

# Varicella Disease Burden and Varicella Vaccines

Jane F Seward, MBBS, MPH  
and Mona Marin, MD

On behalf of the SAGE VZV Working Group

WHO SAGE Meeting  
April 2, 2014



# Context

- SAGE Varicella zoster virus (VZV) Working Group tasked to review evidence to formulate recommendations on the use of varicella vaccines
  - Update the 1998 WHO position paper on varicella vaccine
- Evidence included:
  - Epidemiology & global disease burden
  - Vaccine safety & efficacy
  - Effectiveness and vaccine impact & cost-effectiveness

# Objective

- Present the available evidence related to Varicella

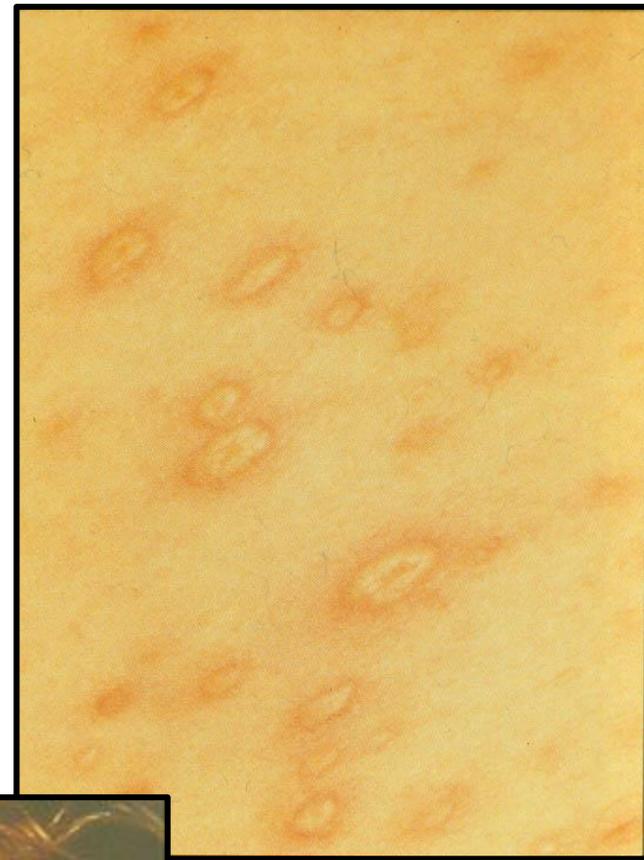
# Varicella

- Etiologic agent = varicella zoster virus, an  $\alpha$  herpesvirus
- Humans only reservoir of infection
  - Primary infection      **Varicella (chickenpox)**
  - Reactivation            **Herpes zoster (shingles)**
- Transmission from patients with varicella and herpes zoster primarily via respiratory route following aerosolization of infective viral particles from skin lesions, also direct contact
- Incubation period 10-21 days
- Highly infectious with  $R_0^* \sim 12-18$  and household secondary attack rates  $> 80\%$  (range 61 – 100%)

\*= the average number of cases generated by one case over the course of its infectious period in a susceptible population

# Varicella

- Febrile pruritic rash illness with macules, progressing to papules, vesicles, crusts
- Lesions in varying stages of development and resolution
- Subclinical infection uncommon



# Severe Disease Burden: Varicella Complications

## Virally mediated

Neurological

Pulmonary

Hemorrhagic

Congenital infection

## Bacterially mediated

Pneumonia

Sepsis

Skin and soft tissue

- More common at extremes of age and in persons with cellular immune deficiencies
- However, most severe complications and deaths occur in healthy persons
- Deaths occur from pneumonia, encephalitis, secondary infections and sepsis and hemorrhagic complications

# Severe Varicella Complications



Pneumonia



Staph aureus



Fatal neonatal varicella



Group A Strep



Severe disseminated varicella  
Child with ALL

# Varicella Epidemiology and Disease Burden

- In most climates, strong seasonality with peak incidence in late spring in temperate climates or in the coolest/driest months in tropical climates
- Because it is very contagious, in most populations, essentially all persons acquire varicella during their lifetime, most commonly during childhood
- Differences in epidemiology described between temperate and tropical climates; later disease acquisition in some tropical settings
- Factors affecting risk of exposure include area of residence (urban vs rural), childcare, school attendance, other
- Disease burden depends on age-specific incidence, age-specific severe morbidity and mortality, and risk factors for severe disease in the population

# Varicella Disease Burden

- Most population-based data on disease burden come from developed countries, methodological issues in comparing data
- **Incidence**
  - Described from developed countries – US, UK, France, Spain, Australia, other, few data otherwise (4-5 countries)
  - Age specific incidence changing (peak incidence moving to younger age groups) in settings with high day care attendance rates
  - Mean number of cases per year average the birth cohort
- **Seroprevalence**
  - Data more widely available globally (studies mainly from North America, Europe, limited from other regions and only 3 from Africa, one commissioned by WHO for this WG)
  - Challenges with sample selection and generalizability of results from studies outside Americas and Europe
- **Severe disease outcomes**
  - Population-based data extremely limited especially from low/middle income countries

# Varicella Public Health Burden

- Direct medical costs
  - Physician visits, hospitalizations, deaths
- Outbreak related costs
  - Schools, other closed settings especially involving adults (hospitals, ships, prisons etc.)
- Healthcare associated costs
  - Exposures and illness in healthcare settings
- Societal costs
  - Days of school and/or work missed for case and caretaker
  - Medications, other
- Public health burden may be greater in communities with higher prevalence of immunocompromising conditions

