Children and Varicella

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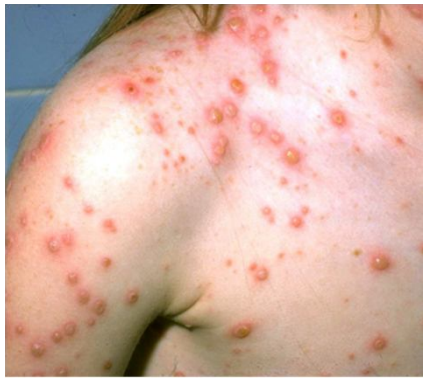
SBIMC – BVIKM. 4/04/2019

Thank you to Philippe Lepage



Photosensitive rash

Maculo-papular lesions

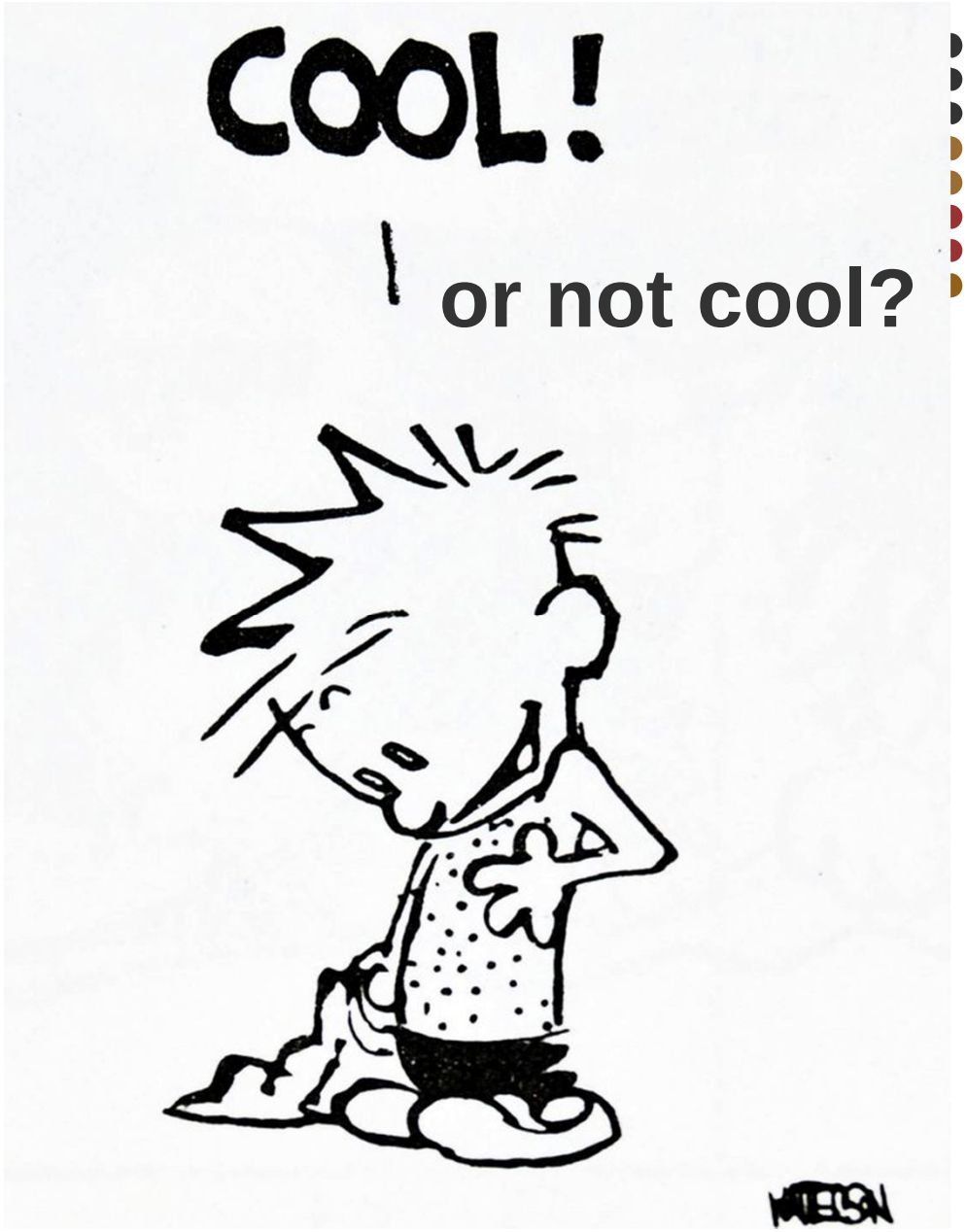
➔ vesicules

➔ crusts

Intense pruritus

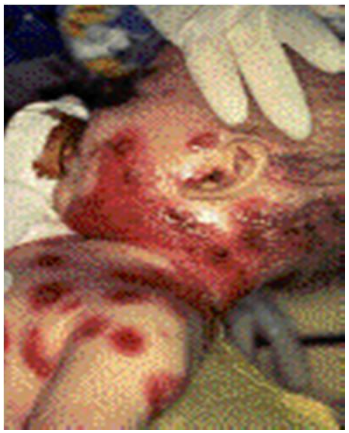
Systemic signs :
Moderate fever

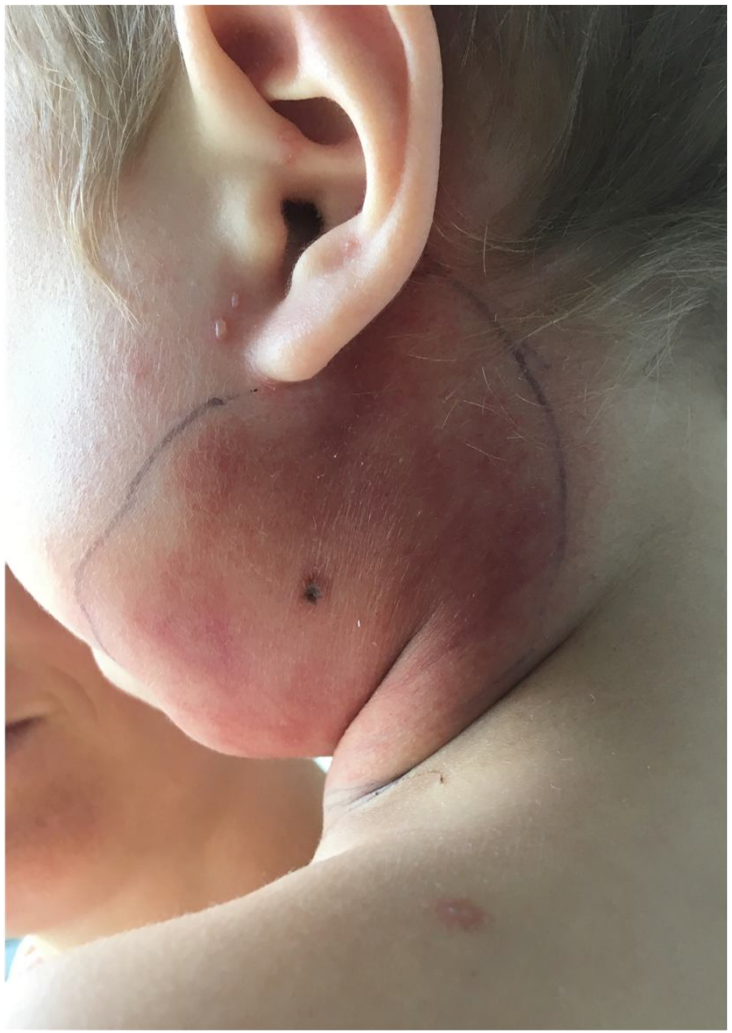
Self-limited infection
in most individuals (10-day course)



Varicella not so benign…

Complications…
Cutaneous superinfection





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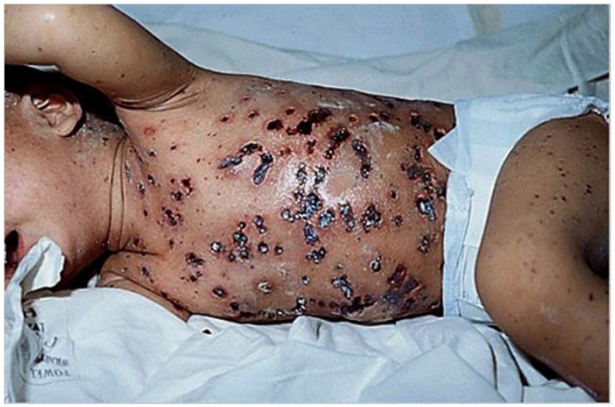
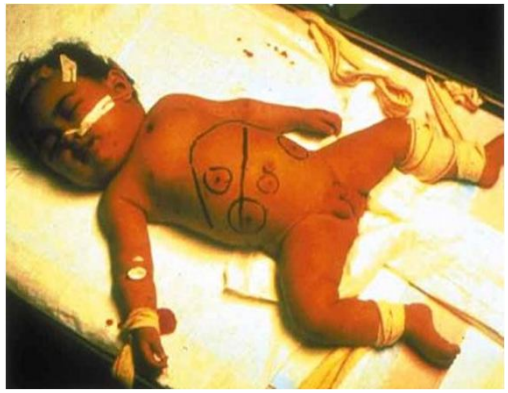
Varicella not so benign…

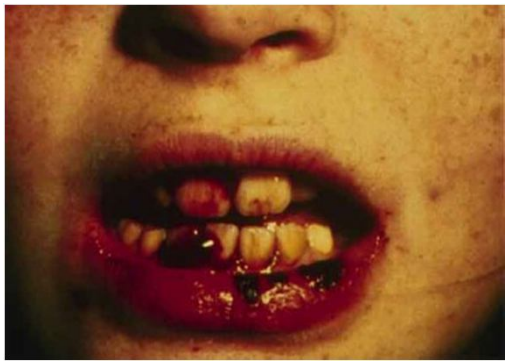
Severe varicella
in healthy subjects



Disseminated
in immuno-
compromised



More severe
in adolescents
and adults



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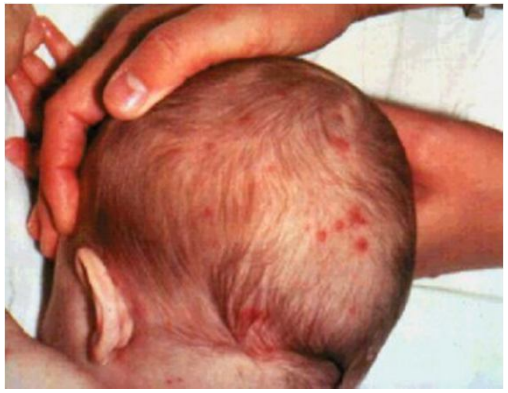
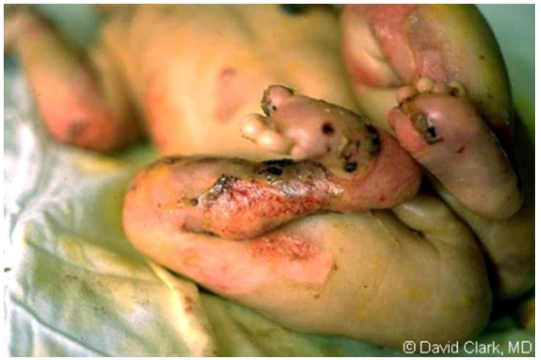
Varicella not so benign…

