Yeni kombine asilar
Combination vaccines

The MMRV vaccine: two doses for optimal protection

Bernd Benninghoff

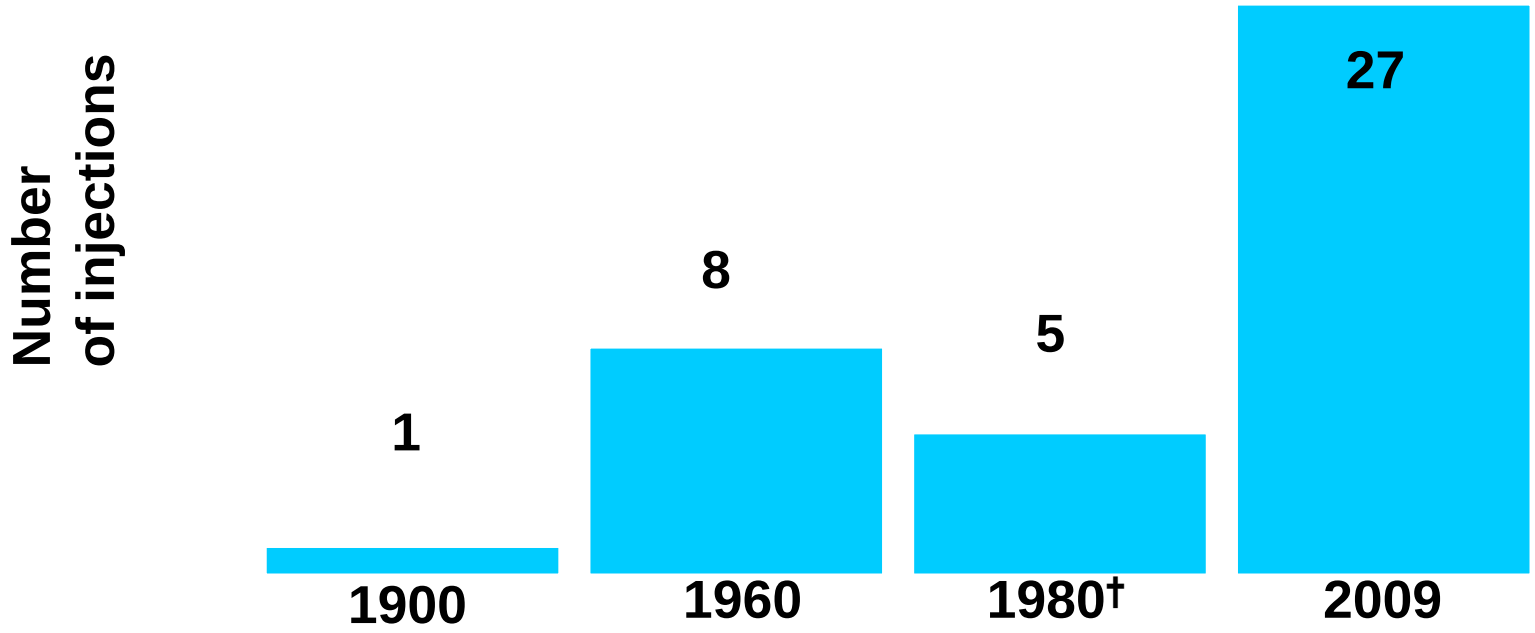
Agenda

- **Advantages of combination vaccines**
- **MMR – The current standard of care**
- **Like MMR, two doses of varicella vaccine may be the optimal strategy for better protection**
  - **immunological evidence suggests that two doses are superior**
  - **MMRV combination vaccines will better facilitate introduction of varicella URV**

URV, universal routine vaccination

Do we need Combination Vaccines?

Recommended injections in first 2 y of life: routine childhood immunisation schedule



†1960–1980: OPV introduced and smallpox vaccine eliminated from schedule

1. Offit *et al*. *Pediatrics* 2002;109:124–9

Impfkalender (Standardimpfungen) für Säuglinge, Kinder, Jugendliche und Erwachsene 2009 (Germany)

Recommended Immunization Schedule infants, adolescent, adults

Combination

Combination

Impfstoff/ Antigen-kombinationen	Alter in Monaten						Alter in Jahren				
	Geburt	2	3	4	11–14	15–23 siehe a)	5–6 siehe a)	9–11 siehe a)	12–17 siehe a)	ab 18	≥ 60
T *		1.	2.	3.	4.		A	A		A *******	
D/d * siehe b)		1.	2.	3.	4.		A	A		A *******	
aP/ap *		1.	2.	3.	4.		A	A		A ********	
Hib *		1.	2. c)	3.	4.						
IPV *		1.	2. c)	3.	4.			A			
HB *	d)	1.	2. c)	3.	4.			G			
Pneumokokken **		1.	2.	3.	4.						S
Meningokokken					1. e) ab 12 Monate						
MMR ***					1.	2.					
Varizellen ***					1.	2.		s. Tab. 2			
Influenza ****											S
HPV *****									SM		

In order to reduce the number of injections available combinations should be used D/d, T, aP/ap, HB, Hib, IPV and MMR or MMR-Varicella

Multiple injections reduce compliance and coverage

- **Additional injections can lead to**
  - **increased discomfort for patients**
  - **greater workload (healthcare staff)**
  - **higher use of consumables**
  - **increased need for large storage capacity**
  - **accumulating costs**
- **These factors could discourage compliance and affect vaccine coverage**

1. André *Vaccine* 1999;17:1620–7
2. Meyerhoff *et al. PIDJ* 2001;20(Suppl):S57–62

What is an acceptable number of injections?

