Red Book Update: 2018

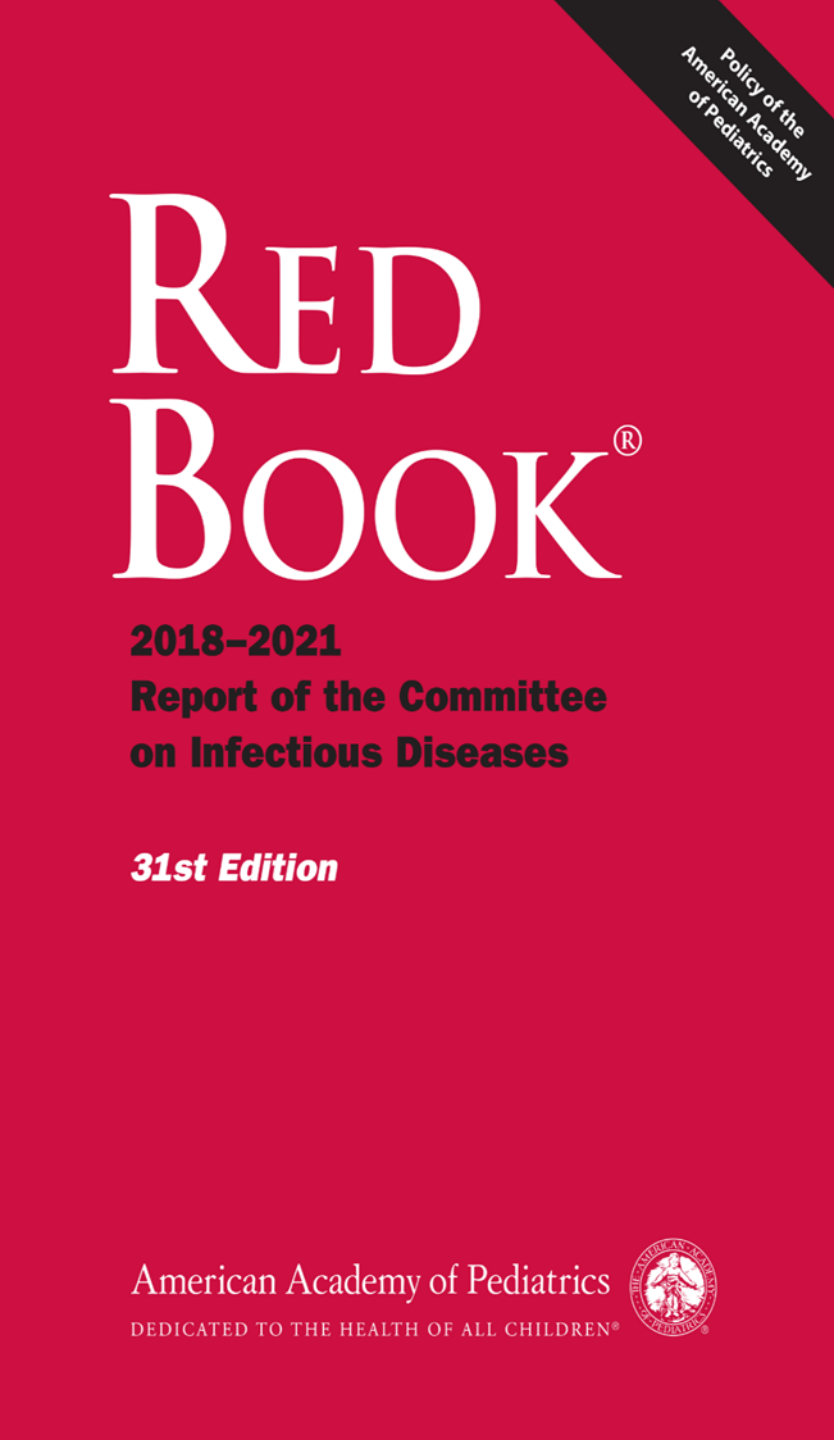
Michael T. Brady, MD
Professor of Pediatrics
The Ohio State University
Associate Medical Director
Nationwide Children's Hospital

Red Book Update: 2018

Michael T. Brady MD

Neither I nor my spouse/partner have any relevant financial relationships with the manufacturer(s) or any commercial product(s) and/or provider of commercial products or services discussed in this CME activity.

I do not intend to discuss unapproved/ investigative use of commercial product(s)/ device(s) in my presentation.



Author: Committee on Infectious Diseases

David W. Kimberlin, MD, FAAP, Editor

Michael T. Brady, MD, FAAP, Associate Editor
Mary Anne Jackson, MD, FAAP, Associate Editor
Sarah S. Long, MD, FAAP, Associate Editor

Hard copy is once again an AAP member benefit.

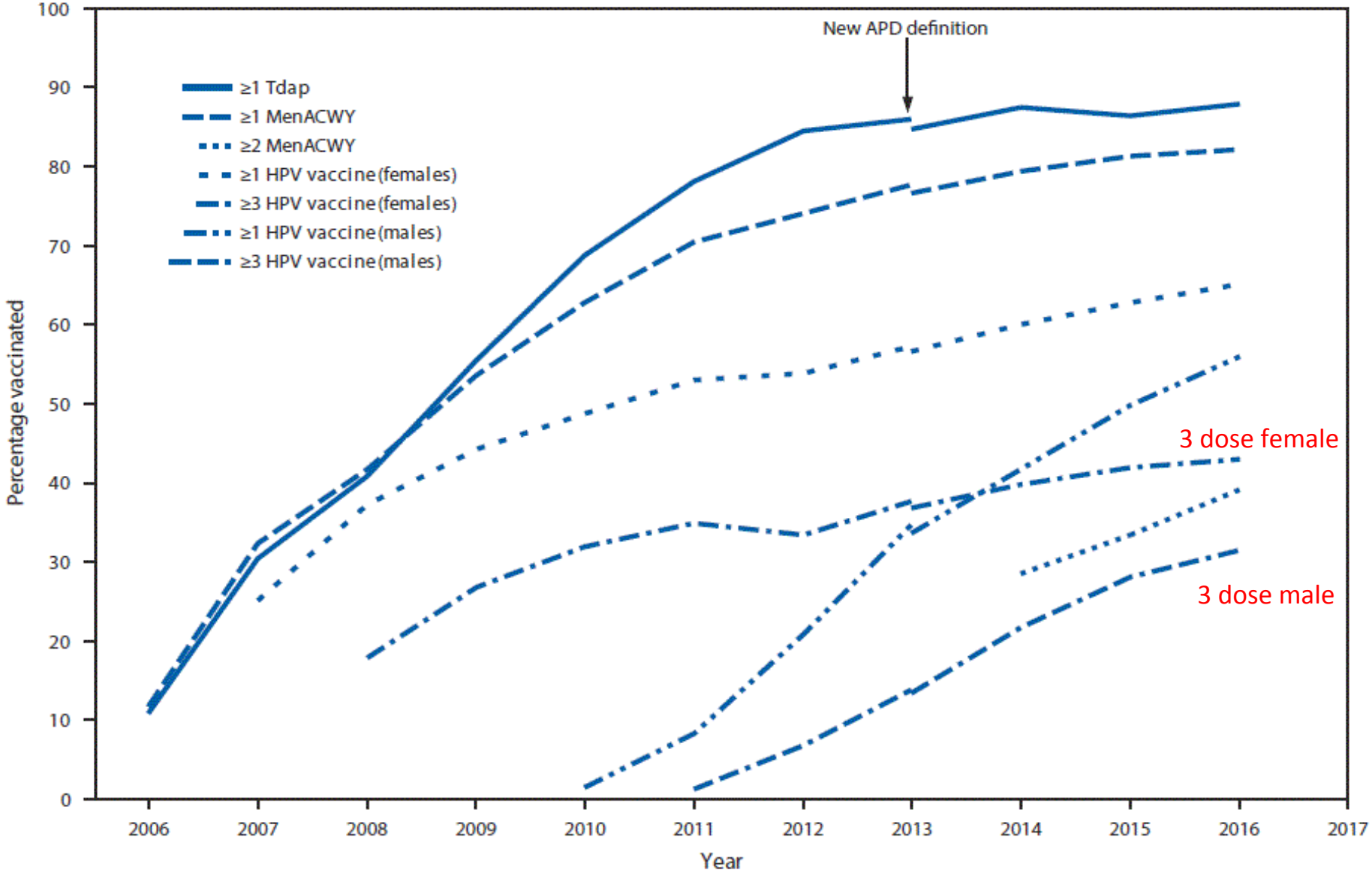
Members need to go online to order their complimentary copy.

Limited "life span" : 2018-2021

2018 Red Book
- **Distribution starts May 1, 2018**
- **Available at PAS**

HPV Vaccine

Adolescent HPV Vaccine Coverage: Still Need To Do Better



Human Papillomavirus Vaccines

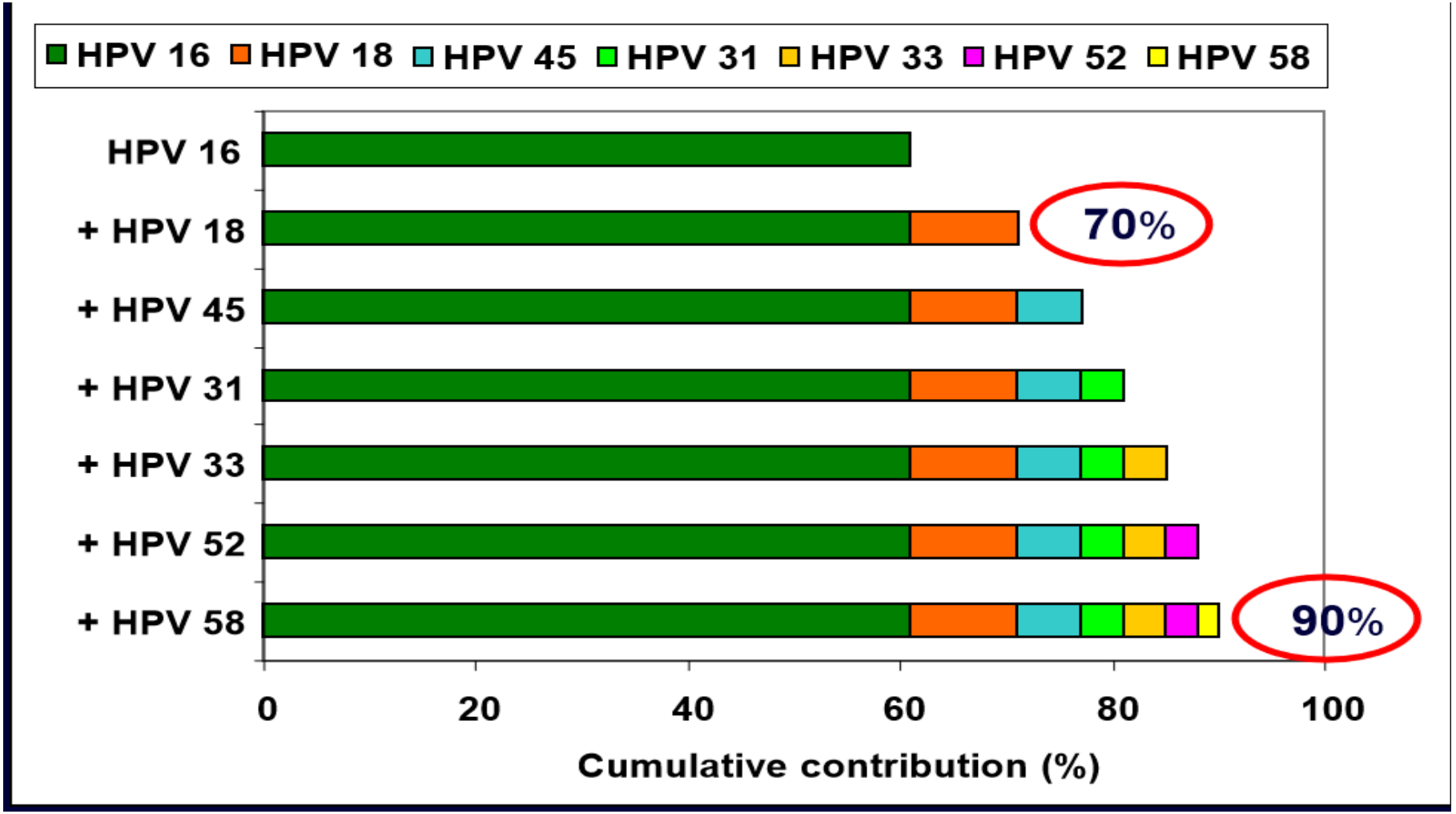
Characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States.

