

Vacunación frente a la varicela, Versión 2.0

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IX
Jornadas de
Actualización
en Vacunas

Vacunas para una Salud Global
"Vaccines for a Global Health"

1-2 octubre 2012
Salón de Actos Casa de las Mariposas
Puerta Purchena s/n. Almería



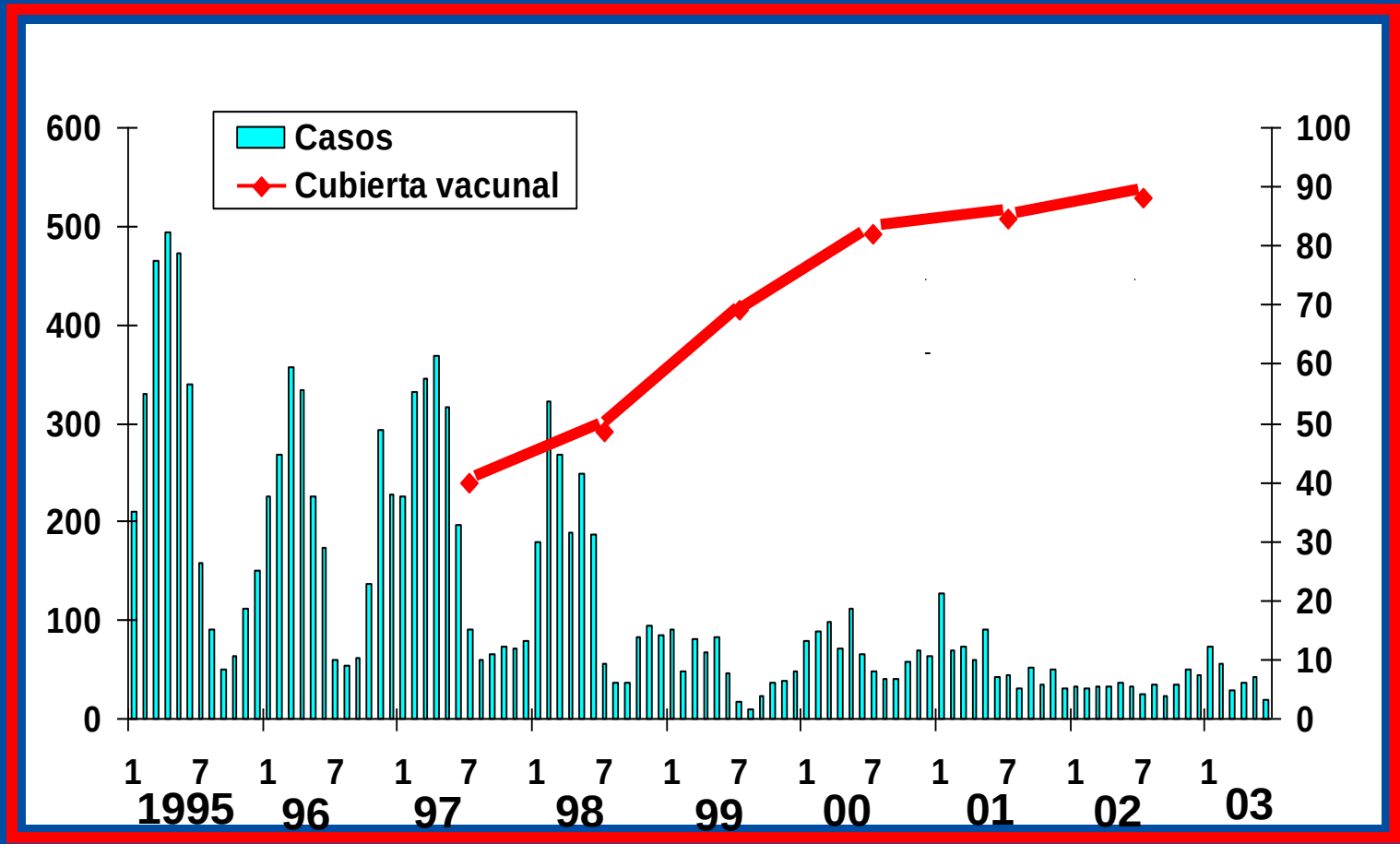
Niño de 4 años con erupción papular, que se tornó vesicular y luego formó costras... eventualmente sanó a los 7 días