- **US survey of 281 parents taking their children to be vaccinated**
- **At a single visit**
  - **92% of parents would allow 2 injections**
  - **58% would allow 3 injections**
  - **only 42% found 4 injections to be acceptable**

1. Melman *et al Arch Fam Med* 1994;3:615–8

Advantages of combination vaccines

- **For children and parents**
  - **comfort: fewer injections**
  - **convenience: fewer clinic visits**
  - **efficacy: avoid interference among vaccine constituents**
- **For healthcare providers**
  - **compliance: increased acceptance/immune coverage**
  - **simplified logistics: surveillance/record keeping**
  - **delivery infrastructure: potential efficiency savings**
- **For the community**
  - **reduced disease burden and healthcare costs**

1.Marcy *Am J Manag Care* 2003;9:314–20
2. Dodd *Am J Manag Care* 2003;9:S6–12
3. Mullany *Am J Manag Care* 2003;9:S23–9
4. André *Vaccine* 1999;17:1620–7

Hexa-combination: seroprotection rates for antigens with established serological markers of protection after primary vaccination

Antibody	Definition of minimal seroprotective titre	% of subjects with seroprotective titre
Anti-D	≥0.1 IU/mL†	100
Anti-T	≥0.1 IU/mL†	100
Anti-HBs	≥10 mIU/mL	97.5
Anti-polio 1	≥1:8 dilution	100
Anti-polio 2	≥1:8 dilution	96.9
Anti-polio 3	≥1:8 dilution	100
Anti-PRP	≥0.15 µg/mL	100

† by ELISA

1. Arístegui *et al. Vaccine* 2003;21:3593–600

Primary childhood vaccine combinations Summary of reactogenicity profile

- ***GSKbio*** **combination vaccines show a similar incidence of local and general reactions, compared with individual vaccines**
- ***Infanrix*™ (combination) vaccines have a lower incidence of local and general reactions, compared with whole-cell (combination) vaccines**

Summary of Product characteristics 2009, Infanrix

Agenda

- Advantages of combination vaccines
- **MMR – The current standard of care**
- Like MMR, two doses of varicella vaccine may be the optimal strategy for better protection
  - immunological evidence suggests that two doses are superior
  - MMRV combination vaccines will better facilitate introduction of varicella URV

URV, universal routine vaccination

MMR – The current standard of care, WHO

- **Immunization against measles is recommended for all susceptible children and adults for whom measles vaccination is not contraindicated[1].**
- **In light of the burden of CRS and the proven efficacy and safety of the RA 27/3 based rubella vaccine, WHO recommends its use in all countries where control or elimination of CRS is considered a public health priority[2].**
- **Based on mortality and disease burden, WHO considers measles control and the prevention of congenital rubella syndrome to be higher priorities than the control of mumps. In countries that decide to use mumps vaccine, the combination of mumps vaccine with measles and rubella vaccines is recommended[3].**
- **The use of such combined vaccines is logistically and programmatically sound and is recommended in areas where the disease burden of mumps and rubella disease burden is high**

1. WHO position paper, Measles vaccines. No. 14, 2004, 79, 129–144 Available at http://www.who.int/wer
2. WHO position paper, Rubella vaccines. No. 20, 2000, 75, 161–172. Available at http://www.who.int/wer
3. WHO position paper, Mumps virus vaccines. No. 7, 2007, 82, 49–60. Available at http://www.who.int/wer

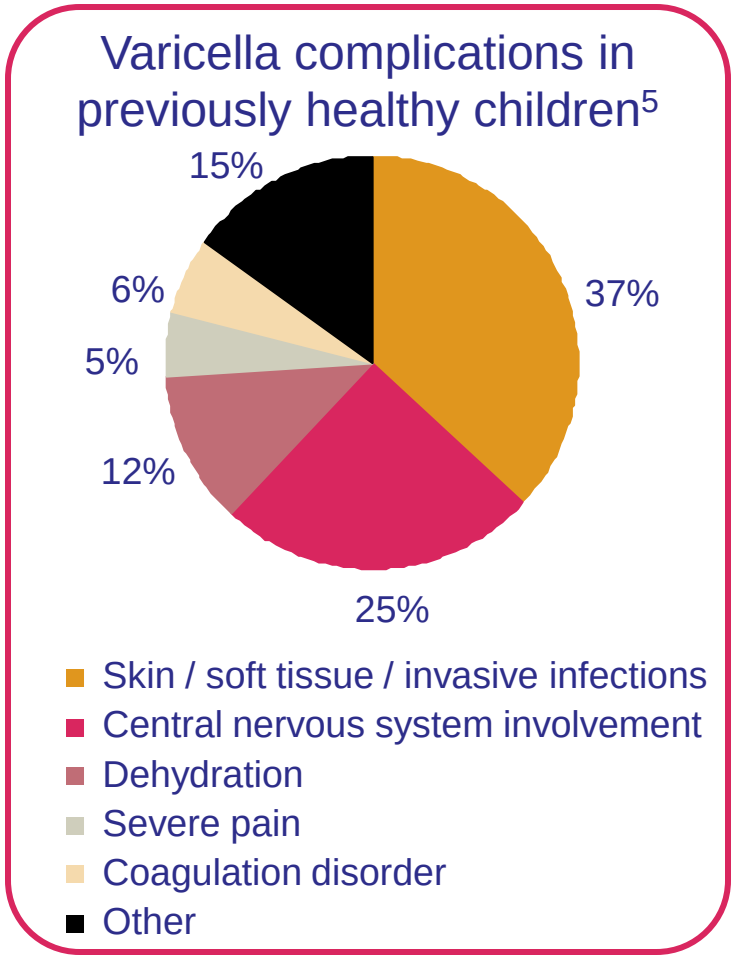
WHO recommendation for Varicella

- **Routine childhood immunization against varicella may be considered in countries where this disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85%-90%) and sustained vaccine coverage can be achieved.**

WHO position paper, Varicella vaccines. 1998, 73, 241-248. Available at http://www.who.int/immunization/wer

Varicella – not a benign disease

- Uncomplicated cases cause considerable discomfort and inconvenience
- Potentially serious complications:
  - occur in 2–6% of infected individuals[1,2]
  - most occur in previously healthy individuals[3–5]
- Can sometimes be fatal[6]



[1]Deguen *et al. J Epidemiol Community Health* 1998**;52 Suppl 1**:46–9**;** [2]Wagenpfeil *et al. Clin Microbiol Infect* 2004;**10**:425–30; [3]Galil *et al. Pediatr Infect Dis J* 2002;**21**:931–5; [4]Boelle & Hanslik *Epidemiol Infect* 2002;**129**:599–606; [5]Bonhoeffer *et al*. *Eur J Pediatr* 2005;**164**:366–70; [6]Heininger & Seward *Lancet* 2006;**368**:1365–76.