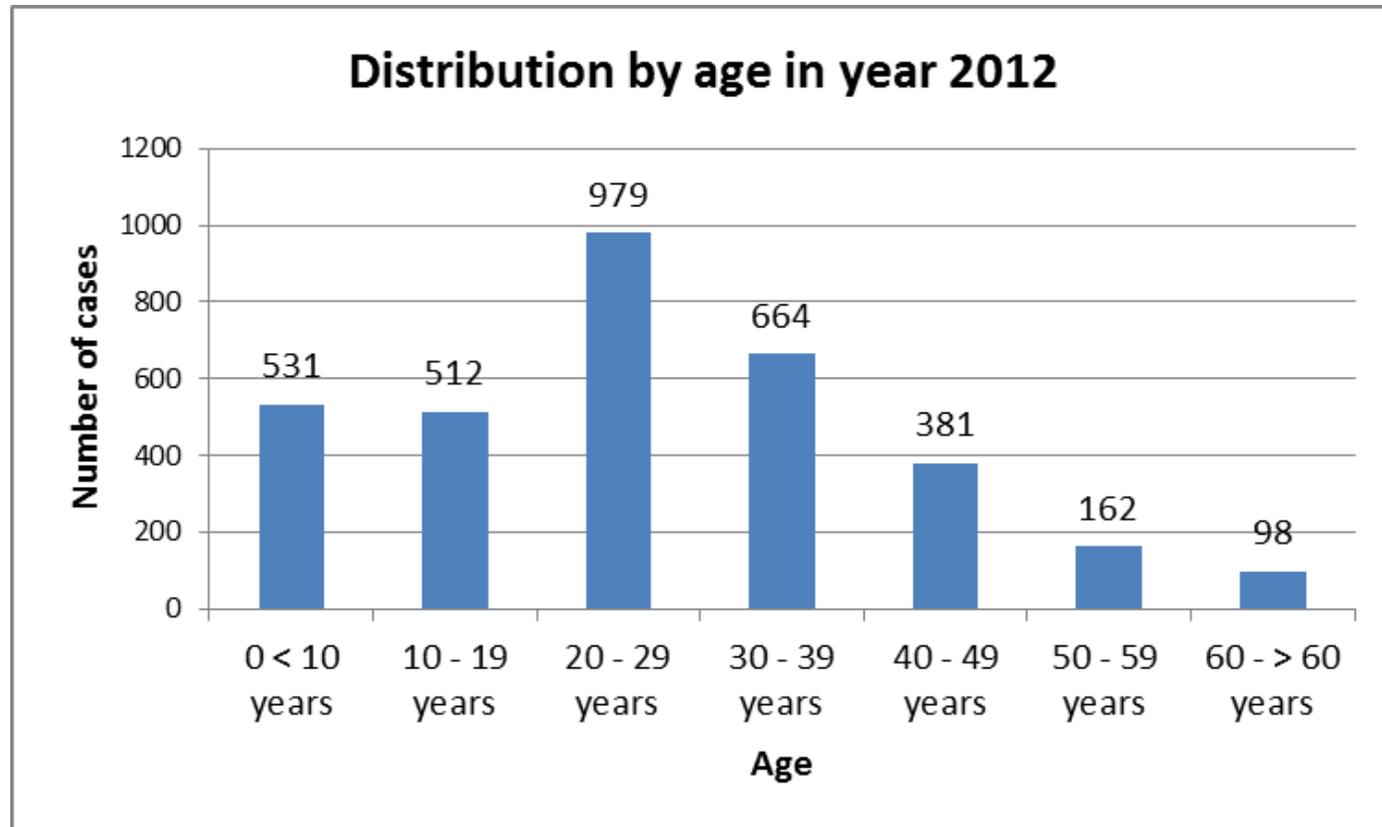
# Varicella Incidence and Case Fatality Rate by Age Group United States, 1990-1994 (pre-Vaccine)



Meyer P et al. JID 2000  
Joseph CA et al BMJ 1988

CFR: overall 2-3/100,000 cases US/UK  
Children = ~ 1/100,000    Adults = 20-25/100,000 cases

# Varicella Cases Notified by Age Sri Lanka, 2012



# VZV Seroprevalance by Age

199 Epidemiology of varicella

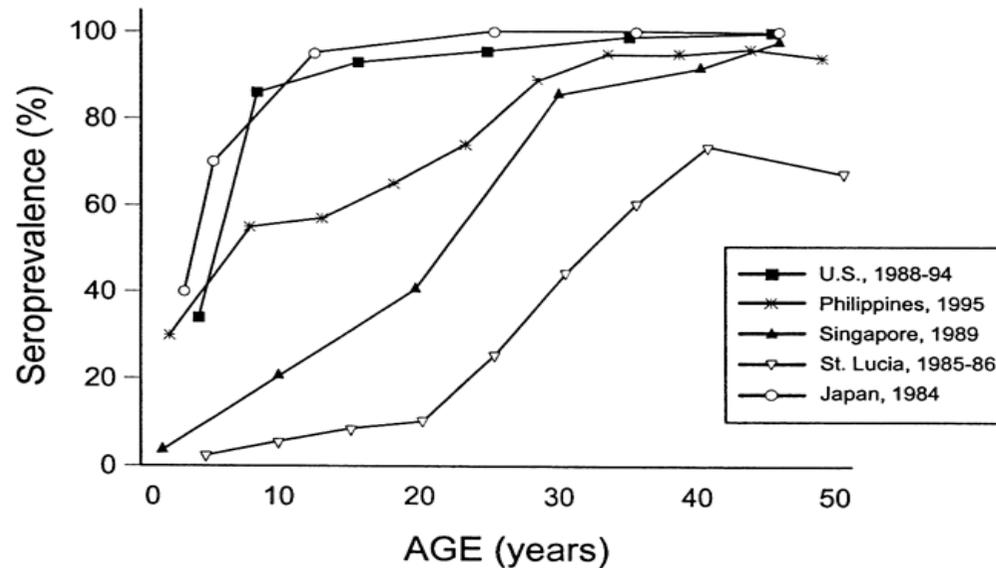


Figure 10.3 Age-related VZV seroprevalance in five countries.

## Susceptibility in Women of Childbearing Age

- < 5% US and UK
- 27% Iran
- 56% Sri Lanka

# Varicella and Healthcare Workers

- Nosocomial VZV transmission is a well recognized medical and public health problem
- Sources of nosocomial exposure: patients, health care workers, and visitors with either varicella or herpes zoster
- Health care workers have high risk of exposure and transmission to susceptible patients at high risk of serious or life-threatening complications

## Susceptibility profiles HCWs

- < 5% US
- 7% Spain (Catalonia)
- 14-19% Saudi Arabia
- 26% India (students)
- ~ 50% Sri Lanka (students)

# Risk Factors for Severe Varicella and Death

- Age
- Altered immunocompetence
  - HIV/AIDS
  - Childhood leukemia, other cancers and immunosuppressive therapies
- Pregnancy
  - Pregnant women – increased severity?
  - Fetus: congenital varicella syndrome with serious sequelae 0-20 weeks pregnancy
  - Newborn: severe infections if mother has varicella around the time of delivery
- Other: lack of access to health care

# Varicella and Herpes Zoster in HIV Infected Children

- Varicella: illness more extensive, longer duration, higher rate of complications compared to healthy children
  - Severity related to immune function
  - Persistent chronic infection may occur with atypical lesions
  - Resistance to acyclovir may develop during prolonged therapy
  - Ophthalmic complications associated with a high rate visual loss
- Herpes zoster: risk in HIV+ patients is >15 times higher than in the general population
  - Risk for disseminated herpes zoster
  - ~20%-30% of HIV-infected patients have one or more subsequent episodes of HZ; CD4 counts correlates with the frequency of HZ recurrences