Casos de Varicela y Tasa de Vacunación California 1995 – 2003

Vemos una disminución de 90% encasos de varicela 1995 a 2003

Seward J et al JAMA 2002



VARICELA

Hospitalizaciones y Coste

Hospitalización 94-'02:

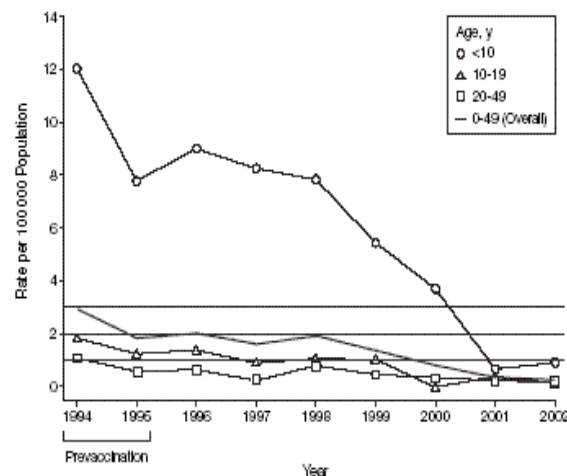
- Disminución 88%
- < 10 yrs 91%
- 10-19 yrs 92%
- 20-49 yrs 78%

Coste de salud asociados a varicela:

- Coste médico en hospitalización y visitas ambulatorias disminuyó un 74%

- 1994-1995 \$85 million
- 2002 \$22 million

Figure 1. Varicella-Related Hospitalization Rates, 1994-2002



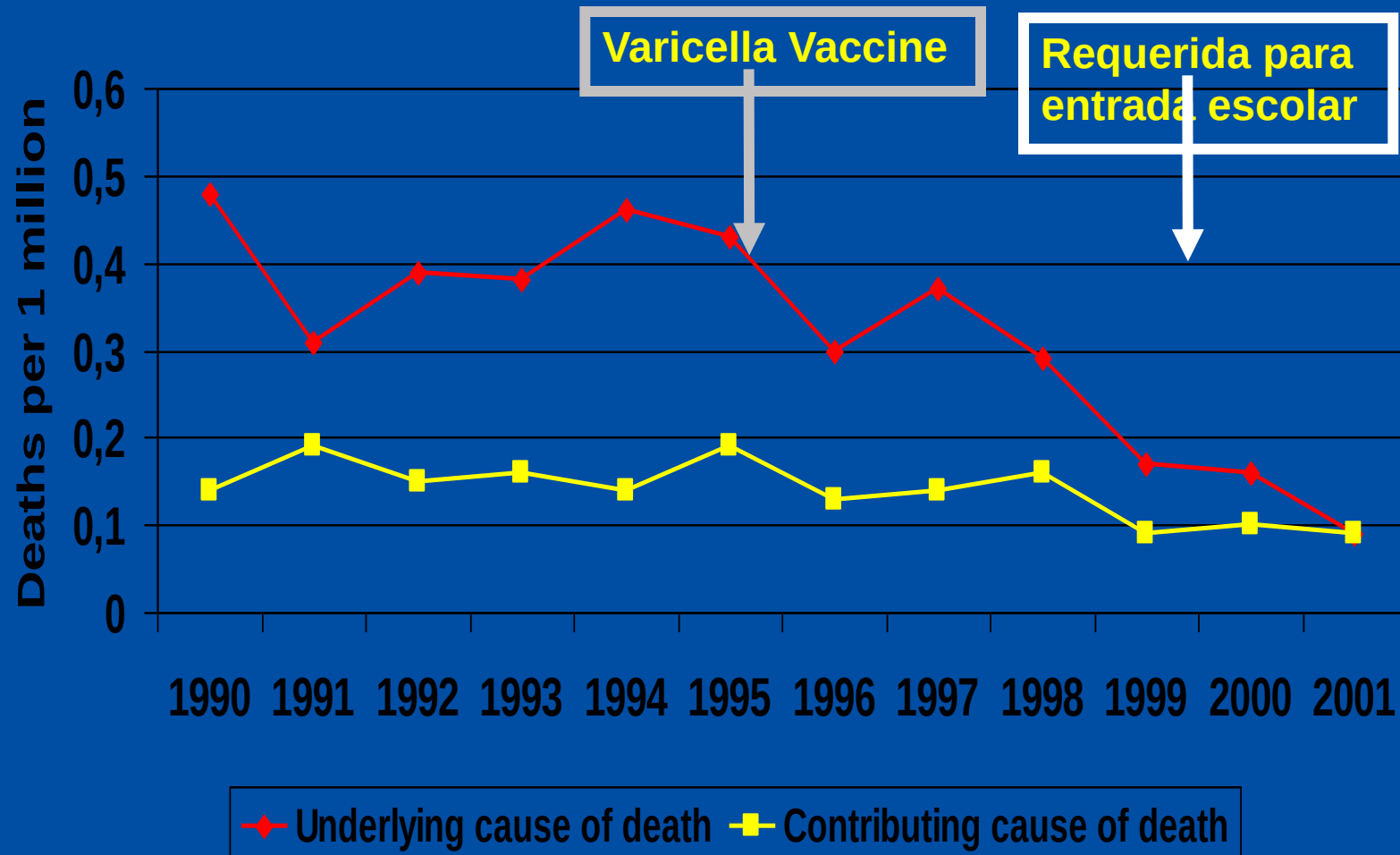
Varicella was the primary diagnosis code for data shown.