Varicella – clinical features

- Highly contagious:
  - 70–90% secondary attack rate[1,2]
- Transmission:[3,4]
  - inhalation of infectious particles
  - direct contact with lesions
  - transplacental
- General symptoms (lasting 5–7 days or more):[3,4]
  - pruritic rash (up to 500 lesions in 2–4 crops, 1500 in severe cases)
  - fever
  - malaise
- More severe in adults than in children[5]

[1]Ross *N Engl J Med* 1962;**267**:369–76; [2]Seward *et al. JAMA* 2004;**292**:704–8; [3]Gershon *et al*. In: Plotkin *et al.* eds. Vaccines 2004:784–823; [4]Macartney *et al*. *J Paediatr Child Health* 2005;**41**:544–52; [5]Marin *et al. J Inf Dis 2008;***197 Suppl 2**:94–100.

Burden of varicella

- Serious complications (including death)
- Impact on infected child
- Impact on family
- Direct medical costs:
  - annual cost to healthcare payers: €78 million[1]
- Indirect (non-medical) costs
  - annual cost to society: €187.5 million[1]

[1]Banz *et al. Eur J Health Econ* 2004;**5**:46–53.

Agenda

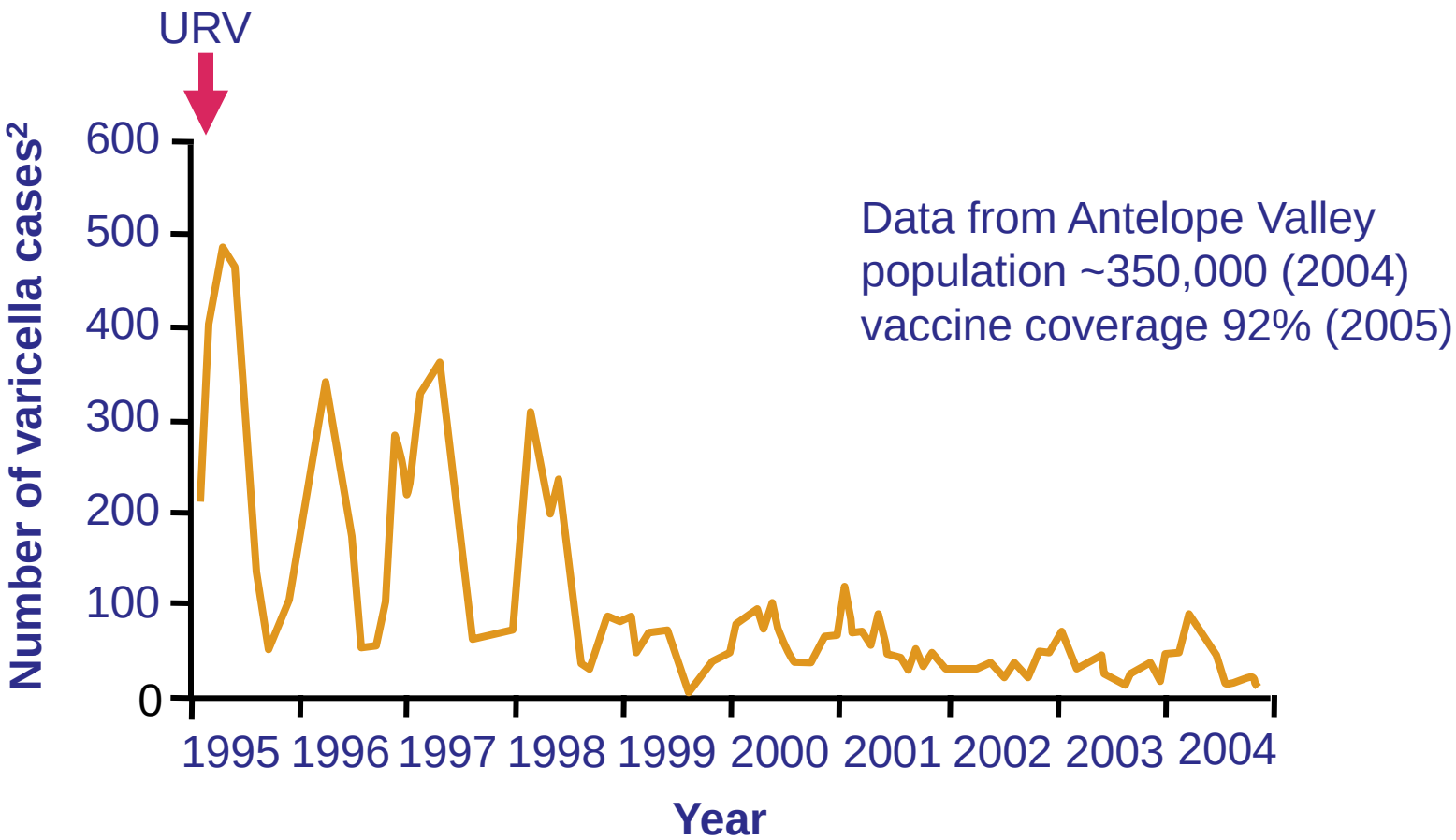
- Advantages of combination vaccines
- MMR – The current standard of care
- Like MMR, two doses of varicella vaccine may be the optimal strategy for better protection
  - immunological evidence suggests that two doses are superior
  - MMRV combination vaccines will better facilitate introduction of varicella URV

URV, universal routine vaccination

Varicella
universal routine vaccination (URV): one-dose schedule

Varicella URV of 1–4-year-olds in the USA – reduced incidence

- Overall varicella incidence 1999–2005 ↓ 89.8%[1]



