

MMR & Shingles

A Tale of Two Vaccines

Melissa Martinez MD

FAAFP

A Tale of Two Vaccines

Chapter 1

Outbreaks of measles and mumps

Rationale for a 3rd MMR

Chapter 2

Comparing 2 Shingles Vaccines

Understanding Adjuvants

Chapter 3

A new Hepatitis B vaccine

Chapter 4

A tale of two influenza vaccines

LAIV4 and Adjuvanted IIV4

Chapter 5

Review of pneumococcal vaccines for adults

Melissa Martinez MD FAAFP
Vaccine Geek

Nothing to declare

- *SHOTS app content expert*
- *National Vaccine Advisory Committee*
US Department of Health and Human Services
- *Liaison Mumps Work Group of the Advisory Council on Immunizations Practices (ACIP,CDC)*
- *Fellow AAFP Vaccine Science*
- *New Mexico Immunization Practice Advisory Committee*
- *UNMH Adult Immunization Task Force*

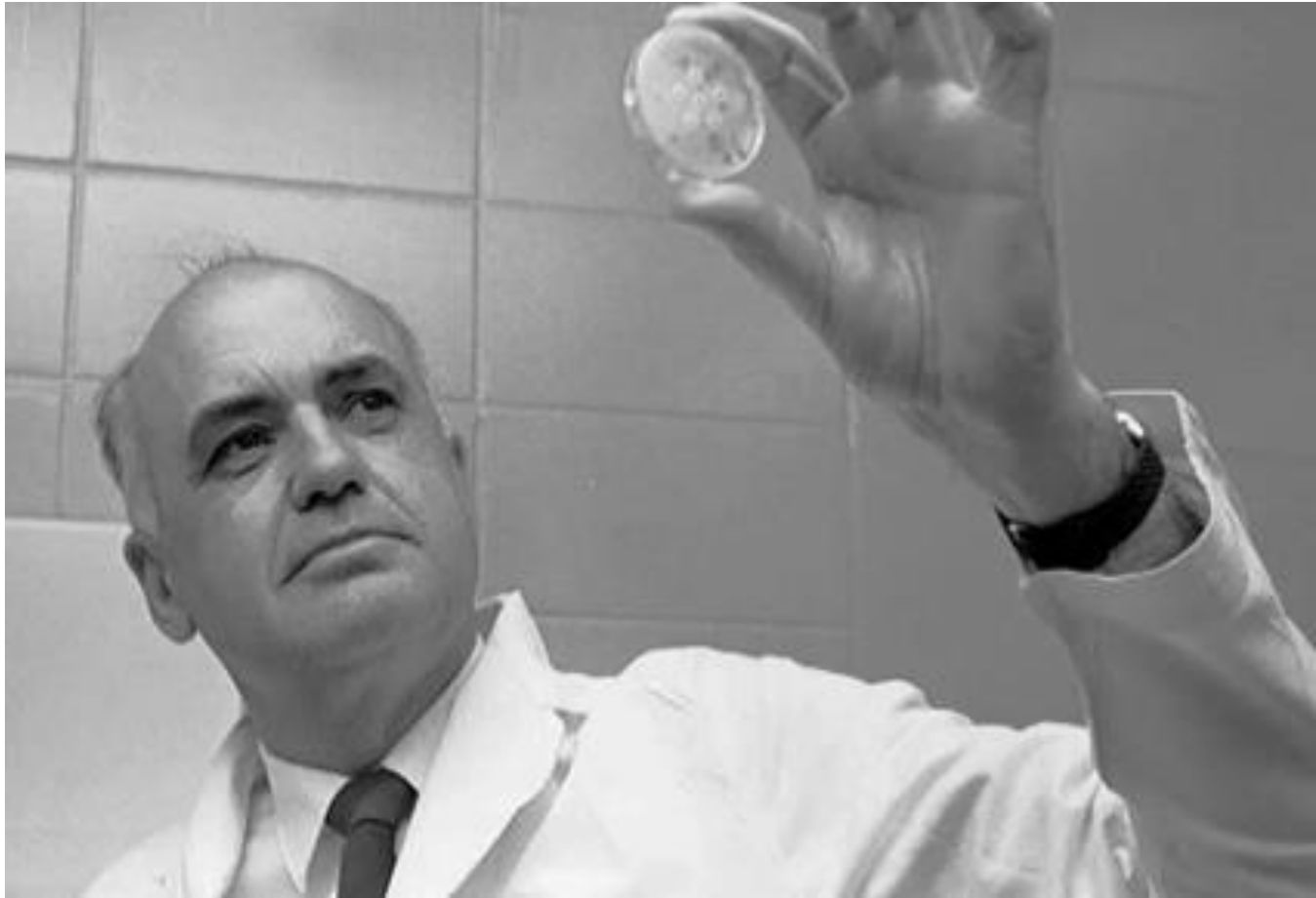


Jeryl Lynn Hilleman

The College of Physicians of Philadelphia

www.historyofvaccines.org/content/mumps-jeryl-lynn-story

1965 Dr. Maurice Hilleman

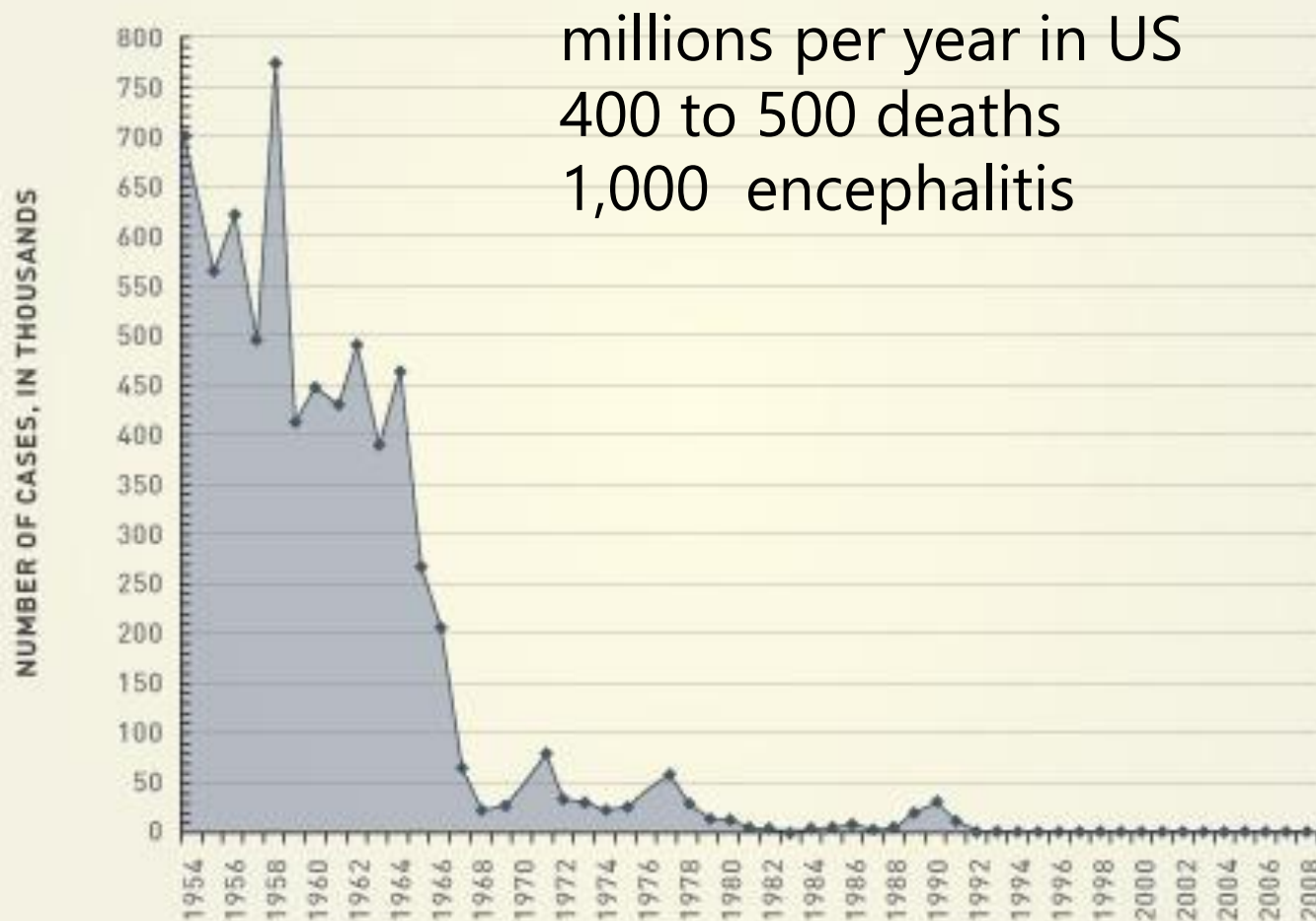


Smithsonian: www.si.edu/spotlight/antibody-initiative/mmr



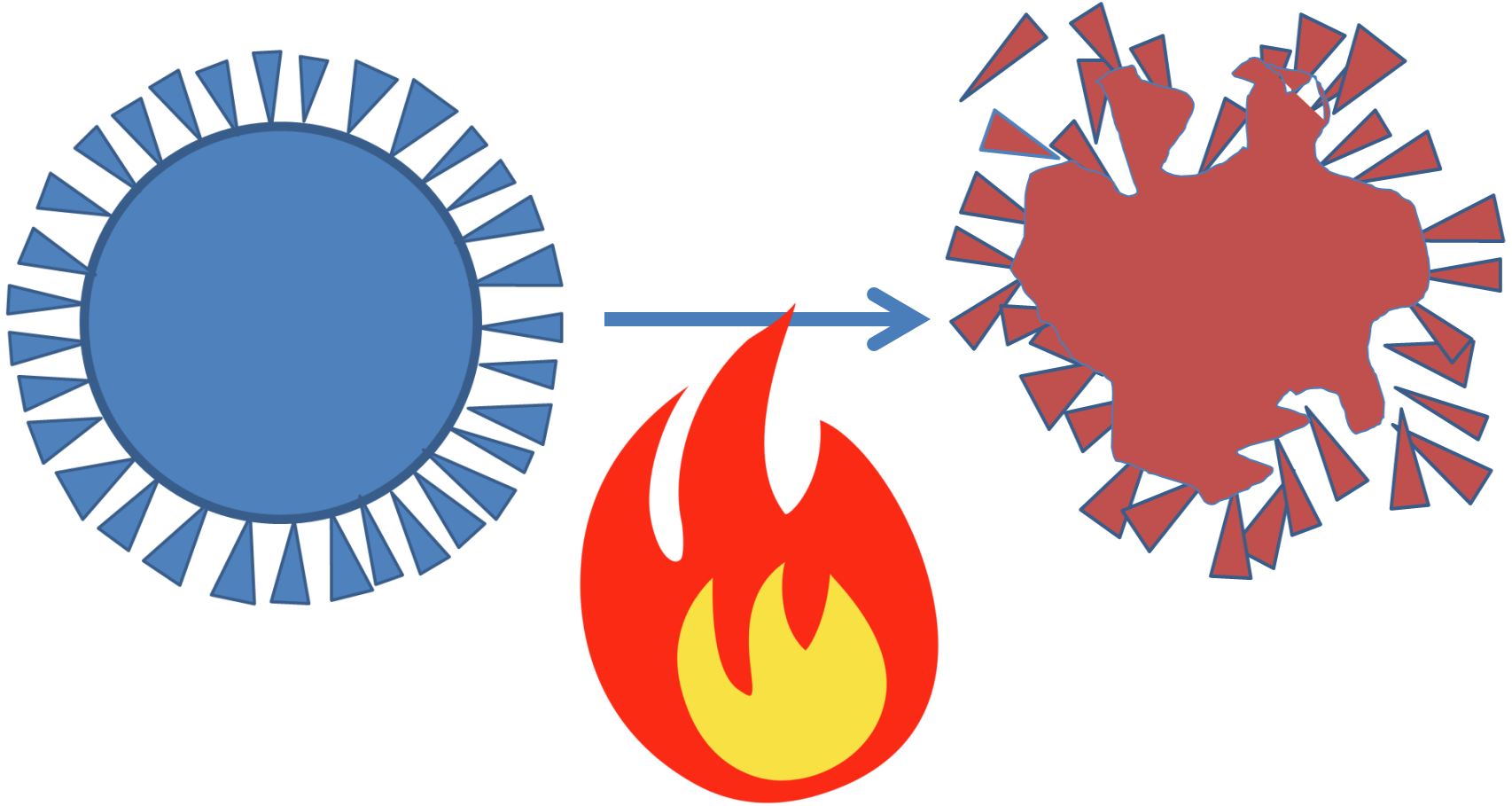
<https://www.historyofvaccines.org/content/mumps-jeryl-lynn-story>
, New York Times May 6 2013