Neonatal varicella



Congenital varicella



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Prospective belgian study

Burden of varicella in Belgium
Analysis of hospitalised cases during a 1-year period
101 hospitals - 97,7% of paediatrics beds in BE

mortality among Belgian children

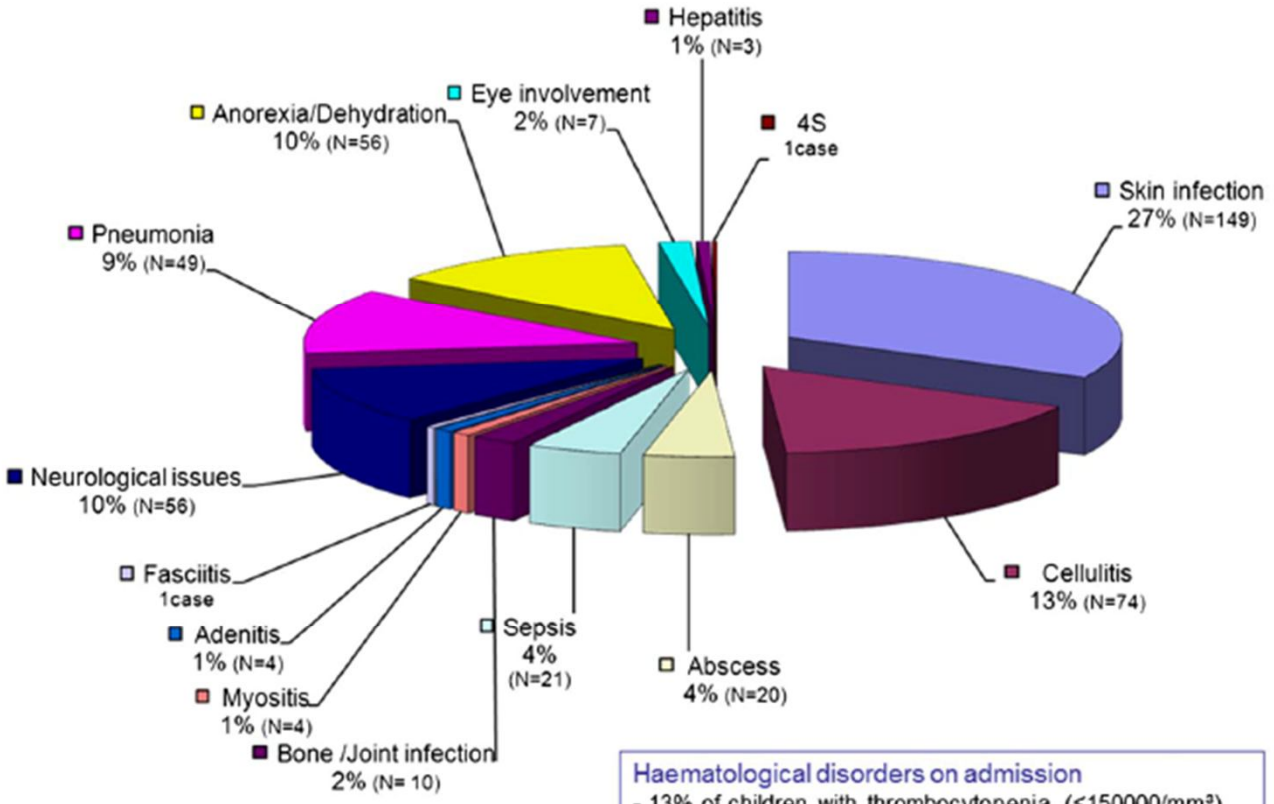
Age group (years)	N Belgian children 2011–2012	Incidence hospitalisation for varicella*	Incidence hospitalisation for complicated varicella*	Mortality rate
0–14	1 873 326	$29.5/10^5$	$19/10^5$	$0.5/10^6$
0–4	647 171	$79/10^5$	$51/10^5$	$1.5/10^6$
5–14	1 226 155	$3.3/10^5$	$2.45/10^5$	0

Blumental et al., 2016

552 hospitalised cases during study period
14% had an underlying condition

65% had 1 or >1 complication(s) justifying their admission
- 49% : bacterial superinfection
- 10% : neurologic disorders

Figure 1 Distribution of varicella-related complications. N=357 patients; 4S=staphylococcal scalded skin syndrome.



Haematological disorders on admission
- 13% of children with thrombocytopenia (<150000/mm³)
- 5% of children with lymphopenia (<1000/mm³)
- 4% of children with leucopenia (<5000/mm³)
- 4% of children with neutropenia (<1500/mm³)

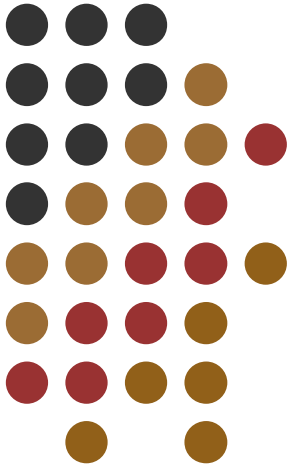
Blumental et al., 2016

Universal mass vaccination (UMV) for varicella.

- Two vaccines are available:
  - *VARILRIX*™ (GlaxoSmithKline Biologicals)
  - *PROVARIVAX*® (MSD)
- Both contain the live attenuated Oka strain
- Varicella added to MMR → MMR-V vaccine
  - *Priorix-Tetra*™ (GlaxoSmithKline Biologicals)
  - *ProQuad*® (Merck & Co., Inc.)

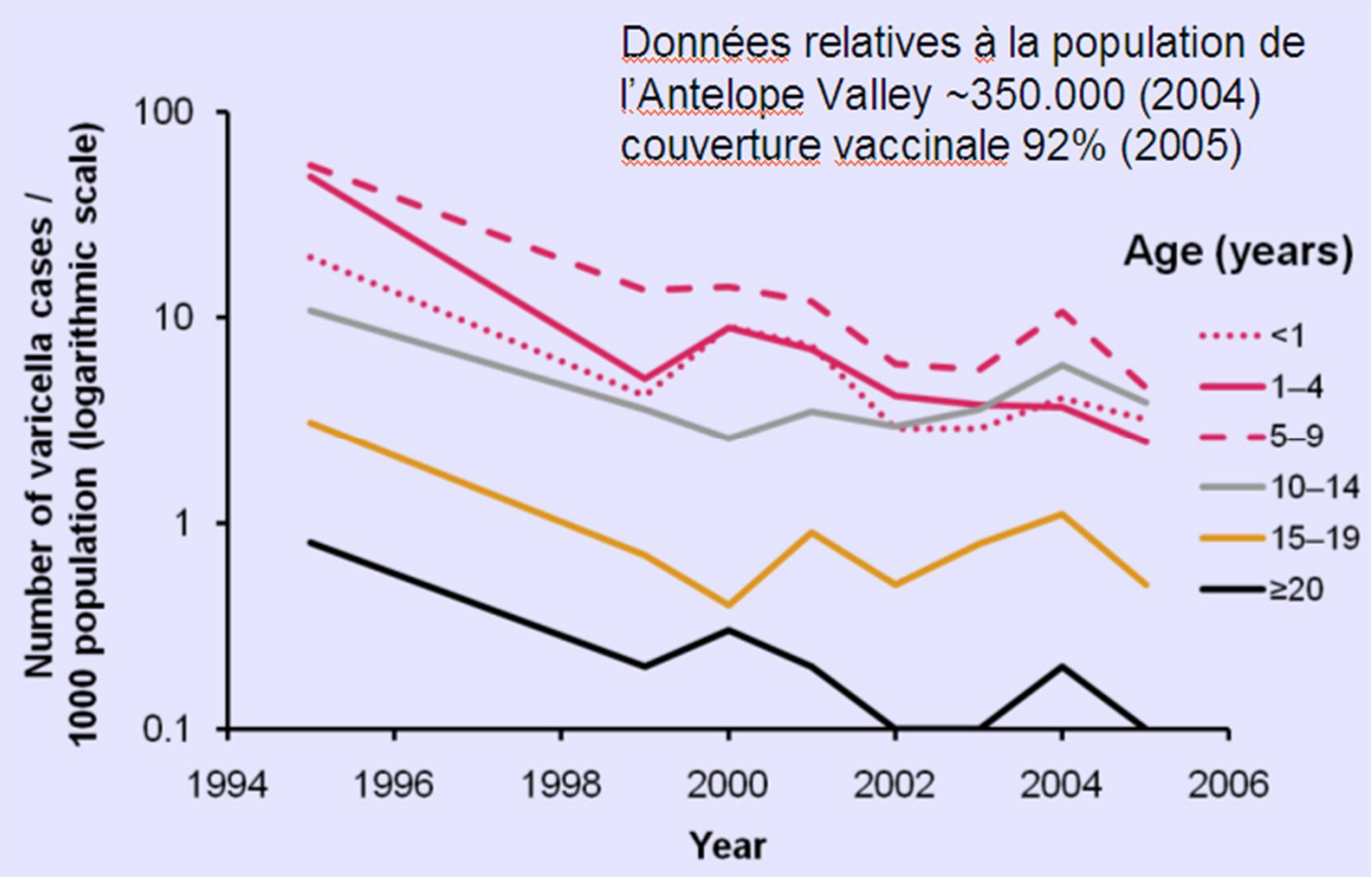
Universal mass vaccination (UMV) for varicella.