URV, universal routine vaccination

[1]Guris *et al*. *J Infect Dis* 2008;**197 Suppl 2**:71–5; [2]CDC In: Eds Atkinson *et al.* Epidemiology and prevention of vaccine-preventable diseases 2007:175–96

Varicella URV in the USA – medical attention

From the pre-vaccination period (1994–1995) to 2002:

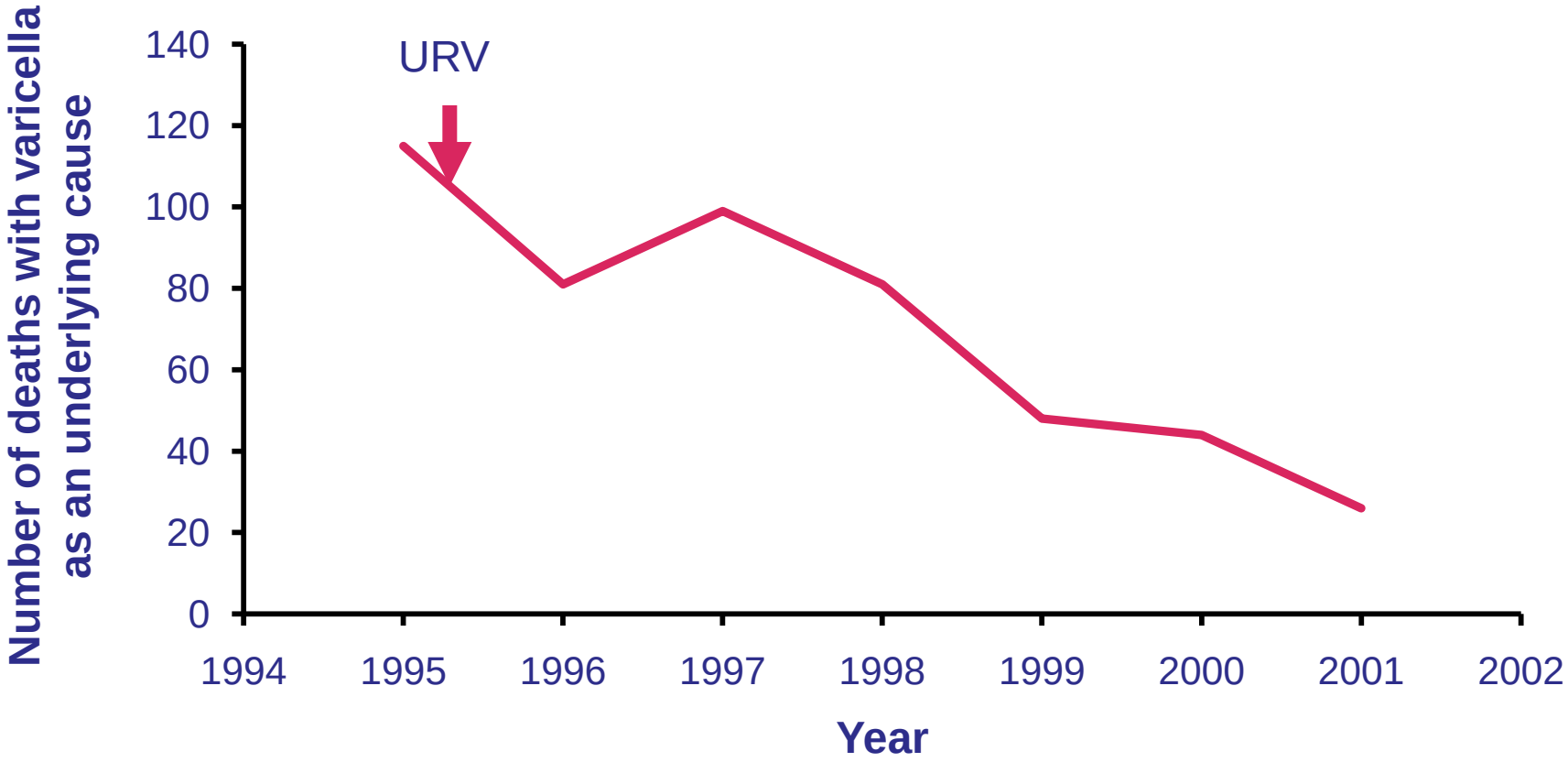
- For all age groups (1–19 years of age):
  - hospitalisations ↓ 88% (from 2.3 to 0.3 per 100,000 population)
  - ambulatory visits ↓ 59% (from 215 to 89 per 100,000 population)
- Greatest reductions in infants aged <1 year
- Annual direct medical expenditure ↓ 74%

  ($US84.9 million to $US 22.1 million)

URV, universal routine vaccination

Zhou *et al*. *JAMA* 2005;**294**:797–802.

Varicella URV in the USA – reduced mortality



URV, universal routine vaccination

Nguyen *et al*. *N Engl J Med* 2005;**352**:450–8.

