

# Varicella Vaccination in the United States – Two Decades of Experience with Program Implementation

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## BACKGROUND

### US Varicella Vaccination Policy

- 1996 - The United States was the first country to introduce a universal childhood varicella vaccination program
  - One dose recommended at age 12-18 months, with catch up vaccination of susceptible older children
  - Two doses for susceptible adolescents and adults
  - Use of the vaccine had a substantial impact on varicella epidemiology
- 2006 - Policy was changed to a routine two-dose program, for additional improvement of disease control
  - First dose at age 12-15 months and the second dose at age 4-6 years
  - Catch up vaccination of unvaccinated children, adolescents, and adults or those who previously received one dose

### WHY A VARICELLA PREVENTION PROGRAM

- Annual Varicella Disease Burden Pre-vaccine**
  - ~4 million cases (approximate the birth cohort)
  - 15.0-16.0/1,000 population
  - 11,000 to 13,500 hospitalizations
  - 4.0-6.0/100,000 population
  - 100-150 deaths
  - 0.4-0.6 /million population
  - Congenital varicella syndrome: ~44
  - Risk=1%-2% for pregnancies affected 0-20 weeks
  - Greatest disease burden in children
  - >90% cases, 70% hospitalizations, 50% deaths
  - Significant societal health burden and costs



## OBJECTIVE

- To describe the two decades of experience with the varicella vaccination program in the United States

## METHODS

- Literature Review
  - PubMed search for articles published during 1996-2016; supplemented by conference papers known to the authors
  - Search terms: varicella, varicella vaccine, herpes zoster
  - Search was limited to data from the United States

## RESULTS - VARICELLA

### ONE-DOSE PROGRAM (1996-2006)

#### Vaccine-related Surveillance

- One-dose vaccine coverage
  - 89% in 2006 among children age 19-35 months (range 76%-96% by state)
- Vaccine effectiveness (metaanalysis)
  - All disease: 82% (95% CI: 79%-85%), range 44%-100%
  - Combined moderate and severe disease: 98% (95% CI: 95%-99%), range 86%-100%
  - Severe disease\*: Median 100%, range 97%-100%
- Vaccine safety: Single antigen varicella vaccine
  - Excellent safety profile with >140 million vaccine doses distributed
  - Rash, fever, and injection-site reactions: 2/3 of all reports in Vaccine Adverse Events Reporting System (VAERS)†
  - Reporting rate for severe adverse events – 2.6/100,000 doses distributed (VAERS)
  - Confirmed vaccine virus rare: rash, hepatitis, pneumonia, herpes zoster, meningitis with herpes zoster; one death in a child with medical history suggestive of primary or acquired immune deficiency
  - Secondary transmission of vaccine virus from healthy vaccine recipients extremely rare (11)
- Vaccine safety: MMRV
  - Increased risk for febrile seizures 5-12 days post dose 1 MMRV compared with same-day administration of MMR and varicella vaccines, in children aged 12-23 months

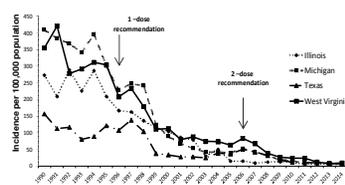
#### Disease-related Surveillance

- Incidence (figure 1)
  - Declined on average 83%-90% in 2005 compared with 1995
  - 90% decline in rates in (unvaccinated) infants
- Hospitalizations (figure 2) - Two studies:
  - Declined 88% in 2002 compared with 1994-1995
    - 91%-92% among persons age <20 years
  - Declined 75% in 2001 compared with 1993-1995
- Mortality (figure 3)
  - Declined 87% in 2004-2006 compared with 1990-1994
    - 96% among persons age <20 years
    - 93% among persons age <50 years
  - Direct inpatient and outpatient medical expenditures
    - 74% decline from 1994-1995 to 2002

\*Definition 1) Varicella with > 500 lesions or a complication requiring physician visit 2) disease severity scale used in clinical trials: # lesions, fever, systemic signs and subjective assessment of illness; metaanalysis not done for severe disease therefore median is reported

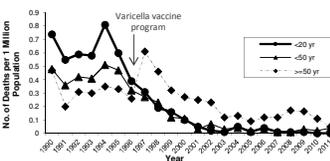
†VAERS is a national vaccine safety surveillance system; reporting is passive #VAERS reports are classified as serious adverse events if one or more of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability

Figure 1. Varicella Incidence in States that Have Consistently Reported Varicella Cases to CDC - 1990-2014



Source: Lopez AS, Zhang J, Marin M. Epidemiology of varicella during the 2-dose varicella vaccination program - United States, 2005-2014. MMWR 2016.