Reported Measles Cases in the United States by Year 1954-2008

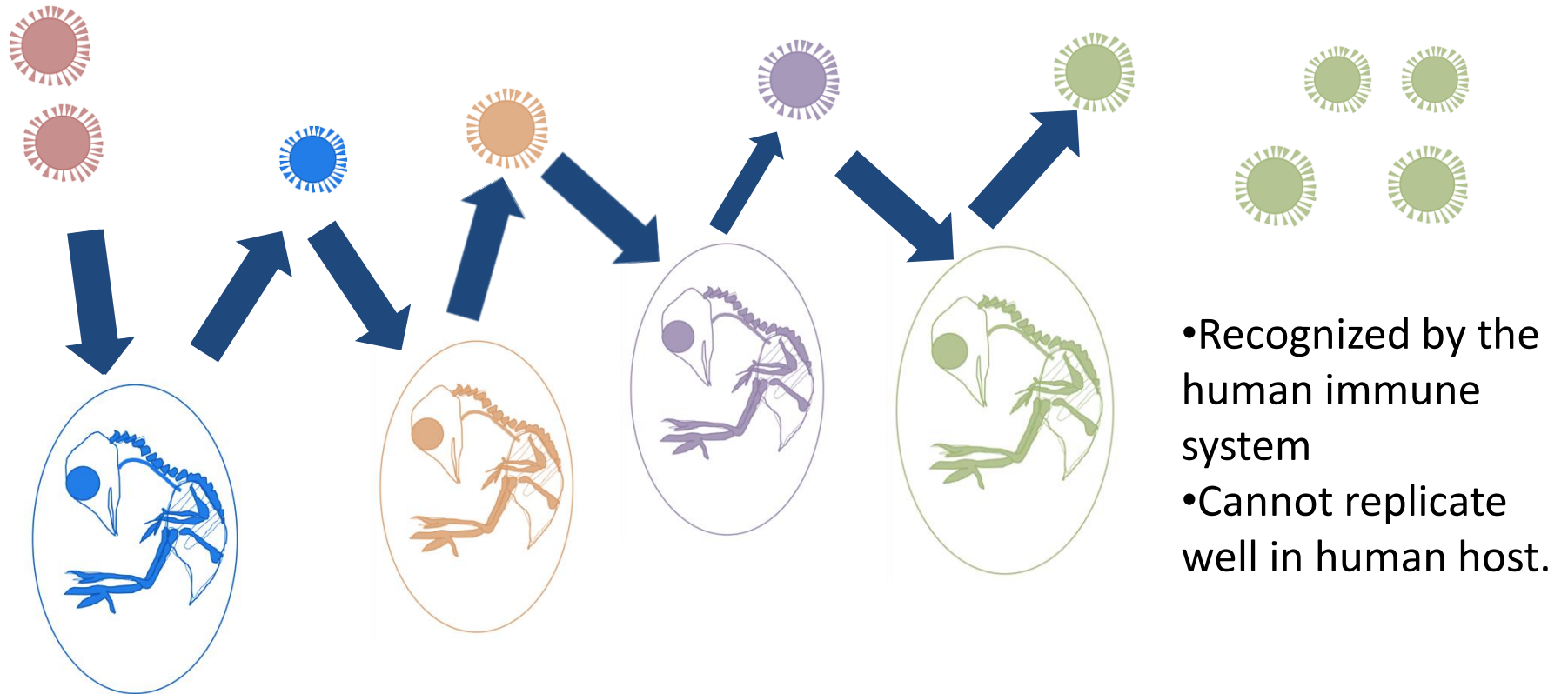


CDC/MMWR Summary of Notifiable Diseases, United States, 1993; CDC/MMWR Summary of Notifiable Diseases, United States, 2008.

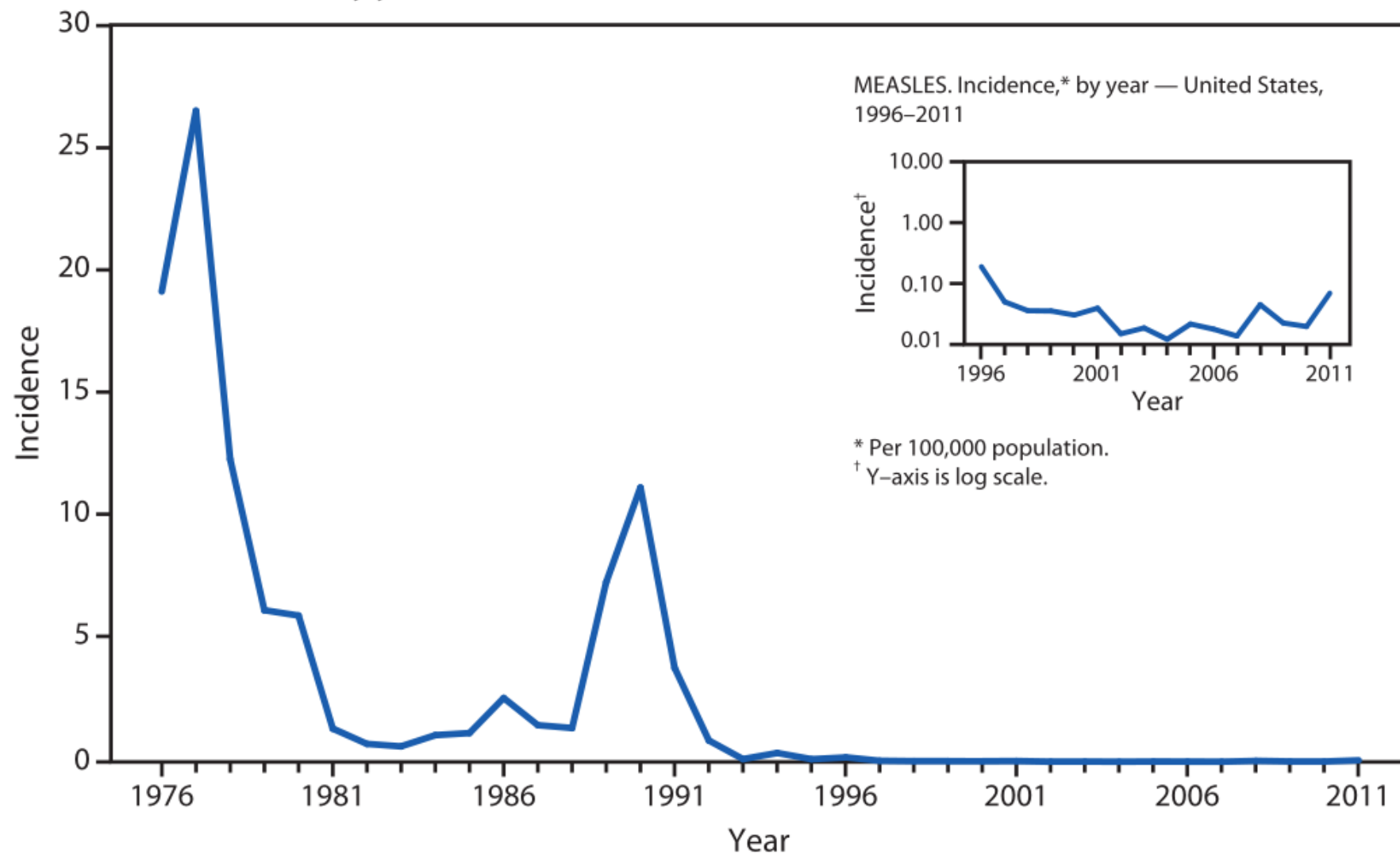
Killed Virus



Live Attenuated Vaccine



MEASLES. Incidence,* by year — United States, 1976–2011



* Per 100,000 population.



Wakefield Lancet

- 12 children with autism-no controls
some clients
- Lots of tests including intestinal biopsy
Ileal lymphoid nodular hyperplasia and non-specific colitis
- Conclusion
MMR weakens intestines
toxin leak through intestines into blood
then to brain
- Others unable to replicate findings
- Data altered

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to granuloid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and low serum IgA in four children.

Interpretation The identical associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351**: 637–41

See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield *mrc*, A Anthony *ms*, J Linnell *mrc*, A P Dhillon *mrc*, S E Davies *mrc*) and the **University Departments of Paediatric Gastroenterology** (S H Murch *ms*, D M Casson *mrc*, M Malik *mrc*), **Child and Adolescent Psychiatry** (M Berelowitz *mrc*), **Neurology** (P Harvey *mrc*), and **Radiology** (A Valentine *mrc*), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to a department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for a few weeks, accompanied by their parents.