Impact of varicella URV in other countries

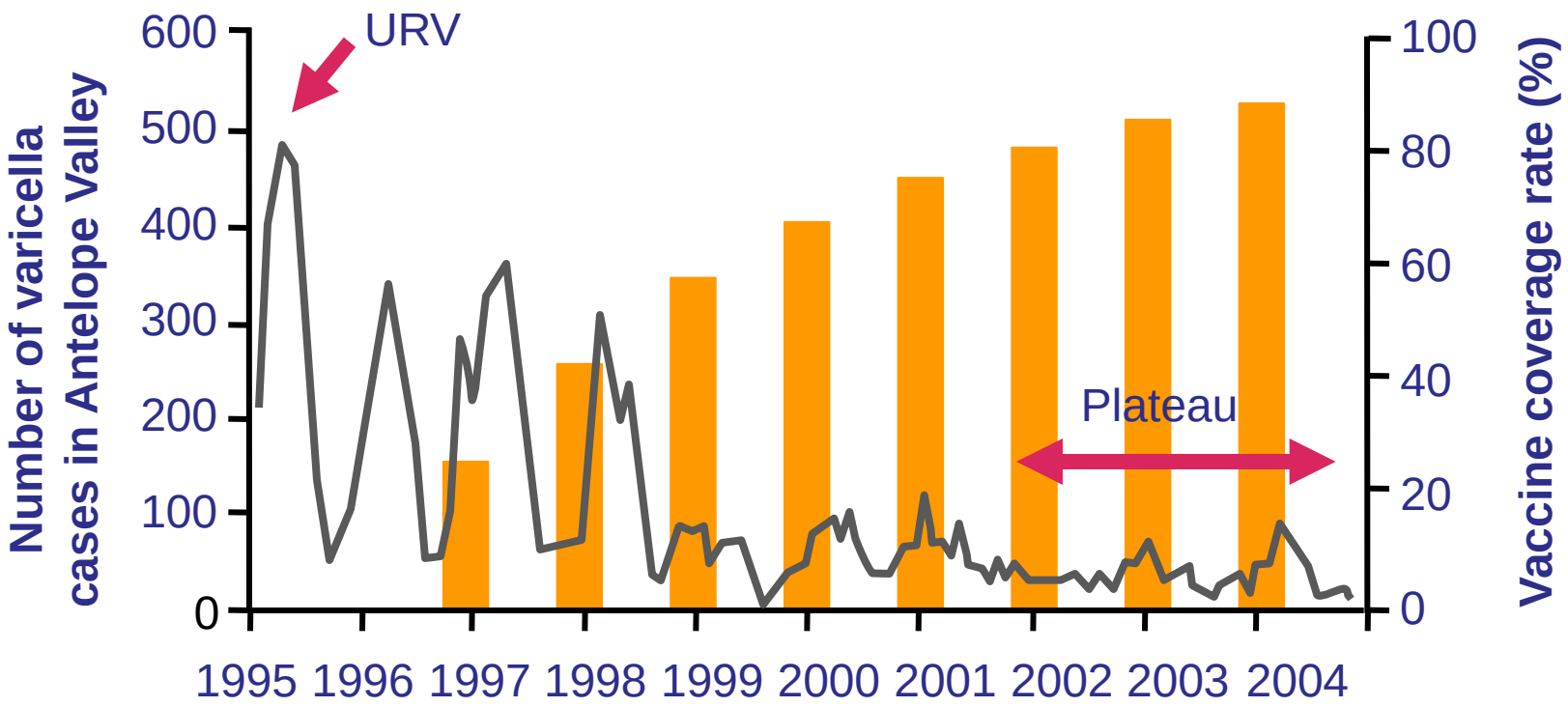
- Sicily, Italy (one-dose URV introduced in 2003)[1]
  - varicella incidence per 1,000 person years↓ 80%
    (from 50.5 in 2005 to 10.2 in first quarter of 2007)
- Uruguay (one-dose URV introduced end of 1999)[2]
  - hospitalisations due to varicella ↓ 81% by 2005
  - varicella-related ambulatory visits ↓ 87% by 2005
  - herd immunity demonstrated
- Germany (one-dose URV introduced in 2004)[3]
  - cases per physician reported via sentinel surveillance system declined from 17 (Apr–Sep 2005) to 9 (Apr–Sep 2007)

[1]Ciriminna *et al.* Presented at ESPID May 13-16, 2008, Graz, Austria [abstract]; [2]Quian *et al*. *Arch Dis Child* 2008;**93**:845–50; [3]Siedler & Arndt Presented at ESPID May 13-16, 2008, Graz, Austria [abstract].

URV, universal routine vaccination

Varicella universal routine vaccination:
Is one dose optimal?

Decline in incidence reached a plateau in the USA



Antelope Valley population: 1995 – approximately 285,000
2005 – approximately 350,000

CDC 2007 In: Eds Atkinson *et al.* Epidemiology and prevention of vaccine-preventable diseases 2007:175–96; CDC 2008 available from: http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm#nis

URV, universal routine vaccination

Breakthrough varicella

- Varicella rash occurring >42 days post-vaccination following exposure to wild-type virus
- Clinical features[1,2]
  - mild symptoms
  - usually fewer lesions (<50) than after primary infection in unvaccinated individuals
  - potentially contagious, so a source of transmission

[1]Chaves *et al*. *N Engl J Med* 2007;**356**:1121–9; [2]CDC 2007 Available from: http://www.cdc.gov/nip/diseases/varicella/faqs-clinic-disease.htm

Primary vaccine failure (‘no take’)

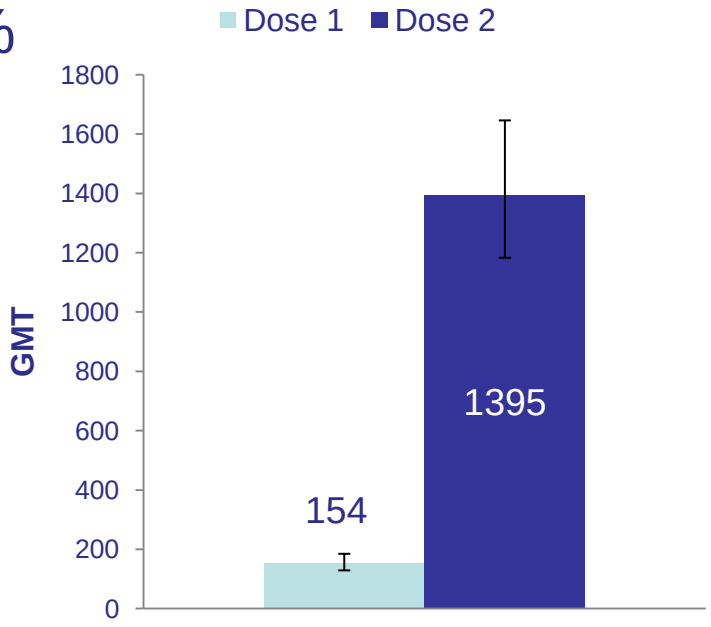
- Pre-licensure studies
  - 96% seroconversion rate (i.e. 4% vaccine failure rate) in children (1–17 years of age)[1]
- Post-licensure studies:
  - 24% vaccine failure rate determined by seroconversion rate[2]
  - could account for most breakthrough cases[3]
- Primary vaccine failure possibly underestimated pre-licensure because:
  - highly sensitive ELISA assay detects non-protective antibodies[3]
  - ideal conditions in clinical trial settings[4]

[1]White *et al*. *Pediatrics* 1991;**87**:604–10; [2]Michalik *et al*. *J Infect Dis* 2008;**197 Suppl 2:**944–9; [3]Gershon & Katz *J Infect Dis* 2008;**197 Suppl 2**:242–5; [4]Torvaldsen & McIntyre *Commun Dis Intell* 2002;**26**:451–7.