Zhou et al, JAMA, 2005



Mortalidad por Varicela en E.U. (90-'01)

Ngyugen H, Jumaan AO, Seward JF, NEJM 2005; 352:450-458



Y entonces llegó “varicela en el individuo previamente vacunado” (*Breakthrough disease*)...

¿Disminución en
concentración de
anticuerpos?
o
¿Fallo vacunal?



Varicela Postvacunal

**Brotes de varicela en grupos vacunados (70-80%)
aumentaron preocupación a cerca de efectividad de
la vacuna**

Study	Vaccine Effectiveness		Study method Setting/Design
	All disease	Mod/severe disease	
Outbreaks N=17	71%-100%	95-100%	Child care centers, schools
Galil, NEJM, 2002	44% (-6, 67%)	86%	Child care center
MD, 2001	59% (-1, 84%)	75%	School

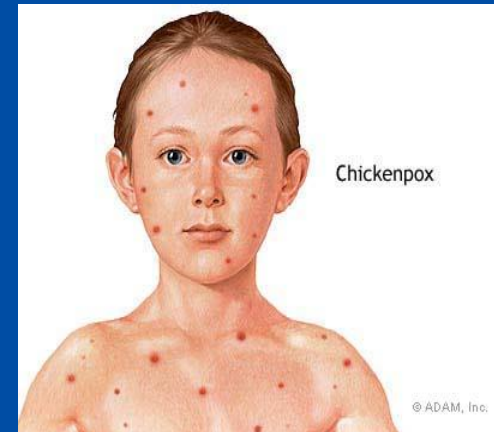


Cambios en manifestación clínica de la Varicela

“Varicela Postvacunal”



La Efectividad de la Vacuna de Varicella



VACUNA VARICELA

Objetivo

- **Evaluar la efectividad, o la eficacia en la práctica diaria, de la vacuna de varicela**
- **Evaluar los efectos de:**
 - **El paso del tiempo después de recibir la vacuna**
 - **La edad del paciente a la hora de la vacunación**



ESTUDIO CASO – CONTROL

Métodos

- Edad 13 meses a 18 años
- Sin historial previo de varicela
- Vigilancia en 30 prácticas pediátricas en CT
- Visitas al día 3-5 de la enfermedad
- Evaluación de severidad de varicela
- 2 controles por caso pareados:
 - prácticas pediátricas
 - edad (+/- 1 mes)
- Muestra de la erupción VZV- PCR





THE EFFECTIVENESS OF THE VARICELLA VACCINE IN CLINICAL PRACTICE

THE EFFECTIVENESS OF THE VARICELLA VACCINE IN CLINICAL PRACTICE

MARIETTA VÁZQUEZ, M.D., PHILLIP S. LARUSSA, M.D., ANNE A. GERSHON, M.D., SHARON P. STEINBERG,
KIMBERLY FREUDIGMAN, PH.D., AND EUGENE D. SHAPIRO, M.D.