Characteristic	Bivalent (2vHPV)	Quadrivalent (4vHPV)	9-valent (9vHPV)
Brand name	Cervarix**	Gardasil**	Gardasil 9
VLPs*	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58

* Virus-like particles

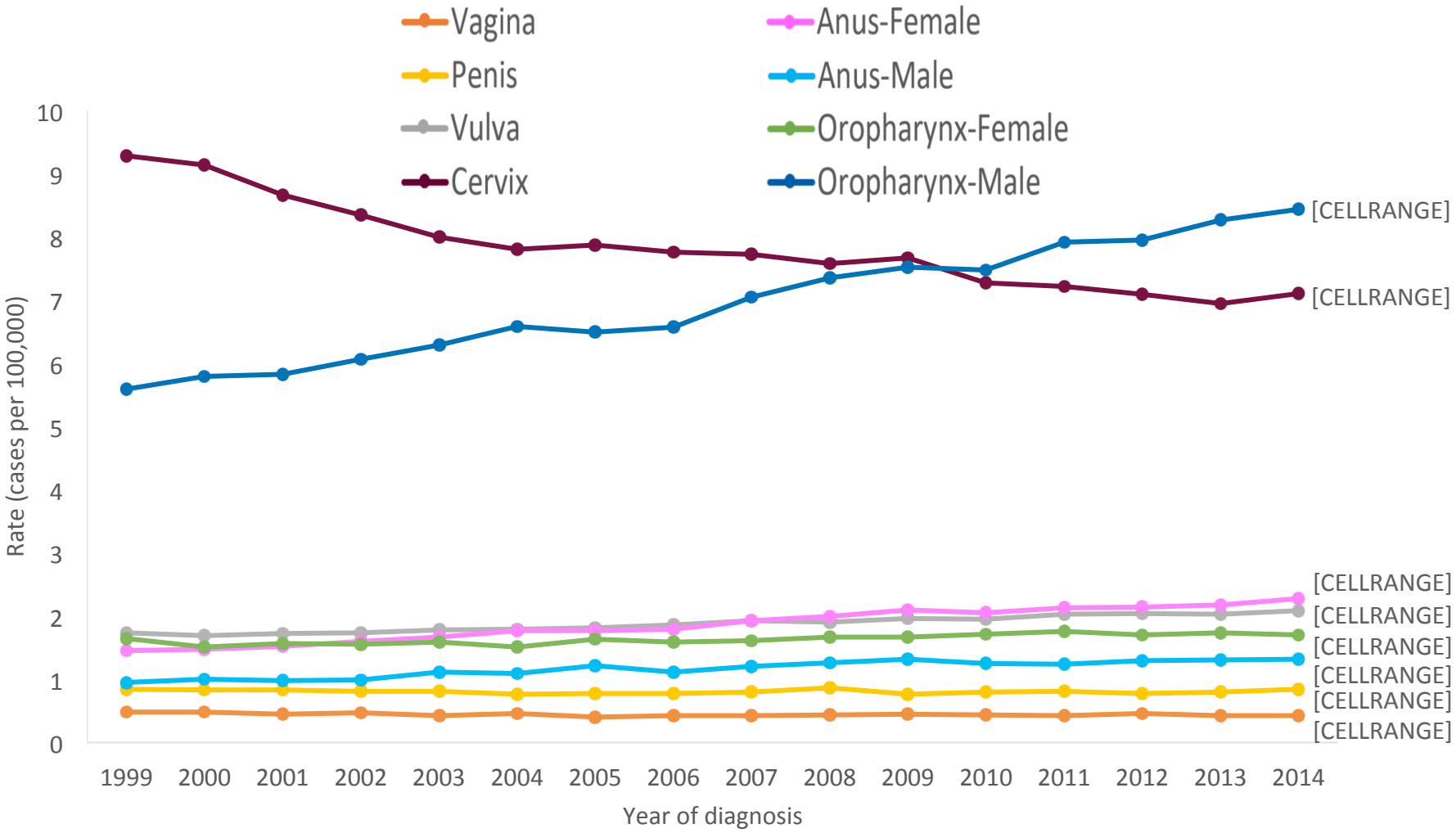
** No longer available in US

Relative Contribution of HPV Types in 9vHPV to Cervical Cancers Worldwide



Lancet Oncol 2010;11:1048-1056
Infect Agent Cancer 2012;7:38

HPV-Associated Cancers Trends — United States, 1999–2014



Rates were considered to increase if annual average percentage change (AAPC) >0 ($p<0.05$) and to decrease if AAPC <0 ($p<0.05$); otherwise rates were considered stable. * = $p<0.05$

AAP Modification of Time of Initiation of HPV Vaccine

ACIP 2018 and 2015 Red Book Wording:

"…recommends starting the series at age 11 or 12 years of age and states that vaccination can be administered starting at age 9 years. When HPV vaccine is begun at 9 or 10 years of age, other adolescent vaccines (e.g., MenACWY and Tdap) are still recommended to be administered only at 11 to 12 years of age.

2018 Red Book Wording:

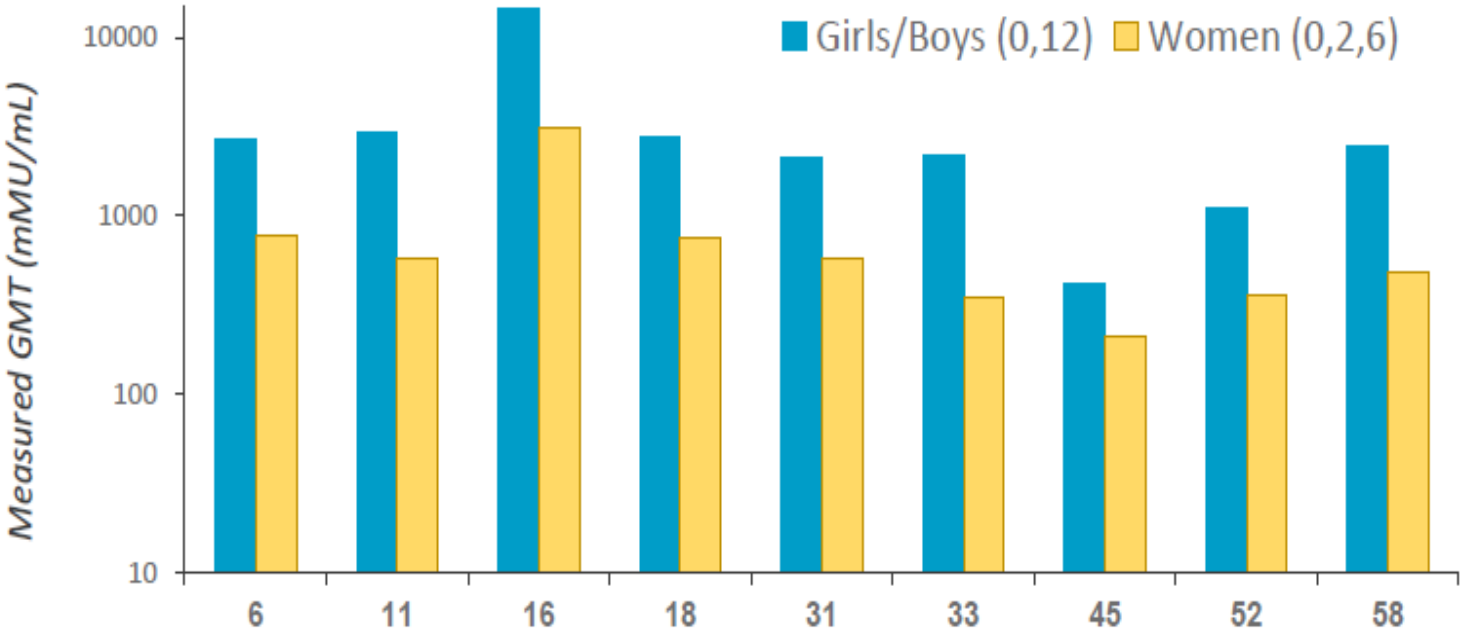
The AAP recommends starting the series between 9 and 12 years, at an age that the provider deems optimal for acceptance and completion of the vaccination series.