A two-dose schedule: An optimal strategy for better protection

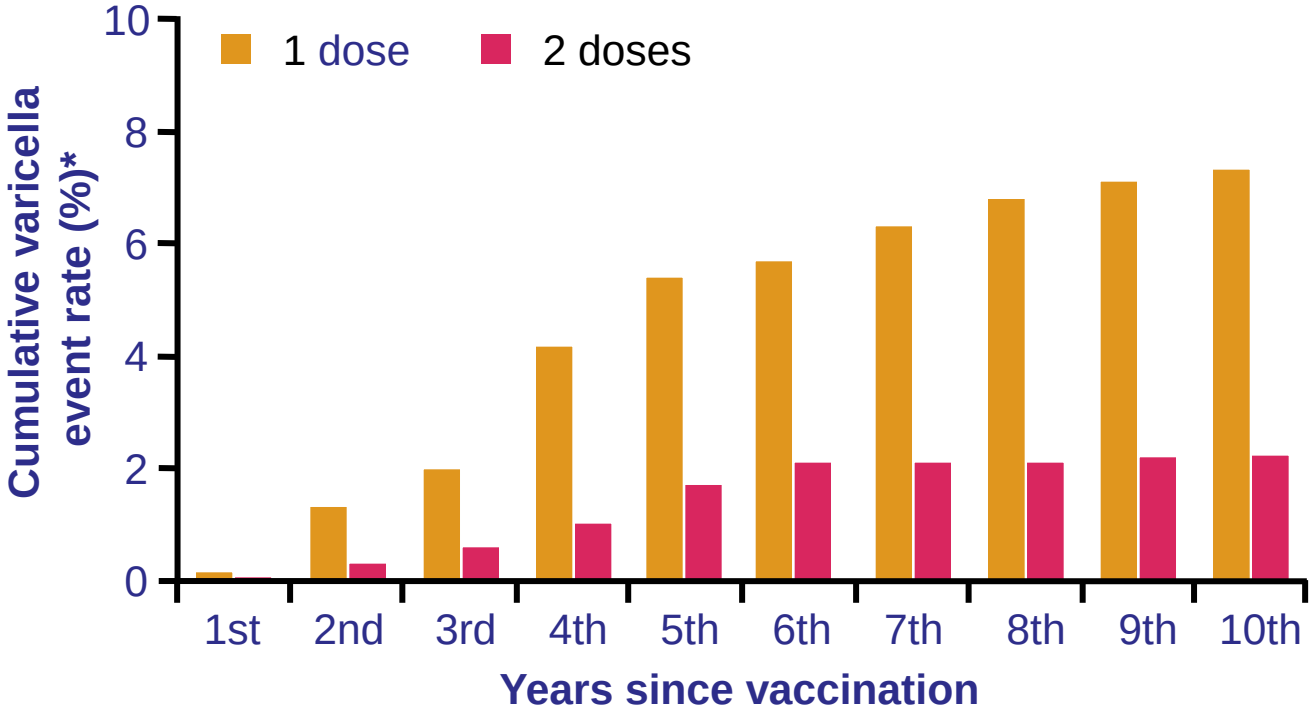
Varicella vaccination with two doses induces an anamnestic response

- 121 young children in the Czech republic and Hungary
- After one dose of *Varilrix*™ 99.1% of vaccinated subjects were seropositive (antibody titre ≥4 dilution^{-1}) by commercial immunofluorescence assay, all were seropositive after second dose
- GMT of anti-varicella antibodies increased approximately 9-fold after second dose



Prymula *et al*. Presented at ESPID 9-13 June 2009, Brussels, Belgium [abstract]

Significantly higher vaccine efficacy and lower breakthrough rates after two doses (10-year projection model)



10-year breakthrough rate 3.3-fold lower after two doses (**2.2%**) *vs* one dose (**7.3%**, p<0.001)

*Varicella event rate = number with actual or expected case of varicella/person-years at risk

Kuter *et al*. *Pediatr Infect Dis* 2004;**23**:132–7.