TABLE 5. EFFECTIVENESS OF THE VACCINE.

CHILD WITH CHICKENPOX	NO. WITH NO VACCINATED CONTROLS*	NO. WITH 1 VACCINATED CONTROL†	NO. WITH 2 VACCINATED CONTROLS	MATCHED ODDS RATIO (95% CI)‡
Vaccinated	5	19	22	0.15 (0.10–0.22)§
Not vaccinated	40	57	59	

*One of the 5 vaccinated children with chickenpox with no vaccinated controls had only 1 matched control, as did 4 of the 40 unvaccinated children with chickenpox with no vaccinated controls.

†Three of the 19 vaccinated children with chickenpox with 1 vaccinated control had only 1 matched control, as did 7 of the 57 unvaccinated children with chickenpox with 1 vaccinated control.

‡CI denotes confidence interval. The odds ratio represents the odds of having received the vaccine among children with chickenpox as compared with controls.

§The vaccine's effectiveness was 85 percent (95 percent confidence interval, 78 to 90 percent; $P < 0.001$); after adjustment with conditional logistic regression for the effects of differences in sex, race, and attendance at group day care, the effectiveness was 87 percent (95 percent confidence interval, 78 to 92 percent; $P < 0.001$).

VE= 85%





The NEW ENGLAND JOURNAL of MEDICINE

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Efectividad 95% CI

Enfermedad leve 81% (68%-89%)

Moderada &
Severa 98% (93%-99%)

Vázquez M, et al NEJM 2001; 344:955-960

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Effectiveness Over Time of Varicella Vaccine

Marietta Vázquez, MD

Philip S. LaRussa, MD

Anne A. Gershon, MD

Linda M. Niccolai, PhD

Catherine E. Muehlenbein, MPH

Sharon P. Steinberg

Eugene D. Shapiro, MD

Table 2. Overall Effectiveness of Varicella Vaccine*

No. of Vaccinated Matched Controls per Case	Cases, No.	Matched Controls, No.	
		Vaccinated	Unvaccinated
Vaccinated Cases			
0	6	0	11
1	27	27	25
2	89	178	0
Unvaccinated Cases			
0	50	0	97
1	69	69	66
2	98	196	0

*Matched odds ratio = 0.13 (95% confidence interval, 0.09-0.20). Unadjusted vaccine effectiveness = 87% (95% confidence interval, 80%-91%), $P < .001$.

JAMA. 2004;291(7):851-855.



Effectiveness Over Time of Varicella Vaccine

Marietta Vázquez, MD

Philip S. LaRussa, MD

Context Reports of outbreaks of varicella in highly immunized groups have in-
Table 3. Effectiveness of the Varicella Vaccine by Time Since Vaccination*

Years Since Vaccination	No. Vaccinated		Effectiveness, % (95% CI)	P Value
	Cases	Controls		
1†	4	84	97 (91-99)	<.001
2	22	108	86 (76-92)	<.001
3	26	92	83 (69-90)	<.001
4	24	68	81 (62-90)	<.001
5	24	65	84 (67-93)	<.001
6	13	33	82 (54-93)	<.001
7-8	9	20	81 (40-94)	.005
2-8†	118	386	84 (76-89)	<.001

Abbreviation: CI, confidence interval.

*Results are adjusted for sex, race, attendance at group day care, asthma, use of steroids, and receipt of varicella vaccine within 28 days after receiving the measles-mumps-rubella vaccine. The *P* values in the table refer to whether the adjusted estimates of the vaccine's effectiveness are statistically significantly different than 0%.

†Difference in overall effectiveness in year 1 vs years 2 to 8 (97% vs 84%; *P* = .003).