Clinical investigations

We took histories including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.¹ Developmental assessments included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.² Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antidiomyseal antibodies and boys were screened for fragile-X if this had not been done

Measles Cases and Outbreaks

January 1 to February 6, 2015*

121

Cases

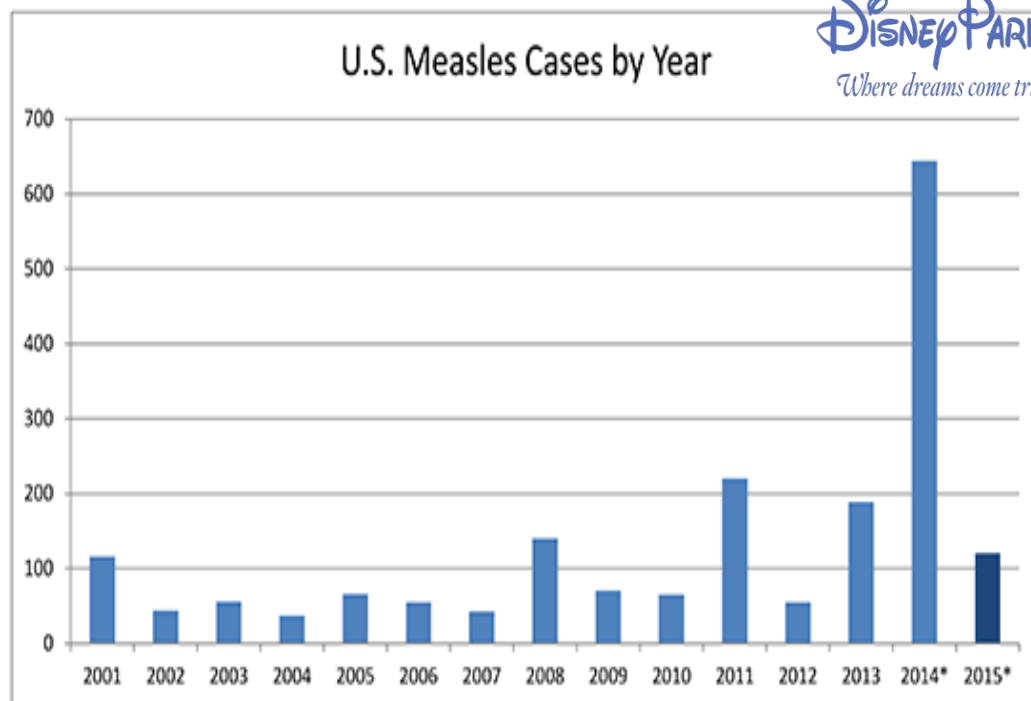
reported in 17 states and Washington DC: Arizona, California, Colorado, Delaware, Illinois, Michigan, Minnesota, Nebraska, Nevada, New Jersey, New York, Oregon, Pennsylvania, South Dakota, Texas, Utah, Washington

1

Outbreak

representing 85% of reported cases this year

2016	86
2017	118
2018*	63



*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases



MMR Adverse Effects

- Hypersensitivity
- Fever
- Rash

~~Autism~~

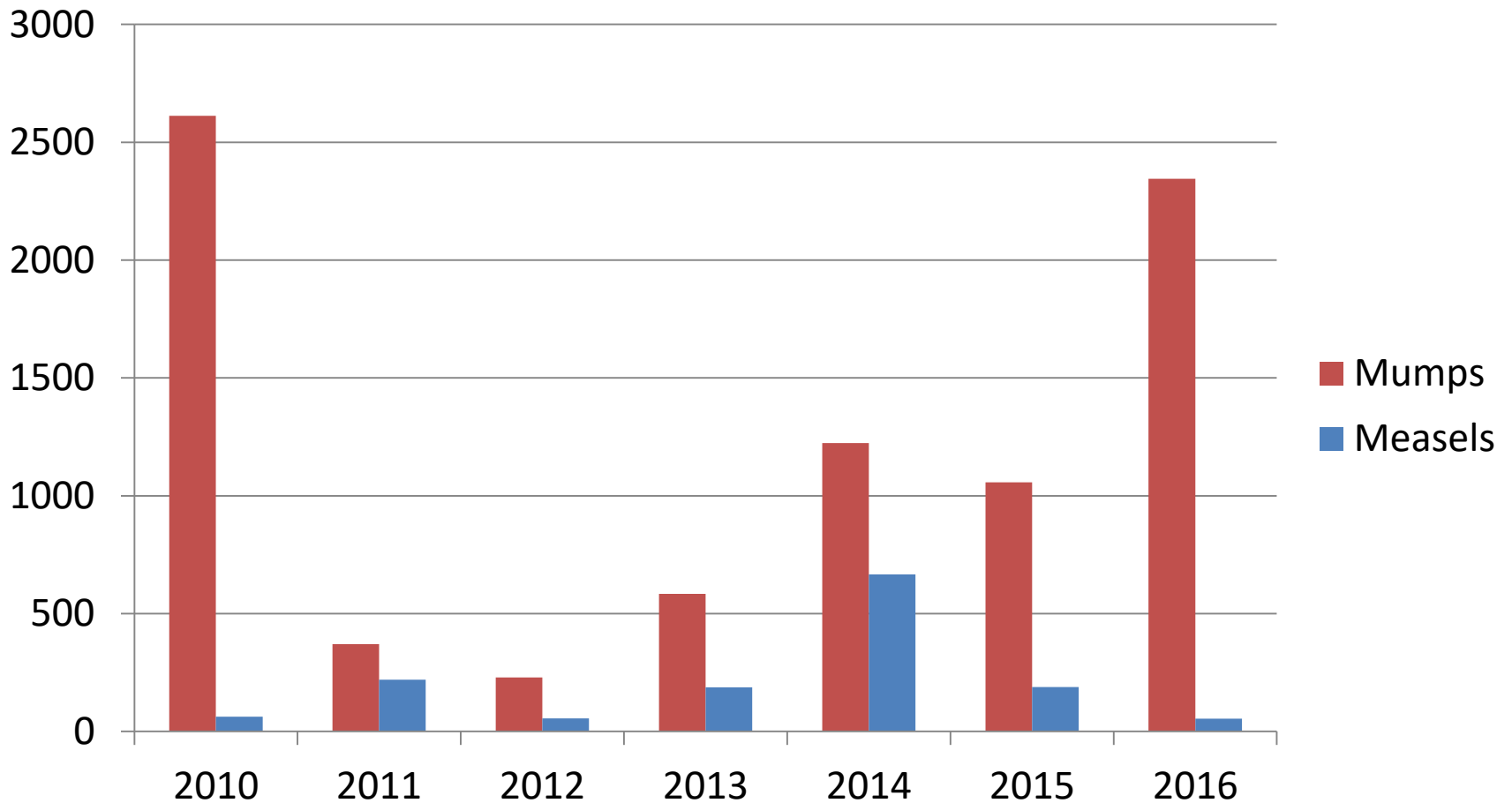
ITP 2.6 in
100,000 doses

Anaphylaxis
3.5 in 1million
doses

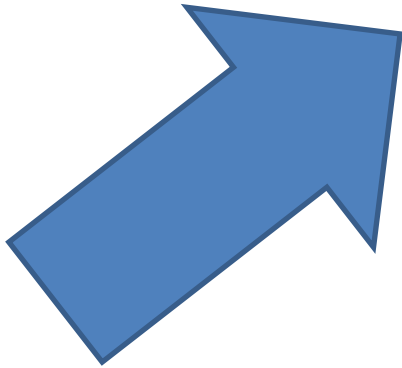
Subacute
sclerosing
panencephalitis
rare if at all

Encephalitis
0.4 in 1
million
doses

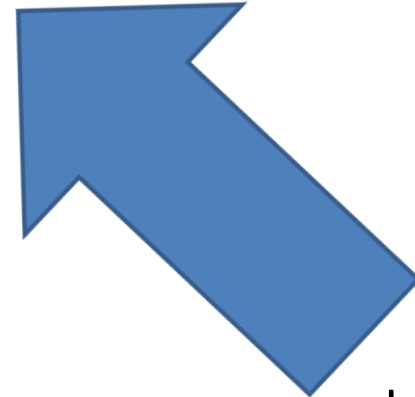
Mumps/Measles cases by Year



MUMPS in persons with two doses of MMR



prolonged contact
(e.g., universities and close-knit communities)



time since 2nd dose

ACIP Recommendation 2018

Third dose of mumps containing vaccine in
persons at increased risk for acquiring mumps
during an outbreak

Chapter 1 Summary

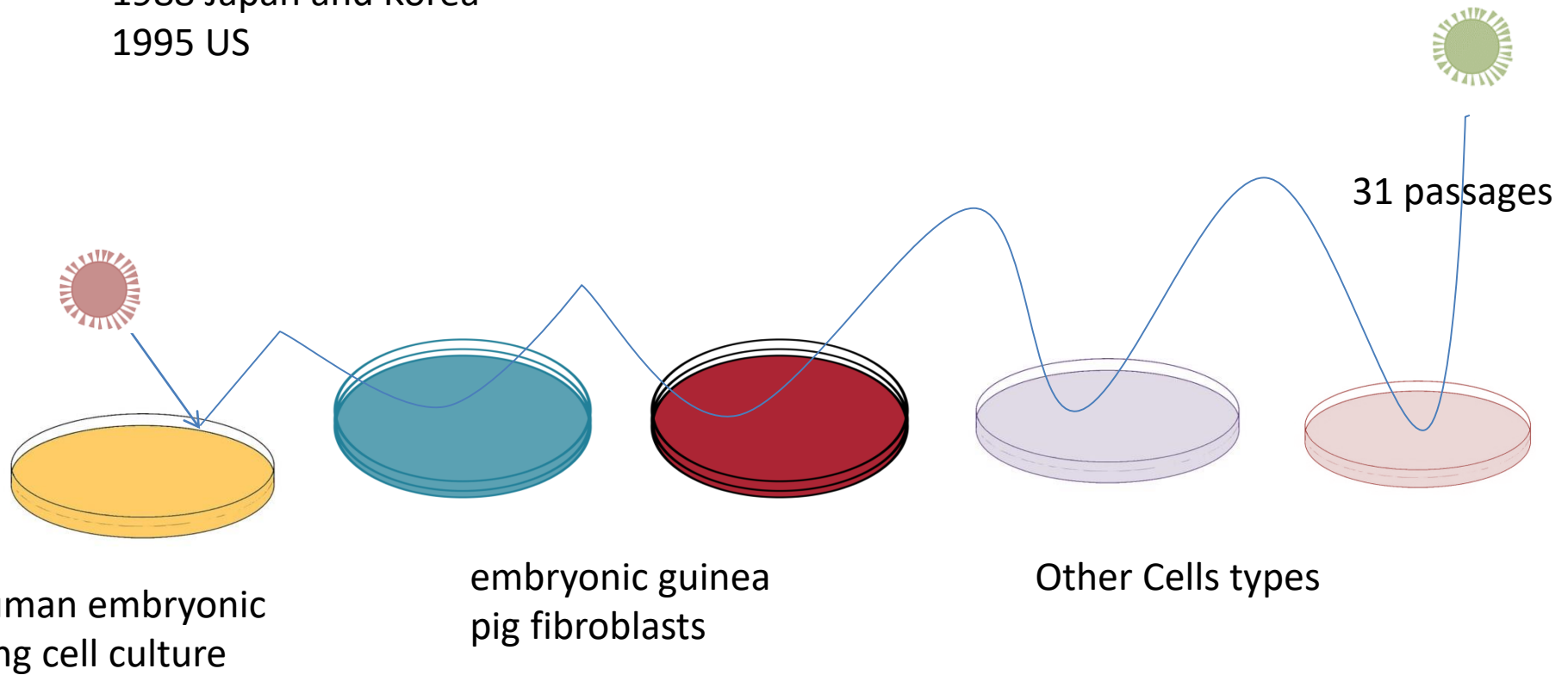
MMR

- *Live Attenuated Vaccine*
- *Does not cause autism*
- *Effective in preventing measles when used*
- *3rd does for preventing mumps in some outbreak settings*