Human Papillomavirus Vaccine
2 Doses vs. 3 Doses

- AAP recommends starting vaccination series **between 9 and 12 years of age**
- For persons initiating vaccination before the 15th birthday, the recommended immunization schedule is **2 doses** of HPV vaccine (0, 6-12 month schedule)
- For persons initiation vaccination on or after the 15th birthday, the recommended immunization schedule is **3 doses** of HPV vaccine (0, 1-2, 6 month schedule)

9vHPV 2-Dose Immunogenicity Trial

Non-inferior GMT at 1 month post-last dose in 2-dose girls/boys vs. 3-dose women



Fold difference (girls & boys /women)	3.47	5.07	4.54	3.69	3.70	6.31	1.96	3.08	4.98
95% CI	*(2.93, 4.11)*	*(4.32, 5.94)*	*(3.84, 5.37)*	*(3.06, 4.45)*	*(3.08, 4.45)*	*(5.36, 7.43)*	*(1.61, 2.37)*	*(2.64, 3.61)*	*(4.23, 5.86)*

Luxembourg, presented at February 2016 ACIP
http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

Age at Initiation of HPV Vaccination and Completion of Vaccine Series

Characteristic	Age at Initiation of HPV Vaccination Series		P-value
	9-10 years	11-12 years	
Completed 3 doses of vaccine by 13.5 years of age	707/725 (97.5%)	1258/1613 (78.0%)	<0.001
Completed 3 doses of vaccine by 15 years of age	722/725 (99.6%)	1517/1613 (94%)	<0.001
Completed 2 doses of vaccine by 13.5 years of age	946/951 (99.5%)	2071/2259 (91.7%)	<0.001
Completed 2 doses of vaccine by 15 years of age	950/951 (99.9%)	2210/2259 (97.8%)	<0.001

Preventive Medicine 2016;89:327-333

Human Papillomavirus Vaccine Immunocompromised Patients

- Immunocompromised females and males aged 9 through 26 years should receive 3 doses of HPV vaccine (0, 1-2, 6 month)
- Persons who should receive 3 doses:
  - Primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity.
  - HIV infection.
  - Malignant neoplasm or transplantation.
  - Autoimmune disease or immunosuppression therapy.
- Recommendation for a 3-dose schedule does not apply to children aged < 15 years with asplenia, asthma, chronic granulomatous disease, chronic heart/liver/lung/renal disease, CNS anatomic barrier defects (e.g. cochlear implant), complement deficiency, diabetes, or sickle cell disease.

Human Papillomavirus Vaccine Additional Information

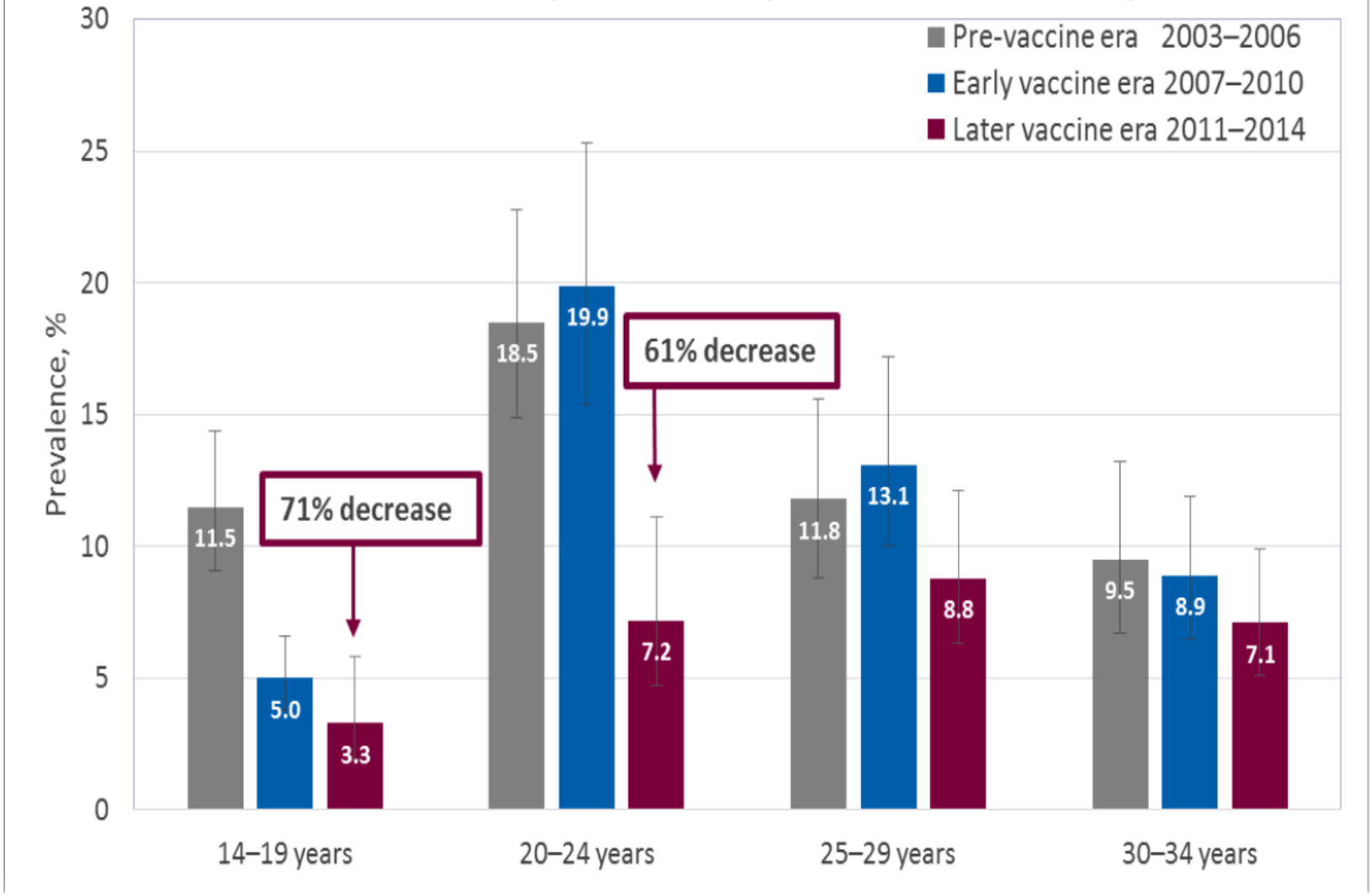
- 9vHPV may be used to continue or complete a series started with 4vHPV or 2vHPV.

- For persons who have been adequately vaccinated with 2vHPV or 4vHPV. **There are no current recommendations for any additional immunizations with 9vHPV.** (9vHPV may be considered if requested for additional HPV strain protection. However, insurance reimbursement could be an issue. Giving 9vHPV to adolescent immunized with 2vHPV or 4vHPV would prevent more disease than providing MenB vaccine to adolescents).

- If the vaccine schedule is interrupted for any duration, the vaccination series does not need to be restarted.

Vaccine type prevalence (HPV 6,11,16,18), NHANES

Later vaccine era compared to pre-vaccine era, females



Oliver et al. JID 2017;216: 594-603 NHANES, National Health and Nutrition Examination Survey

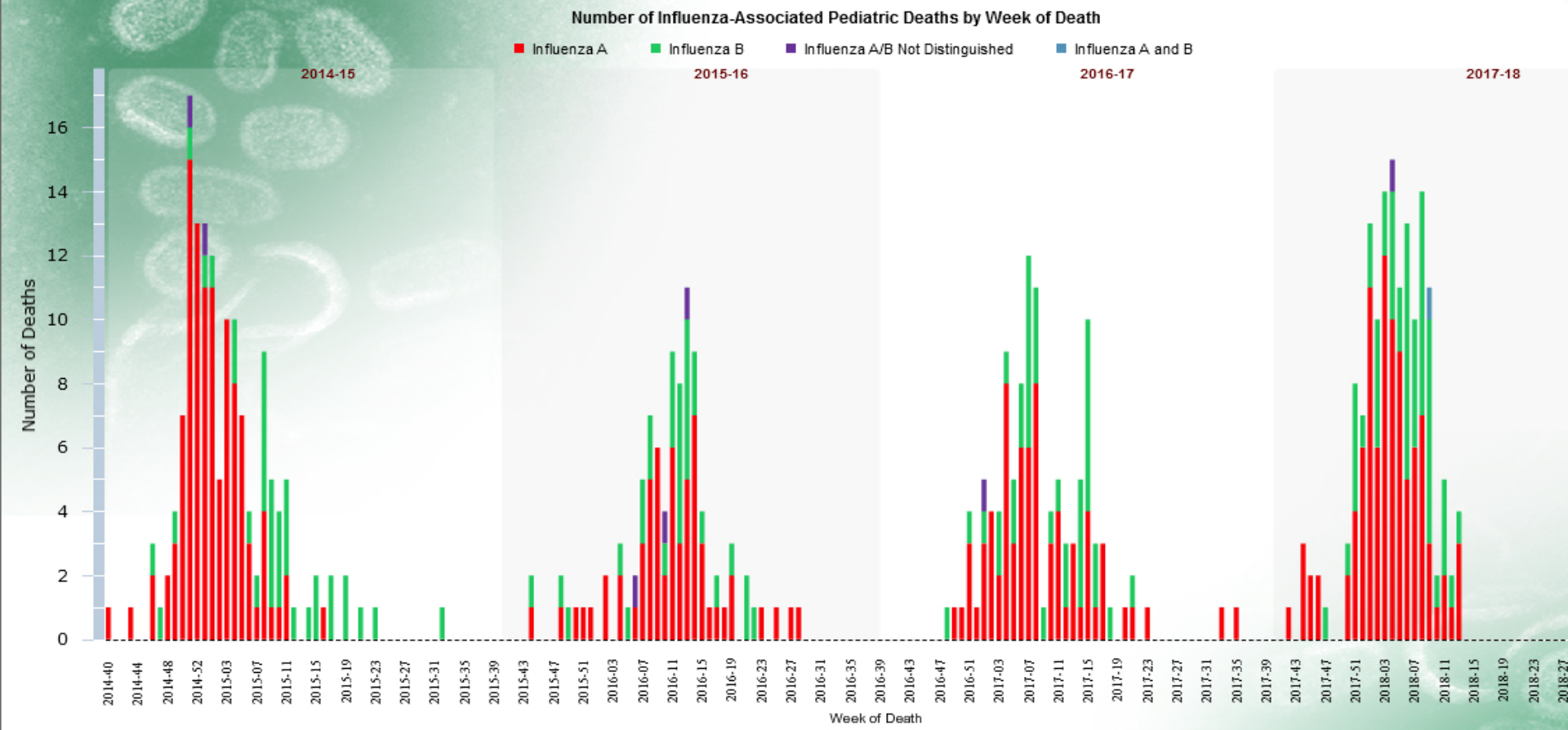
Question

Which vaccine-preventable infection is most likely to cause the death of one of your patients in 2018.