Effectiveness data



UMV (1 dose) varicella in USA: Direct effect & herd immunity

UMV from 1996
Global incidence reduced from 89.8% (1995 to 2004)
(Coverage 92% in 2005, 1-dose schedule)



- Guris *et al.* 2008

UMV (1 dose) varicella in USA : Impact on mortality

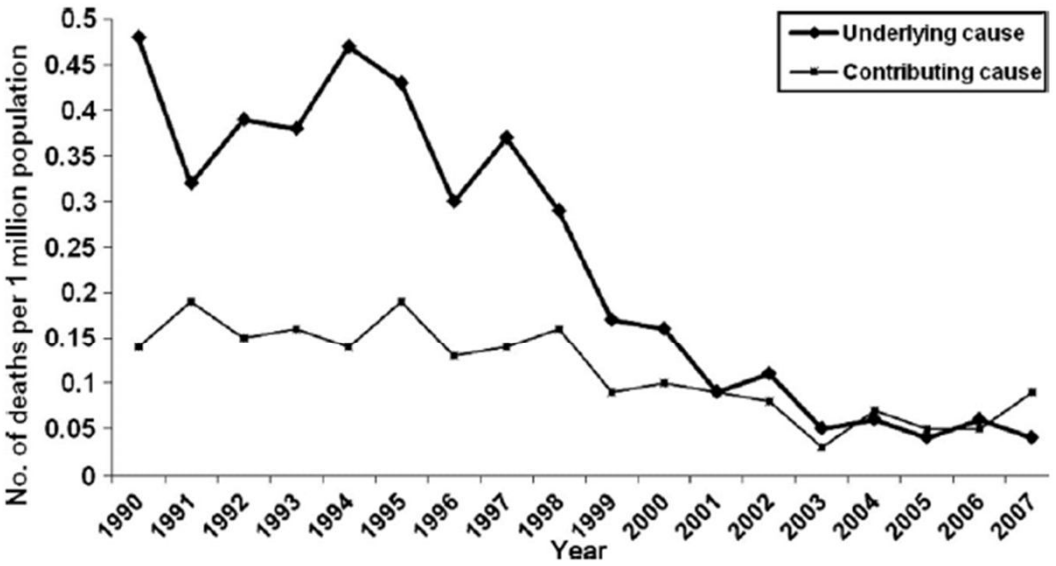


FIGURE 1
Varicella-related mortality rates in the United States, 1990–2007 (age adjusted to the 2000 US population).

Mortality :
1990-94 : 0.41/1 million

-88%

2005-2007 : 0.05/1 million

In all age groups:
<20 yrs : -97%
<50 yrs : -96%
>50 yrs : -67%

Mortality related to varicella almost eliminated

Marin et al. Pediatrics 2011; 128: 214-220

Data for all Germany

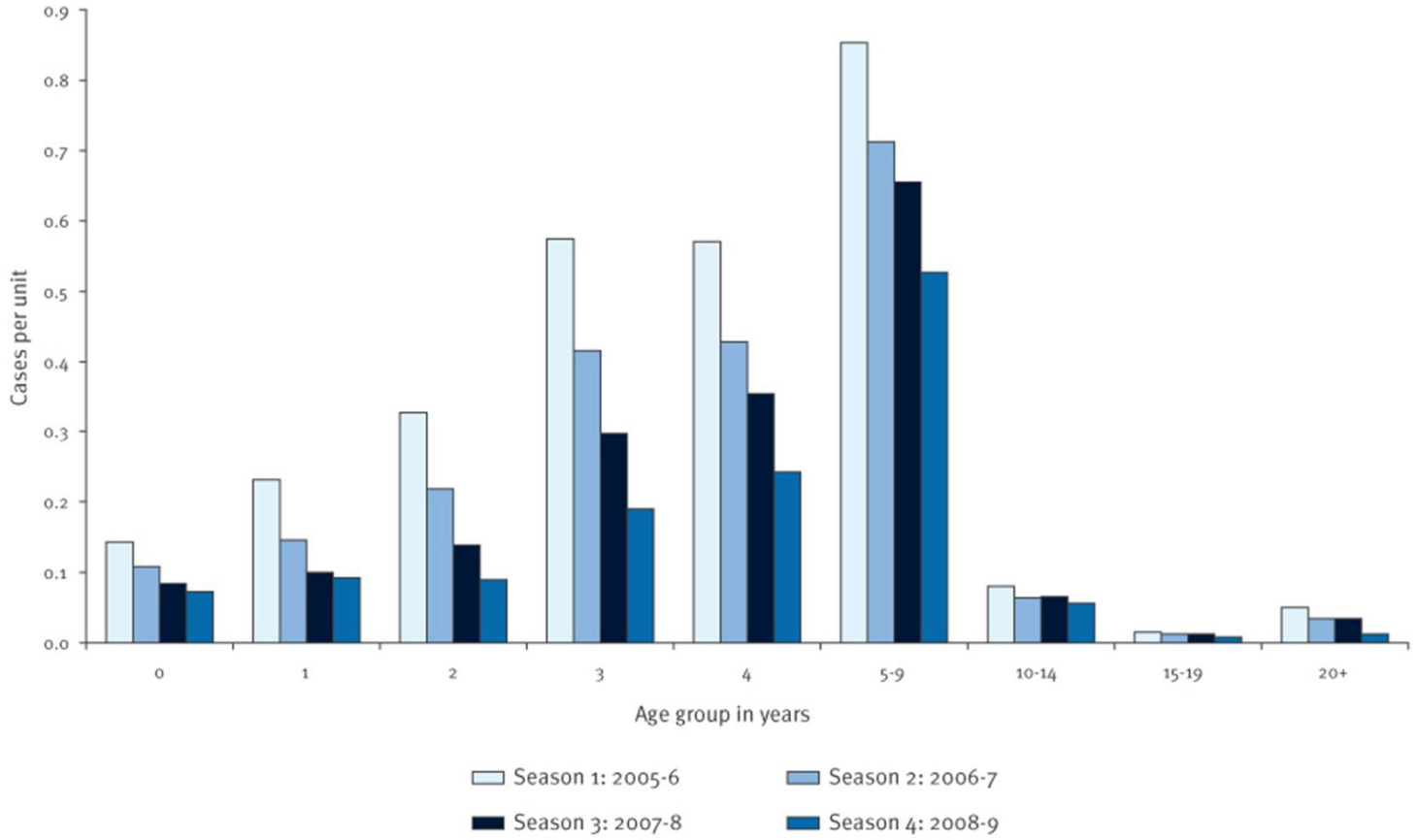
(Sentinel network = 1000 pediatricians & GPs)

Data from 2005 to 2009 (4 seasons; coverage <80%)

UMV from July 2004

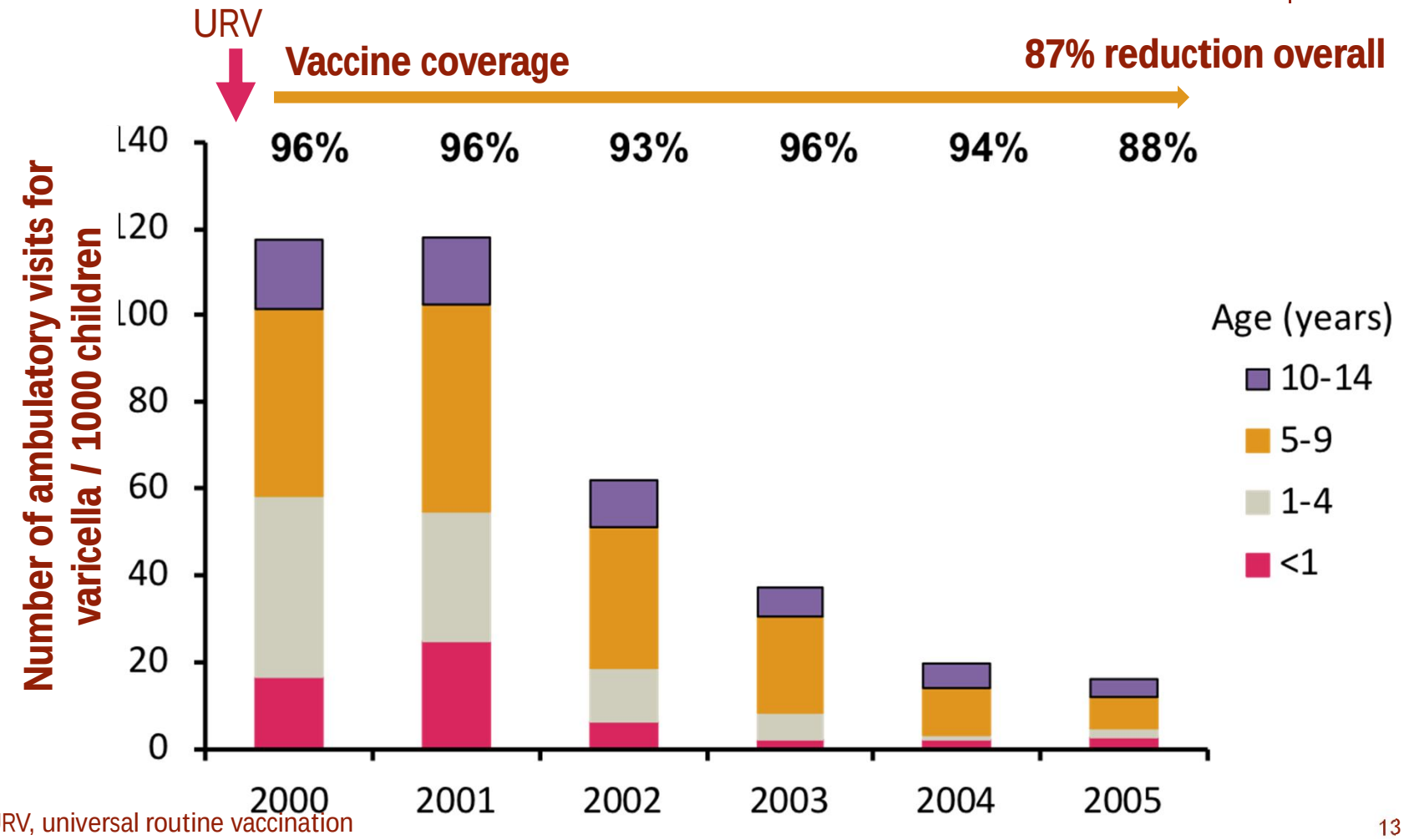
55% reduction in all age groups:

64% (0-4 yrs), **38%** (5-9 yrs) (herd immunity)



Siedler, A. & Arndt, U., 2010.
Impact of the Routine Varicella Vaccination Programme on Varicella Epidemiology in Germany. *Euro Surveill*,

Varicella URV in Uruguay
Ambulatory visits



URV, universal routine vaccination

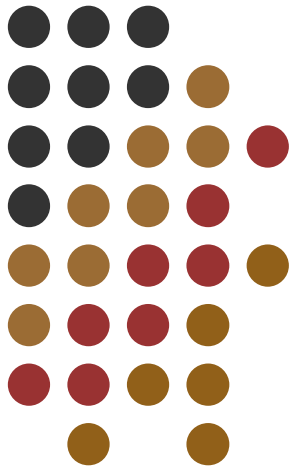
Quian J *et al*. *Arch Dis Child* 2008; **93**: 845–50.

Universal mass vaccination (UMV) for varicella.

Effectiveness data

Vaccine efficacy (VE) : GOOD

- VE all cases 80%
- VE severe cases 99%



Universal mass vaccination (UMV) for varicella.