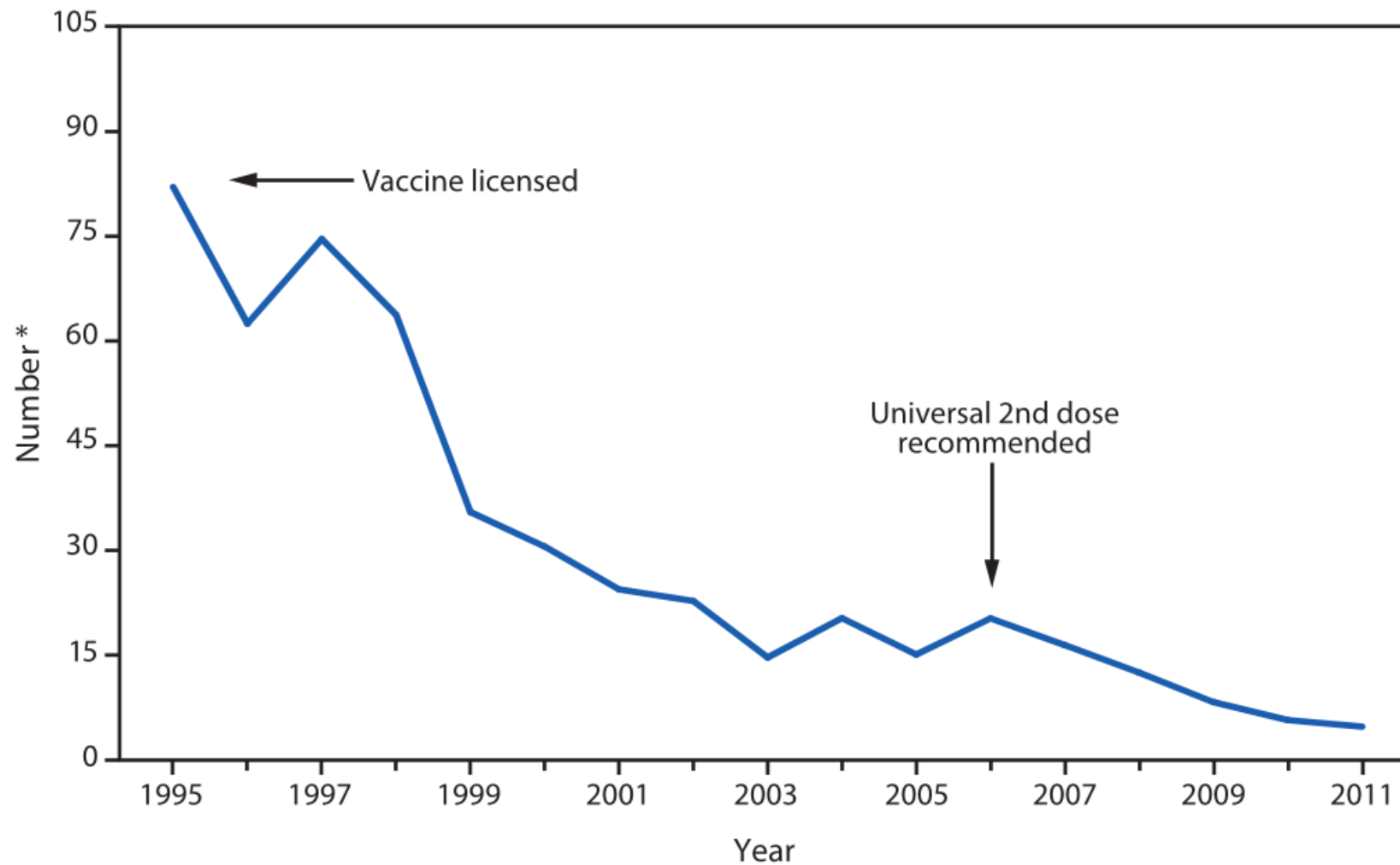
Chapter 2 Shingles Vaccines

Varicella

Takahashi
1988 Japan and Korea
1995 US



VARICELLA (CHICKENPOX). Number of reported cases — Illinois, Michigan, Texas, and West Virginia, 1995–2011



* In thousands.

Zoster Vaccine (Zostavax®) #1

- 2006
- Age 50 and up
- Live Attenuated



- 14X the dose of varicella

Shingles Vaccine HZV (Zostavax®)

- Herpes Zoster Efficacy
51.3%
- 41% (age 70-79)
- 4 years duration
- Post Herpetic Neuralgia
66.5%

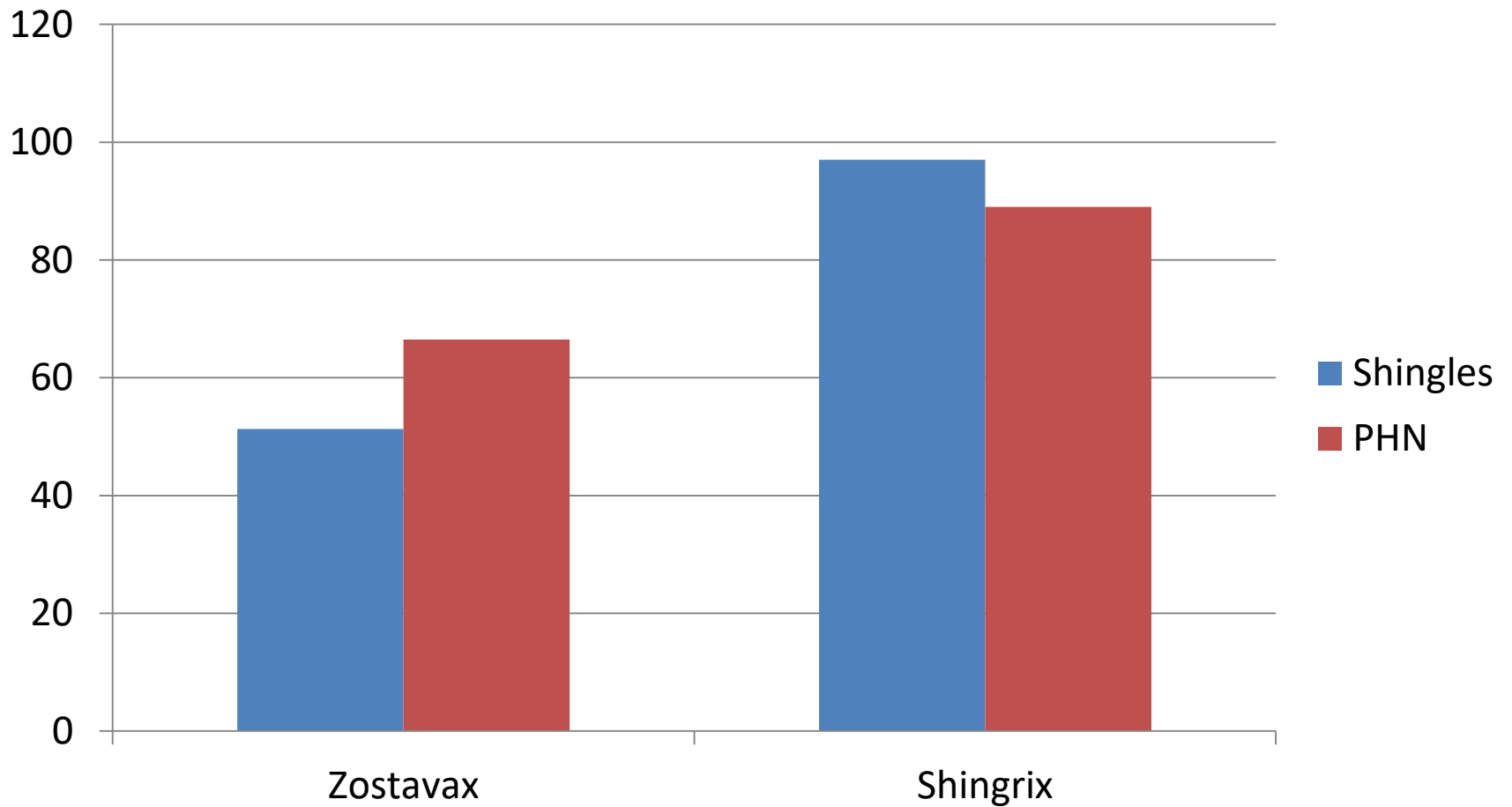
N Engl J Med. 2015;372:2087-96

N Engl J Med. 2016;375:1019-32.

N Engl J Med 2005; 352: 2271-84



Efficacy %



Shingles Vaccines

HSV live attenuate (Zostavax®)

- Herpes Zoster
Efficacy 51.3%
- 4 years duration
- Post Herpetic Neuralgia
Efficacy 66.5%

HSV Sub unit(Shingrix®)

- Herpes Zoster
Efficacy 97%
- 3.7 years and going
- Post Herpetic Neuralgia
Efficacy 89%

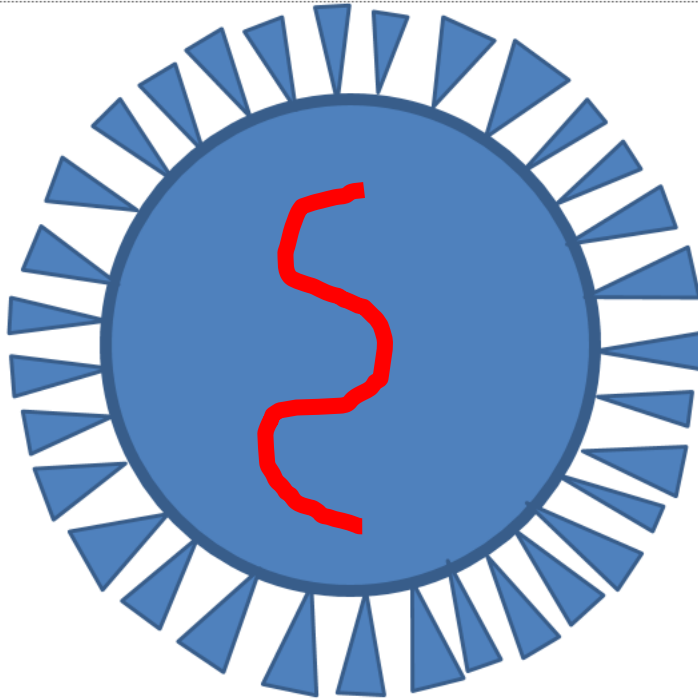
N Engl J Med. 2016;375:1019-32.

N Engl J Med 2005; 352: 2271-84.