# Varicella Hospitalizations Developing Countries

- Studies from hospital or clinic populations (case series)
  - Nigeria: 1970-80, 65% of admissions were in persons > 15 years
  - South Africa: 1985-96, retrospective review of admissions in a pediatric hospital in Durban
    - Measles accounted for 58% and varicella for 23% of admissions
    - 1% measles and 15% varicella admissions were HIV+ and 56% and 75% of measles and varicella deaths were in HIV+ children respectively
  - Sri Lanka 2000-2001 review admissions to Infectious Disease Hospital
    - 65% of 1690 hospital admissions were due to VZV infection (91% varicella and 9% HZ)
    - mean age 33 years, range 3 days to 94 years; 69% were 11-40 years
    - 10 were pregnant
    - Secondary bacterial infections, extensive rash in persons with other skin diseases, pneumonia, carditis, neurological complications

# Varicella Mortality Developing Countries

## Case Fatality Rates from Selected Studies

- Guinea Bissau 2000 (small study 2 deaths/1539 cases –6 months and 17 years)
  - ~ 129/100,000 case, 50 times higher than US/UK
- India late 1970s enhanced rash illness surveillance post smallpox eradication 433 deaths/862,155 reported cases; 80% deaths adults
  - 52/100,000 cases, 20 times higher than US/UK
- Brazil 2008: estimated CFR 4/100,000 (deaths from vital statistics, cases from modeling)

### Deaths in hospital admissions

- Nigeria (1970s): 14 deaths among 2,153 hospital admissions
- Sri Lanka (2000-2001): 41 deaths among 989 varicella admissions (4.2%)
- Papua New Guinea (1980s): 10 deaths in adults at small hospital over 2 years in population 130,000

# Varicella Disease Burden: Developed Countries

- Incidence
  - 15.0 – 16.0/1,000 persons per year
  - Highest incidence < 10 years
- Complications
  - 2-4% of cases
- Hospitalizations
  - 3-6 hospitalizations per 1,000 cases
- Congenital varicella syndrome
  - Risk = 1-2% for pregnancies affected 0-20 weeks
- Deaths
  - ~ 3 deaths per 100,000 cases
  - Most deaths occur in healthy people

**Greatest disease burden in children  
>90% cases, 70% hospitalizations, 50% deaths**

# Global Burden of Disease Study

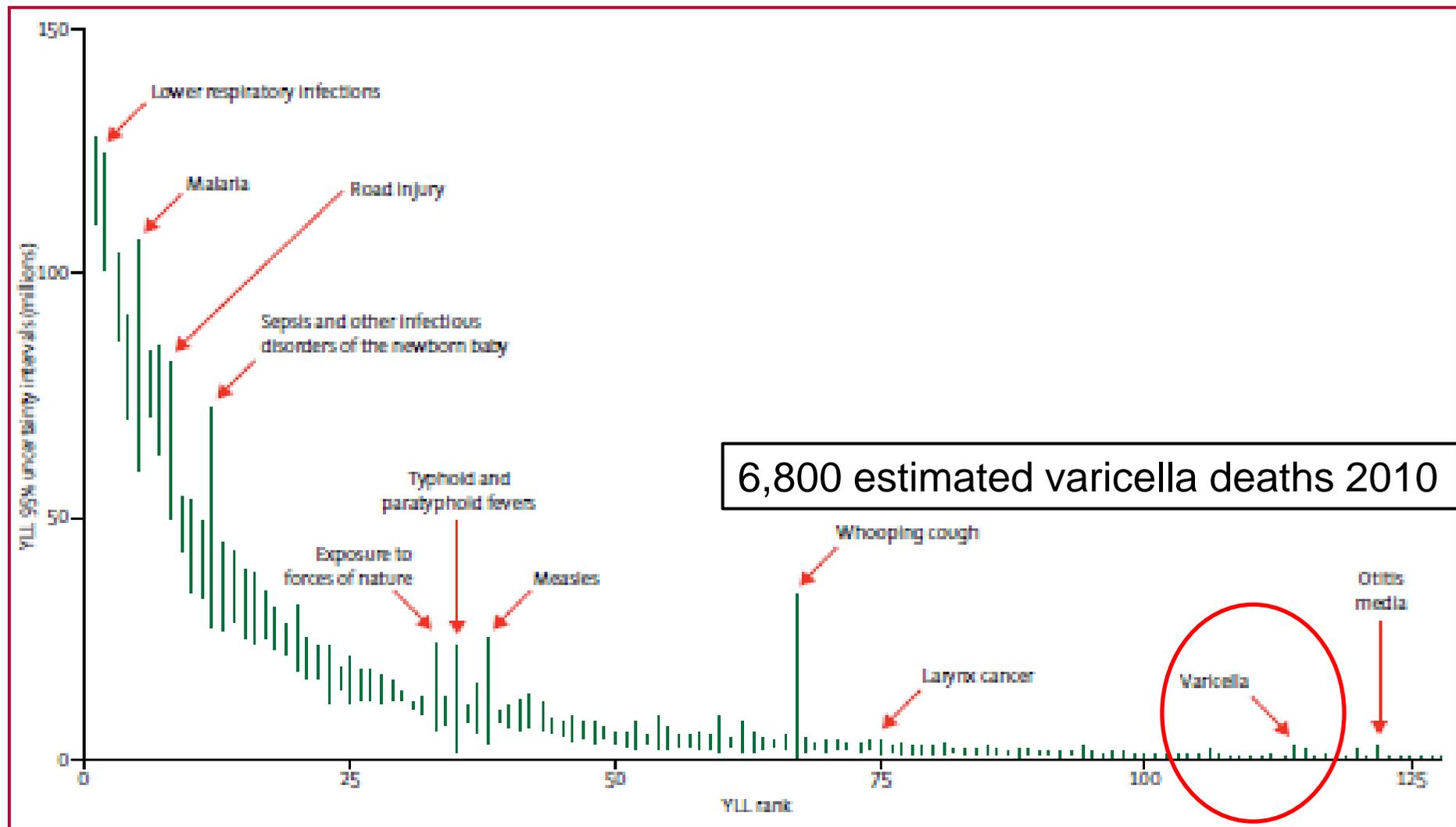


Figure 7: Global YLLs (millions) with 95% uncertainty intervals versus rank by cause in 2010

YLLs—years of life lost. An interactive version of this figure is available online at <http://healthmetricsandevaluation.org/gbd/visualizations/regional>.