Safety data

Most common adverse reactions :

- local reactions (pain and erythema)

Monovalent & combined varicella vaccines are generally well tolerated

- Of note : MMRV

Infants of 12-23 months
Administration of a first dose of MMR or MMRV or MMR + V or VV

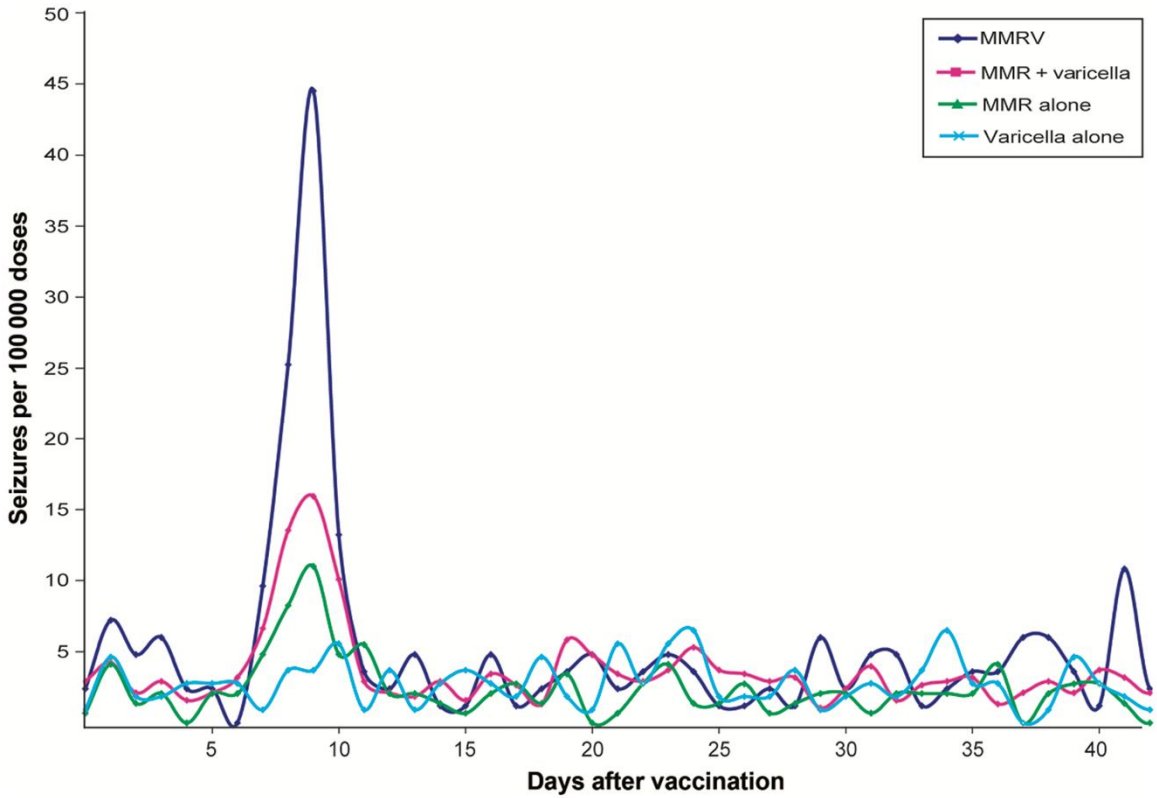


FIGURE 1
Postvaccination seizures among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

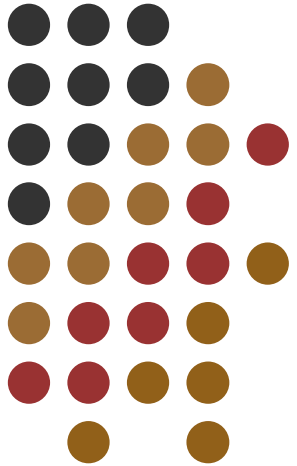
Increased risk of 1 febrile seizure among every 2300 children

Klein et al., Pediatrics 2010

Universal mass vaccination (UMV) for varicella.

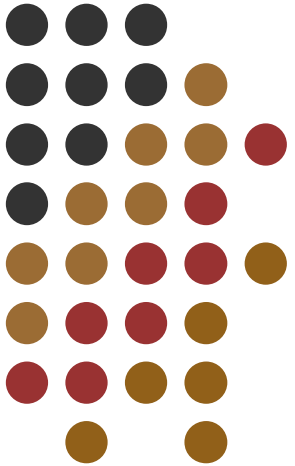
Safety data

Security of Vaccine : GOOD



Universal mass vaccination (UMV) for varicella.

Who follows WHO recommendations to introduce the vaccine in routine immunization program ?



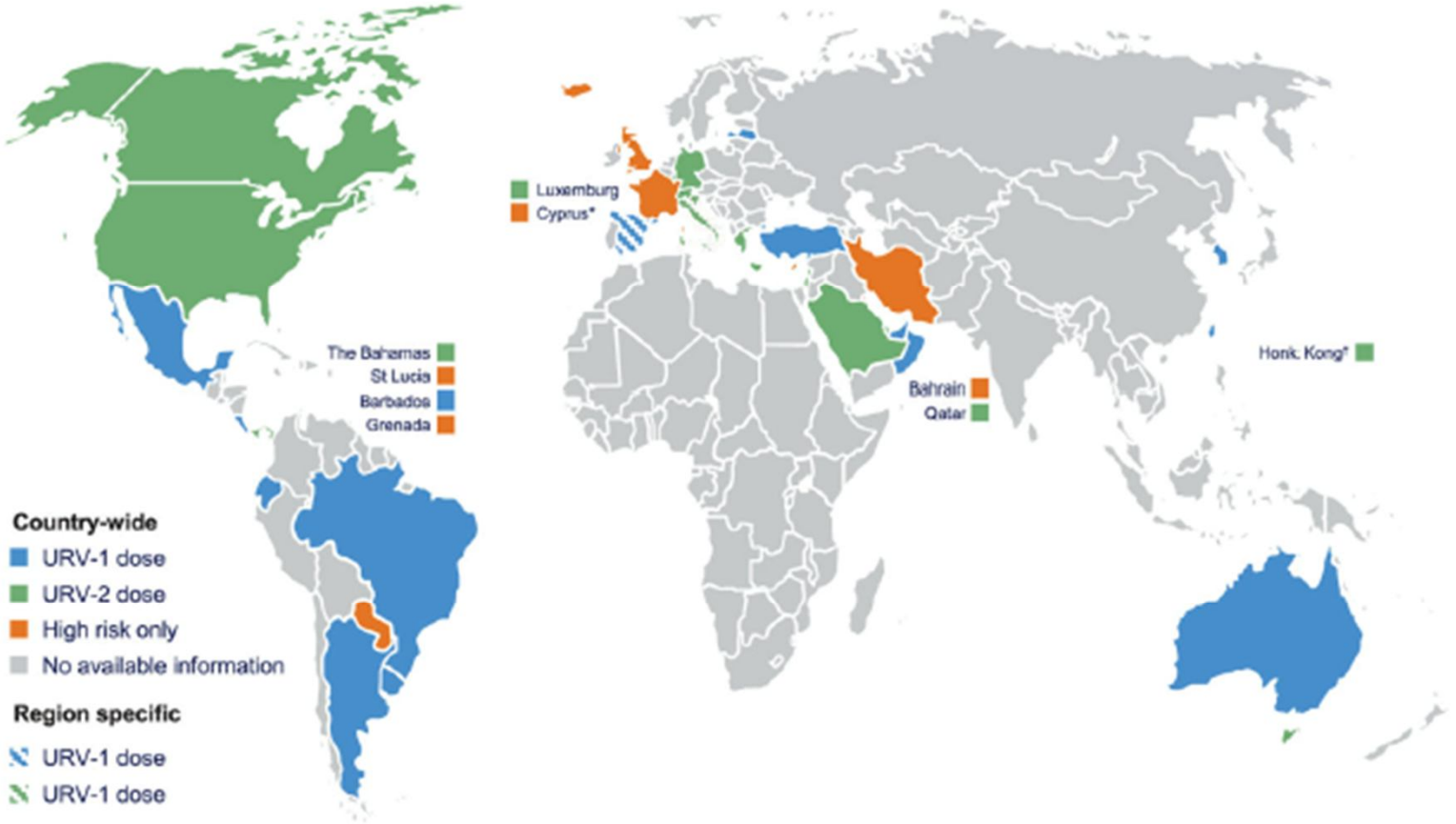
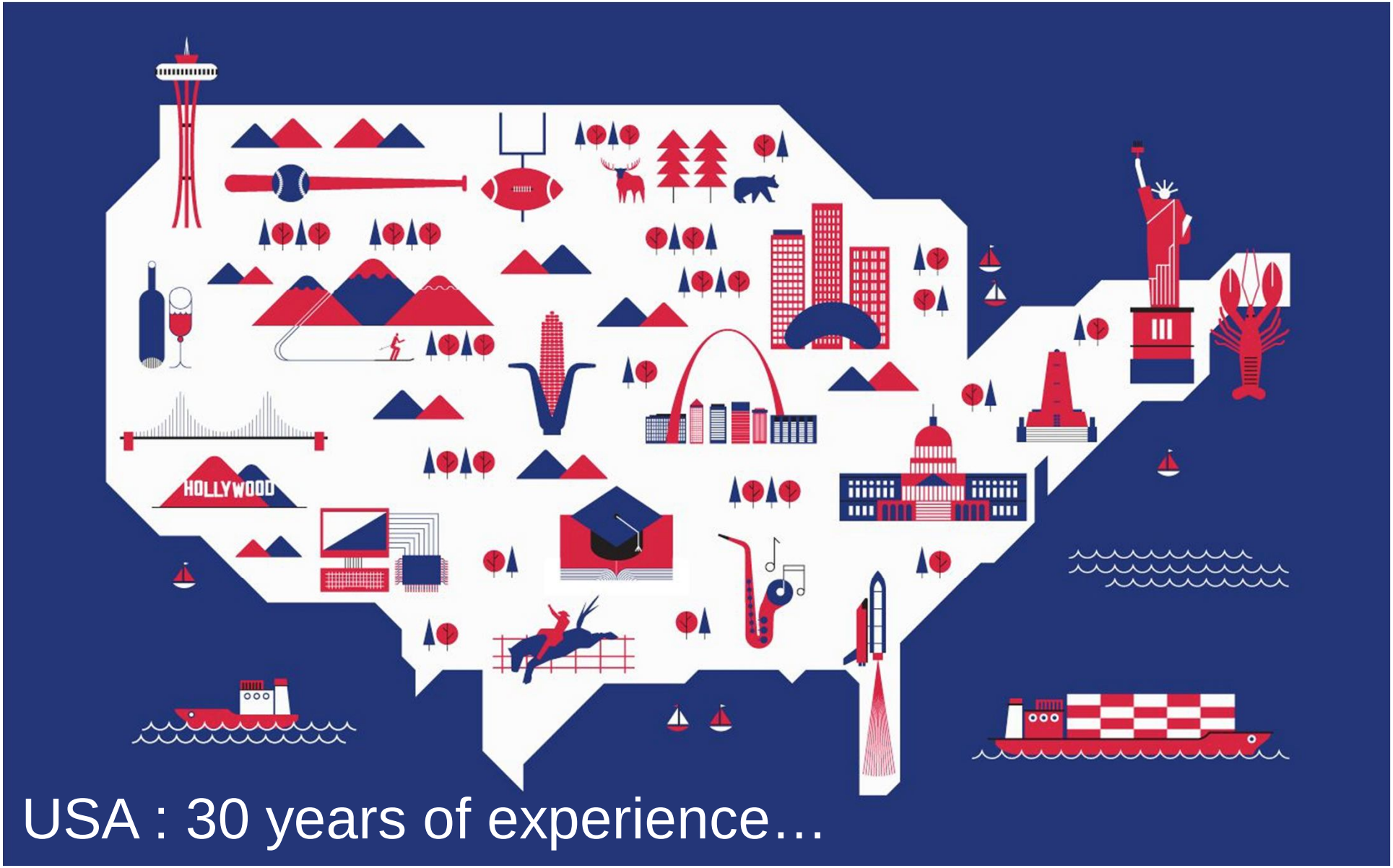


Figure 1.