Herpes Zoster subunit vaccine

Shingrix[®]

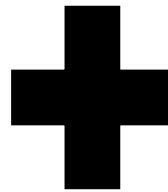
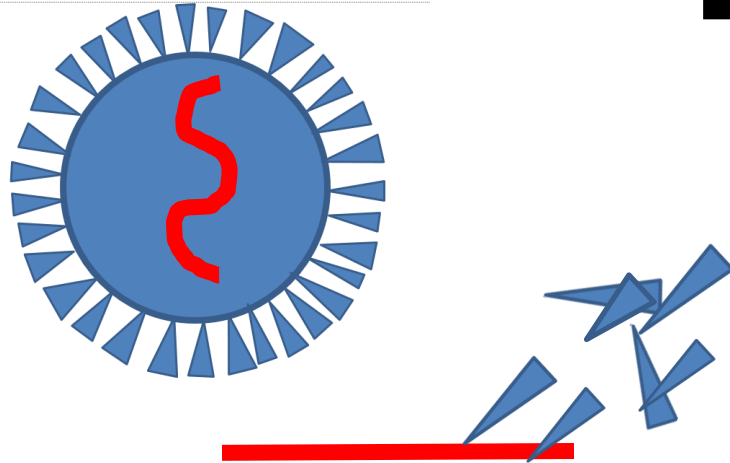
- Recommended for the prevention of herpes zoster and complications in immunocompetent adults aged 50 up
- **Preferred over Zoster Vaccine Live (Zostavax[®])**
- Recommended for immunocompetent even if they have Received Zostavax[®]



Glycoprotein E (gE)
most abundant
glycoprotein on the
surface of infected cells



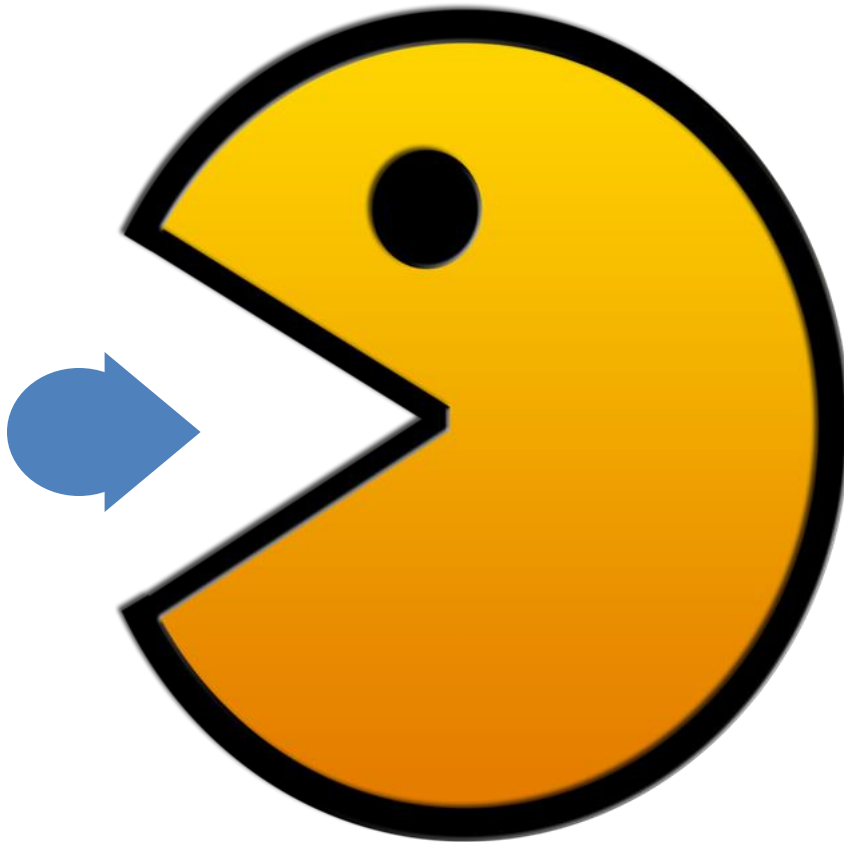
Glycoprotein E (gE)
most abundant
glycoprotein on the
surface of infected cells



ADJUVANT

Substances included in a vaccine formulation to enhance the quality and strength of the immune response induced by the vaccine antigen(s)

- less immunogenic antigens
- lower antigen doses needed
- enhancing immune response in
 - elderly
 - young children
 - chronic diseases
 - immunocompromised



- T Cells
- release cytokines
- stimulate B cells
- create memory cells
-
- B Cells
- make antibodies



Adjuvants

- Oil-in-water emulsions (MF59, AS03)
- Virosomes
- AS04
- AS01
- MPRC
- 529
- Liposomes (AS01)
- CpG ODN (1018 ISS)
- TLR7 ligand



Shingrix

Antigen

- Glycoprotein E (gE)



Adjuvant: AS01



HZV sub unit

More reactions:

HZsu 79.0% Placebo 29.5%



HSV Sub unit (Shingrix[®])

Price=\$130 whole sale X 2 $\pm$ \$300

Questions

- Coverage

Medicare D?

- Availability

Long term duration and safety

Chapter 2 Summary

New shingles vaccine

- *2 vials*
2 dose (1-6m apart)
- *adjuvanted*
- *higher efficacy*
- *reactive side effects*
- *Coverage still not clear*
- *Current shortage*

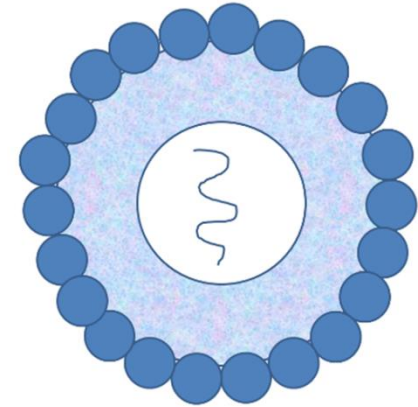
Chapter 3

Hepatitis B Vaccine

Hepatitis B Vaccines

EngenrixB[®]

Recombivax HB[®]



Combination:

Pediarix 6 weeks–6 years Tdap/IPV

Twinrix ≥18 years -Hep A and Hep B

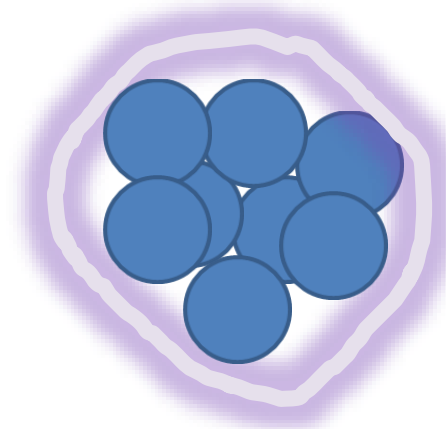
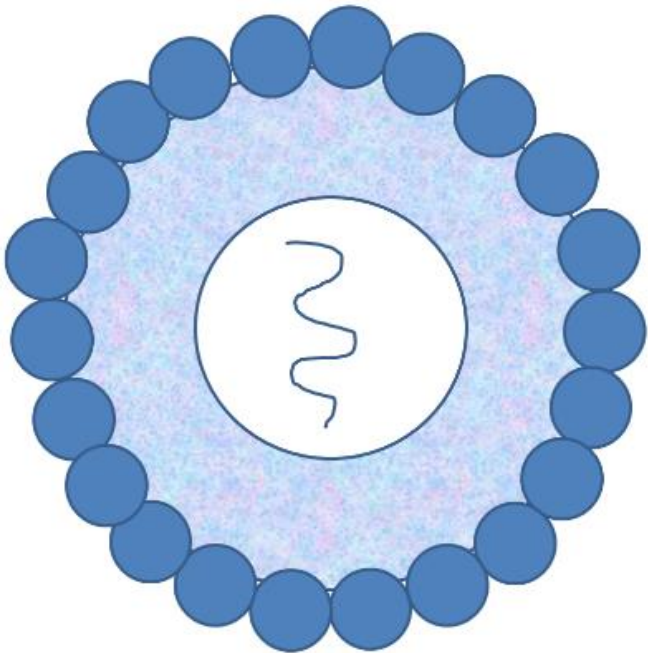
New

Heplisav[®]

Heplisav-B[®]

HepB surface antigen (HBsAg) 1018 adjuvant

- synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN) motifs



Heplisav B[®] versus Engerix-B[®]

Outcome: Anti-HBS Ab >10mIU/MI

Study 7,056 2 doses Heplisav[®]

Control 3,214 3 doses Engerix-B[®]

Results

90.0%–100.0% Heplisav[®]

70.5%–90.2% Engerix-B[®]

Safety

9,871 Hheplisav[®]

Mild 45.6%

Serious 5.4%

Cardiac 0.27%

4,385 Engerix-B[®]

Mild 45.7%

Serious 6.3%

Cardiac 0.14%

Not statistically significant

Heplisav B[®]

- May be used as a HepB vaccine in persons aged ≥ 18 years for vaccination against HBV
- When feasible, the same manufacturer's vaccines should be used to complete the series
- No data on pregnancy
- Use serologic testing as usual

Non-responders

- Celiac: lower response rate compared to controls
 - Low HBSab titers
- Compliance with gluten free diet improved response
- No studies to date of Non-responders and test for celiac or trial of gluten free diet

Chapter 3 Summary

New Hepatitis B Vaccine

- *2 doses*
- *adjuvanted*
- *higher efficacy (serologic studies)*
- *cardiovascular events not statistically significant*
- *Trial of gluten free diet in non-responders*

Chapter 4

Influenza Vaccines

LAIV

Adjuvanted Seasonal
Flu

2009 H1N1 safety
signal

LAIV (FluMist)

- 2003: LAIV3 licensed
- 2012: LAIV4 replaced LAIV3 for 2013-14
- 2014: Preferential recommendation for healthy 4-49 year olds
- 2015: Preferential recommendation removed
- 2016-17 and 2017-18 not recommended