# Varicella Annual Disease Burden

## Developed Countries

- Incidence 16/1000/year or birth cohort equivalent
- Complications (3%)
- Hospitalizations (5/1,000 cases)
- Congenital varicella syndrome
  - 1-2% first trimester affected pregnancies)
- Deaths (3/100,000 cases)

## Global minimum estimate)

- Cases
  - 140 million
- Complications
  - 4,200,000
- Severe complications (hospitalization)
  - 4.2 million
- Congenital varicella syndrome
  - ???
- Deaths
  - 4,200

# Summary Varicella Disease Burden

- Considerable disease burden especially as burden due to other vaccine preventable disease declines, well described problem in healthcare settings
- Epidemiology, especially population-based estimates of severe disease and deaths, mainly described from temperate climates, developed countries
- However, disease burden described from developed countries is likely the minimum disease burden that a country will experience
- Risk factors affecting severity of disease and outcomes may increase disease burden
  - Proportion of cases among infants and adults including pregnant women
  - Prevalence of immunocompromising conditions HIV, other?
  - Access to case and appropriate treatment

# Varicella Vaccines

- Live, attenuated vaccine, developed in Japan by Dr Takahashi
- Oka VZV strain used for all vaccine production except in South Korea
- Manufacturers in the US, Belgium, Japan, South Korea and China
- ~ 31 million doses annual average distributed worldwide 2007-2011
- Refrigerator and freezer stable vaccines
- Vaccines
  - **Monovalent vaccines**: licensed on basis of efficacy and safety
  - **Combination (MMRV)**: licensed on basis of safety and of non-inferior immunogenicity compared with MMR and V vaccines

# Varicella Vaccines

## Indications

Monovalent vaccine:

- Prevention of varicella in healthy persons  $\geq 9$  months or  $\geq 12$  months
- 9 or 12 months – 12 years: 1 dose
- $\geq 13$  years: 2 doses 4-8 weeks apart

MMRV vaccine:

- Prevention MMRV in children
  - 12 months – 12 years (ProQuad)
  - 9 months – 6 years (Priorix-tetra)

## Contraindications\*

- Anaphylactic reaction to vaccine components
- Pregnancy
  - Avoid for 1 month after vaccination
- Primary and acquired immunodeficiency states

\*Some vaccines licensed for use in leukemic children who meet certain criteria

Some advisory groups recommend use in immunocompromised populations who meet certain criteria e.g. HIV+ with CD4  $\geq 15\%$  , leukemia in remission

# Varicella Vaccine Performance

- Vaccine efficacy (pre-licensure studies)
  - Preventing varicella (phase 3 RCTs)
  - Preventing herpes zoster (observational study, children ALL)
- Vaccine effectiveness (postlicensure, real world conditions)
  - Preventing varicella and severe outcomes of varicella (severe clinical illness, hospitalization, death)
  - Preventing herpes zoster in healthy children

# Vaccine Efficacy

## Randomized Controlled Clinical Trials in Healthy Children

- United States (high potency vaccine)
  - 914 children 12 months – 14 years (mean 4.7 years)
  - One year f/u: VE 100%
  - Two years f/u: VE 98% overall and 92% in households
- Finland: (high and low potency vaccines)
  - 513 children 10 – 30 months
  - 29 months f/u: calculated VE 88% and 55% respectively
- China: high potency vaccine
  - 5,000 children 3-7 years
  - f/u 12 months: VE 90.8%

Wiebel R et al NEJM 1984, Varis T et al JID 1996; Ma FB et al Zhongguo Yi Miao He Mian Yi 2009

US: 17430 plague forming units (pfus), Finland: high: 10,000 – 15,850 pfus; low: 630-1,260 pfus  
China 10,000 pfus

# Post-licensure Varicella Vaccine Effectiveness One Dose, Prevention of Varicella

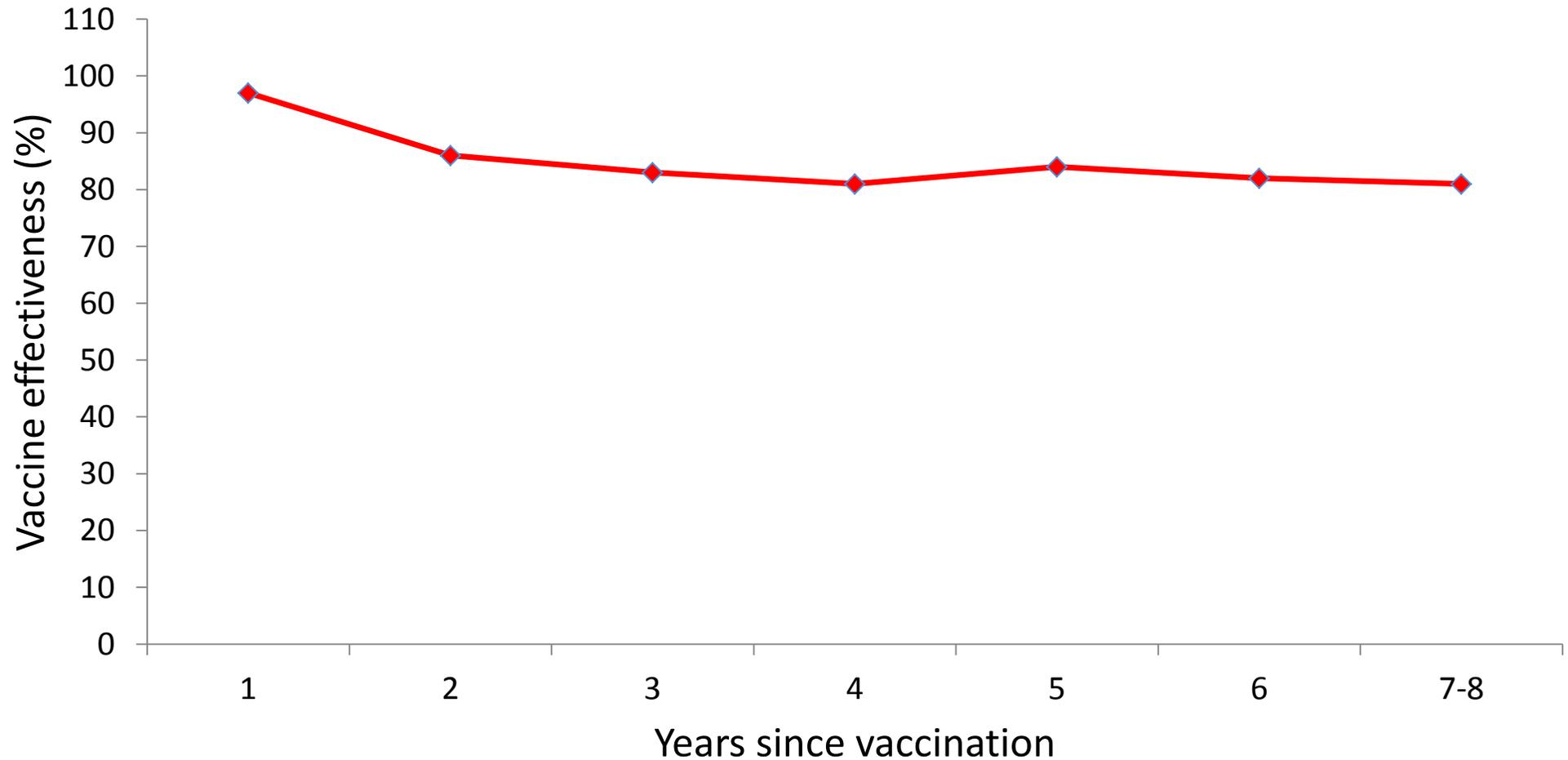
## Healthy children

## HIV+ children

- All disease  
Median ~ 82.5% (range 20%-100%)  
52 estimates
  - Severe disease (clinical severity score, > 500 lesions complications/hospitalization)  
Median 100% (range 85-100%)  
18 estimates
- 82% (95% CI 24-100%)  
1 study

No differences in vaccine effectiveness across vaccine manufacturers though number of studies are small for many vaccines

# Effectiveness of Varicella Vaccine by Time Since Vaccination



# Varicella Vaccine Efficacy/Effectiveness One Dose Prevention of Herpes Zoster

## Healthy children

- Civen et al children < 10 years
  - Method 1: VE 92% (95% CI: 89–94%)
  - Method 2: VE 77% (95% CI: 68–84%)
- Weinman et al children 0-17 years
  - VE 79% (P < 0.001, vaccinated vs unvaccinated cohorts)

## Immunocompromised children

### HIV

- Son et al
  - 100% (95% CI 67%-100%)

### Acute Lymphocytic Leukemia

- Hardy et al
  - 67.5%

# Varicella Vaccine Effectiveness: One vs Two Doses

<b>Study</b>	<b>Country/Setting</b>	<b>1 dose VE</b>	<b>2 dose VE</b>
<b>Vaccine Efficacy</b>			
Kuter	US, Community	94%	98%
Prymula	10 European countries, Community - MMRV	-	95%
<b>Vaccine Effectiveness</b>			
Gould	US, School outbreak	84%	88%
Nguyen	US, School outbreak	79%	95%
Shapiro	US, Community	86%	98%
Mahamud	US, School outbreaks	80%, 81%	84%, 95%
Cenoz	Spain, Community	87%	97%
Spackova	Germany, Day care outbreaks - MMRV	62%	93%

# Varicella Vaccine Safety

## Pre- and Post-licensure

- Placebo-controlled trials: small risk rash, fever, injection site reactions in appropriate time windows
- Post-licensure safety monitoring from the US (mainly)
  - Rare/extremely rare confirmed serious adverse events
    - Rash, hepatitis, pneumonia, herpes zoster, meningitis, encephalitis, secondary transmission
    - 2 vaccine strain VZV deaths, one immunocompromised and one with significant medical history suggestive of immunocompromise
- Reported but not confirmed vaccine virus
  - Ataxia, thrombocytopenic purpura
- Increased risk (X 2) of febrile seizure in 5-12 (or 7-10) day window following first dose MMRV vaccine in children 12-23 months
  - One additional febrile seizure for every 2,500 children vaccinated with MMRV vaccine compared with MMR+V vaccines

# Varicella Vaccine in Immunocompromised Children

- Because diseases caused by wild type VZV are more severe and fatal in persons with defects in cell mediated immunity, varicella vaccine has been studied for safety and efficacy in select immunocompromised populations
- Compared to healthy children, varicella vaccine is associated with higher risk of adverse events, some severe, in selected subpopulations of children with deficiencies in cell mediated immunity
- Two doses of varicella vaccine are effective and safe in preventing varicella in children with HIV with CD4%  $\geq 15\%$
- In countries with routine childhood varicella vaccination programs, many children will be vaccinated before acquiring their immune deficiency states

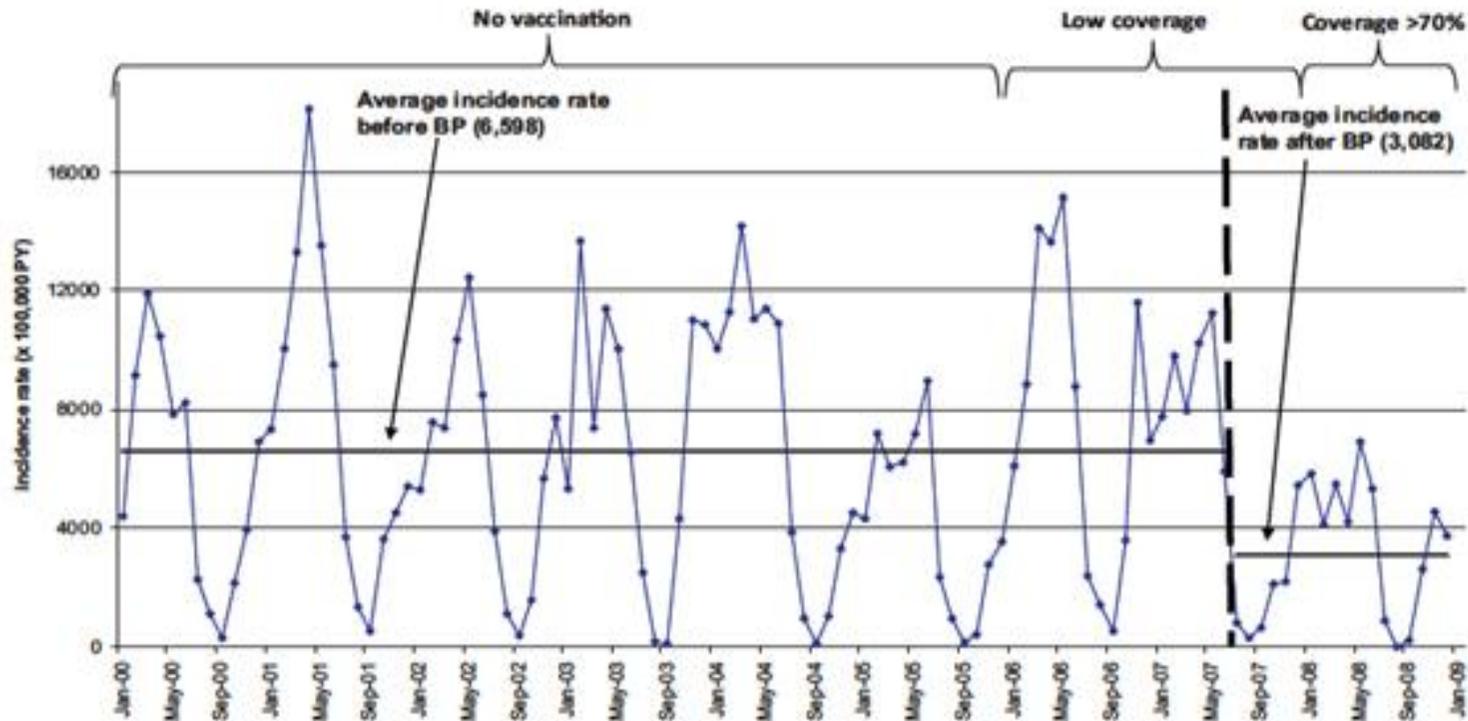
# Cost Effectiveness of Varicella Vaccine

- Two major reviews Thiry *et al.* (2003) & Rozenbaum *et al.* (2008) summarizing 41 studies: most from Europe and North America, 2 studies from Taiwan, 1 from Israel and 1 from Singapore
- Consistent Results:
  - Cost saving (or cost-effective) under the societal perspective
  - Cost-effective under the health payer perspective when excluding potential impact on zoster
  - Cost-ineffective (or increased morbidity) when including potential impact on zoster
- Recent studies produced similar results

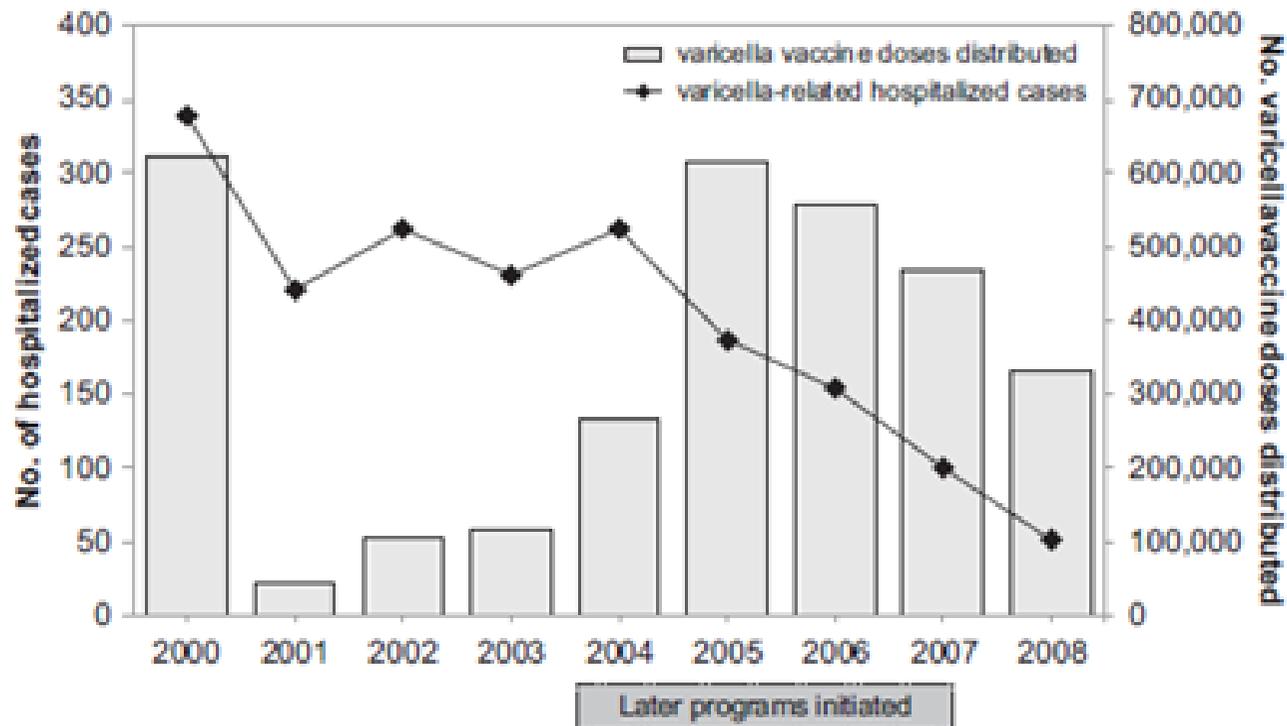
# Varicella Vaccine Impact

# Varicella Incidence

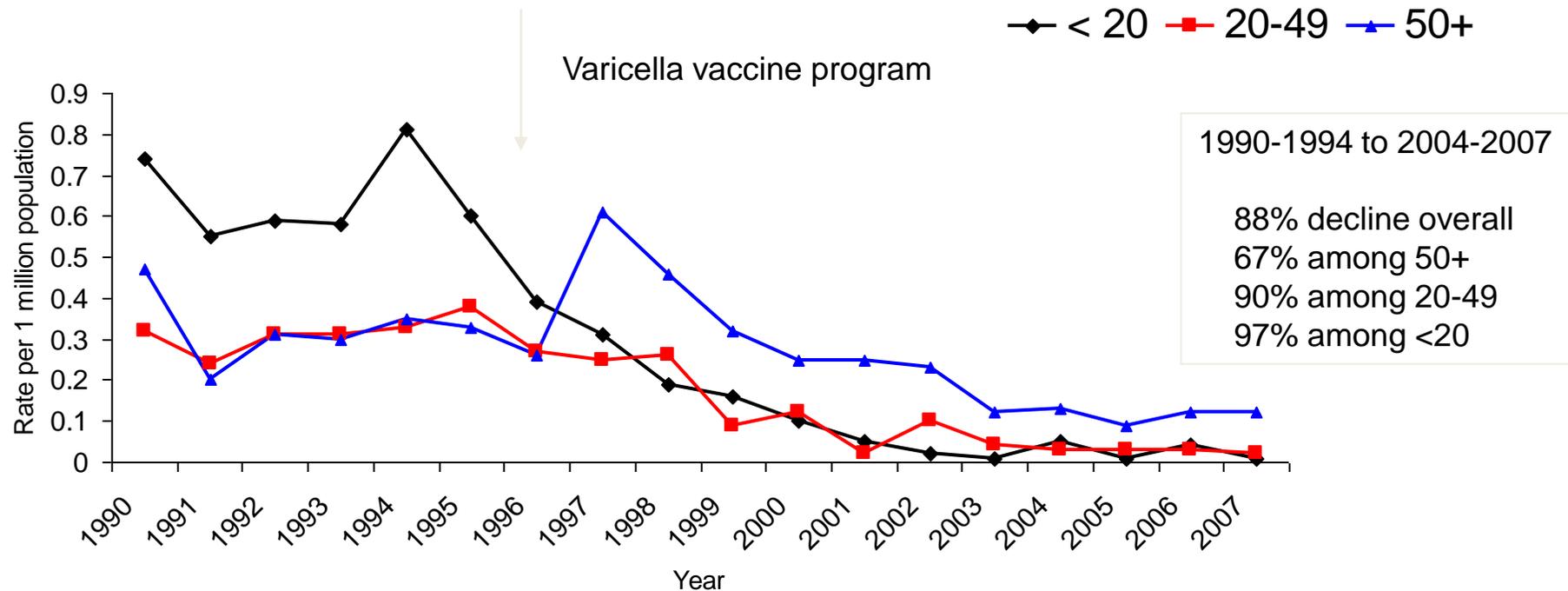
## Veneto region, Italy, 2000-2008



# Varicella-related Hospitalizations 8 Canadian Provinces/territories, 2000-2008



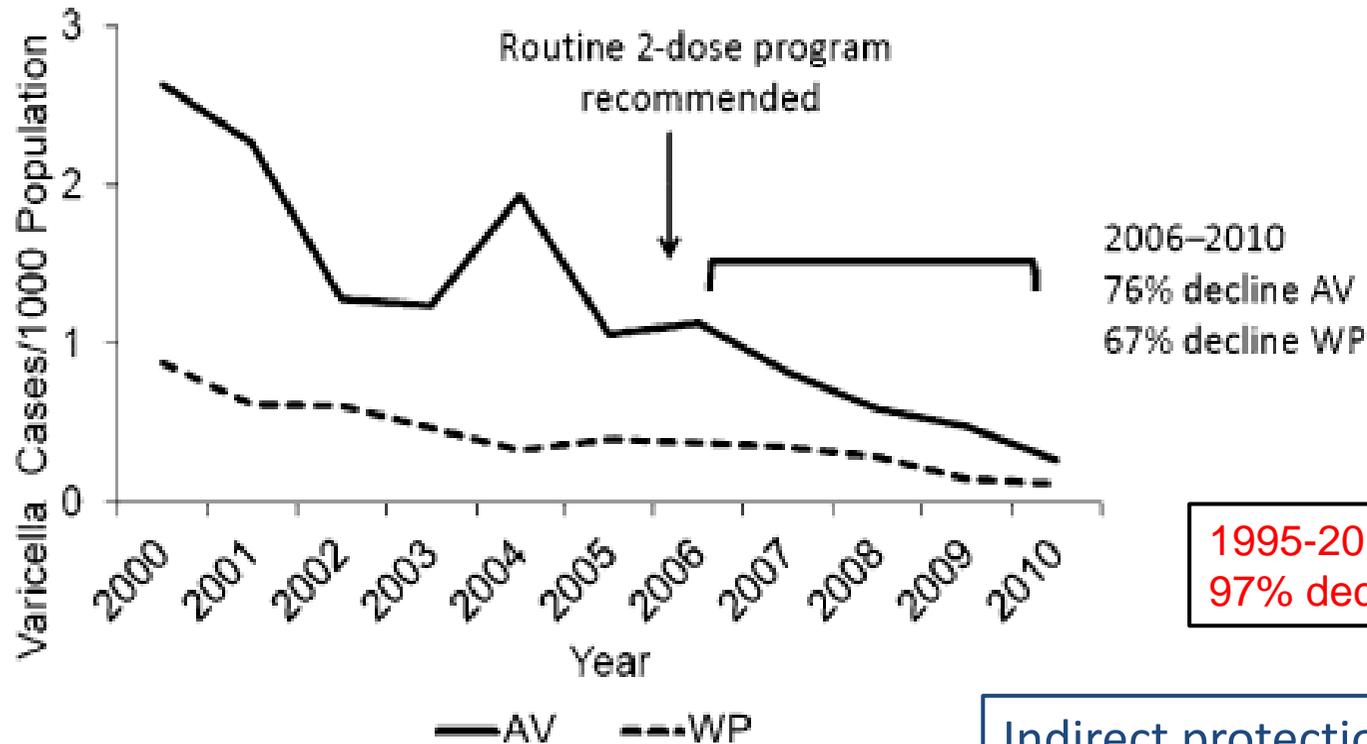
# Varicella-Related\* Mortality Rates, by Year and Age Group - United States, 1990–2007



Nguyen HQ et al NEJM 2005, Marin M et al Pediatrics 2011

\*Varicella as the underlying cause of death

# Varicella Incidence 2000-2010 Active Surveillance Sites, U.S.



# Surveillance for Herpes Zoster

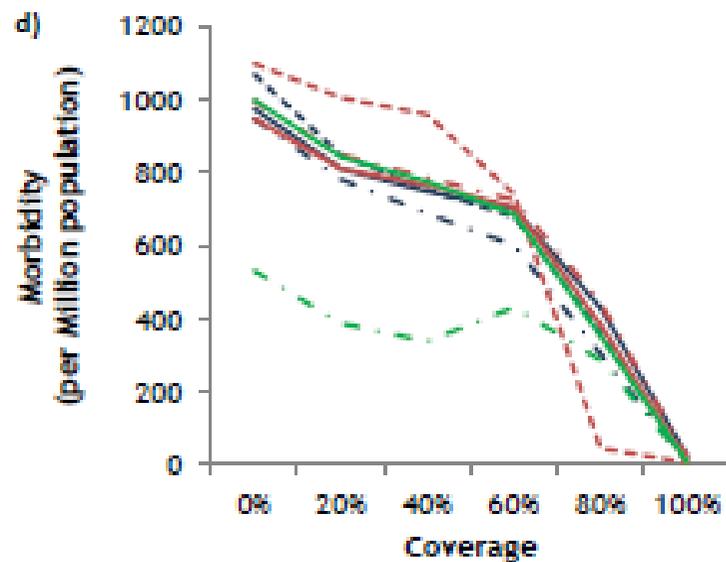
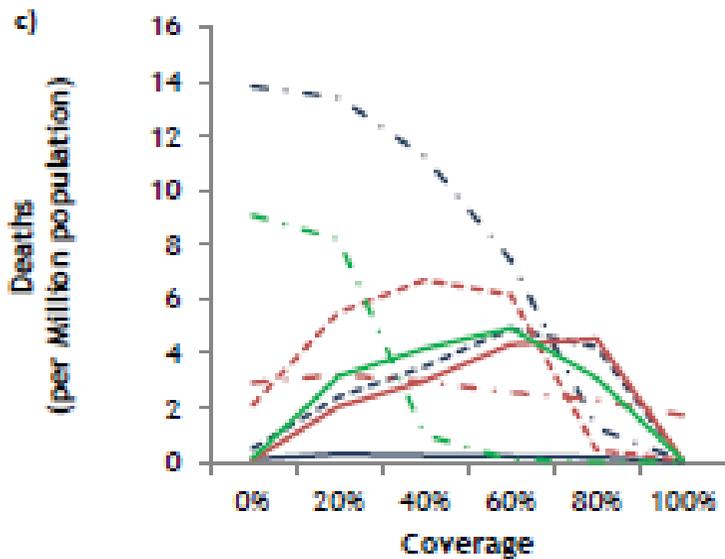
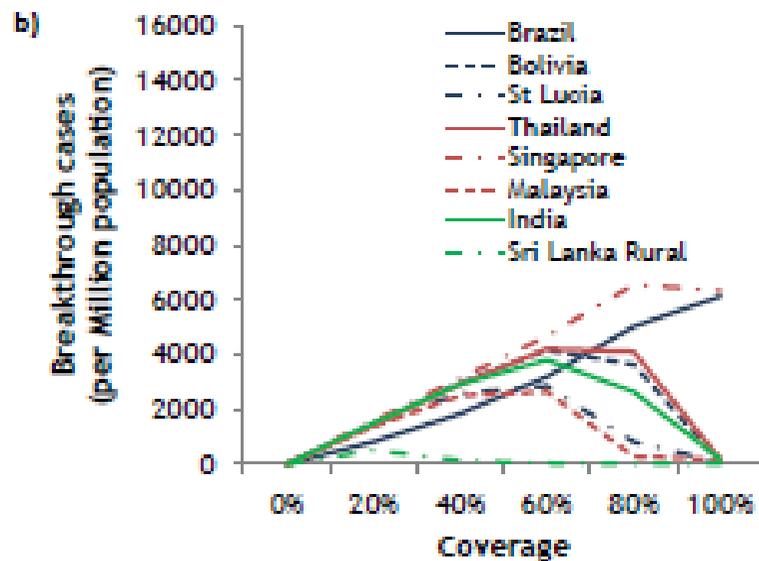
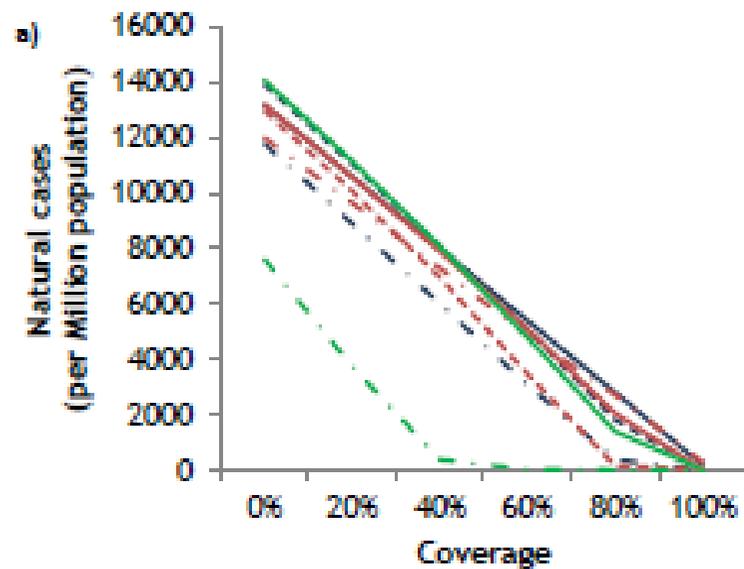
# Varicella Vaccine and Herpes Zoster

- Effect in community will depend on effect in vaccinated and unvaccinated cohorts
- In vaccinated healthy and immunocompromised children
  - Varicella vaccine also prevents herpes zoster
    - VE 68% - 100%
  - Declines in HZ incidence in vaccinated cohorts described US, Canada
- In persons with history of varicella
  - Model predictions based on assumptions about role of and duration of external boosting from exposure to children with varicella
  - Real world data?

# Summary Varicella Vaccine and Impact

- There is now almost 20 years of experience with use of varicella vaccine on a population basis
- Varicella vaccine
  - Good safety profile with rare confirmed serious adverse events, most commonly in immunocompromised children
  - Markedly decreases the risk and severity of varicella and, over the short term, herpes zoster in vaccinated children
  - One dose is ~ 85% effective in preventing all varicella and ~ 100% effective in preventing severe varicella and 67-100% effective in preventing HZ
- Vaccine impact documented in developed countries:
  - Declines in varicella incidence, hospitalizations and mortality to very low levels
  - Herd immunity effect, no increase in incidence or severe outcomes in adults
  - Increases in herpes zoster can't be attributed to varicella vaccination programs

Vaccine Coverage and Varicella Disease Burden  
in Low/Middle Income Countries: A Modelling Study  
commissioned by WHO for SAGE WG



# Study Conclusions

- In lower and middle income countries (LMICs), with a one dose program in children 12-18 months, when coverage is between 20% and 80%, there is a high risk of shifts in the age at infection and increased mortality
- However, LMIC with very low seropositivity (less than 20-30% in 20 year olds) and the highest burden of disease are expected to have little to no shifts in the age at infection and important reductions in varicella-related mortality and morbidity, at intermediate levels of vaccination coverage

# Summary

- Varicella disease burden
  - considerable especially as burden due to other VPDs declines , well described problem in healthcare settings
- Risk factors affecting severity of disease and outcomes likely to increase disease burden in low income countries
  - Proportion of cases among infants and adults including pregnant women
  - Prevalence of immunocompromising conditions HIV, other?
  - Access to care and appropriate treatment
- Safe and effective vaccine:
  - Severe adverse effects and deaths reported very rarely
  - Decline in varicella deaths, hospitalizations and incidence and herd immunity effect
  - Impact on herpes zoster incidence in healthy and immunocompromised children
  - Current evidence does not support adverse impact varicella vaccine on HZ epidemiology