World map representing different national universal routine vaccination (URV) schedules against varicella (national-level guidelines are represented, unless specific region data was publically available). *In Cyprus, varicella vaccination is administered universally in the private sector. †Varicella URV is recommended in Hong Kong, but not yet implemented [7,37,42,70,72,115,116].

Wutzler et al., Expert Rev Vaccines 2017



USA : 30 years of experience…

1996 : 1-dose schedule

2006 : 2-dose schedule

Figure 1. Varicella vaccination recommendations in EU/EEA countries, 2012

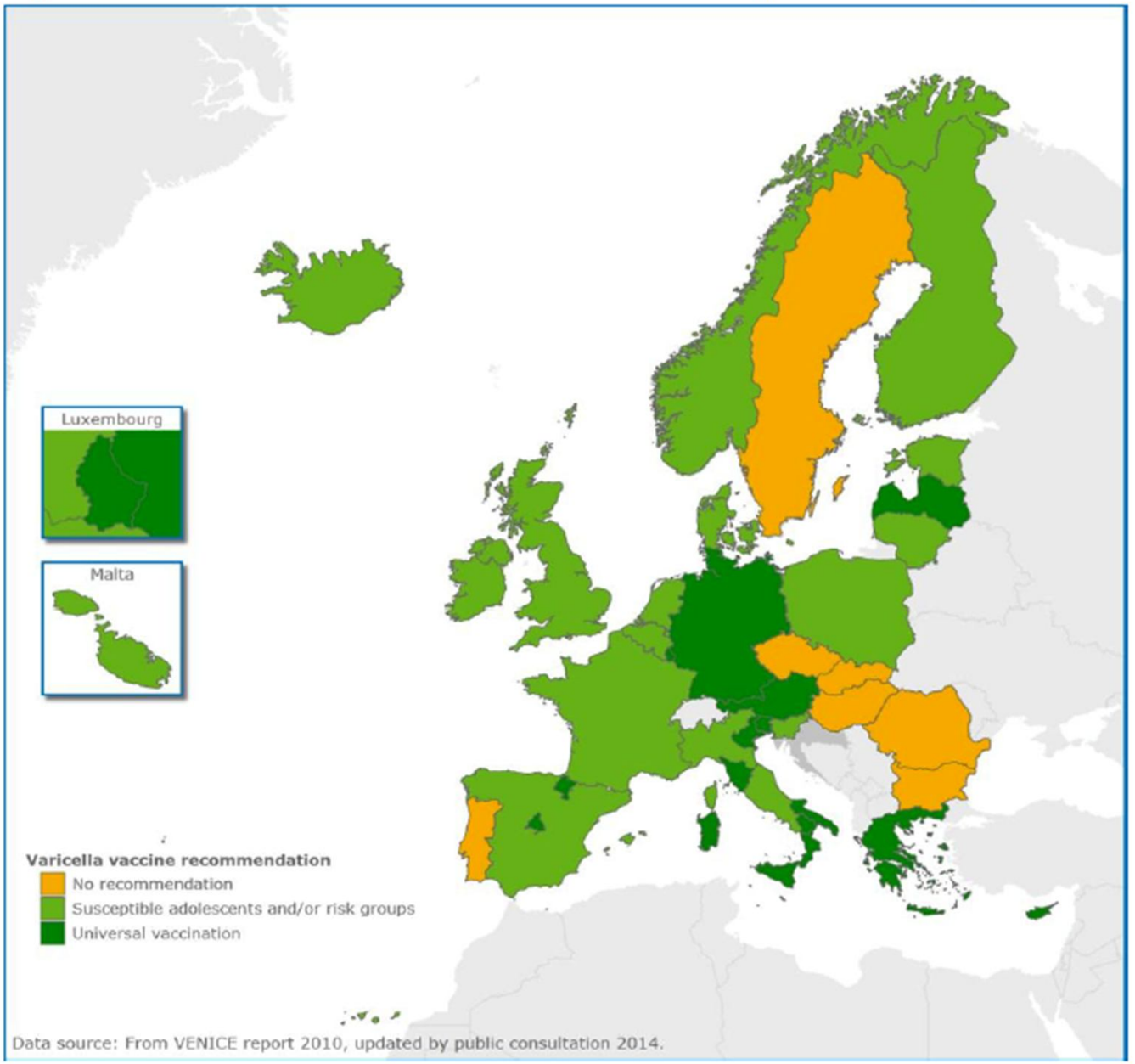


Table 1. Year of introduction, number of doses and age of varicella vaccination in EU and EEA countries with childhood universal vaccination, 2014


Universal mass vaccination for varicella.
What does Belgium recommend?

Conseil
Supérieur de la Santé

AVIS DU CONSEIL SUPERIEUR DE LA SANTE N° 9212

Vaccination des enfants, des adolescents et des personnes à risque contre la varicelle

In this scientific advisory report on public health policy, the Superior Health Council of Belgium provides recommendations on the prevention of varicella infections in children, adolescents and people at risk in the Belgian population.

This report aims at providing public authorities with specific recommendations on varicella vaccination

Version validée par le Collège de
Mars - 2017[1]

No UMV

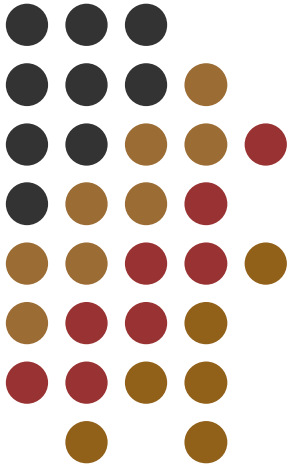
Recommended for individuals at higher risk

- People and HCW in contact with Immuno-compromised
- Child-bearing unimmunized women
- Unimmunized individuals in contact with young children

Universal mass vaccination for varicella.

What are the issues?

- MMR Vaccine coverage rate
- Breakthrough infection
- Waning immunity and age shift
- Increase incidence of shingles



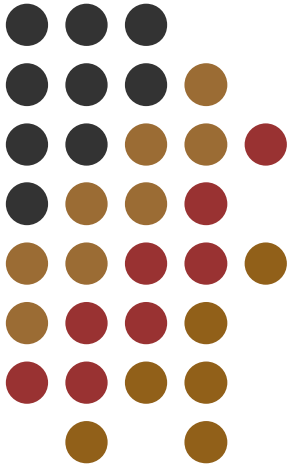
MMR – Measles vaccine coverage

Risk of decrease…

- MMR Vaccine coverage rate : currently >95% for the first dose
- Adding varicella vaccine could stimulate parent dose

- Combined vaccine
  - Increase/maintain current coverage rates
  - Febrile seizure

Currently no distribution of MMR-V



Klein et al., 2010

Universal mass vaccination for varicella.

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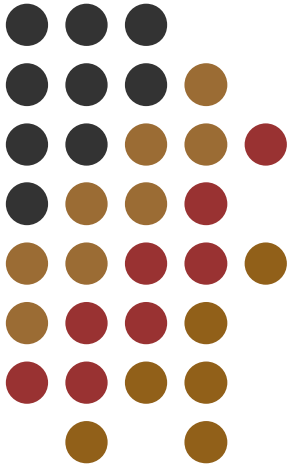
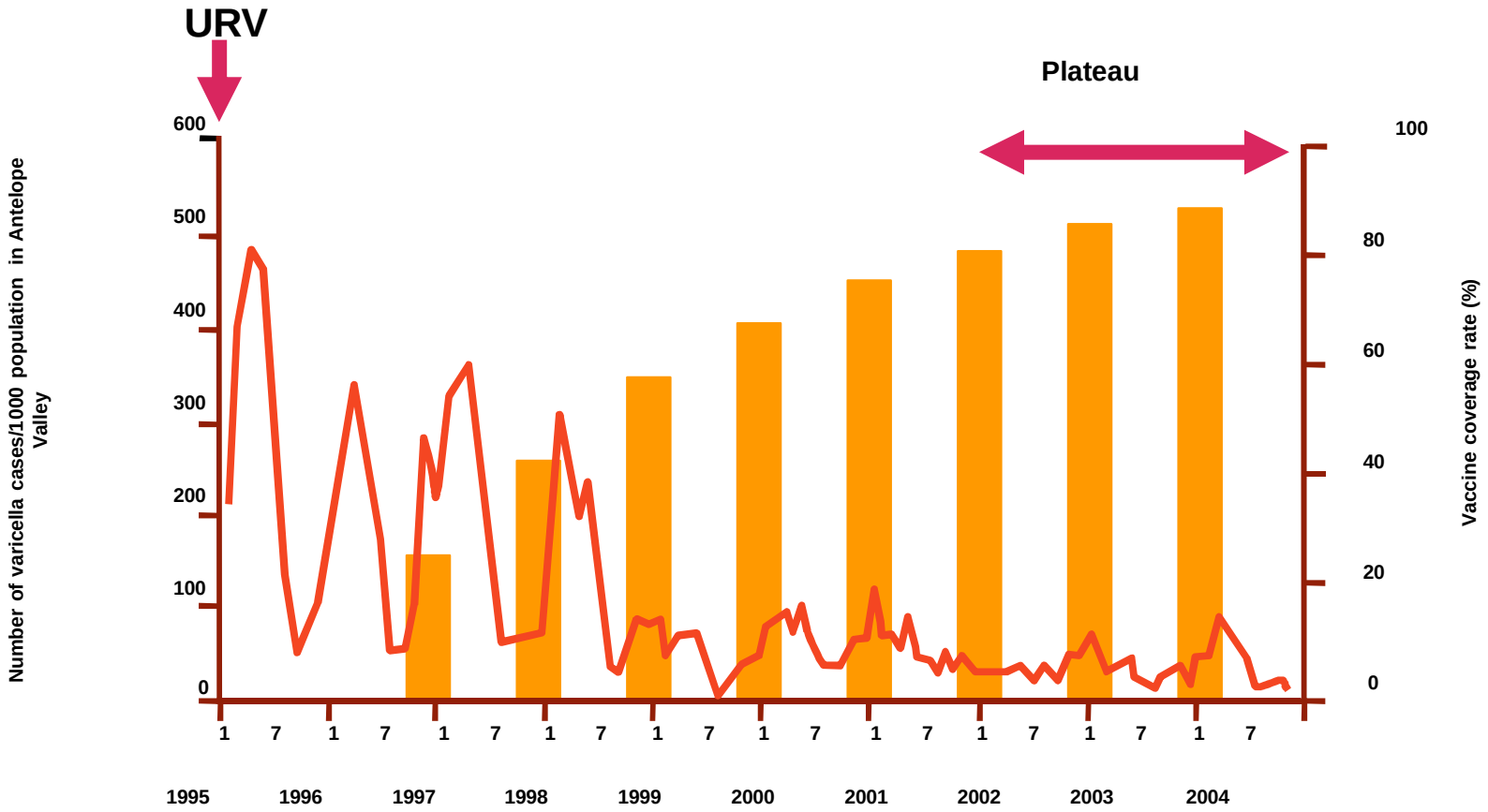