Influenza

Pediatric Deaths

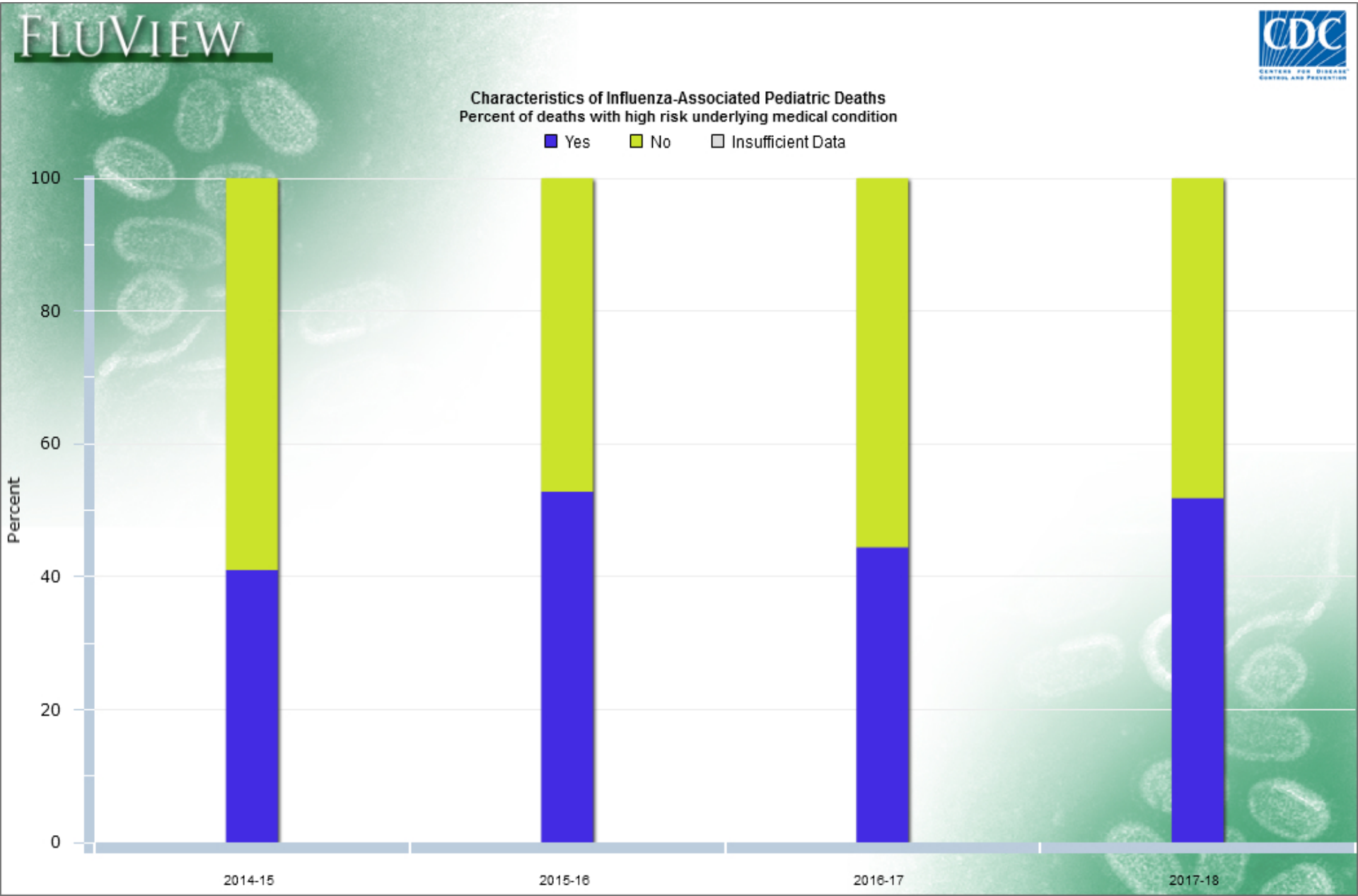
FLUVIEW



Season	Total Deaths	Influenza A	Influenza B	Influenza A/B Not Distinguished	Influenza A and B
2014-15	0	109	36	2	0
2015-16	0	59	31	3	0
2016-17	0	71	38	1	0
2017-18	0	96	53	1	1

Influenza Season	Predominant Strain	Pediatric Deaths	Hospitalizations (0-4 years old) per 100,000	Hospitalizations (5-17 years old) per 100,000
2017-2018 (up to: 4/15/2018)	H3N2	156	47.1	12.3
2016-2017	H3N2	98	44.1	16.7
2015-2016	pH1N1	85	42.5	9.6
2014-2015*	H3N2	148	57.3	16.6
2013-2014	pH1N1	111	47.3	9.4
2012-2013	H3N2	171	67	14.6
2011-2012*	H3N2	37	16	4
2010-2011	H3N2	123	49.5	9.1
2009-2010	pH1N1	288	77.4	27.2
2008-2009	H1N1	137	28	5
2007-2008	H3N2	88	40.3	5.5
2006-2007	H1N1	77	34.6	2.3

Pediatric Deaths By High Risk Medical Conditions

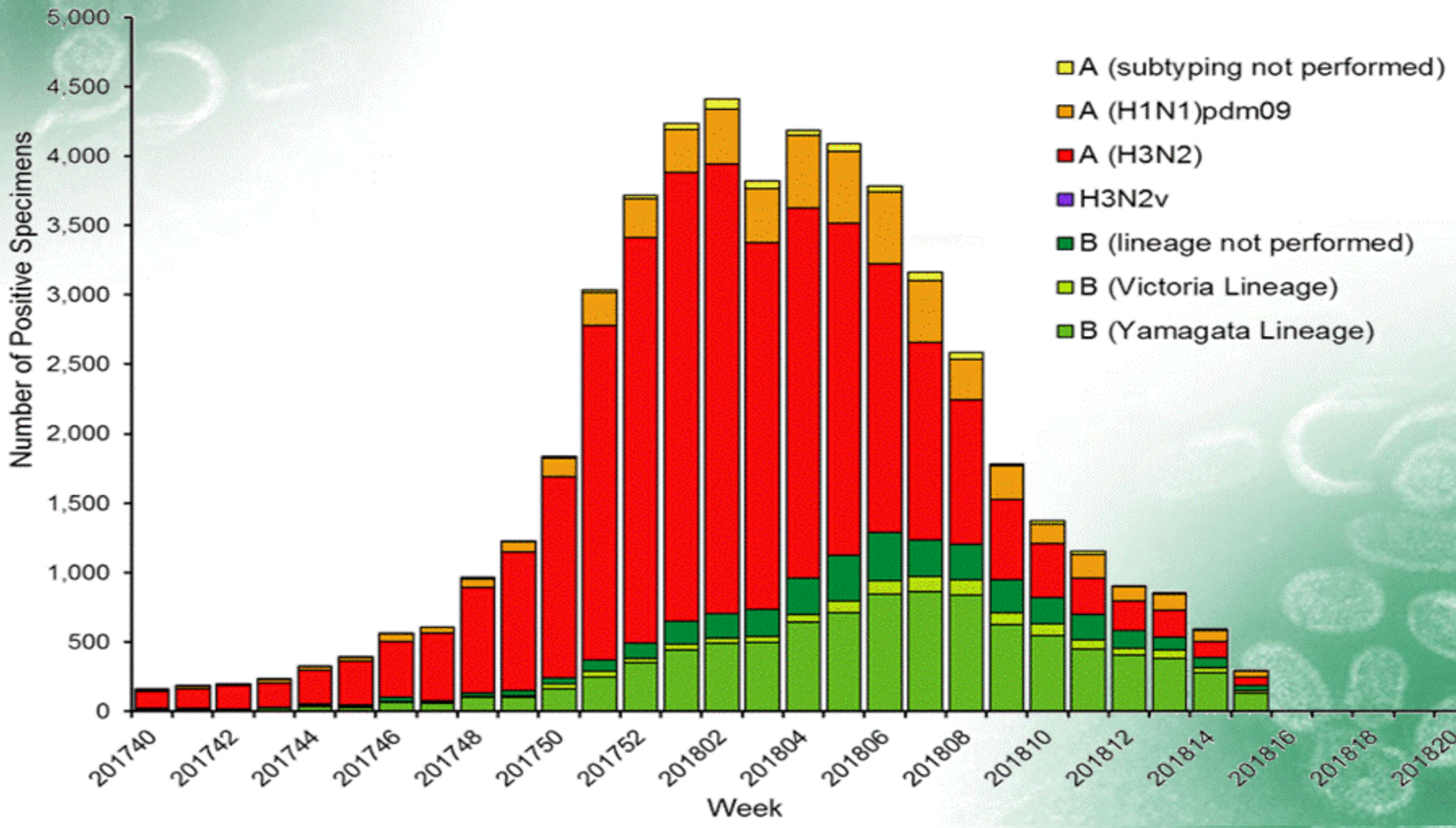


FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season



2017-18 Language in AAP Policy

Annual universal influenza immunization is indicated with either a trivalent or quadrivalent (no preference) inactivated vaccine.

Quadrivalent live attenuated influenza vaccine (LAIV4) **is not recommended** for use in any setting in the United States during the 2017–2018 influenza season. This interim recommendation, originally made in 2016, followed observational data from the US Influenza Vaccine Effectiveness Network revealing that LAIV4 performed poorly against influenza A (H1N1)pdm09 viruses in recent influenza seasons;

Influenza Vaccination Coverage by Age Group, Children 6 months–17 years, NIS-Flu, United States, 2016–17 Season

Age Group	Unweighted Sample Size	%* ±95% CI†	Difference from the 2015–16 Season ±95% CI
6 months–17 years	143,169	**59.0** ± 0.7	-0.3 ± 1.1
6 months–4 years	44,094	**70.0** ± 1.3	0.0 ± 1.9
6–23 months	16,374	**76.3** ± 2.0	1.0 ± 2.6
2–4 years	27,720	**66.2** ± 1.6	-0.6 ± 2.4
5–17 years	99,075	**55.6** ± 0.8	-0.3 ± 1.2
5–12 years	63,130	**59.9** ± 1.0	**-1.9 ± 1.6‡**
13–17 years	35,945	**48.8** ± 1.3	**2.0 ± 1.9‡**

* Percentage vaccinated.
† Confidence interval half-widths.
‡ Statistically significant difference between the 2016–17 season and the 2015–16 season by t test

Possible Reasons for Low Vaccine Efficacy (VE) of LAIV to A/ H1N1pdm09

- **Differences in viral replication and infectivity affect VE.**
- During and after 2009, pre-pandemic A/H1N1 in LAIV was replaced with A/H1N1pdm09 HA and NA proteins →poorer replication and shedding.
- An amino acid sequence was identified in the **HA stalk region** of wild-type A/ California/7/2009 H1N1pdm09 virus that **reduced thermal stability and infectivity** of the LAIV vaccine virus containing the HA gene. Likely not the problem.
- Change in strain in 2015-16 to A/Bolivia/559/2013/H1N1pdm09 for 2015-16 did NOT improve vaccine efficacy.
- **Change from LAIV3 to LAIV4 without dose change.**
- **Effect of repeated vaccinations in children.**
- **Other unknown immunologic effects.**

Chung JR, Flannery B, Thompson MG, et al. Seasonal Effectiveness of Live Attenuated and Inactivated Influenza Vaccine. Pediatrics. 2016;137(2):e20153279

Any influenza (all 3 seasons)

A/H1N1pdm09 (2013-14 and 2015-16)

Influenza (sub)type/ Age group	Total	Influenza Positive N Vaccinated (%)	Influenza Negative N Vaccinated (%)	aOR (95% CI)
Influenza A and B				
2-17 y				
LAIV	1979	476 (24)	1503 (76)	1.48 (1.28 ,1.7)
IIV	4579	727 (16)	3852 (84)	
2-4 y				
LAIV	625	121 (19)	504 (81)	2 (1.5 ,2.67)
IIV	1950	199 (10)	1751 (90)	
5-8 y				
LAIV	727	196 (27)	531 (73)	1.39 (1.11 ,1.74)
IIV	1216	252 (21)	964 (79)	
9-17 y				
LAIV	627	159 (25)	468 (75)	1.19 (0.92 ,1.56)
IIV	1413	276 (20)	1137 (81)	
A/H1N1pdm09				
2-17 y				
LAIV	868	140 (16)	728 (84)	2.66 (2.06 ,3.44)
IIV	2397	156 (7)	2241 (94)	
2-4 y				
LAIV	283	43 (15)	240 (85)	3.12 (1.62 ,6.01)
IIV	1057	61 (6)	996 (94)	
5-8 y				
LAIV	331	67 (20)	264 (80)	2.79 (2.09 ,3.71)
IIV	621	56 (9)	565 (68)	
9-17 y				
LAIV	254	30 (12)	224 (88)	2.19 (1.26 ,3.81)
IIV	719	39 (5)	680 (95)	

VE Meta-Analysis (2011-2016 seasons) Summary

A(H1/N1)pdm09

- LAIV was better than no vaccine for 2-17 year olds in US-IPD; but not in other surveillance systems.
- IIV better than LAIV for all age groups in the US.
- A/Slovenia was in LAIV4 for 2017-18 season (used in UK, Finland, Canada).
- No US VE data for LAIV since 2015, or with A/Slovenia in other countries.

H3N2

- LAIV = IIV, except for 2-4 year olds where IIV was better.

B strains

- LAIV *might* be better than IIV (not statistically significant).

There are 13 licensed influenza vaccines. Recommendations for individual influenza vaccines *are not* generally based upon comparative effectiveness data.

ACIP Vote February 2018

"For the 2018-19 season, immunization providers **may choose to administer any licensed, age appropriate, influenza vaccine** (including LAIV, IIV, and RIV).

LAIV4 *is an option* for influenza vaccination for persons for whom it is otherwise appropriate."

This additional language will be in the Background Information in the Influenza Statement:

"Although the **effectiveness of the new formulation of LAIV4 against H1N1pdm09** viruses **is not yet known**, available data suggests that the new LAIV4 containing A/Slovenia may provide protection more comparable to that observed with pre-2009 [LAIV] influenza vaccines."

Suggestion for preferential recommendation for IIV was voted down.

Discussion of COID 4/12/2018

- Most COID members would not "**recommend**" LAIV4 based on new available data.
- COID needs to comment on ACIP's recommendation on LAIV4.
- Must provide guidance to providers.
- However, review of old and new data shows that there is potential protection against influenza strains H3N2 and B by use of LAIV even if VE for H1N1 is unknown.
- Policy statement will be published in September with online availability in August. AAP News article will be published as soon as AAP Board approves.

Language “approved by COID” April 2018

- AAP recommends influenza vaccination for all children ≥ 6 months.
- ACIP approved new formulation of LAIV4 as an option for the 2018-2019 season.
- The effectiveness of the new LAIV4 formulation for protection against A/H1N1 for 2018-2019 is unknown.
- The AAP “prefers” IIV (trivalent or quadrivalent) for influenza vaccination in children because effectiveness of quadrivalent live attenuated influenza vaccine (LAIV4) against A/H1N1 was inferior in prior seasons.
- LAIV4 may be used for children who would not otherwise receive influenza vaccine and for whom it is appropriate.
- Final wording of the policy will be contingent upon reviews from multiple AAP Committees/Sections/Councils and approval by the AAP Board.

Influenza Vaccine Strains 2018-2019

TRIVALENT

- **A/Michigan/45/2015 (H1N1)pdm09-like virus (same as 2017-2018)**
- **A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus (NEW)**
- **B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) (NEW)**

QUADRIVALENT

- **B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)**

Vaccines for Young Travelers

Immunizations for Young Travelers

(6 months to 12 months of age)

Previous

- MMR (off label) is recommended for infants 6 to 12 months of age if travelling to a country with endemic measles. This dose does not count towards requirement for the first dose of the 2 dose series to be given at or after 12 months of age.

- Immune globulin (IGIM) is recommended for infants 6 to 12 months of age if travelling to a country with endemic hepatitis A.

Immunizations for Young Travelers (6 months to 12 months of age)

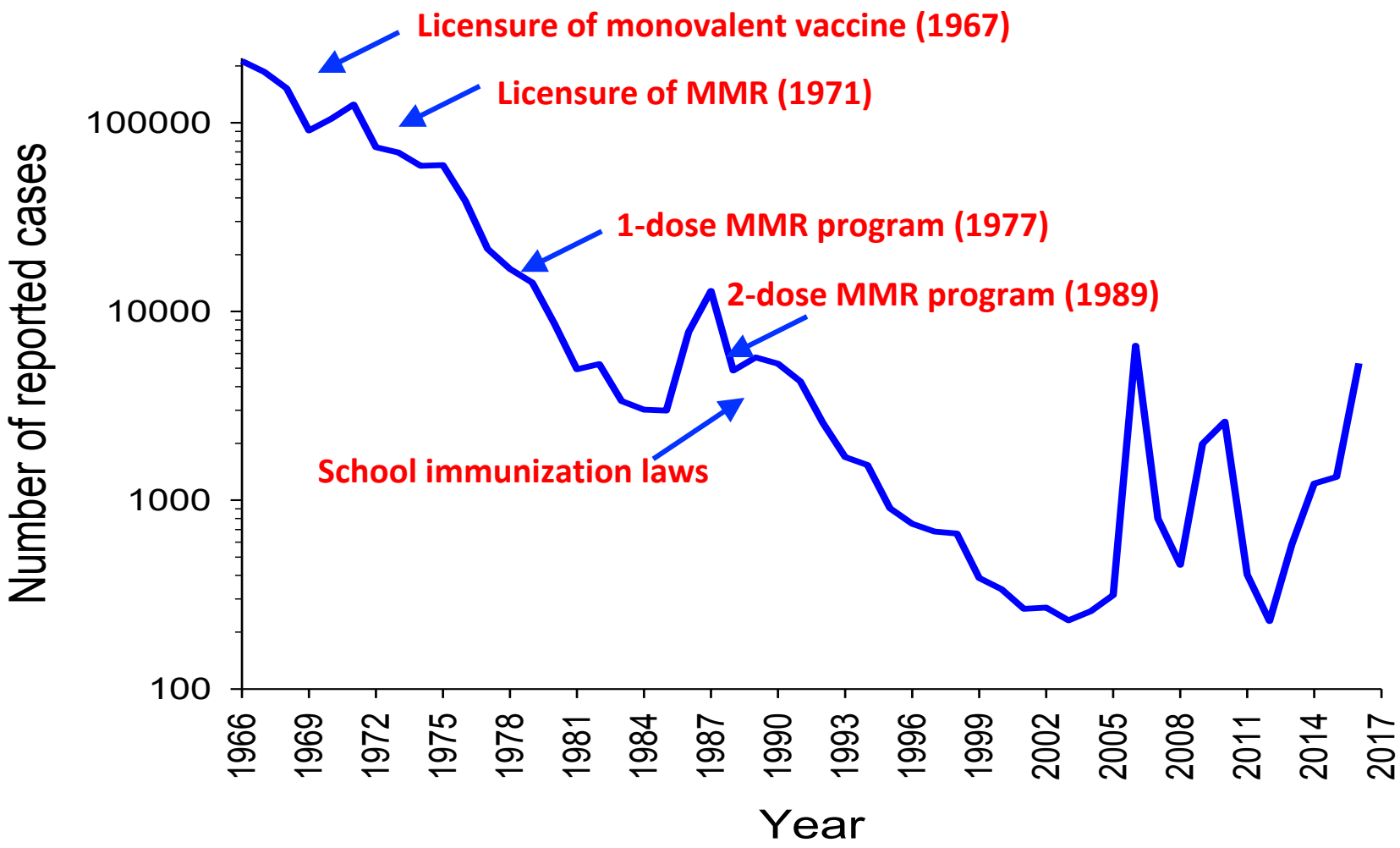
New

- Since many countries may have both endemic measles and endemic hepatitis A, prophylaxis for both infections needs to be administered.

- Since MMR cannot be given simultaneously with IGIM and if IGIM is given, there needs to be a 3 month time period after IGIM before MMR can be given, there are 3 options:
  - Give MMR and give IGIM at least one month later.
  - Give IGIM and give MMR 3 months later.
  - Give MMR and hepatitis A vaccine (off label). Like the MMR, the off label hepatitis A vaccine does not count as the first dose of the 2 dose series.

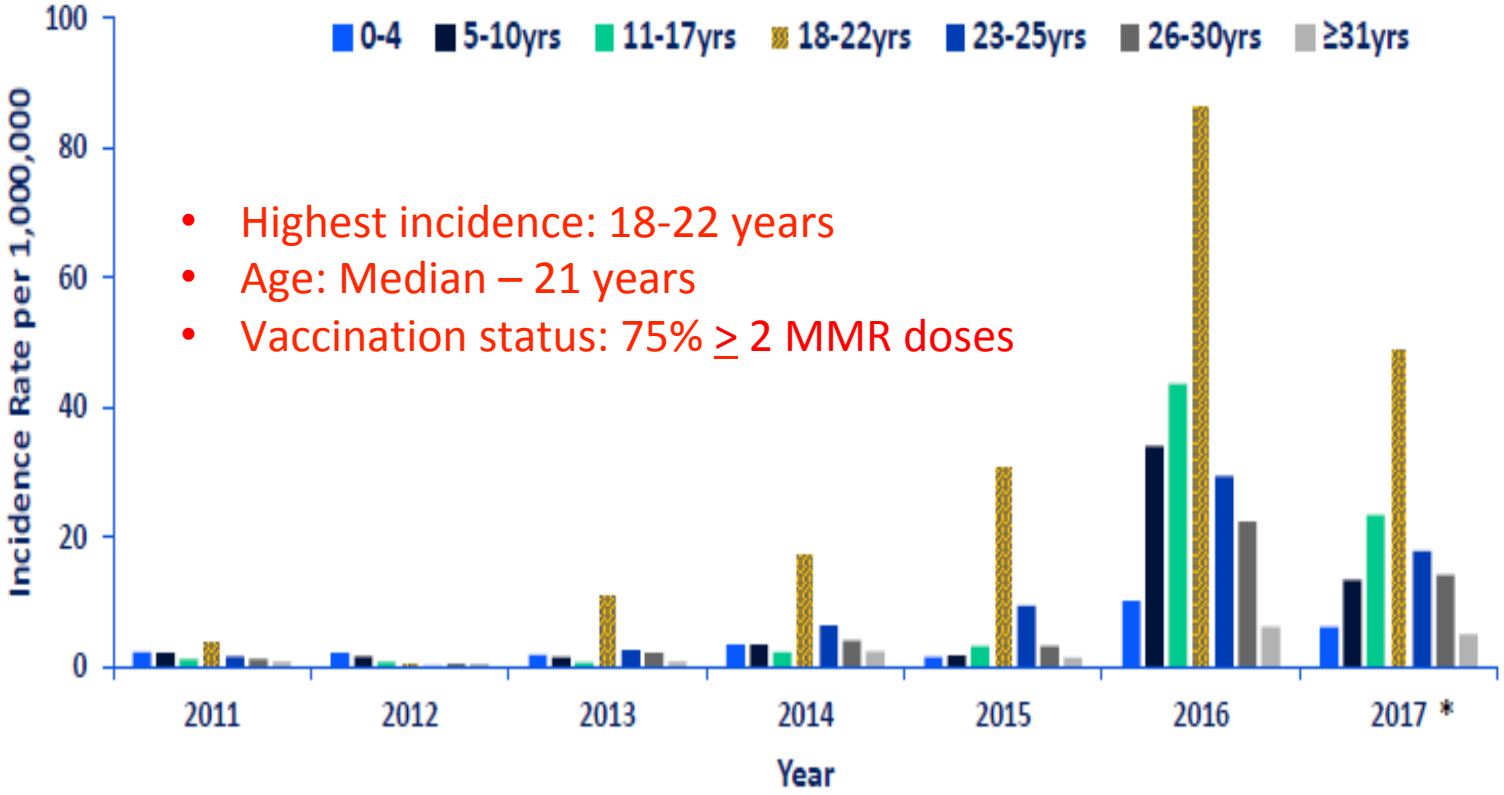
Mumps

Mumps Cases in the U.S. 1966–Present



Characteristics of Reported Mumps Cases, 2011-2017

*In 2017, 75% had received ≥ 2MMWR doses



- Highest incidence: 18-22 years
- Age: Median – 21 years
- Vaccination status: 75% ≥ 2 MMR doses

Source: National Notifiable Disease Surveillance System (passive surveillance); 2017 data as of October 12, 2017.
Vaccination status calculated as percent of persons with known vaccination status and for whom information on number of doses was reported.
IQR=Interquartile range

Mumps Outbreaks by Setting, United States, January 2016 - June 2017

Setting	Outbreaks (N=150)		Cases (N=9,200)	
	N	%	N	%
University	**75**	**50**	**3,664**	**40**
Sports team	4	3		
Greek organizations	3	2		
Community	**48**	**32**	**5,238**	**57**
Organized groups*	25	15		
Close-knit	16	11		
Sports teams	2	1		
Other (wide-spread)	7	5		
Schools (other than university)	**19**	**13**	**272**	**3**
Sports teams	6	4		
Households	**8**	**5**	**26**	**0.3**

*Organized groups include: churches, workplace, theater groups, parties, fitness centers, other.

Mumps Complications – Before and After Implementation of the MMR Vaccine Program

Complications	Pre-vaccine Era (%)*	Published 2006-2015 Outbreaks (%)†	Jan 2016-June 2017 Outbreaks (%)
Orchitis‡	up to 30	3-11	4.3
Oophoritis	~5	≤1-1	0.3
Mastitis‡	up to 30	≤1	0.4§
Hearing loss	4	≤1	0.4
Pancreatitis	4	≤0.1	0.4§
Aseptic meningitis	1-15	0.2-0.5	0.1
Encephalitis	0.03-0.5	0-0.3	0.02
Hospitalizations	5.5	<1-2	0.8

*McLean HQ et al. *MMWR* 2013; †Data from published US outbreak investigations 2006-2015; ‡Assessed in postpubertal male/female patients; §Data from 2016-2017 ELC Enhanced Mumps Surveillance Group (9 states = 33% of outbreak cases).

Recent Mumps Cases

- Majority of “identified” mumps cases are associated with outbreaks.
- Young adults are at highest risk.
- Half of all outbreaks occurred in university setting.
- 80% of cases occurred in outbreaks of $\geq$ 50 cases.

MMR Vaccine (2 Dose) Effectiveness

- Median 2-dose mumps vaccine effectiveness is 88% (20 estimates : range 31-95%).
- Most effectiveness studies included individuals who had received MMR2 <10 years prior.
- Increased risk of mumps and decreased mumps effectiveness (waning immunity) is related to time since MMR2 (mean of 27 years for loss of immunity with wide variability).
- 2 Dose MMR has not been **efficient** in preventing mumps outbreaks.

Lewnard, G Sci Transl Med ePub March 21, 2018 doi:10..1126/scitranslmed.aao594

Molecular Epidemiology of Wild-type Virus

- Mumps vaccine is genotype A (Jeryl Lynn strain).
- Recent circulating mumps strains have been genotype G.
- Neutralizing antibodies following mumps immunizations neutralize both genotype A and genotype G; higher levels of antibodies are required to neutralize genotype G as compared to genotype A.
- Relevance of higher antibody levels to neutralize genotype G is unclear because levels needed to protect against mumps has not been established.
- If mis-matched genotype (G vs. A) was responsible for lack of protection against mumps then more children should be affected during outbreaks.

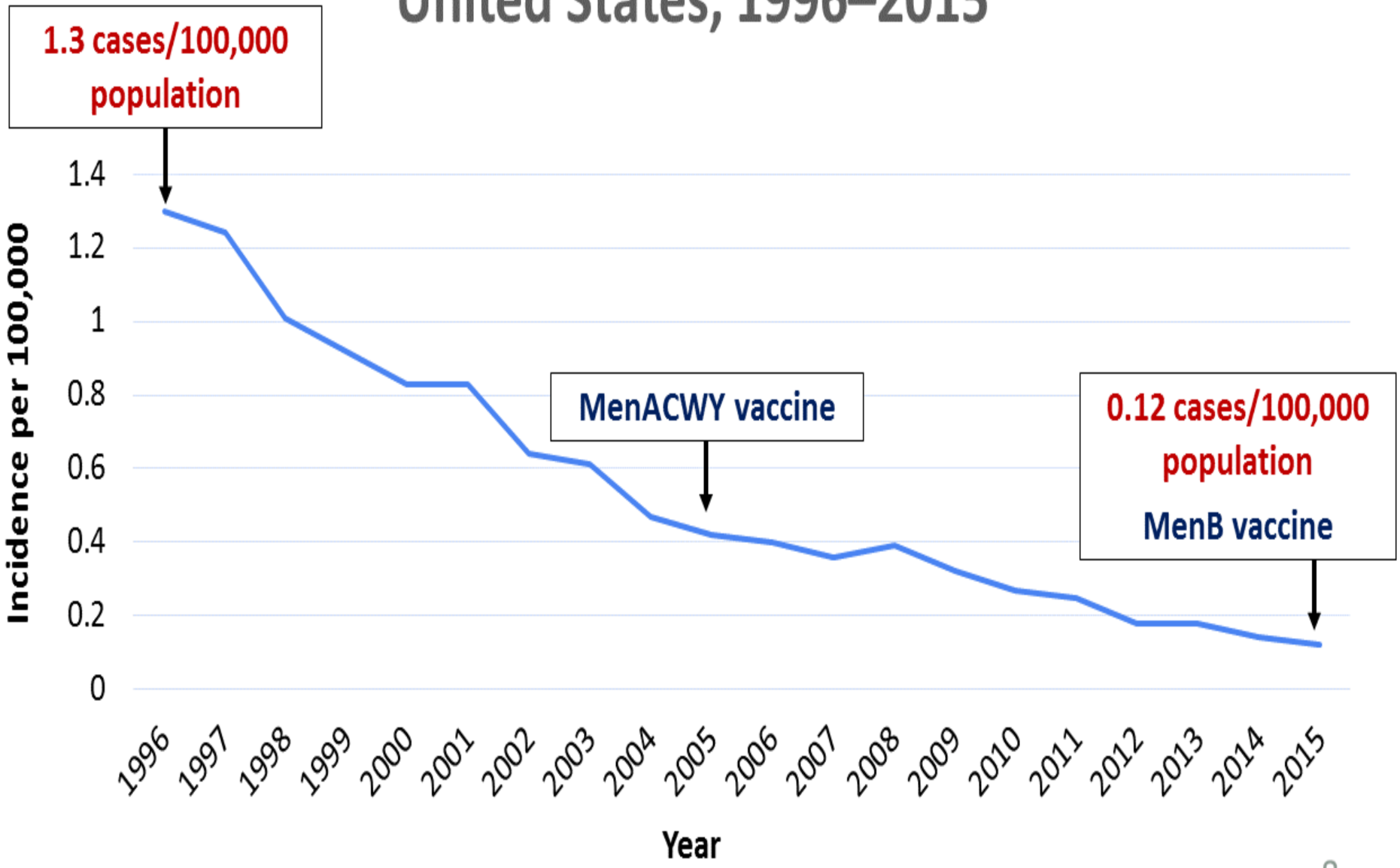
Lewnard, G Sci Transl Med ePub March 21, 2018 doi:10..1126/scitranslmed.aao594

New ACIP Mumps Recommendations

Anyone previously vaccinated with two doses of mump-containing vaccine who are identified by public health at increased risk for mumps because of an outbreak should receive a third dose of a mump-containing vaccine to improve protection against mumps disease and related compilations.