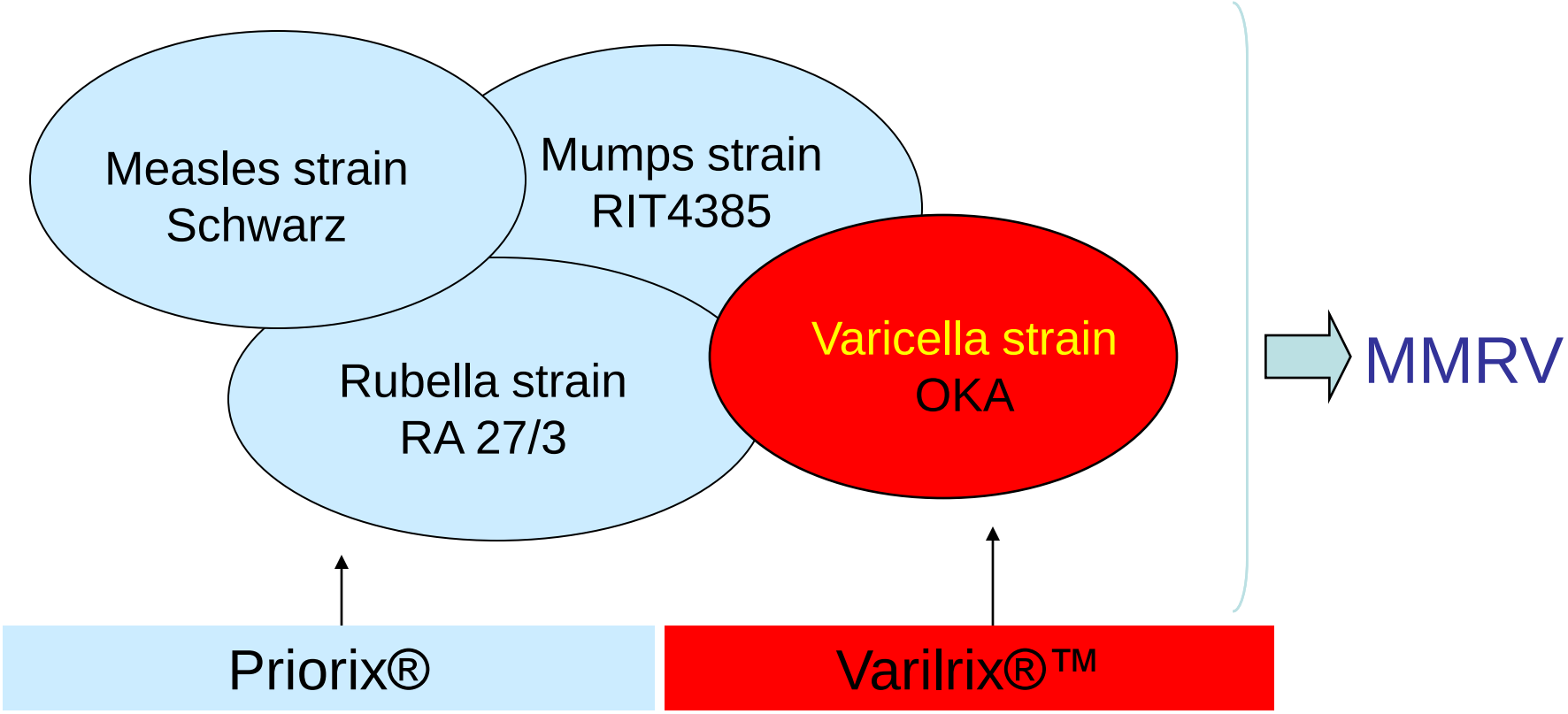
Impact of varicella UMV similar in the US and Uruguay

- Varicella incidence before UMV was similar in the US[1] and Uruguay[2]
- Percent reduction of varicella incidence in Uruguay was also similar to US by age groups[1,2]

Age-group (yrs)	Uruguay[2]	US[1]
<1	63–80	68–81
1–4	94–97	83–90
5–9	73–81	63–77
10–14	62–65	65–80

[1]Seward *et al.* 2002
[2]Quian *et al.* 2008

MMRV


Measles strain
Schwarz
Mumps strain
RIT4385
Rubella strain
RA 27/3
Varicella strain
OKA
MMRV
Priorix®
Varilrix®™

MMRV– immunogenicity

- **Healthy children (n=970, 10–21 months of age at dose 1)**
  - ***N=732*: two doses of MMRV vaccine *(VaMMRix™ / Priorix™Tetra*) -day 0 and day 42**
  - ***N=238: one dose of MMR vaccine (Priorix™*) and one dose of varicella vaccine (V*arilrix™*) -day 0- followed by*one dose of MMR vaccine (Priorix™*) -Day 42**

TABLE 2. Seroconversion Rates and Antibody GMTs in Initially Seronegative Subjects 42 Days After Administration of the First Vaccine Dose (ATP Immunogenicity Cohort)

Antibody	MMRV Group			MMR + V Group			Difference in SC Rate (MMR + V − MMRV)
	N	SC (%) (95% CI)	GMT (95% CI)	N	SC (%) (95% CI)	GMT (95% CI)	Value (%) (95% CI)
Measles (≥150 mIU/mL)	670	94.5 (92.5–96.1)	2584.7 (2364.7–2825.2)	213	93.4 (89.2–96.4)	1645.4 (1399.2–1935.0)	−1.05 (−5.46 to 2.26)
Mumps (≥28 ED_{50})	558	96.1 (94.1–97.5)	157.9 (143.0–174.4)	187	93.6 (89.1–96.6)	124.1 (103.6–148.7)	−2.47 (−7.14 to 0.87)
Rubella (≥4 IU/mL)	667	99.7 (98.9–100.0)	62.9 (59.1–67.0)	212	98.1 (95.2–99.5)	83.2 (73.4–94.3)	−1.59 (−4.47 to −0.27)
Varicella (≥4 $dilution^{-1}$)	624	95.5 (93.6–97.0)	80.4 (72.6–89.0)	204	95.6 (91.8–98.0)	84.0 (70.3–100.3)	0.08 (−3.91 to 2.94)

N indicates number of initially seronegative subjects with prevaccination results available; GMT, geometric mean titer calculated on all subjects (with an arbitrary value of half the cut-off for seronegative titers); SC, seroconversion rates: percentage of subjects with antibody concentrations above the specified cut-off; CI, confidence interval.

TABLE 3. Seroconversion Rates and Antibody GMTs in Initially Seronegative Subjects 42 Days After Administration of the Second Vaccine Dose (ATP Immunogenicity Cohort)

Antibody	MMRV Group			MMR + V Group*			Difference in SC Rate (MMR + V − MMRV)
	N	SC (%) (95% CI)	GMT (95% CI)	N	SC (%) (95% CI)	GMT (95% CI)	Value (%) (95% CI)
Measles (≥150 mIU/mL)	657	98.3 (97.0–99.2)	3755.9 (3473.2–4061.6)	209	97.6 (94.5–99.2)	2176.0 (1878.2–2520.9)	−0.72 (−3.89 to 1.18)
Mumps (≥28 ED_{50})	541	99.4 (98.4–99.9)	589.4 (542.9–640.0)	182	99.5 (97.0–100.0)	449.0 (390.4–516.5)	0.01 (−2.51 to 1.18)
Rubella (≥4 IU/mL)	653	99.7 (98.9–100.0)	122.6 (116.4–129.3)	209	100.0 (98.3–100.0)	135.6 (124.4–147.9)	0.31 (−1.50 to 1.11)
Varicella (≥4 $dilution^{-1}$)	615	99.7 (98.8–100.0)	1903.3 (1716.3–2110.7)	199	97.5 (94.3–99.2)	80.3 (66.0–97.6)	−2.19 (−5.44 to −0.60)

*Eighty-four day postdose 1 for varicella vaccine administration, no second dose of varicella vaccine given.