UMV (1 dose) varicella in USA : Despite high coverage decrease in incidence of varicella is plateauing



URV, universal routine vaccination

[1] CDC In: Atkinson W *et al.* eds. Epidemiology and prevention of vaccine-preventable diseases, 10th edn. Washington DC: Public Health Foundation, 2007: 175–96. [2] CDC 2008 Available from: http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm#nis

Breakthrough Varicella

Case of wild-type varicella

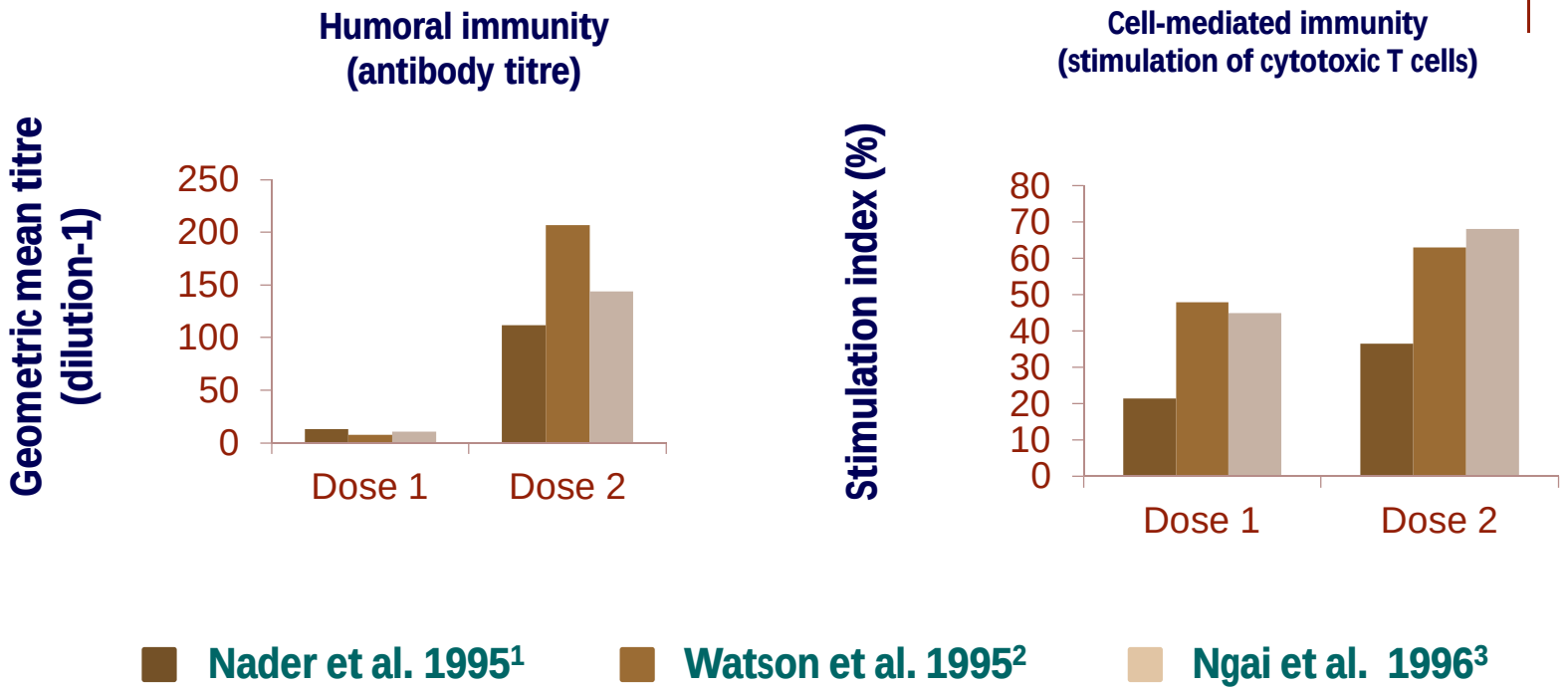
- Occurring in a vaccinated person >42 days after varicella vaccination
- Following exposure to wild-type virus

Effectiveness of 1-dose schedule: **80%**

- Risk of breakthrough infection in 1/5 children
- Primary failure or waning immunity or both?

Kuter B *et al*, Pediatr Infect Dis J 2004
Shapiro E *et al*, J Infect Dis 2011

Robust anamnestic response after 2-dose schedule



- 2 doses of vaccine mimicks natural response to infection[4]
- Increased response after 2nd dose suggests uncomplete immunity after 1 dose[5]

[1]Nader S, et al. J Infect Dis 1995;171:13–7; [2]Watson B, et al. Clin Infect Dis 1995;20:316–9; [3]Ngai AL, et al. Pediatr Infect Dis J 1996;15):49–5; [4]ACIP, 2006; [5]Gershon A & Katz S. J Infect Dis 2008;197(Suppl2):S242–S245

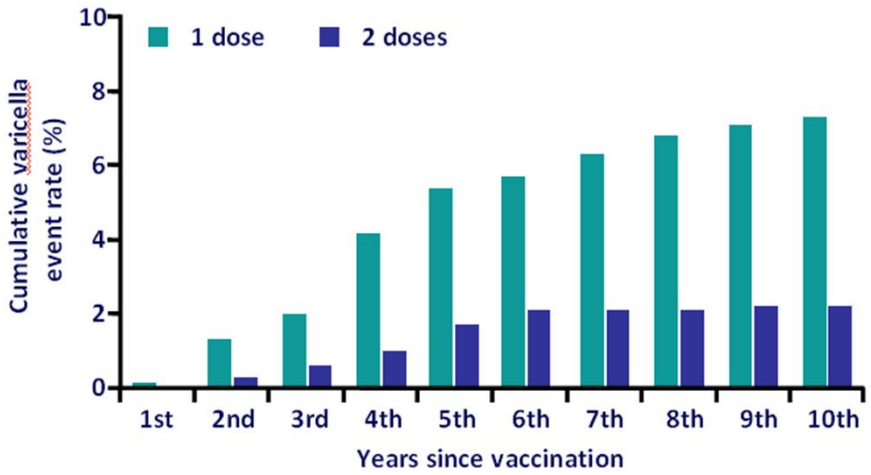
Varicella vaccine: why 2 doses?

- Effectiveness of 2-doses schedule: **98.3%** (USA)

- Significant reduction of breakthrough infections

- Odds of developing varicella : ↓↓ lower if 2 doses versus 1

- ↓↓ virus transmission and risk of late herpes zoster



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

Kuter B *et al*, Pediatr Infect Dis J 2004
Shapiro E *et al*, J Infect Dis 2011

Summary: 1 vs 2 doses of varicella vaccine

One dose

→ **↓ Incidence, hospitalisations and death[1,2]**
BUT
Outbreaks (breakthrough varicella)[3–6]

↓

Two doses in the USA[7]

←

Advantages of two doses

- **Robust anamnestic response[8–10]**
- **Significantly higher efficacy ($p<0.001$)[11]**
- **Reduction in breakthrough cases[12]**

[1]Seward *et al*. 2002; [2]Nguyen *et al*. 2005; [3]LaRussa *et al*. 2000;
[4]Vazquez *et al*. 2005; [5]Galil *et al*. 2002; [6]Tugwell *et al*. 2004;
[7]Marin *et al*. 2007; [8]Ngai *et al*. 1996; [9]Nader *et al*. 1995;
[10]Watson *et al*. 1995; [11]Kuter *et al*. 2004; [12]AAP 2007

Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial

Roman Prymula, Marianne Riise Bergsaker, Susanna Esposito, Leif Gothefors, Sorin Man, Nadezhda Snegova, Mária Štefkovičova, Vytautas Usonis, Jacek Wysocki, Martine Douha, Ventzislav Vassilev, Ouzama Nicholson, Bruce L Innis, Paul Willems

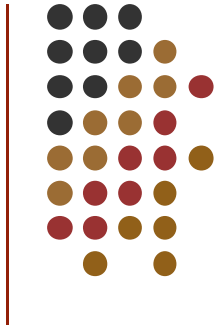
- Study in 10 European countries with endemic varicella.
- Healthy children aged 12–22 months randomised to receive 42 days apart
  (1) two doses of MMRV
  (2) MMR at dose one and monovalent varicella vaccine at dose two
  (3) two doses of MMR.

- Participants and their parents, Observers were blinded

- Primary efficacy endpoint : confirmed varicella cases from 42 days after the second vaccine dose to the end of the first phase of the trial. Efficacy analyses were per protocol

Lancet 2014; 383: 1313–24

RESULTS



- 5803 children (mean age 14·2 months) were vaccinated.
- Mean follow-up : 35-36 months
- Efficacy against all varicella
  - 2 doses MMRV : **94·9%** (97·5% CI 92·4–96·6),
  - 1 dose Varicella vaccine : **65·4%** (57·2–72·1)
- Efficacy against moderate to severe disease
  - 2 doses MMRV : **99·5%** (97·5–99·9).
  - 1 dose Varicella vaccine : **90·7%** (85·9–93·9).