Quadrivalent Influenza

Influenza A



H1N1



H2N3

Influenza B



Yamagata



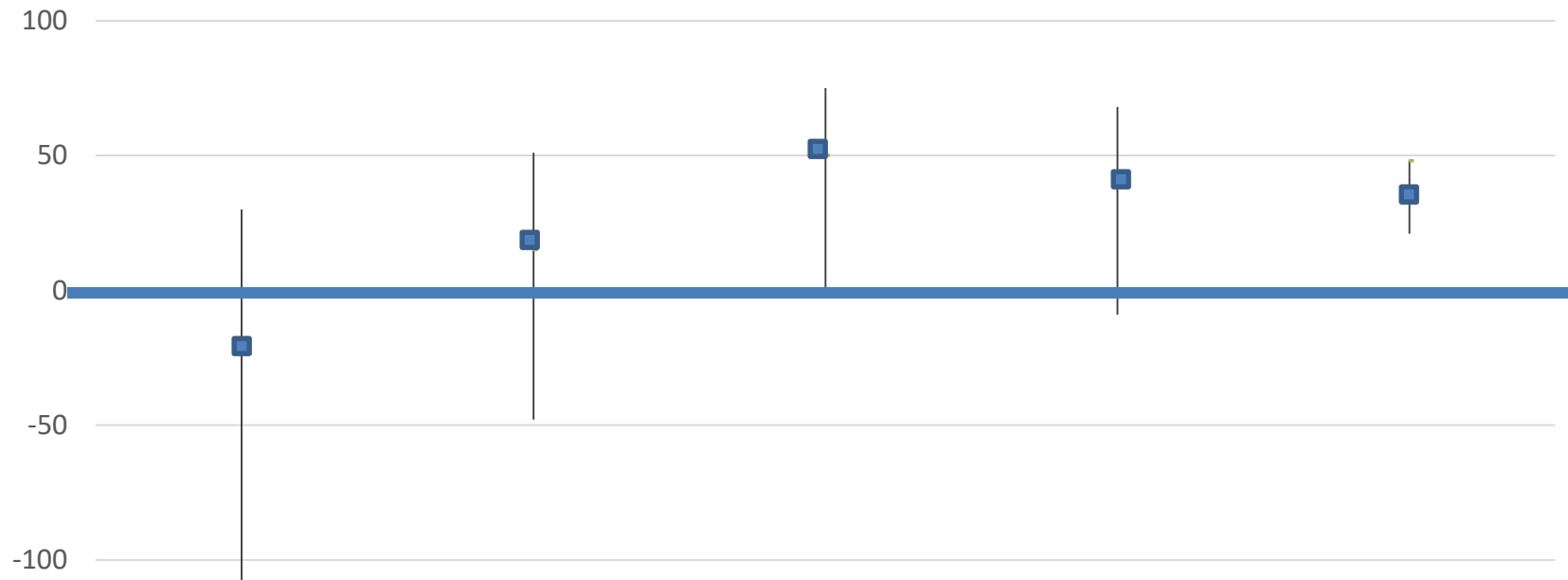
Victoria

2013-14 and 2015-16 Seasons

- **A(H1N1)pdm09 predominates**

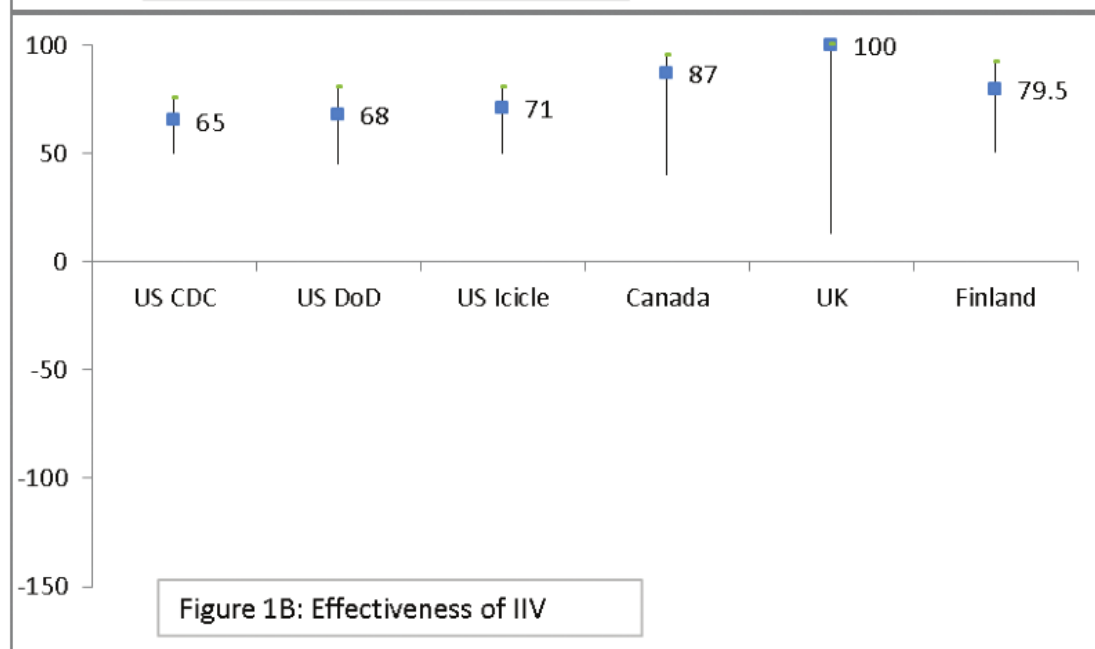
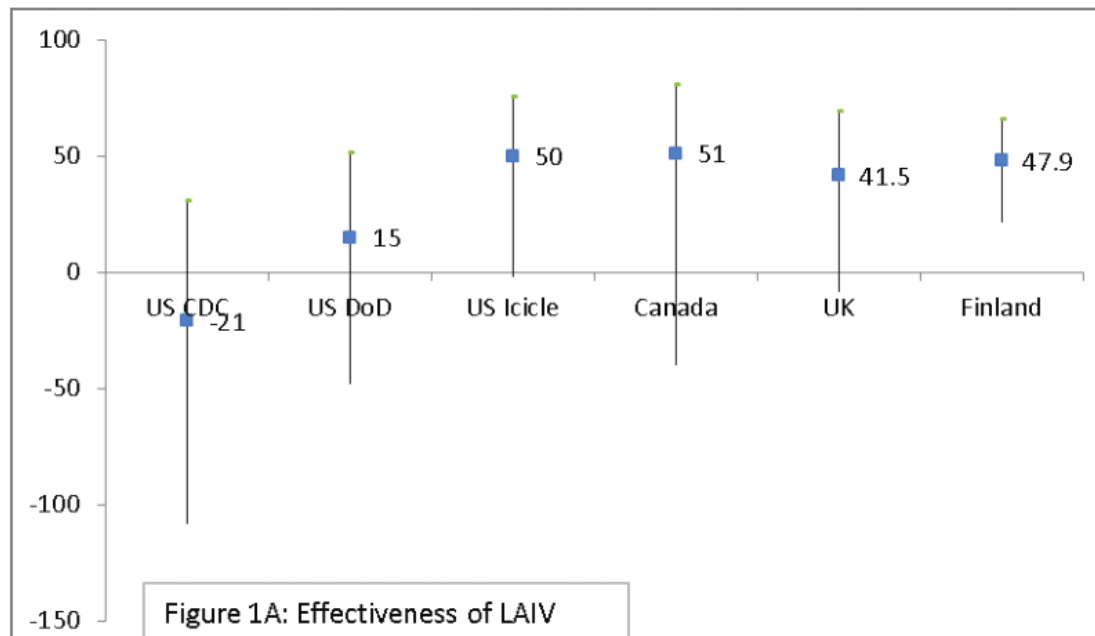
VE:LAIV against H1N1 2015-16

Ages 2-17



-150	CDC	Dod	ICICLE	PHE	THL
High	30	51	75	68	46
Low	-108	-48	-2	-9	21
Close	-21	15	50	42	48

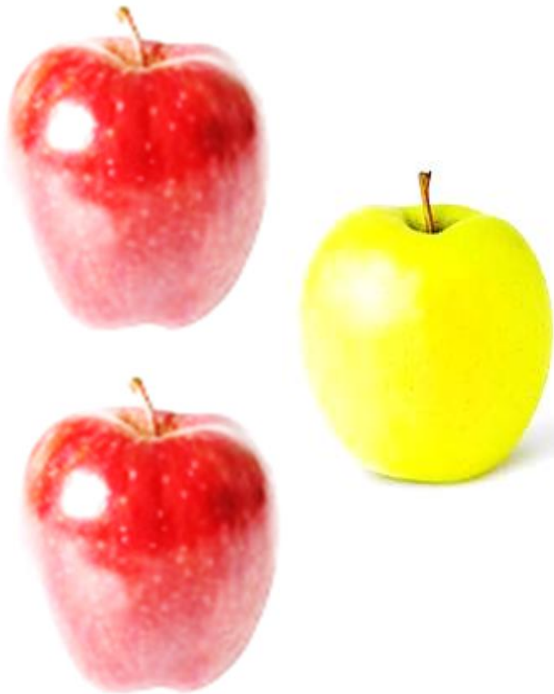
A(H1N1)pdm09
Children 2-17 years
2015-16 season



2017-18 Season

- New H1N1 in LAIV4
- A(H2N3) predominates
- LAIV not tested clinically but did well in serologic and shedding studies
- ACIP: LAIV4 is **an option** for those for whom it is otherwise appropriate. No preference is expressed for any influenza vaccine product.

Fluad[®]: Adjuvanted Flu Vaccine

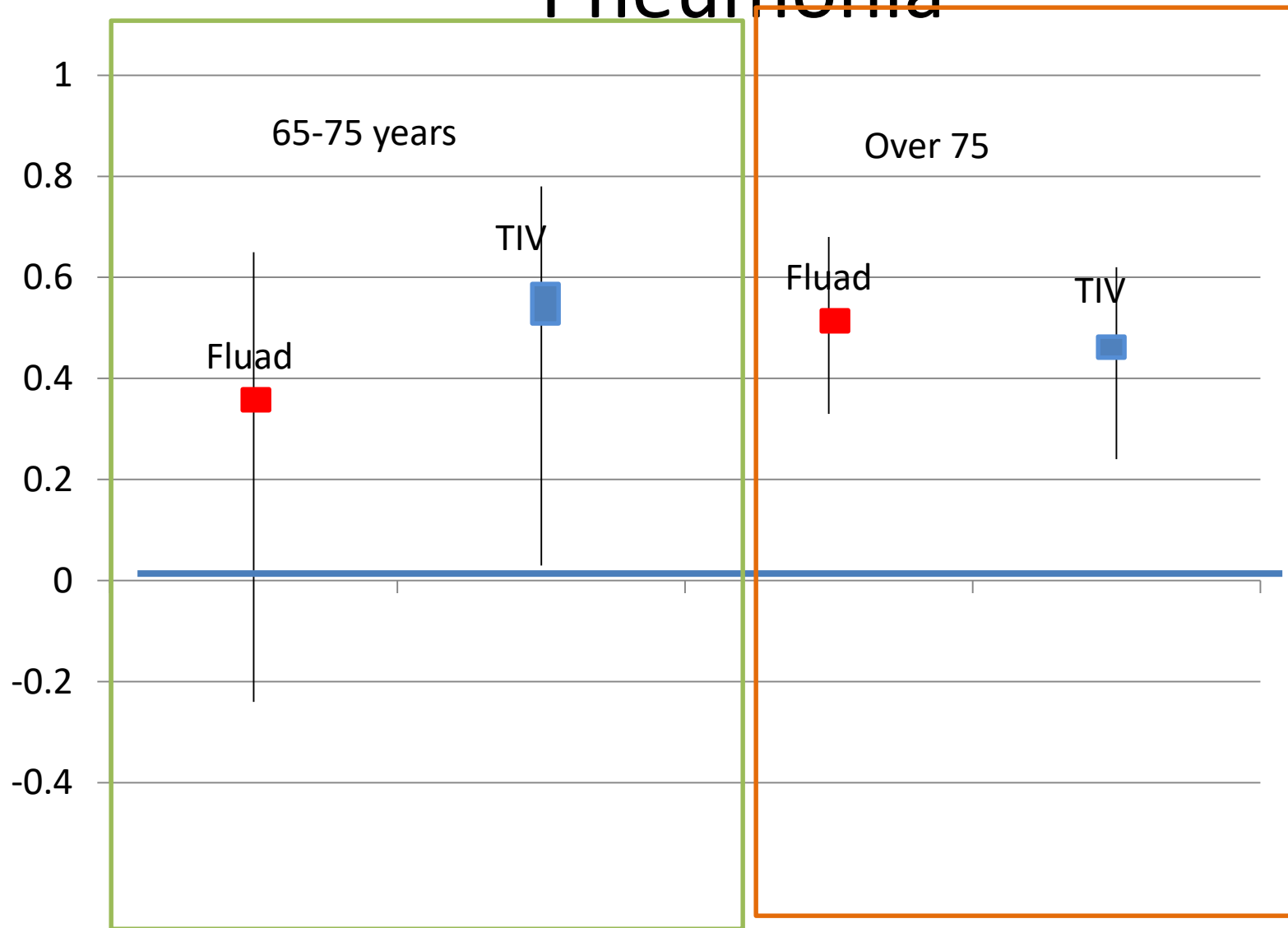


MF596.1



Age 65+

VE for Hospitalization, Flu or Pneumonia



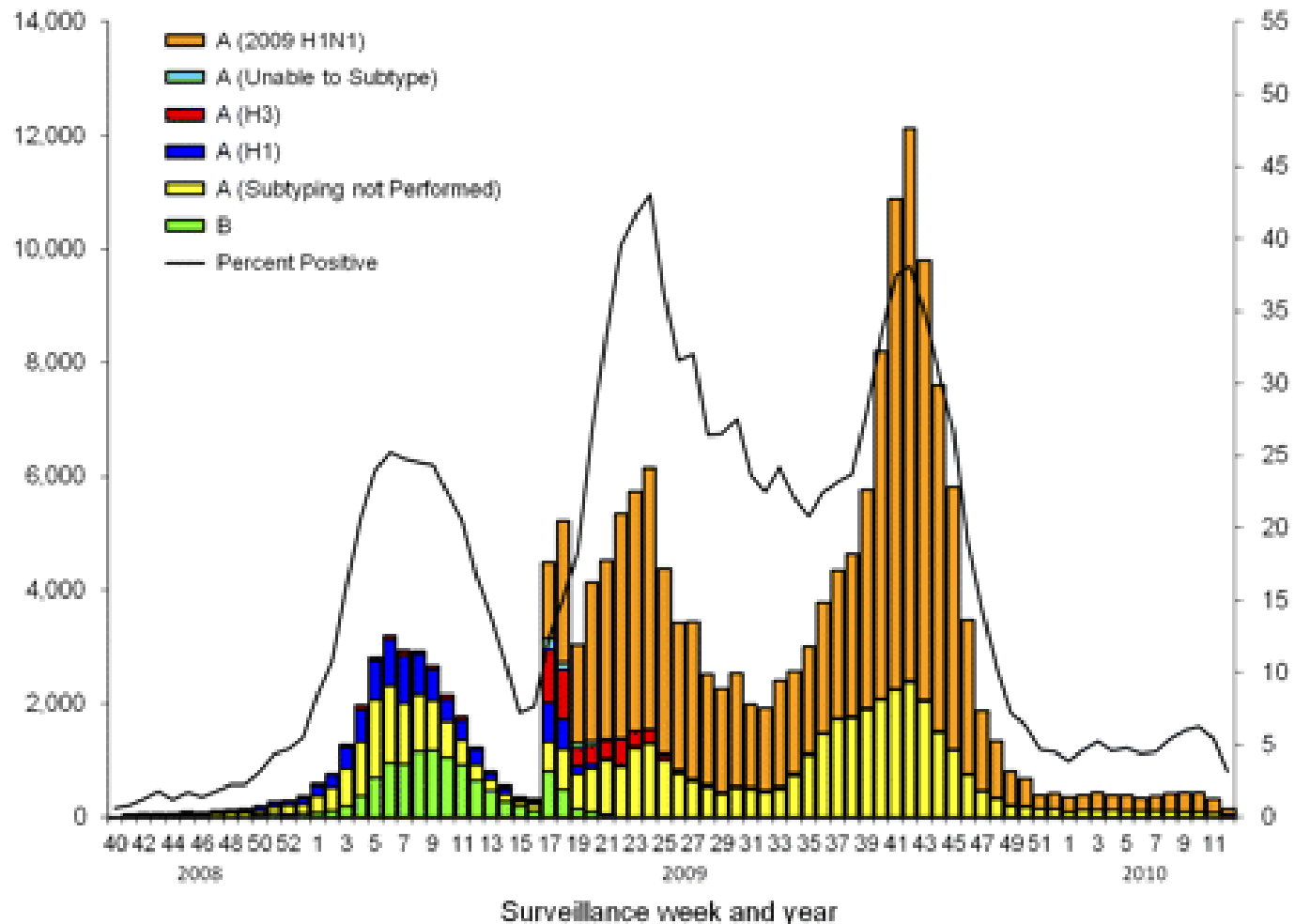
Adjuvanted Influenza Vaccine

- Option for over 65
- Trivalent
- Better in serologic studies
- Clinical studies

Slightly better in those over 75

More side effects

2009-2010





H1N1 Vaccines for 2009-10

Non Adjuvant

ASO3 Adjuvanted (not used in US)

European-Narcolepsy

Canadian-no narcolepsy

<1 in 10,000 vaccine recipients

H1N1 AS03



- Genetics
- H1N1 disease
- None in Canada
- Rare disease
- Up to 10 years to diagnosis

Harris 2014 Eurosurveillance .org

Ahmed et al Journal of Autoimmunity 50 (2014)

Adjuvant and Safety?

MF59

AS03

Virosomes

AS04

TLR7 ligand

AS01

MPRC 529

Liposomes

CpG ODN

1018 ISS

TLR7 ligand

Determined with each vaccine

Combined in vaccines

Cumulative and net effect?

Flu + HepB + Shingles

Chapter 4 Summary

Influenza Vaccines

LAIV okay to use

*Adjuvanted Seasonal Flu
okay to use*

2009 H1N1 Safety signal

*Watching adjuvant
vaccines*

Chapter 5

Review of pneumococcal vaccines for adults

Pneumococcal Vaccine



Between October 1 and March 1

Offer Influenza and Pneumococcal Vaccine

All hospitalized patients 65 and up

NMSIIS

One Clinic –check NMSIIS

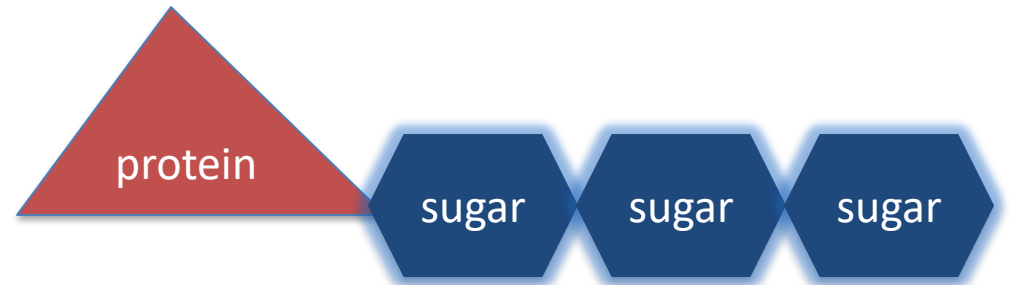
Study uncovered many vaccines previously given

Two Pneumococcal Vaccines

Pneumovax® PPSV23



Prevnar® PCV13

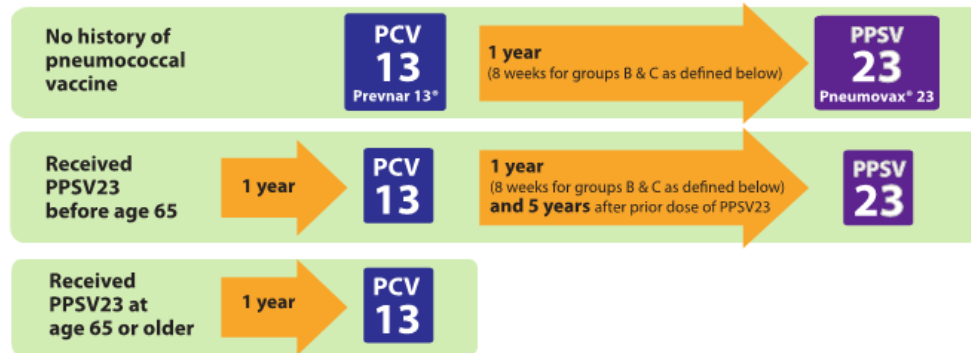


Pneumococcal Vaccine Timing For Adults

DO NOT administer PCV13 and PPSV23 at the same visit.

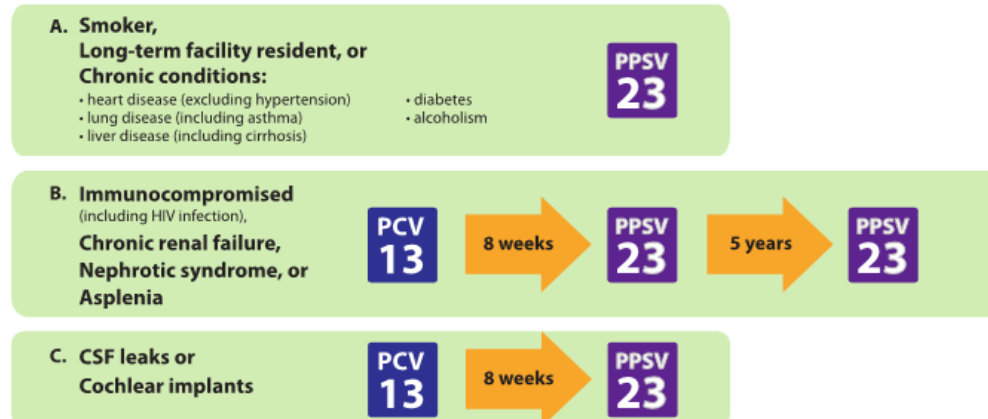
Age 65 Years or Older

- If PCV13 was given before age 65 years, no additional PCV13 is needed.



Age 19-64 Years With Underlying Condition(s)

- Prior doses count toward doses recommended below and do not need to be repeated.
- If PPSV23 given previously – wait one year before giving PCV13
 - for group B, wait at least five years before giving a second dose of PPSV23
- No more than two doses of PPSV23 recommended before 65th birthday and one dose thereafter.



For further details, see: www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html

Reproduced with permission from the California Department of Public Health, Immunization Branch. Development was supported by Grant H23/COH922507 from the Centers for Disease Control and Prevention.

This material was adapted by HealthInsight, the Medicare Quality Improvement Network (QIN) Quality Improvement Organization for Nevada, New Mexico, Oregon and Utah, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services. The contents presented do not necessarily reflect CMS policy. 11SOW-11-16-02-NM

66 year old female with type II diabetes, hypertension, low back pain, and elevated cholesterol. Smokes 1 pack per day for 30 years. She has never received a pneumococcal vaccine.

Pneumococcal Vaccine Timing For Adults

DO NOT administer PCV13 and PPSV23 at the same visit.

Age 65 Years or Older

- If PCV13 was given before age 65 years, no additional PCV13 is needed.

No history of
pneumococcal
vaccine

PCV
13
Prevner 13®

1 year
(8 weeks for groups B & C as defined below)

PPSV
23
Pneumovax® 23

Received
PPSV23
before age 65

1 year

PCV
13

1 year
(8 weeks for groups B & C as defined below)
and 5 years after prior dose of PPSV23

PPSV
23

Received
PPSV23 at
age 65 or older

1 year

PCV
13

Age 19-64 Years With Underlying Condition(s)

- Prior doses count toward doses recommended below and do not need to be repeated.
- If PPSV23 given previously – wait one year before giving PCV13
 - for group B, wait at least five years before giving a second dose of PPSV23
- No more than two doses of PPSV23 recommended before 65th birthday and one dose thereafter.