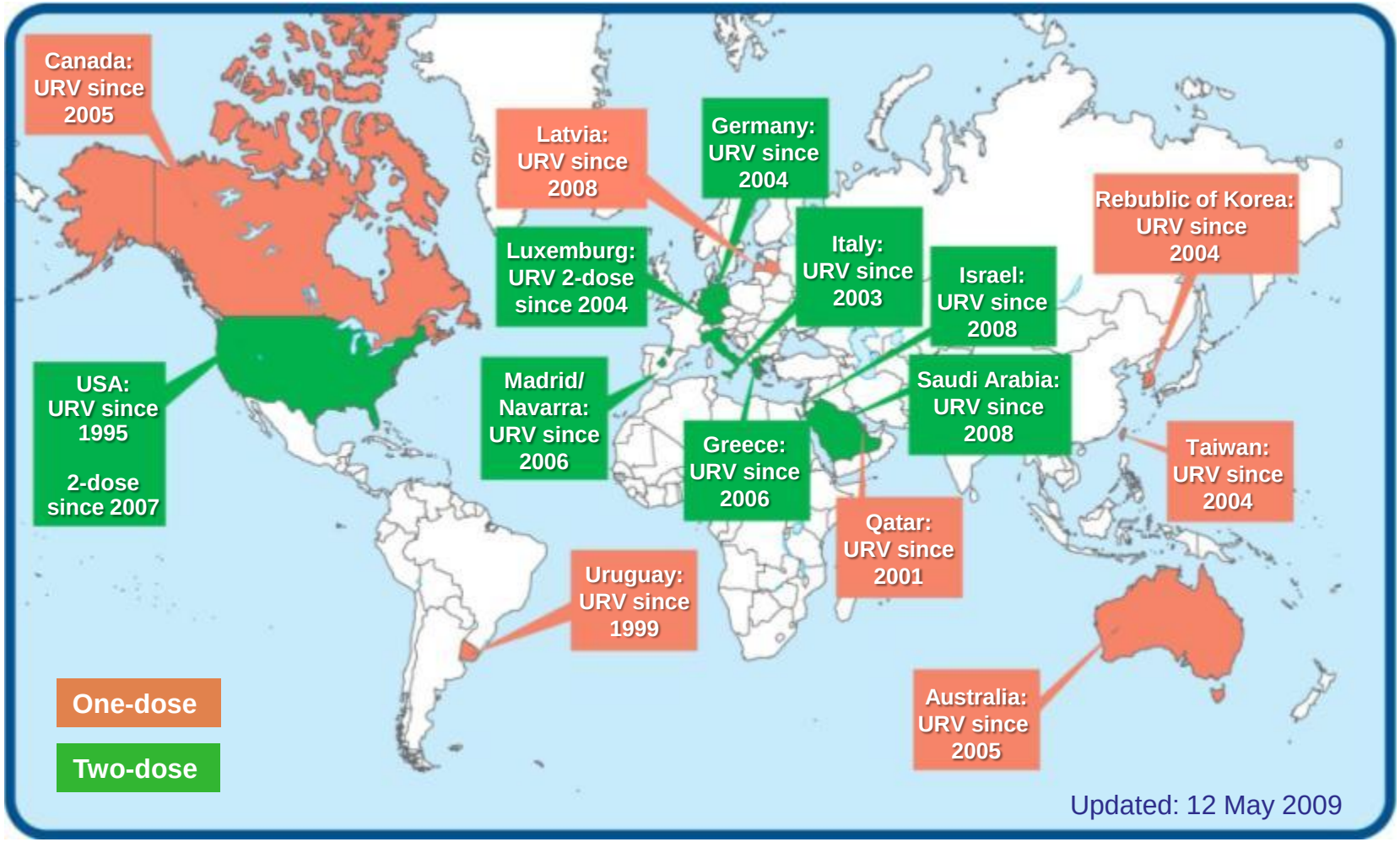
Schuster et al. The Pediatric Infectious Disease Journal 2008, 27(8):724-730

MMRV safety and immunogenicity conclusion

- **After each dose, immunogenicity was similar to the individual MMR and varicella component vaccines Priorix® and Varilrix®**

- **The safety profile remained similar to coadministration of Priorix® and Varilrix®, except for a slight increase in mild local reactions an increase in incidence of fever after the first dose between Day 4 and Day 11 post-vaccination.**

Varicella URV recommendations



URV, universal routine vaccination

Summary and conclusions

- Advantages of combination vaccines
- A one-dose varicella vaccination strategy:
  - has been effective in the USA[1,2]
  - may not be optimal because concerns remain (e.g. breakthrough)
- Like MMR, two doses of varicella vaccine may be the optimal strategy for better protection
  - immunological evidence suggests that two doses are superior[3]
- MMRV combination vaccines:[4,5]
  - will better facilitate introduction of varicella URV

[1]Seward *et al*. *JAMA* 2002;**287**:606–11; [2]Zhou *et al*. *JAMA* 2005;**294**:797–802; [3]ACIP 2006 Available from:http://www.cdc.gov/vaccines/recs/acip/downloads/min-jun06.pdf; [4]Vesikari *et al*. *Pediatr Infect Dis J* 2007;**26**:632–8; [5]Zepp *et al*. Presented at ESPID May 13-16, 2008, Graz, Austria *ESPID* 2008 [abstract].

URV, universal routine vaccination