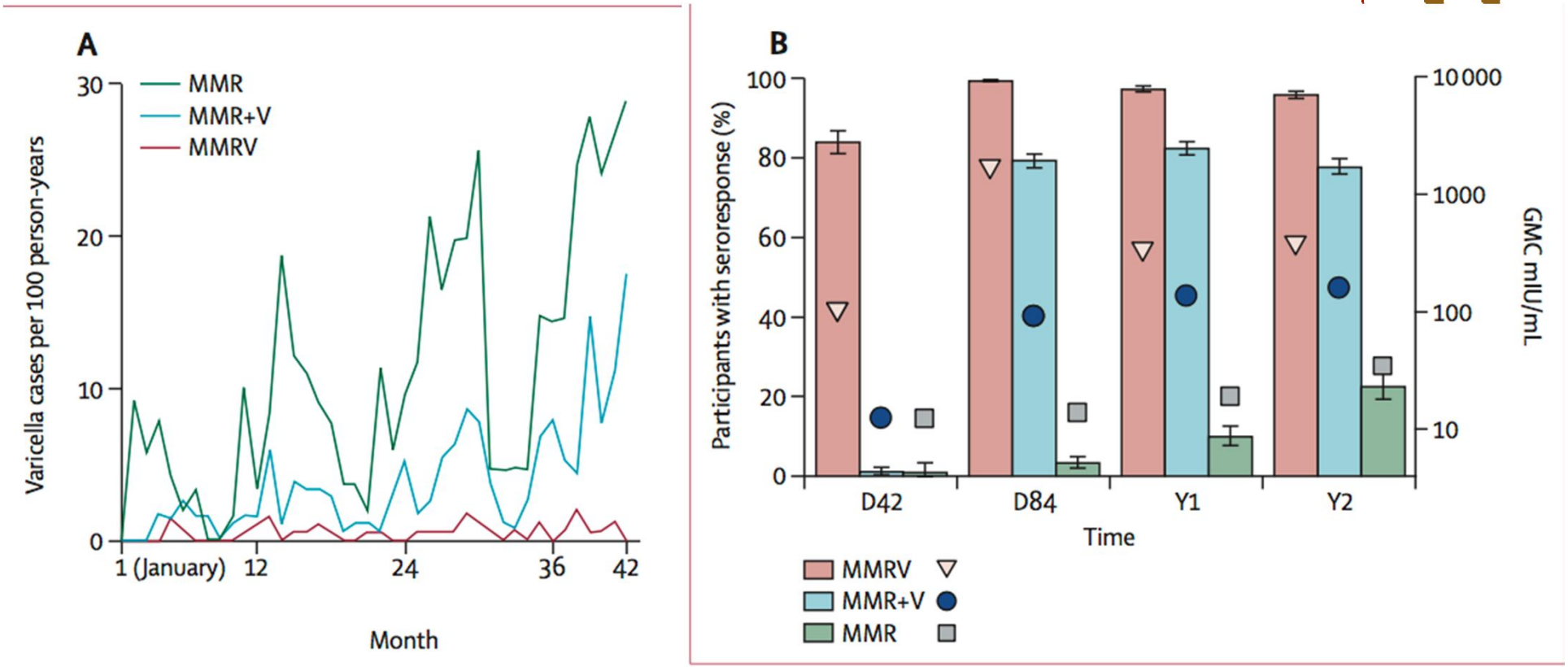
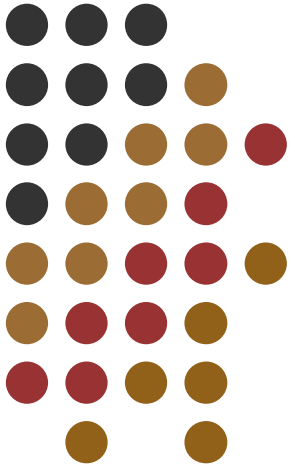


***Figure 4*: Anti-VZV antibody responses to vaccination**

Universal mass vaccination for varicella.

What are the issues?

- MMR Vaccine coverage rate
- Breakthrough infection
- Waning immunity and age shift
- Increase incidence of shingles



Age Shift

TABLE 3 Reported Annual Incidence Rates of Varicella by Age Category and Survey Year, KPNC, 1995–2009

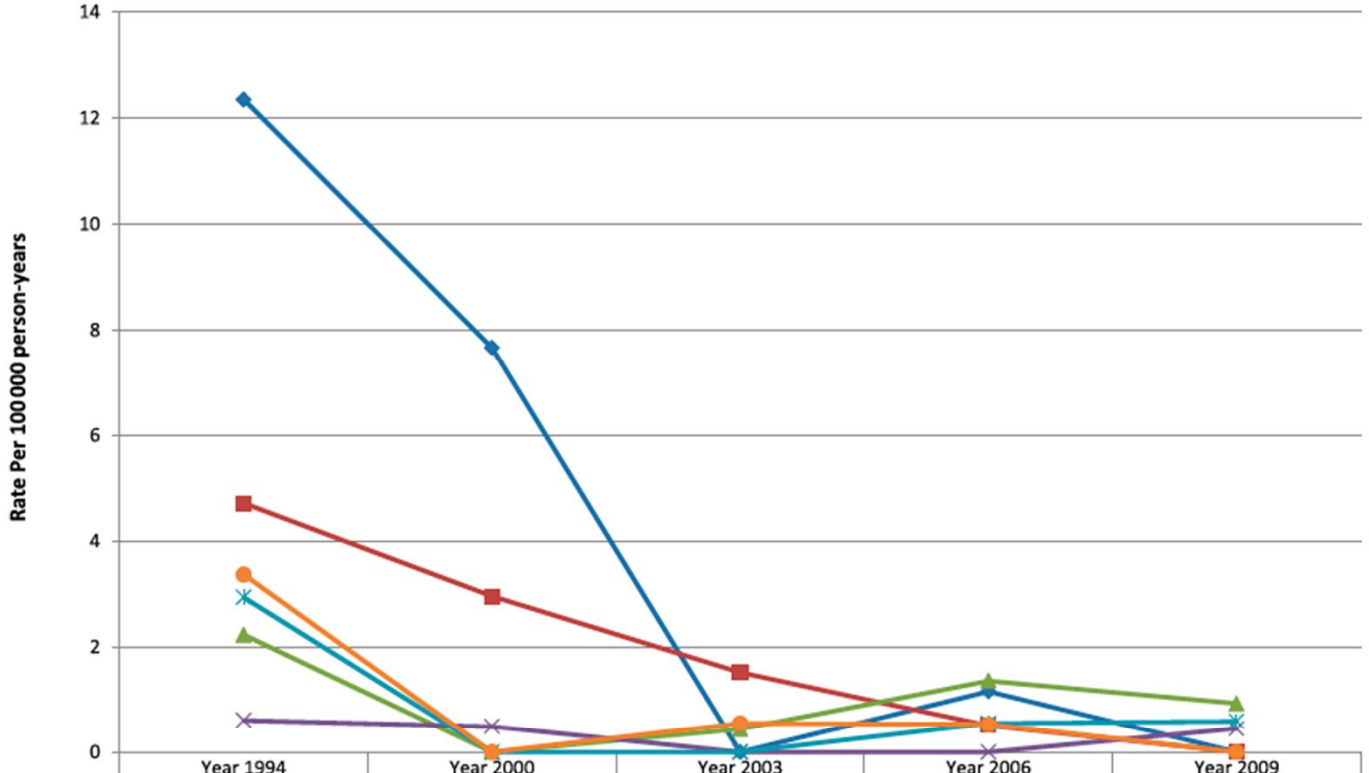
Survey year	5–9 Years of Age			10–14 Years of Age			15–19 Years of Age		
	Cases	Children	Rate[a]	Cases	Children	Rate[a]	Cases	Children	Rate[a]
1995	116	1125	103.1	21	1085	19.4	72	5879	12.3
2000	19	1123	16.9	8	1108	7.2	7	5984	1.2
2003	8	1263	6.3	5	1270	3.9	7	7131	1.0
2006	12	1181	10.2	6	1136	5.3	6	6350	0.9
2009	5	1076	4.6	2	1082	1.8	4	6049	0.7

[a] Rate per 1000 person-years.

In individuals 5 to 19 years of age
Between 1995 and 2009
In all age groups

Incidence of varicella decreased by ~90% to 95% (~10- to 20-fold decrease)

Baxter *et al*, Pediatrics 2015



	Year 1994	Year 2000	Year 2003	Year 2006	Year 2009
0–4	12.35	7.67	0	1.16	0
5–9	4.72	2.96	1.52	0.51	0
10–14	2.23	0	0.44	1.36	0.93
15–19	0.61	0.49	0	0	0.45
20–24	2.94	0	0	0.55	0.59
25–29	3.37	0	0.55	0.53	0
All ages	2.23	0.87	0.46	0.51	0.25

FIGURE 1
Rates of hospitalization with a primary diagnosis for varicella at KPNC, by age group, 1994–2009.

Hospitalization rates with a primary diagnosis of varicella decreased in all age categories, **including in adults**.
Average, **decrease of 13% annually between 1994 and 2009** (incidence rate ratio, 0.87; 95% CI: 0.84–0.90, *p* 0.001)

Baxter *et al*, Pediatrics 2015

Waning immunity

Length of protection is supposed to be 15-20 years…

Baxter *et al*, Pediatrics 2015

Universal mass vaccination for varicella.

What are the issues?

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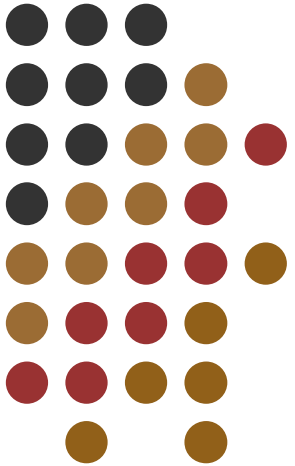
- Waning immunity
- Increase incidence of shingles



Increased risk of herpes zoster?

- Importance of “exogen boosting”

Thomas et al. Lancet 2002

- US surveillance:

Slight increase in incidence before UMV

Donahue JG et al, Arch Intern Med 1995

- No increase since the pre-vaccine era

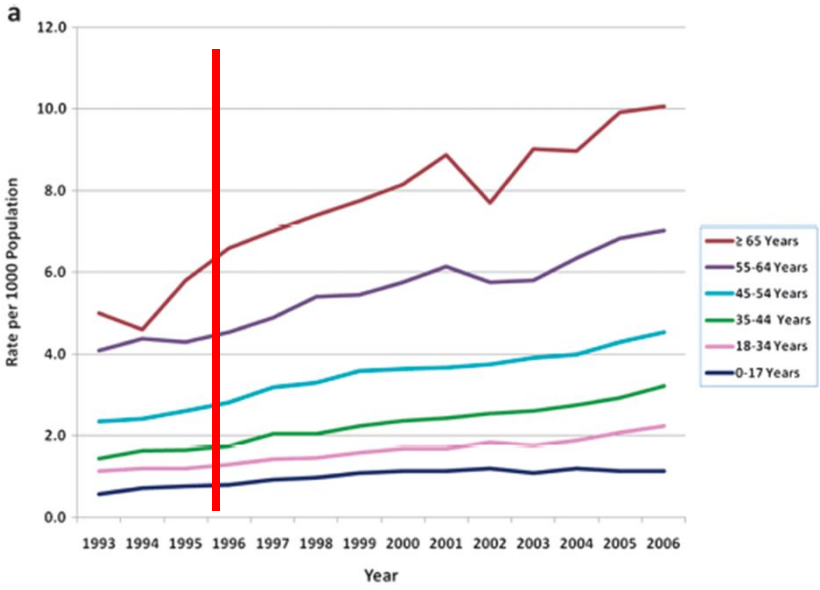
Hambleton S et al, J Infect Dis 2008

US experience : data after 10 years of varicella UMV implementation

ACIP[3]

"Numerous studies and surveillance data have failed to demonstrate systematic increases in the incidence of herpes zoster infection in the USA since the implementation of UMV against varicella in 1995"

- **USA : increase in HZ cases does not appear to be linked to vaccination :**
  - Already present before vaccination
  - High coverage States = Low coverage States
  - Incidence in children from States with high coverage confirms protective effect of vaccination



[2]Donahue *et al*. 1995; [3]Marin *et al*. 2007; [4]Hambleton *et al.* 2008
Leung et al. Clin Infect Dis 2011

Areas covered—This literature review summarizes the effectiveness and epidemiological impact of varicella immunization programs.

