
  - Infant was breastfed at any time (for any length of time)
  - Someone in the home diagnosed with pertussis

*slide provided by Tami Skoff, MS (MVPDB/CDC)

# PRELIMINARY VE of Tdap During Pregnancy at Preventing Pertussis in Infants <2 Months

*slide provided by Tami Skoff, MS (MVPDB/CDC)

# PRELIMINARY VE of Tdap During Pregnancy at Preventing Pertussis in Infants <2 Months, Stratified by Trimester

*slide provided by Tami Skoff, MS (MVPDB/CDC)

# Possible Contributing Factors

- **Surveillance bias**
  - ***However***, changes in risk by age strongly suggest a cohort effect
- **Vaccine refusal or under-vaccination**
  - ***However***, coverage is excellent and majority of cases are vaccinated and outbreaks are widespread
- **Waning of immunity after vaccination**
  - Studies provide strong evidence of waning of protection
- **Type of immune response**
  - Animal models suggest aP vaccines may not prevent infection and transmission
- **Molecular changes in the population of *B. pertussis***
  - Yes, ***but*** impact on disease and transmission is still uncertain

# Thank You

## www.cdc.gov/pertussis

## www.cdc.gov/pregnant

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov