



# **The Impact of the U.S. Varicella Vaccination Program on the Incidence of Herpes Zoster**

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June 21, 2017



**Dr. Edgar Hope-Simpson  
(1908 –2003)**

# Background

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- Herpes zoster (HZ): caused by reactivation of Varicella Zoster Virus (VZV)
- Process under immunological control
  - Influenced by subclinical VZV reactivation (ie, endogenous boosting) and/or by exposure to others with varicella (ie, exogenous boosting)
- If correct, by reducing VZV circulation, varicella vaccination could reduce exogenous boosting and thus plausibly increase the risk of HZ
- This (among other concerns) made ACIP cautious about introducing routine varicella vaccination in early 1990s
  - Continues to make vaccine policy-makers in Europe and elsewhere cautious about introducing varicella vaccination today

# Background

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Vaccine 20 (2002) 2500–2507

Vaccine

[www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

## Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox

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Received 22 October 2001; received in revised form 8 March 2002; accepted 11 March 2002

### Abstract:

“...Mass varicella vaccination is expected to cause a major epidemic of herpes-zoster, affecting more than 50% of those aged 10-44 years at the introduction of vaccination...”

# Background

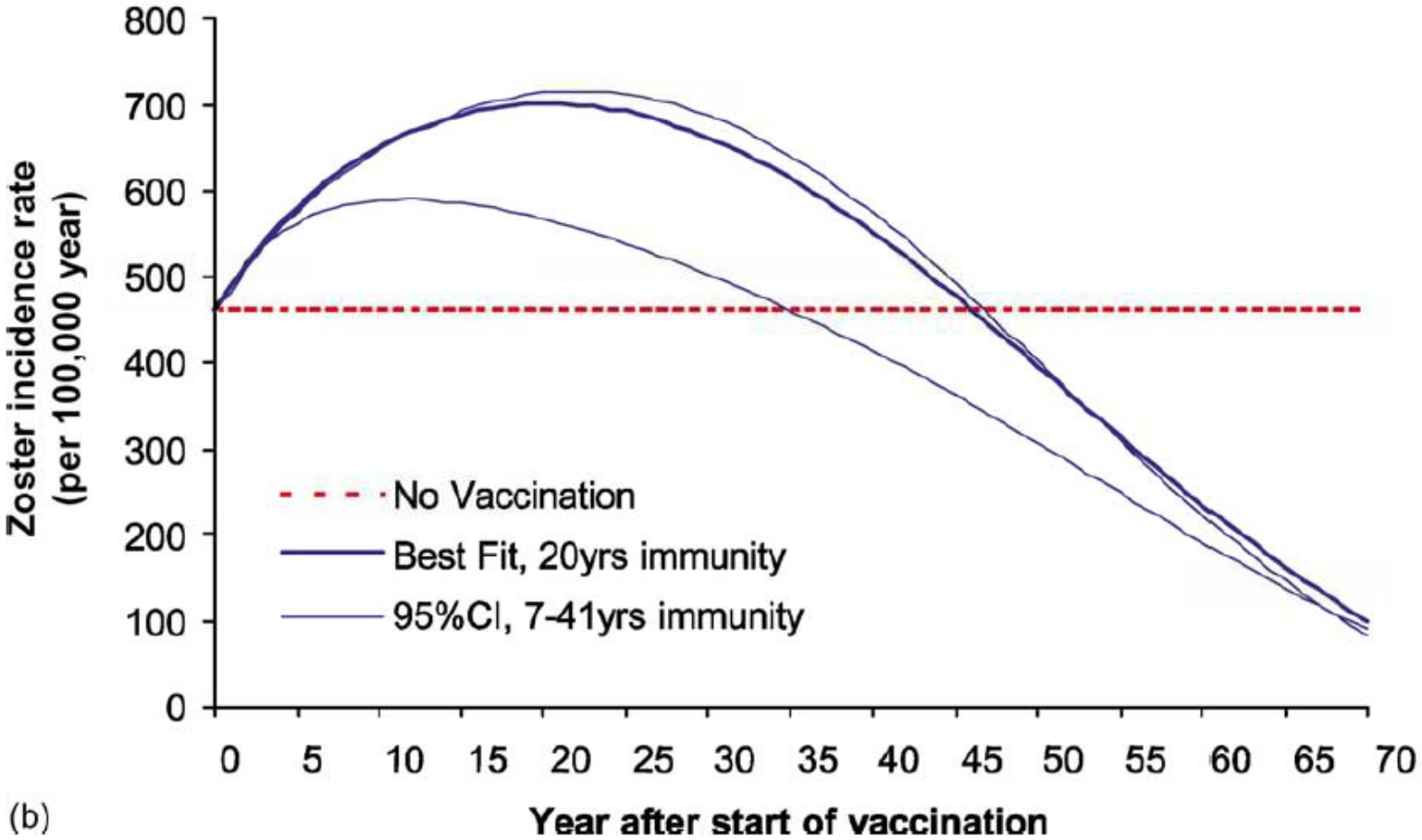


Fig. 4. Prediction of post-vaccination incidence of herpes-zoster. (a) Lifetime risk of zoster among unvaccinated individuals of different ages at the start of vaccination by different durations of immunity to zoster after exposure to varicella. (b) Incidence of zoster over time after the introduction of vaccination for the 'best-fit' model ( $1/\sigma = 20$  years) and the 95% confidence bounds of  $1/\sigma$  (7 and 41 years). The no vaccination scenario is represented by the dotted line.

# Outline

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- Background
  - Varicella in the US
    - Burden
    - Introduction of varicella vaccination
    - Impact on VZV circulation
  - HZ in the US
    - Epidemiology and risk factors including baseline rates
    - Introduction of zoster vaccination and vaccine uptake
- The impact of the US varicella program on HZ trends
- Conclusions

# Background on Varicella in the U.S.



# Burden of Varicella During Pre-Vaccine Era

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- Cases ~4 million annually
- Hospitalizations ~11,000 to 13,500 annually
- Deaths ~100 – 150 annually
- Greatest disease burden in children
  - >90% cases, 70% hospitalizations, 50% deaths
- Congenital varicella syndrome ~44 annually

Refs: Wharton ID Clin N Am 1996; Galil PIDJ 2002; Davis Pediatrics 2004; Meyer JID 2000; Nguyen NEJM 2005; Enders G & Miller E (2000) Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM and Gershon AA (eds) Varicella-zoster virus;

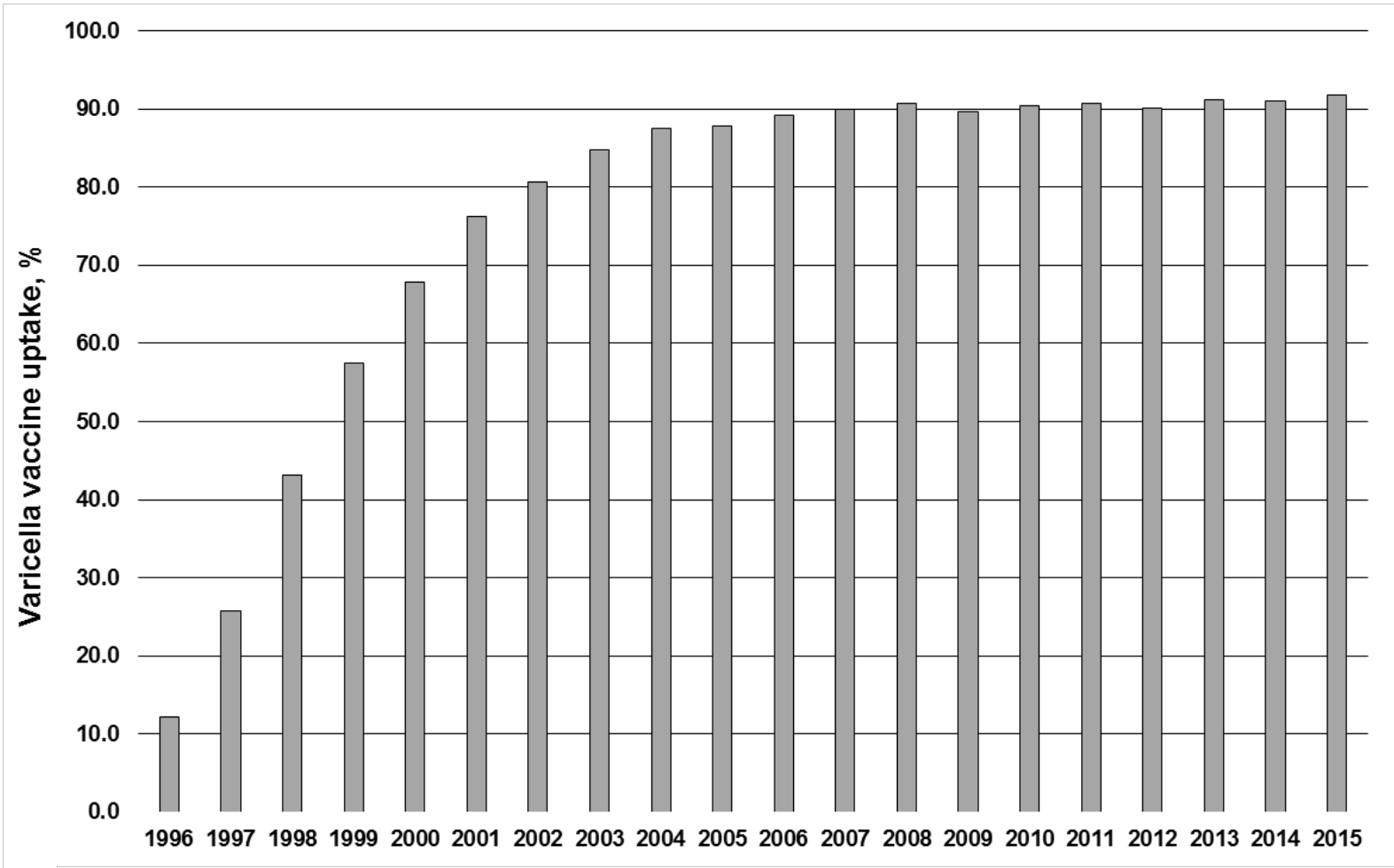


# Varicella Vaccination Policy and Uptake

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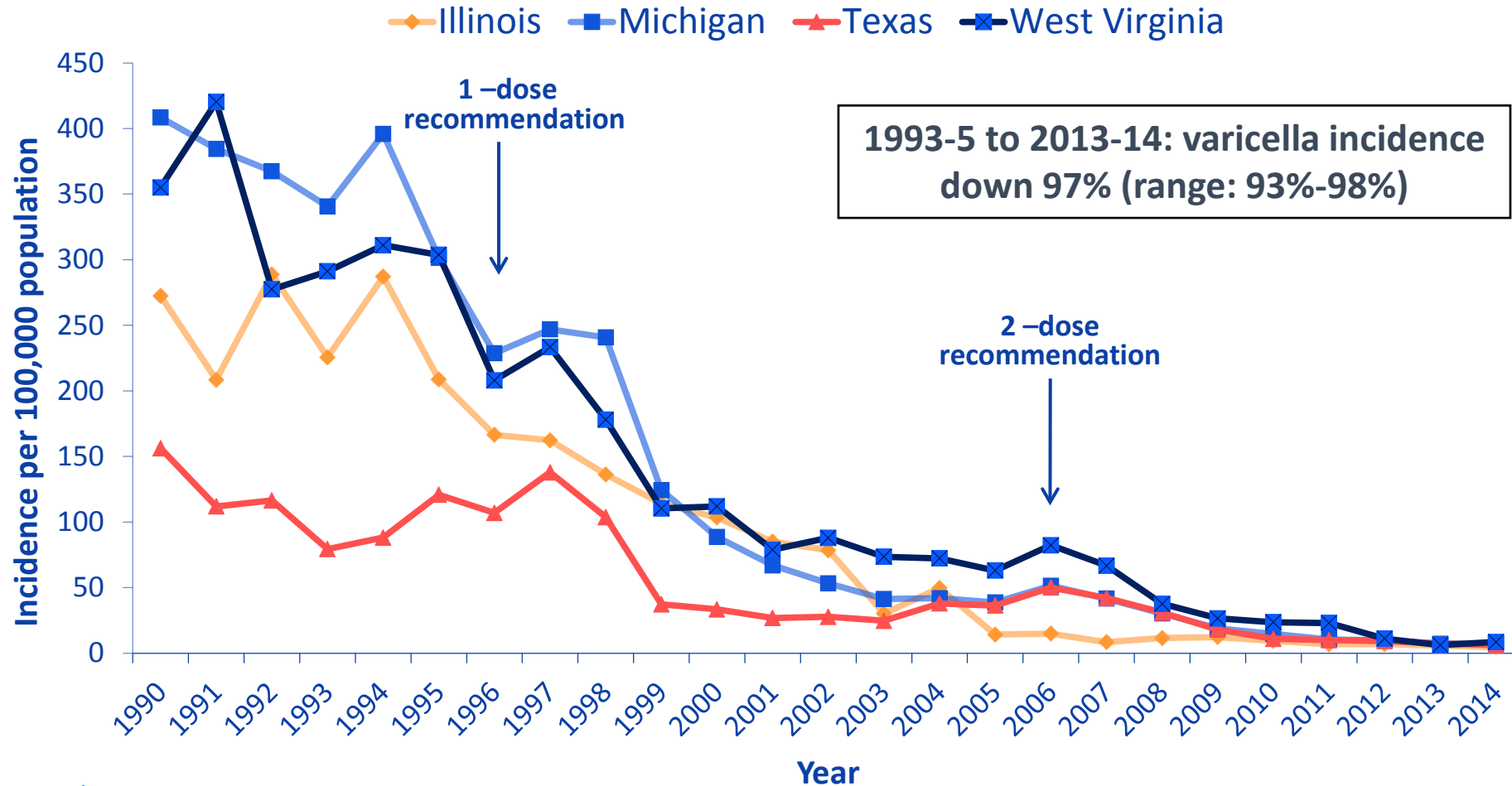
- 1996: 1-dose varicella vaccine for all children
  - At age 12-18 months
  - Catch-up vaccination of susceptible children
  - 2 doses for susceptible persons  $\geq 13$  years
  
- 2006: 2-doses varicella vaccine for all children
  - 1<sup>st</sup> dose at age 12-15 months
  - 2<sup>nd</sup> dose at age 4-6 years
  - Catch-up for persons who received 1 dose

# Varicella vaccine coverage, children 19-35 months of age U.S., 1996-2015



[www.cdc.gov](http://www.cdc.gov)

# Reported Varicella Incidence, 4 U.S. States 1990-2014



# Reduction in Varicella Rates by Age, Varicella Active Surveillance Projects (VASP), 1995 vs. 2010

Age group	Antelope Valley, CA (%)	West Philadelphia (%)
<1	-97	-94
1-4	-98	-97
5-9	-99	-99
10-14	-93	-99
15-19	-86	-94
20+	-94	-91
Total	-97.5	-98

# Background on Herpes Zoster in the U.S.



# Overview of Herpes Zoster Epidemiology and Burden

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- Incidence: ~4 per 1000 population annually (lifetime risk: ~30%)<sup>1</sup>
  - ~1 million cases of HZ annually
  - Postherpetic neuralgia (90 day duration): ~110,000
  - Hospitalizations: ~10,000 – 30,000
  - Eye complications: ~90,000<sup>2</sup>
- Risk factors<sup>1</sup>
  - High magnitude (increased several-fold): age, immunosuppression
  - Moderate magnitude (increased 20%-60%): gender, race
  - Uncertain magnitude (disparate reports): genetics/family history
- We do not have any idea what distinguishes most of ~1/3 individuals who develop HZ from the ~2/3 individuals who do not<sup>1</sup>

1 Harpaz et al., MMWR Recomm Rep. 2008

2 Yawn et al. Mayo Clin Proc 2013

# Instability of Baseline Herpes Zoster Incidence

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- Increasing trends in HZ incidence preceding availability of varicella vaccine
  - Five of six US studies<sup>1</sup>
    - All adult age groups
    - Explanation unknown (obvious ones ruled-out) <sup>1,2</sup>
  - Most but not all studies in Canada, UK, Spain, Taiwan, Japan, Australia, Czech Republic, S. Korea<sup>3</sup>

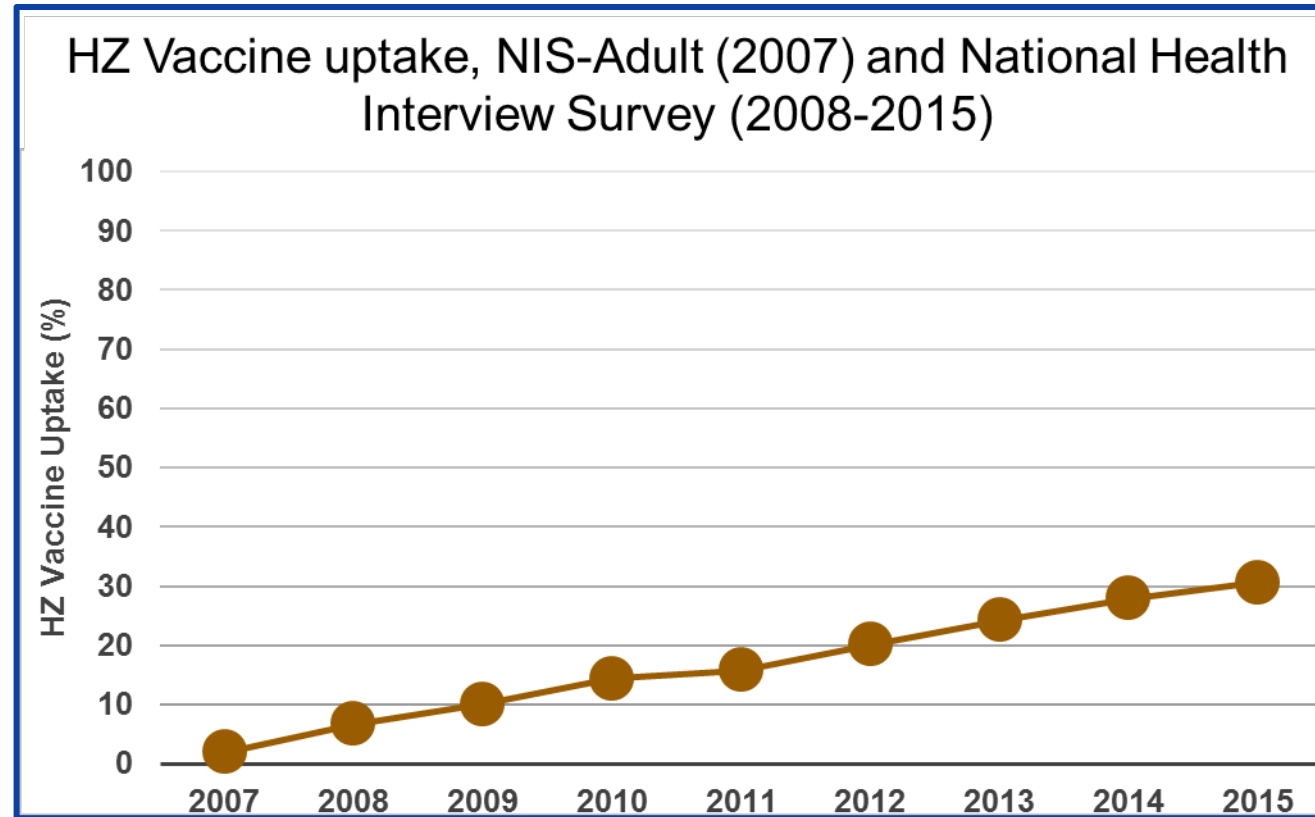
1 Ragozzino MW, *Medicine (Baltimore)*, 61(1982):310-6; Kawai K, *CID*, 63(2016):221-6; Singleton J, 41<sup>ST</sup> Annual Meeting IDSA 2003, Abstract 899; Leung J, *CID*, 52(2011):332-40; Hales CM, *Ann Intern Med* 160(2014):582-3; Hales CM (unpublished thesis, 2015, [http://scholarworks.gsu.edu/math\\_theses/149/](http://scholarworks.gsu.edu/math_theses/149/)); Jumaan AO, *JID* 191(2005):2002-7.

2 Joesoef RM, *Mayo Clin Proc.* 87(2012):961-7

3 Kawai K, *BMJ Open.* 4(2014):e004833; Park SY, *Korean J Dermatol*, 42(2004):1531-5 (in Korean); Smetana J, *Epidemiol Mikrobiol Imunol*, 59(2010):138-146 (in Czech)

# Herpes Zoster Vaccine Uptake

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Lu P, Vaccine, 2009; Lu P, AJPM, 2011; Williams W, MMWR, 2012; Williams W, MMWR, 2014; Lu P, Vaccine, 2015; Williams W, MMWR, 2016; Williams W, MMWR, 2017.



# Impact of Varicella Vaccination on the Epidemiology of HZ in the U.S.



# Trends in Herpes Zoster Incidence in the U.S.

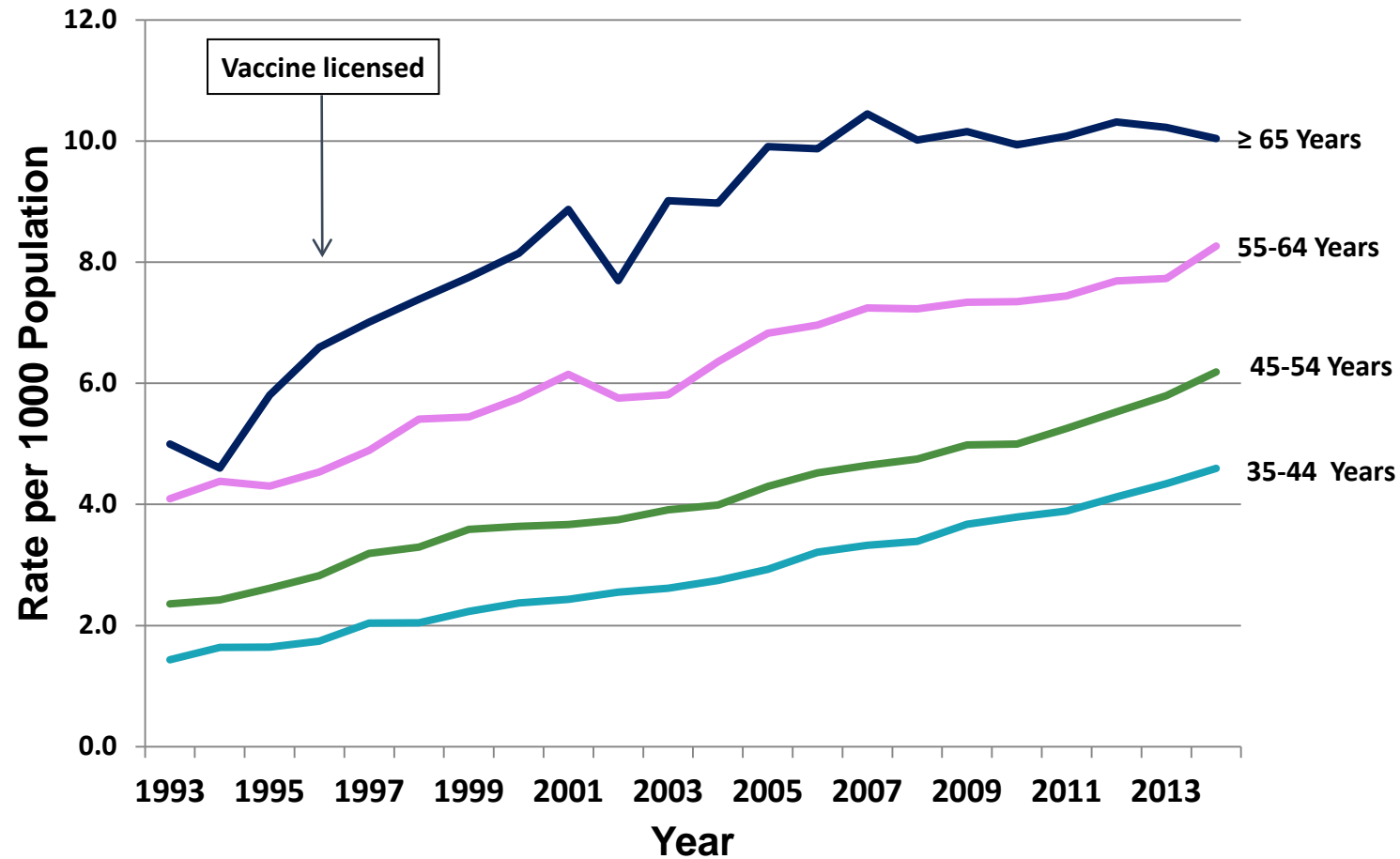
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- Seven studies show HZ trends following availability of varicella vaccine
  - None of these show evidence of an accelerating trend following introduction of varicella vaccination<sup>1</sup>
    - Five of these 7 studies actually suggest a deceleration<sup>2</sup>
    - These HZ trends cannot be attributed to Zostavax given its slow uptake and moderate effectiveness
  - None of these show evidence of an accelerating trend following introduction of varicella vaccination<sup>1</sup>

1 Kawai K, CID, 63(2016):221-6; Jumaan AO, JID 191(2005):2002-7; Leung J, CID, 52(2011):332-40; Harpaz R, OFID 2015:2 (suppl\_1): 1052; Hales CM, Ann Intern Med 160(2014):582-3; Zhang J (unpublished); Izurieta HS, CID, 64(2017):785-793; Moanna A, OFID 2016: 3 (suppl\_1): 628; Yih WK, BMC Public Health. 5(2005):68; Mass DPH (unpublished); Tseng HF, JID, 213(2016):1872-5.

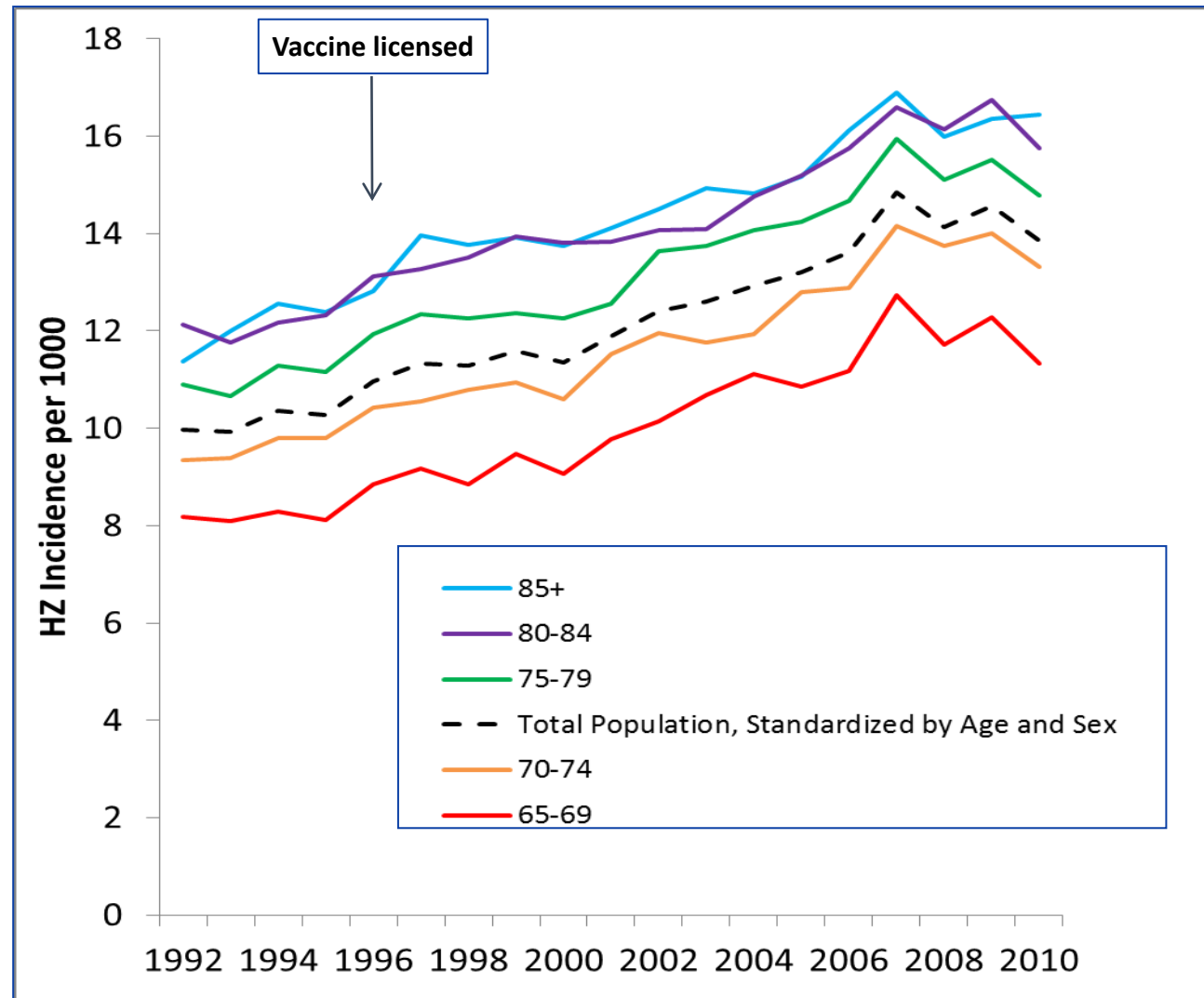
2 Leung J, CID, 52(2011):332-40; Harpaz R, OFID 2015:2 (suppl\_1): 1052; Hales CM, Ann Intern Med 160(2014):582-3; Zhang J (unpublished); Izurieta HS, CID, 64(2017):785-793; Moanna A, OFID 2016: 3 (suppl\_1): 628; Yih WK, BMC Public Health. 5(2005):68; Mass DPH (unpublished); Tseng HF, JID, 213(2016):1872-5.

# HZ Rate by Age, Adults $\geq 35$ Years, MarketScan U.S., 1993-2014



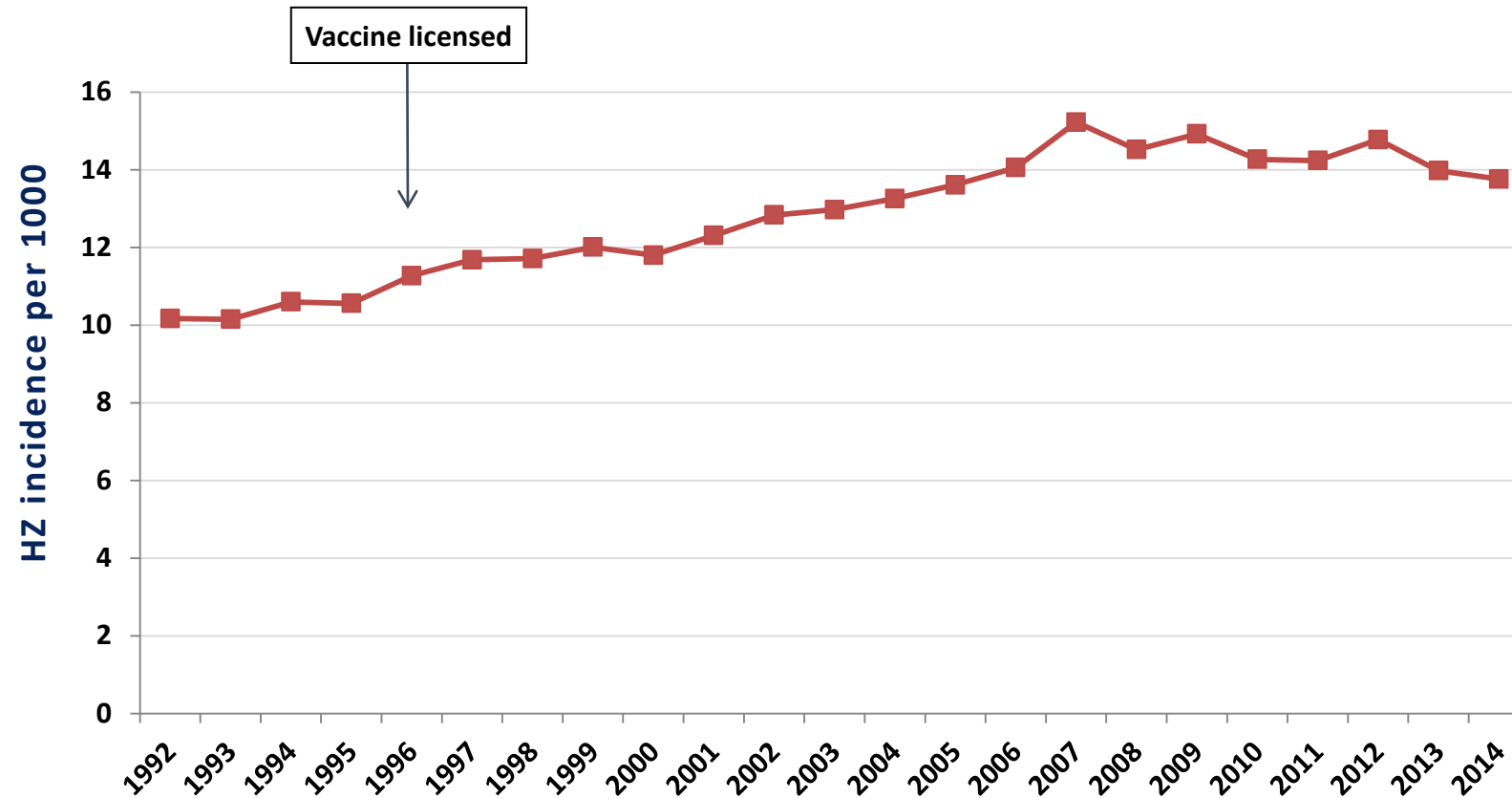
Harpaz R, IDWEEK 2015

# HZ Incidence, Medicare (Adults $\geq 65$ ), 1992 - 2010



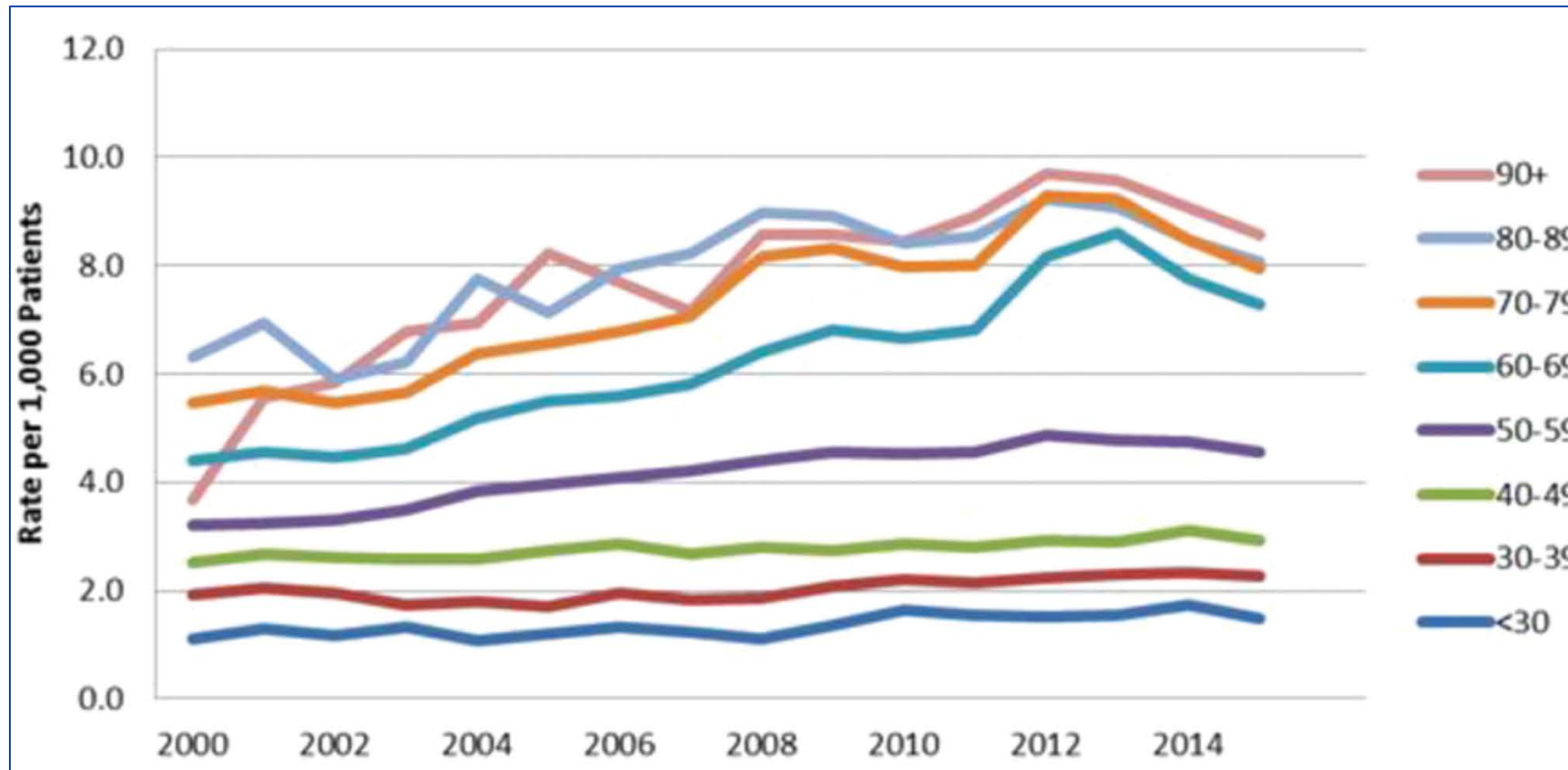
Hales C. et al., *Ann Intern Med.* 2013;159:739-745.

# HZ Incidence, Medicare (Adults $\geq 65$ ), 1992 - 2014



CDC, Unpublished

# HZ Rates, by Age, Veterans Administration U.S., 2000 - 2015



# Conclusions



# Possible Reasons for Lack of Varicella Vaccine Impact on HZ

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1. Hope-Simpson's hypothesis is incorrect
  - VZV exposure has little/no impact on HZ control, or impact of short duration
  - Endogenous boosting compensates when exogenous boosting declines
2. In the pre-vaccine era, there were too few sufficiently-intense VZV exposures to noticeably alter HZ rates at the population level
  - Limited to parents of young children, occupational groups
  - Older adults have fewer VZV contacts (and immune senescence?)
3. Hope-Simpson hypothesis at least partially manifest as a decline in mean age of HZ cases (ie, younger = milder HZ = less health care seeking per episode)
4. Inadequate time to see an impact
  - Most models predict effect by 20 years (it was immediate in household studies)
5. US studies all incorrect: missing a true impact due to cross-study artifacts



# Conclusion: the Impact of Varicella Vaccination

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- Varicella:
  - Incidence, outbreaks, and severe disease have declined to low levels in all age groups
- Herpes zoster:
  - Among children, rates have been declining to low levels
  - No evidence that the varicella program has increased HZ rates in the general population
    - At a minimum, models can be updated and constrained using the US data to allow for more realistic assumptions
- The US experience can provide reassurance for countries considering adoption of varicella vaccination

**Thank You!!**



**Questions??**