Figure 3. Varicella-related Mortality\* Rates Among Persons Age <50 Years, by Age Group, United States, 1994-2012

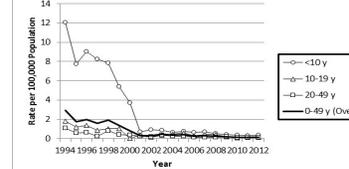


\*Varicella underlying cause of death: 99% decline among <20 year-olds  
Source: Leung J, Bialek SR, Marin M. Trends in varicella mortality in the United States: data from vital statistics and the national surveillance system. Human vaccines and immunotherapeutics 2015.

### EVIDENCE CONSIDERED FOR VACCINE POLICY CHANGE

- Program goal may not be met and sustained with 1-dose
  - Incidence plateaued between 2003 and 2006
- Varicella epidemiology
  - Ongoing endemic transmission, outbreaks in highly vaccinated school populations (coverage >96%)
- Breakthrough cases are contagious
- Vaccine performance
  - One dose did not provide sufficient herd immunity to interrupt community transmission; 15%-24% of children did not have antibodies after one dose
- Improved immune response following the second dose
  - Both proportion of children with detectable antibody and antibody titer
- Some evidence of waning immunity
  - Evidence remains weak even today; no additional data showing waning of immunity

Figure 2. Varicella-related Hospitalizations\* Rates Among Persons Age <50 Years, by Age Group, United States, 1994-2012



\*Varicella as the primary diagnosis code  
Source: Leung J, Harpaz R. Impact of the maturing varicella vaccination program on varicella and related outcomes in the United States: 1994-2012. J Pediatric Infectious Diseases Society 2015.

Table 1. Characteristics of Varicella Outbreaks in an Active Surveillance Site by 4-Year Time Periods, 1995-2010

Characteristic	1995-1998	1999-2002	2003-2006	2007-2010
# of outbreaks	236	52	47	12
# of cases median (range)	15 (5-124)	11 (5-56)	9 (5-45)	9 (5-11)
Duration outbreak	45 (7-198)	39 (1-149)	30 (3-90)	43 (5-52)
% cases vaccinated	2%	22%	59%	65%

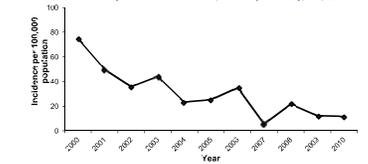
Number of outbreaks declined 75% and 95% during 2007-2010 compared with 2003-2006 and 1995-1998, respectively.  
Source: Bialek SR et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. Pediatrics, 2013.

### TWO-DOSE PROGRAM (2007-present)

- Further declines in morbidity after implementation of the two-dose program (figures 1, 2)
  - Incidence: declined 85% during the two-dose period through 2013-2014; an overall decline of 97% (range 93%-98%) in 2013-2014 compared with prevaccine years
  - Hospitalizations: declined 38% during the two-dose period through 2012; an overall decline of 93% in 2012 compared with prevaccine years, with 91%-99% among <20 year-olds
  - Outpatient visits: declined 60% during the two-dose period through 2012; an overall decline of 84% in 2012 compared with prevaccine years
- Outbreaks (table 1)
  - Number, size, and duration reduced compared with the one-dose program

## RESULTS - HERPES ZOSTER

### Herpes Zoster Incidence Among Children Age <10 Years, Trends and Risk by Vaccination Status, Antelope Valley, CA, 2000-2010



Source: Civen R et al. Update on incidence of herpes zoster among children and adolescents after implementation of varicella vaccination, Antelope Valley, CA, 2000 to 2010. PIDJ 2016.

- Among children
  - Declining trend: 69% reduction in herpes zoster incidence 2007-2010 vs. 2000-2006
  - Herpes zoster risk 4-12 times lower in vaccinated children compared with those with varicella history
  - Potentially less pain and pain severity in vaccinated than unvaccinated children
- Among adults
  - No evidence that the varicella program is contributing to changes in the epidemiology of herpes zoster

## CONCLUSIONS

- >90% reductions in varicella morbidity and mortality during the two decades of vaccination program
  - Declines highest among children but they occurred in all age groups including infants not recommended for vaccination indicating substantial herd immunity
- Annually, >3.5 mil varicella cases, 9,000 hospitalizations and 100 deaths are now prevented in the United States
- Excellent safety profile: confirmed serious adverse event rare
- One dose is sufficient to reduce mortality and severe morbidity from varicella but not to prevent limited virus circulation and outbreaks
- The two-dose program has provided additional disease reduction
- Lower incidence of herpes zoster in cohorts who received varicella vaccine

## FUTURE TASKS

- Improving diagnostics for varicella in vaccinated persons
- Developing tools to measure vaccine-induced immunity and monitor its duration
- Understanding correlates of protection
- Monitoring severe disease, especially in adults to make sure waning is not occurring (or susceptibles escaping to adulthood)
- Monitoring herpes zoster epidemiology in both vaccinated persons and persons previously infected with wild-type varicella-zoster virus

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