Meningococcal B Vaccine

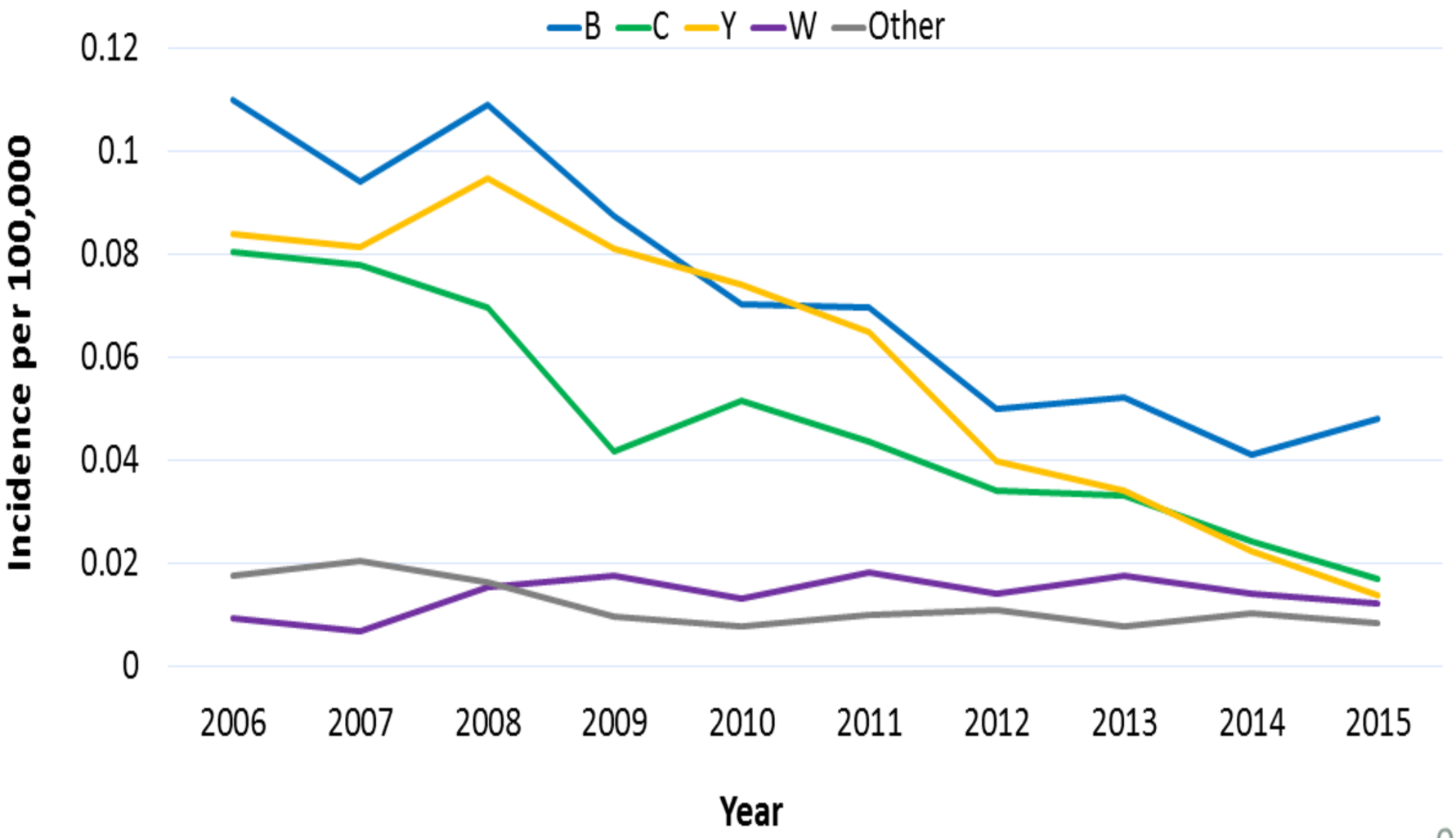
Meningococcal Disease Incidence – United States, 1996–2015



Abbreviations: MenACWY = quadrivalent meningococcal conjugate vaccine; MenB vaccine = serogroup B meningococcal vaccines

Source: 1996-2015 NNDSS Data

Trends in Meningococcal Disease Incidence by Serogroup – United States, 2006-2015



Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

Meningococcal Serogroup B Vaccines

- MenB-FHbp (Trumenba®, Pfizer), licensed on October 29, 2014
  - 3-dose (increased risk) or 2-dose (not increased risk) series
- MenB-4C (Bexsero®, Novartis/ GSK), licensed on January 23, 2015
  - 2-dose series
- Both licensed for 10 through 25 year olds
- Protection based on developing immunity to bacterial proteins rather than capsular polysaccharides (as with MenACWY)

Pediatrics 138(3); September 2016

Meningococcal Serogroup B Vaccines Recommendations

- When used, MenB-4C should be administered as a 2-dose series, with second dose given at least one month following the first.

- When used, MenB-FHbp should be administered as a 3-dose series in high risk patients (0-, 1- to 2-, and 6 months), and as a 2-dose series in non-high risk patients (with second dose given at least 6 months following the first).

Pediatrics 138(3); September 2016

Meningococcal Serogroup B Vaccines Recommendations

- Persons ≥ 10 years of age at increased risk of meningococcal B disease **should** receive a MenB vaccine routinely (Category A)

- A MenB vaccine series is **not routinely recommended but may** be administered to adolescents and young adults 16 through 23 years of age to provide short-term protection against diverse strains of meningococcal B disease (Category B)

Pediatrics 138(3); September 2016

Current ACIP vaccination recommendations for persons at increased risk for meningococcal disease

Population	MenACWY (aged ≥ 2 months)	MenB (aged ≥10 years)
Persistent complement component deficiencies (including eculizumab)	X	X
Functional or anatomic asplenia (including sickle cell disease)	X	X
HIV infection	X	
Unvaccinated first year college students living in dorms	X	
Military recruits	X	
Microbiologists routinely exposed to *N. meningitidis*	X	X
Travel to endemic or hyperendemic countries	X	
Persons at risk due to an outbreak	X	X

Uncertainties Regarding Meningococcal Serogroup B Vaccines

- Both vaccines licensed under accelerated approval pathways.
- Duration of immunogenicity uncertain; antibody levels decrease by 50% by 1-2 years – varies by antigen.
- Breadth of coverage across MenB strains in different geographic regions uncertain.
- Long-term safety uncertain:
  - Theoretical concerns regarding autoimmune disease with MenB-FHbp vaccine.

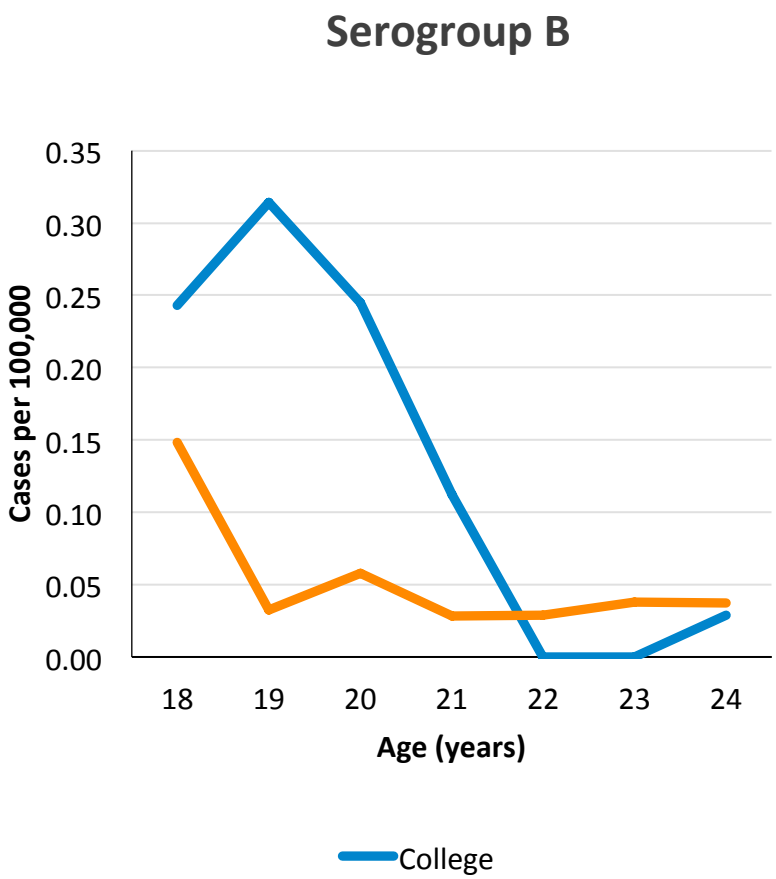
Pediatrics 138(3); September 2016

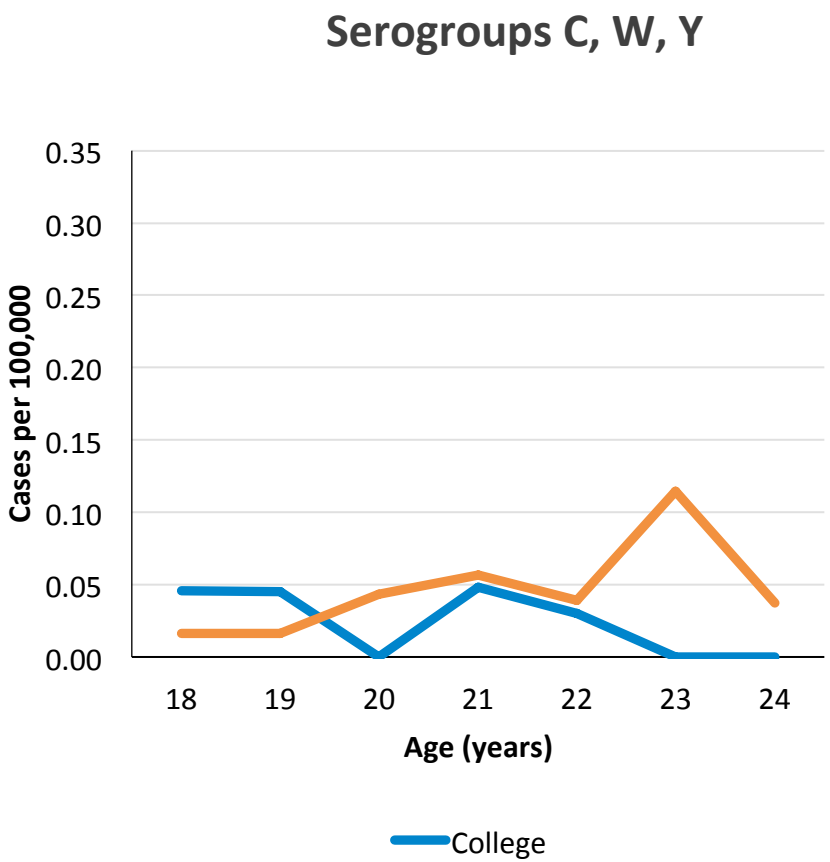
MenB Vaccine: What's Next

- Both manufacturers are planning studies in order to get FDA approval for MenB Vaccines down to age 1 year.

- ACIP is discussing:
  - What to do with persons already immunized with MenB during an outbreak due to concern for Ab waning?
  - Will MenB vaccine boosters be needed to protect adolescents/ young adults throughout college years due to Ab waning ?
  - If MenB vaccines are approved for ages 1 through 9 years, what recommendations would be appropriate?