**A. Smoker,
Long-term facility resident, or
Chronic conditions:**

- heart disease (excluding hypertension)
- lung disease (including asthma)
- liver disease (including cirrhosis)
- diabetes
- alcoholism

PPSV
23

B. Immunocompromised
(including HIV infection),
**Chronic renal failure,
Nephrotic syndrome, or
Asplenia**

PCV
13

8 weeks

PPSV
23

5 years

PPSV
23

C. CSF leaks or

PCV

PPSV

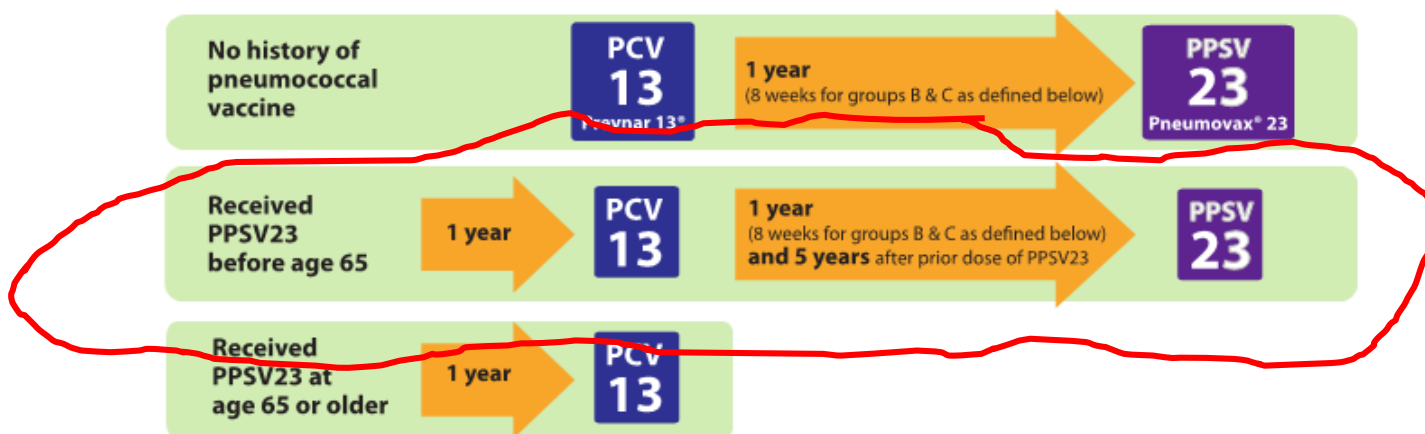
66 year old female treated with mastectomy, chemotherapy and radiation for breast cancer at age 50. Given PPSV23 at age 55

Pneumococcal Vaccine Timing For Adults

DO NOT administer PCV13 and PPSV23 at the same visit.

Age 65 Years or Older

- If PCV13 was given before age 65 years, no additional PCV13 is needed.



Age 19-64 Years With Underlying Condition(s)

- Prior doses count toward doses recommended below and do not need to be repeated.
- If PPSV23 given previously – wait one year before giving PCV13
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A. Smoker, Long-term facility resident, or Chronic conditions:

- heart disease (excluding hypertension)
- lung disease (including asthma)
- liver disease (including cirrhosis)
- diabetes
- alcoholism

PPSV 23

B. Immunocompromised (including HIV infection), Chronic renal failure, Nephrotic syndrome, or Asplenia

PCV 13

8 weeks

PPSV 23

5 years

PPSV 23

C. CSF leaks or

PCV

PPSV

Timeline

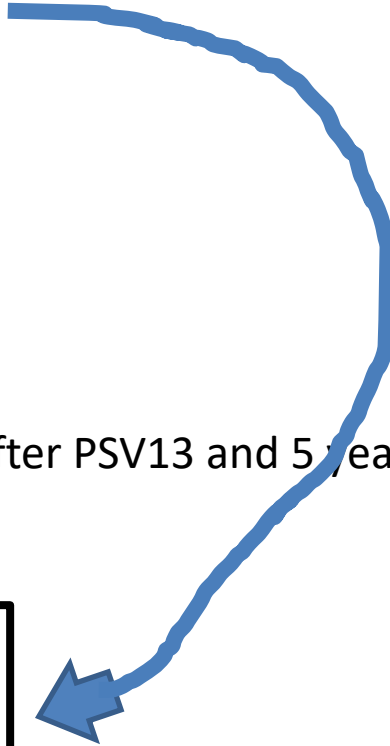
Age 55
PPSV23

>1 year

Age 66
PCV13 Today

1 year after PSV13 and 5 years after
PPSV23

Age 67
PPSV23 # 2



CASE 3

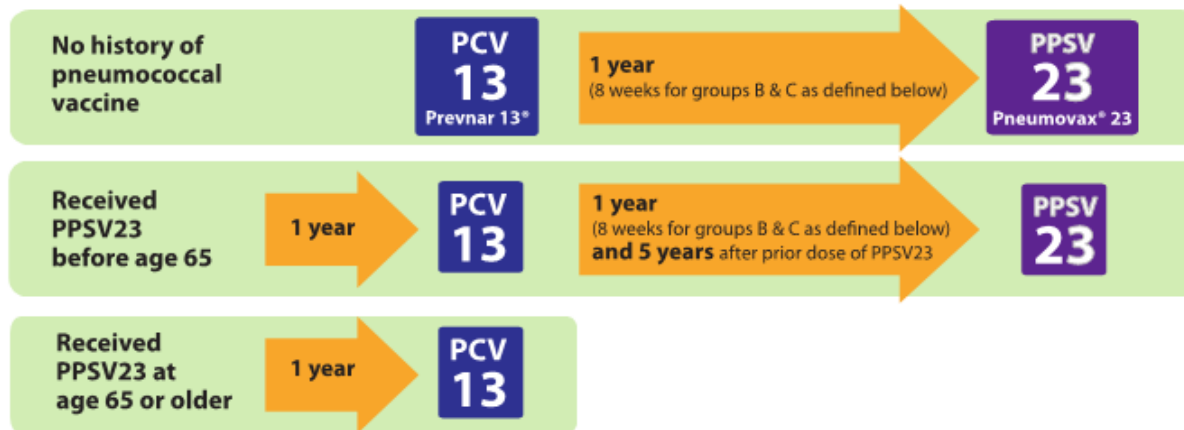
~~66~~56 year old female with type II diabetes, hypertension, low back pain, and elevated cholesterol. Smokes 1 pack per day for 30 years. She has never received a pneumococcal vaccine.

~~66~~56 year old female with type II diabetes, hypertension, low back pain, and elevated cholesterol. Smokes 1 pack per day for 30 years. She has never received a pneumococcal vaccine.

DO NOT administer PCV13 and PPSV23 at the same visit.

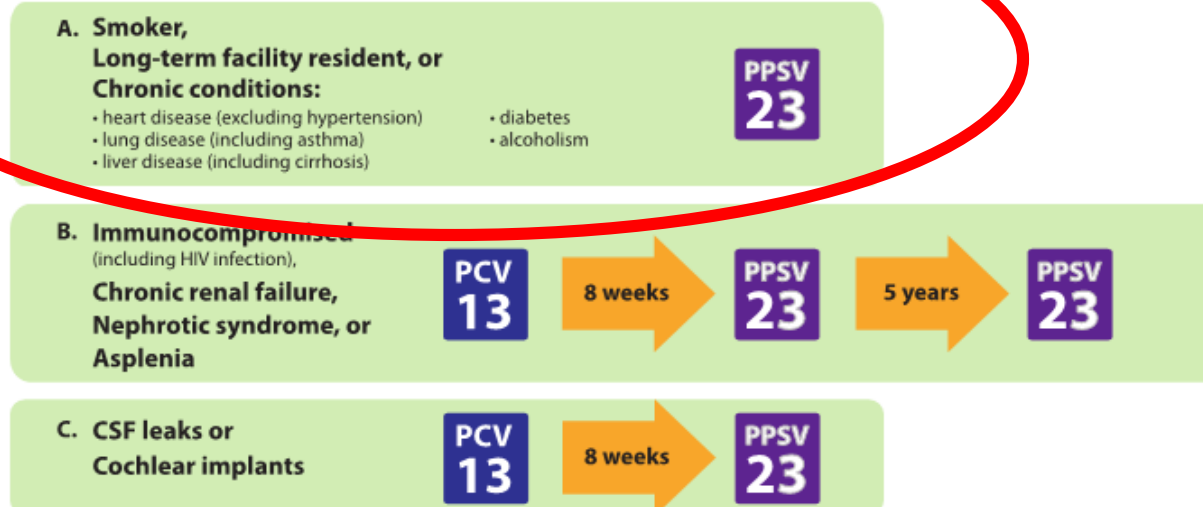
Age 65 Years or Older

- If PCV13 was given before age 65 years, no additional PCV13 is needed.



Age 19-64 Years With Underlying Condition(s)

- Prior doses count toward doses recommended below and do not need to be repeated.
- If PPSV23 given previously – wait one year before giving PCV13
 - for group B, wait at least five years before giving a second dose of PPSV23
- No more than two doses of PPSV23 recommended before 65th birthday and one dose thereafter.



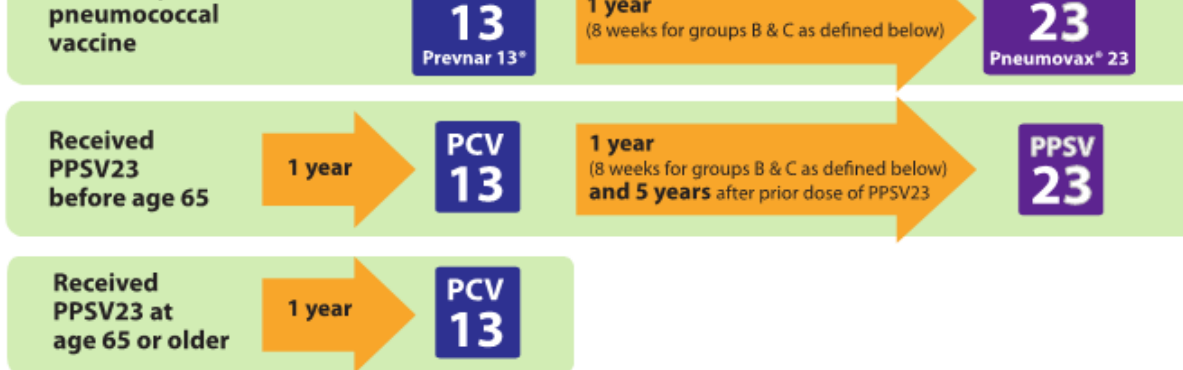
66-56 year old female with type II diabetes, hypertension, low back pain, and elevated cholesterol. Smokes 1 pack per day for 30 years. She has never received a pneumococcal vaccine.

PPSV23 only until she turns 65

Then PCV13 followed by PPSV23 at least 5 years

After 1st PPSV23

46 year old with lung cancer. In remission after chemotherapy



Age 19-64 Years With Underlying Condition(s)

- Prior doses count toward doses recommended below and do not need to be repeated.
- If PPSV23 given previously – wait one year before giving PCV13
 - for group B, wait at least five years before giving a second dose of PPSV23
- No more than two doses of PPSV23 recommended before 65th birthday and one dose thereafter.

A. Smoker, Long-term facility resident, or Chronic conditions:

- heart disease (excluding hypertension)
- lung disease (including asthma)
- liver disease (including cirrhosis)
- diabetes

PPSV 23

B. Immunocompromised (including HIV infection), Chronic renal failure, Nephrotic syndrome, or Asplenia

PCV 13

8 weeks

PPSV 23

5 years

PPSV 23

C. CSF leaks or Cochlear implants

PCV 13

8 weeks

PPSV 23



For further details, see: www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html

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Chapter 5 Summary

Pneumococcal and Influenza to
Hospitalized patients over 65

Check NMSIIS

Use flow sheet for pneumococcal vaccine
guidance



The End

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