Expert commentary—Varicella vaccines are immunogenic with acceptable safety profiles. One and two dose schedules are highly effective against varicella and large reductions in disease incidence, particularly moderate-severe disease, have been widely reported. There is currently no evidence to suggest that the introduction of varicella vaccination results in a shift of varicella disease burden to older age groups. Although epidemiological studies have shown an increased incidence of herpes zoster since the vaccines were launched, there are many other contributing factors, and indeed, this secular trend was evident before their introduction. In conclusion, varicella vaccination easily fits into existing immunization programs and significantly reduces the often underestimated burden of varicella.

Wutzler et al., Expert Rev Vaccines 2017

Conclusion

VZV is a **highly contagious virus** infecting nearly all individuals

Varicella is **generally a mild disease** but with potential serious complications and a **high societal burden**

- individual discomfort
- potentially severe complications
- societal burden for patients, parents and caregivers

Varicella vaccines proved to be **safe** and **effective** in preventing the morbidity and mortality associated with the disease

Where implemented : **impressive reductions** in disease incidence, as well as fewer hospitalizations and deaths

Currently **no evidence of age shift**

Shingles incidence to be followed

Conclusion

Vaccine recommendations currently exist in 33 countries

Varicella vaccine program :

- 2-dose schedule
- (4)-6 weeks minimum between doses
- If not combined with MMR, at least 4 weeks in between
- If varicella disease between doses, no need for boosting

Long-term protection and herd immunity

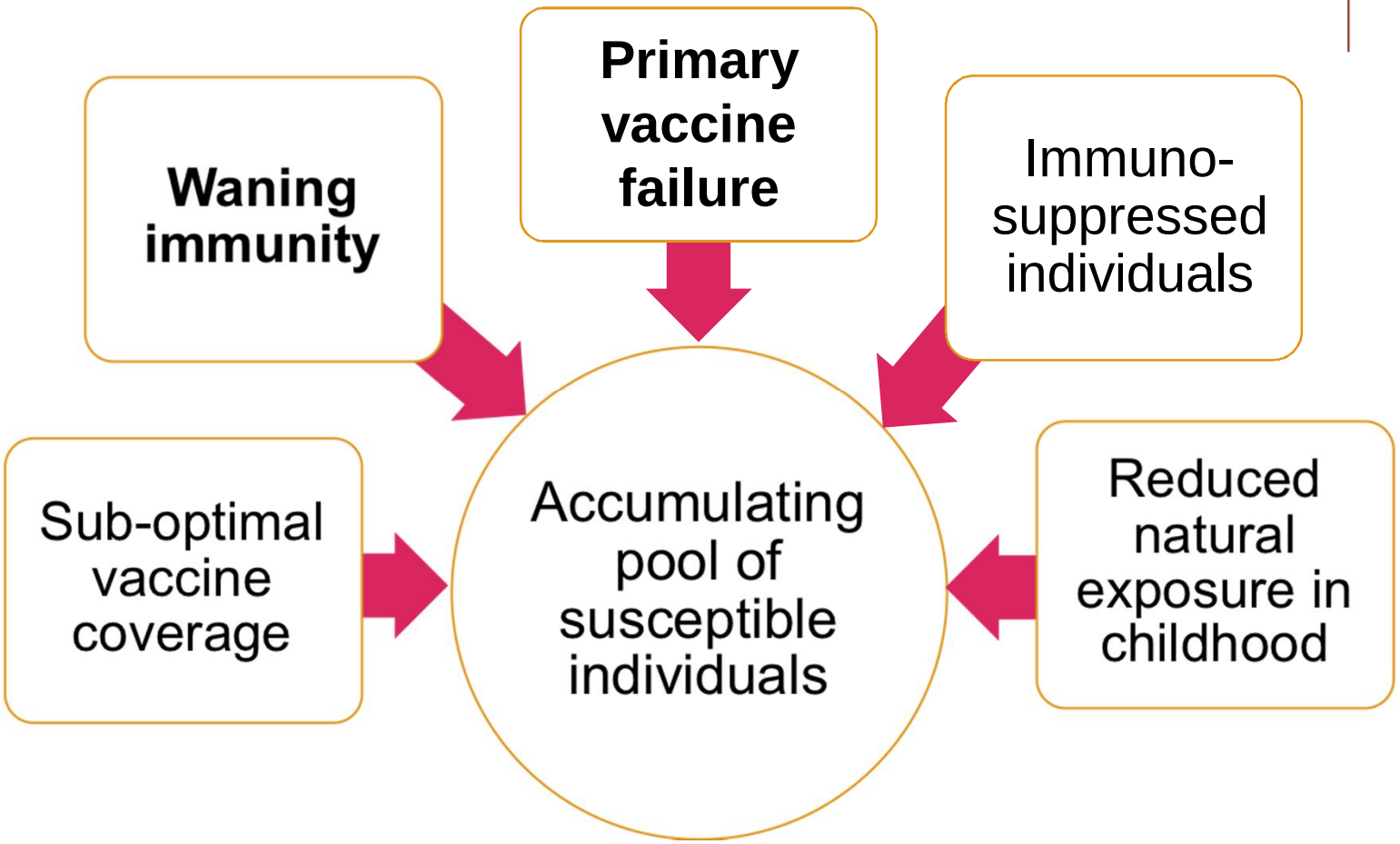
Importance of a high population coverage rate (>80%)

"In case the hypothesis of an essential exogen boosting will not be confirmed, the UMV in Belgium following a 2-dose schedule will be cost- efficient, according to the current fares of vaccine doses." KCE Report 151A 2010

Thank You!

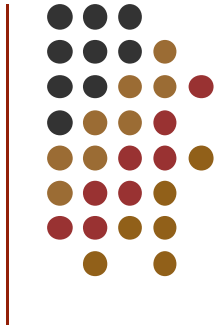
Thank you to Philippe Lepage

Reasons for increase in at risk subjects with a 1-dose schedule:



ACIP 2006 Available from: http://www.cdc.gov/vaccines/recs/acip/downloads/min-jun06.pdf

Current European recommendations for varicella vaccine



- **SIEVE 2008 (Society of Independent European Vaccination experts)**

"the SIEVE recommends such a policy as soon as financially and practically possible"

Sengupta N et al, Eur J Pediatr 2008

- **BMC Medicine 2009, Review article (Experts opinion)**

Bonanni P et al, BMC Medicine 2009

"The clinical burden of varicella in Europe demonstrates a medical need for prevention strategies against the disease"....."Targeted vaccination in susceptible adolescents or high-risk groups is a strategy that does not have the potential to interrupt viral transmission and is far less effective in achieving high coverage rates when compared with childhood programmes"

- **Current statement in Belgium**
  - **Varicella vaccination kept for risk groups**
  - **KCE (report 151A, 2010):**

"In case the hypothesis of an essential exogen boosting will not be confirmed, the UMV in Belgium following a 2-doses schedule will be cost- efficient, according to the current fares of vaccine doses."

In countries providing UMV: cost-efficiency of the vaccine was confirmed

Does Monastic Life Predispose to the Risk of Saint Anthony's Fire (Herpes Zoster)?

Background. The consequences of the epidemiology of varicella for zoster epidemiology are still debated. We therefore compared the frequency of herpes zoster in an adult population with virtually no varicella zoster virus (VZV) exposure with that in the general population (GP).

Methods. We performed a national, multicenter, observational, exposed versus nonexposed, comparative study. The nonexposed population consisted of members of contemplative monastic orders (CMO) of the Roman Catholic Church living in 40 isolated monasteries in France. The exposed population consisted of a sample of the GP representative of the French population in terms of age group, sex, socio-occupational categories, and regions.

Results. The primary analysis population comprised 920 members of CMO (41.5% nuns; mean age, 64.2 years) and 1533 members of the GP (51.9% women; mean age, 64.6 years). The reported frequency of zoster was 16.2% among CMO and 15.1% in the GP ($P = .27$, adjusted for sex and age). The reported mean age of onset of zoster was 54.8 and 48.6 years, respectively ($P = .06$).

Conclusions. This study failed to demonstrate an increased risk or earlier onset of zoster in members of CMO not exposed to VZV, compared with that in the GP. Although adults highly exposed to VZV could have a reduced risk of zoster, compared with the GP, our results suggest that the opposite is not true: adults not exposed to VZV are not at increased risk of zoster when compared with the GP, challenging the relevance of the assumptions and forecasts of current epidemiological models.

- Gaillat *et al*. Clin Infect Dis 2011

Interval between 2 doses of varicella vaccine (or MMR-V) depends of local recommendations for MMR administration...

- **Accelerated interval :** D1 (11-23 mo) et D2 (12-24 mo): example Luxemburg, Germany
- **Standard interval :** D1 (12-24 mo) et D2 (3-7 yrs): example USA
- **Long interval :** D1 (12-18 mo) et D2 (8-13 yrs): example Belgium

- **Priorix Tetra and Varilrix advertisement : minimum interval = 6 weeks**

N	82	83	
Age (mo), Median (interquartile range)	49.0 (22.7–74.0)	52.0 (27.0–84.0)	.95
Gender			
Female, N (%)	42 (51.2)	28 (33.7)	.03
Male, N (%)	40 (48.8)	55 (66.3)	
Varicella-related IGASI, N (%)	24 (29.3)	7 (8.8)	.001
Underlying chronic disease, N (%)	7 (8.5)	9 (11)	.34
Clinical features of IGASI, N (%)			
SSTI	41 (50.0)	15 (18.1)	<.001
NF	24 (29.3)	3 (3.6)	<.001
SSTI other than NF	17 (20.7)	12 (14.5)	.31
IGASI other than SSTI	41 (50.0)	68 (81.9)	<.001
Pleuropulmonary	15 (18.3)	24 (28.9)	.14
Osteoarticular	14 (17.1)	21 (25.3)	.25
Streptococcal toxic shock syndrome	9 (11)	3 (3.7)	<.001
Death, N (%)	3 (3.7)	4 (4.8)	1
*Emm*1 genotype,[a] N (%)	13 (26.0)	28 (38.4)	1.18
Virulence factor genes,[a] N (%)			
speA	18 (32.7)	34 (46.6)	.15
speC	21 (38.2)	32 (43.8)	.59
ssa	11 (20)	45 (61.6)	<.001
smeZ	55 (43.3%)	72 (56.7%)	.002

Abbreviations: IGASI, invasive group A streptococcal infection; NF, necrotizing fasciitis; SSTI, skin and soft tissue infection; VV, varicella vaccine.

[a] *Emm*1 genotype and presence of virulence factor genes were screened in 140 and 128 Group A Streptococcal strains, respectively.

Frère et al. 2015