Estimated incidence of meningococcal disease among persons aged 18-24 years by serogroup and year of life – United States, 2014-2016





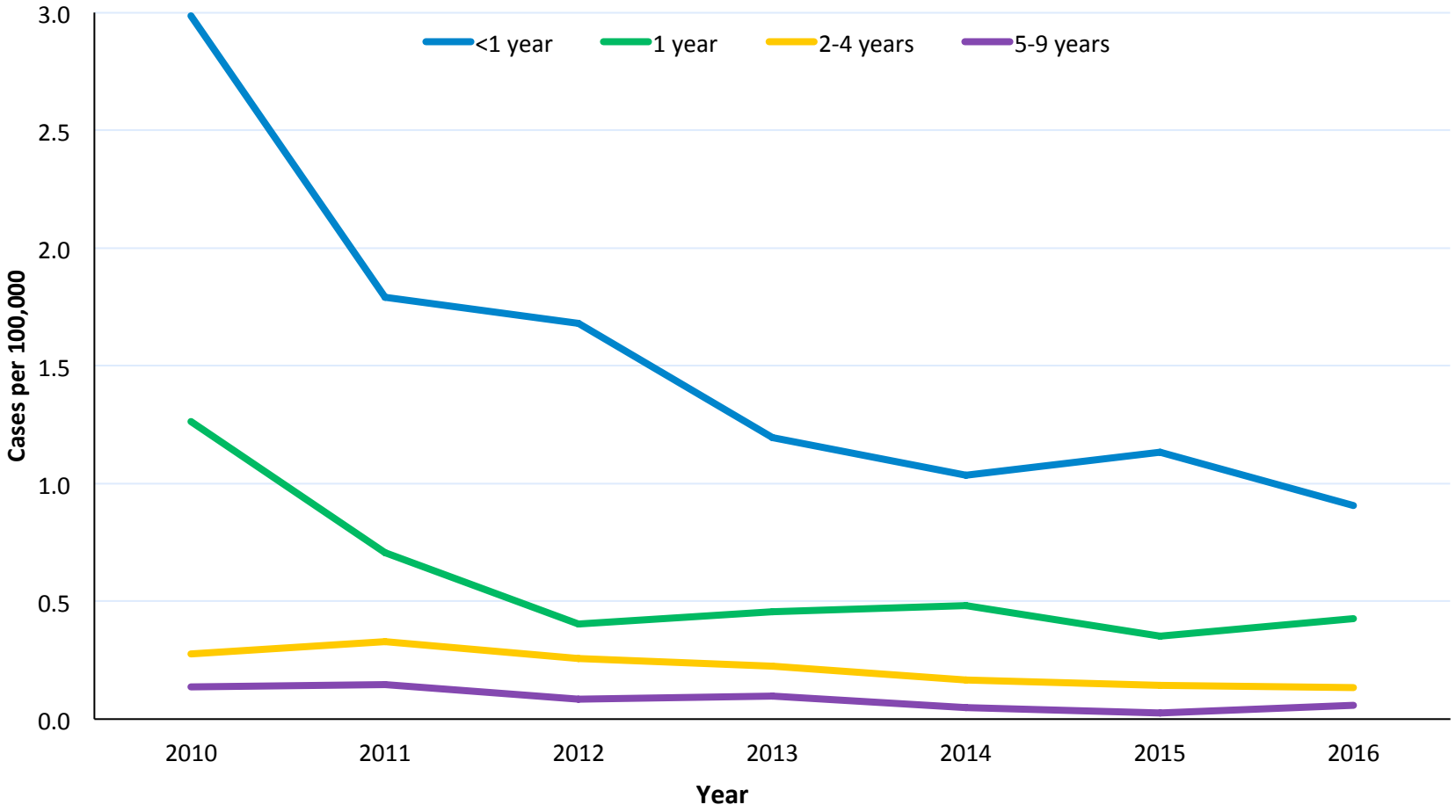
University Based Serogroup B Clusters/Outbreaks†, 2008–2016

State of University Location	Outbreak Period	Cases (deaths)	# Undergraduates
Ohio	Jan 2008 – Nov 2010	13 (1)	24,000
Pennsylvania	Feb – Mar 2009	4	10,000
Pennsylvania	Nov 2011	2	5,000
New Jersey	Mar 2013 – Mar 2014	9 (1)	5,000
California	Nov 2013	4*	18,000
Rhode Island	Jan – Feb 2015	2	4,000
Oregon	Jan – May 2015	7 (1)	20,000
California	Jan – Feb 2016	2**	5,000
New Jersey	Mar – Apr 2016	2	35,000
Wisconsin	Oct 2016	3	30,000
Oregon	Nov 2016 – Feb 2017	3	25,000

MenB Vaccination

†Where CDC consulted; *1 additional associated case identified after retrospective case review; **1 additional patient with inconclusive laboratory results

Trends in incidence of meningococcal disease among children aged <10 years by age group – United States, 2010-2016



Source: National Notifiable Diseases Surveillance System (NNDSS) data

Reported meningococcal disease cases in persons at increased risk for meningococcal disease[1]

Population	Complement deficiency[2] /eculizumab use[3]	Asplenia, including sickle cell disease[4]
Serogroup B cases		
Age <10 years	0	0
Age ≥ 10 years	0	3
Serogroup A, C, W, Y cases		
Age <10 years	0	0
Age ≥ 10 years	6	14

[1] Source: Active Bacterial Core surveillance (ABCs)
Since [2]2005, [3]2017, [4]1995

Cost-per-QALY in adolescent vaccines in the US Base-case Comparisons

Vaccine	Target group	Cost per QALY gained (compared to no vaccination)
Hepatitis B	College freshmen	<$0 (cost-saving) to ≈ $10,000
Hepatitis A	College freshmen	<$0 (cost-saving) to ≈ $15,000
HPV	12-year-old females	≈ $4,000 to $46,000
Influenza (LAIV)	12- to 17-year olds, high risk	≈ $11,000
HPV	12-year-old males (+ low female coverage)	≈20,000 to $40,000
TDaP	All 11-year-olds	≈ $26,000
HPV	12-year-old males (+ high female coverage)	≈75,000 to >$250,000
Meningococcal (MCV4)*	All 11- to 17-year-olds	≈ $97,000
Influenza	12- to 17-year olds, healthy	≈ $133,000
Meningococcal (MCV4)	2-dose, all 11 & 16-year-olds	$230,000
Meningococcal (MenB)	Series, all freshman college in 4yr and 2yr	$9.6 Million
Meningococcal (MenB)	Series, all 11-year-olds +booster	$10.8 Million
Meningococcal (MenB)	Series, all 18-year-olds	$11.2 Million
Meningococcal (MenB)	Series, all 16-year-olds	$12.7 Million

Source: Ortega-Sanchez et al. *Pediatrics* (2008), HPV (MMWR, Dic 2011) and new Mening Recom (MMWR, March 2013)

* includes Herd Immunity & duration 10 years (Ortega-Sanchez et al., *CID* 2008)

All figures were adjusted to December 2016 US$

Hepatitis B vaccine

Hepatitis B vaccine: Birth Dose

Maternal HBsAg Status	Birth weight	Timing (Age in hours)
Positive	≥ 2000gm	≤ 12 hrs*
Unknown	≥ 2000gm	≤ 12 hrs**
Negative	≥ 2000gm	**≤ 24 hrs**
Positive	<2000gm***	≤ 12 hrs*
Unknown	< 2000gm***	≤ 12 hrs**
Negative	< 2000gm***	1 month of age or hospital discharge, whichever is sooner

***HBIG < 12 hrs of age**

**** HBIG <12 hrs of age, if STAT HBsAg is positive or HBsAg is not available by 2hrs of age**

***** If HepB vaccine is given at birth, 3 additional doses would be needed to complete series**

HBsAg+-exposed Infants

- Serologic testing following 3 or 4 dose series at 9-12 months of age or 1-2 months following last dose if completion of HepB vaccine series is delayed:
-
  - anti-HBs - $\geq$ 10 mIU/mL-immune/protected
  - anti-HBs - < 10 mIU/mL-need additional HepB vaccine dose(s)

HBsAg+-exposed Infants

Option A for Infants with anti-HBs <10mIU/mL at age 9-12 months of age or after 1-2 months after last dose

- Give a single dose of HepB vaccine and repeat anti-HBs 1-2 months later:
  - anti-HBs -> 10 mIU/mL-immune/protected
  - anti-HBs -< 10 mIU/mL- give 2 additional doses of HepB vaccine and repeat anti-HBs 1-2 months after last dose
- If anti-HBs < 10 mIU/mL after 6 doses of HepB vaccine, no more doses should be given a this time.

HBsAg+-exposed Infants

Option B for Infants with anti-HBs<10mIU/mL at age 9-12 months of age or after 1-2 months after last dose

- Give an additional 3 doses of HepB vaccine and repeat anti-HBs 1-2 months later

- If anti-HBs <10mIU/mL after 6 doses of HepB vaccine, no more doses should be given at this time.

Doxycycline

Preferred Therapies for Rickettsial Infections

Disease	Treatment
Rocky Mountain spotted fever	Doxycycline
Rickettsialpox	Doxycycline
Murine (endemic) typhus	Doxycycline
Epidemic typhus	Doxycycline
Scrub typhus	Doxycycline
Human monocytic ehrlichiosis	Doxycycline
Anaplasmosis	Doxycycline
Q-fever	Doxycycline
Mediterranean tick fever	Doxycycline
African tick fever	Doxycycline

2018 Report of the Committee on Infectious Diseases

Doxycycline and Tooth Staining

- Retrospective cohort study of Native American reservation in Arizona.
- 58 children exposed to doxycycline:
  - 107 total courses of doxycycline **before the age of 8 years old**
  - Average duration 7.3 days (range 1-10, SD = 2.8)
  - Average age of doxycycline administration 4.5 years old (range 0.2-7.9, SD 2.4)
  - Average of 1.8 courses per child
  - Mean age at time of dental exam 9.8 years old (range 8.1-15.6, SD 1.7)
- 213 children who never received doxycycline
  - Mean age at time of dental exam 11.8 years old (range 8.0-16.9, SD 2.2)

J Pediatr 2015;166:1246-51

Doxycycline and Tooth Staining

- No visible tetracycline-like staining patterns were seen on any teeth from either group (95% CI: 0% to 5%)

	Doxycycline <8 y, N (%)	**No Doxycycline, N (%)**	**Age-Adjusted Prevalence Ratio (95% CI)**	**Age-Adjusted Prevalence Ratio, P value**
Enamel hypoplasia	2 (4)	8 (4)	1.6 (0.2-13.5)	0.65
Fluorosis	5 (9)	28 (13)	0.86 (0.4-2.0)	0.72

J Pediatr 2015;166:1246-51

Doxycycline and Tooth Staining

- Blind, randomized, controlled study of children treated with doxycycline for controlling asthma.
- 4 mg/kg BID on Day 1, then 2 mg/kg QD on Days 2-10.
- 31 treated vs. 30 control non-doxycycline exposed.
- No tooth staining detected in any of the children in either group

Clin Pediatr (Phila) 2007;46:121-6

Liberalization of Doxycycline Recommendations

Doxycycline binds less readily to calcium compared with other members of the tetracycline class, but because of concern for a drug class effect with tetracyclines, its use previously has been limited largely to patients 8 years and older, and these older children have been studied more thoroughly than younger children. Recent comparative data in younger children, however, suggest that doxycycline is not likely to cause visible teeth staining or enamel hypoplasia in children younger than 8 years. **These reassuring data support the revised recommendation by the American Academy of Pediatrics, reflected throughout the 2018 *Red Book*, that doxycycline can be administered for short durations (i.e., 21 days or less) without regard to the patient's age.** When used, patients should be careful to avoid excess sun exposure due to the photosensitivity associated with doxycycline.

2018 Report of the Committee on Infectious Diseases. Rickettsial Diseases