Effectiveness Over Time of Varicella Vaccine

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Table 4. Effectiveness of the Varicella Vaccine by Time Since Vaccination and Age at the Time of Vaccination*

Effectiveness	Age at Time of Vaccination, mo			P Value, <15 vs ≥15 mo
	≥12	<15	≥15	
Year 1, % (95% CI)	97 (91 to 99)	73 (–43 to 95)	99 (93 to 100)	.01
P value†	<.001	.12	<.001	
Years 2-8, % (95% CI)	84 (76 to 89)	81 (62 to 90)	85 (77 to 90)	.47
P value†	<.001	<.001	<.001	
P value, year 1 vs years 2-8	.003	.71	.007	
Overall, % (95% CI)	87 (81 to 91)	81 (64 to 90)	88 (82 to 92)	.17
P value†	<.001	<.001	<.001	

Abbreviation: CI, confidence interval.

*Results are adjusted for sex, race, attendance at group day care, asthma, use of steroids, and receipt of varicella vaccine within 28 days after receiving the measles-mumps-rubella vaccine.

†The P values refer to whether the adjusted estimates of the vaccine's effectiveness are statistically significantly different than 0%.





ORIGINAL ARTICLE

Loss of Vaccine-Induced Immunity to Varicella over Time

Sandra S. Chaves, M.D., M.Sc., Paul Gargiullo, Ph.D., John X. Zhang, Ph.D., Rachel Civen, M.D., Dalya Guris, M.D., M.P.H., Laurene Mascola, M.D., M.P.H., and Jane F. Seward, M.B., B.S., M.P.H.

- 1995-2004, 10 años de data
- 9% de vacunados desarrolló varicela
- Enfermedad en vacunados más común ≥ 5 años después vacunación
- Tasa de enfermedad aumenta:
 - 1 año (1.6 casos/1,000 personas años)
 - 5 años (9.0 casos/1,000 personas años)
 - 10 años (58.2 casos/1,000 personas años)

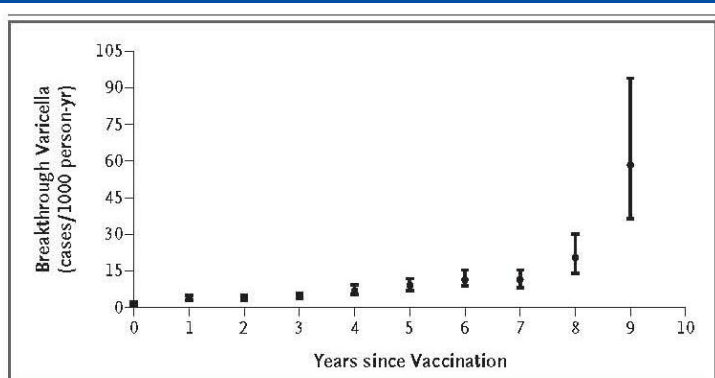


Figure 3. Adjusted Rates of Breakthrough Varicella among Children Vaccinated between the Ages of 12 Months and 12 Years, According to the Year after Vaccination.

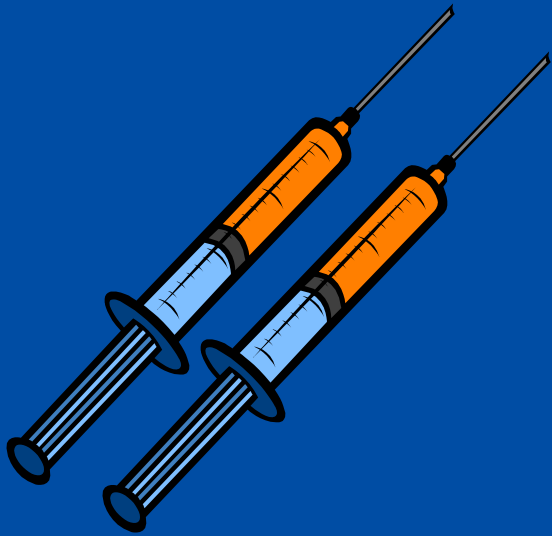
Rates of disease were adjusted for the age at disease onset and the calendar year with the use of a Poisson regression model. All 95% confidence intervals, which are indicated by I bars, were calculated with the use of the Wald chi-square test.



VACUNA DE VARICELA *ITINERARIO desde e l 2006*

- Régimen:
 - 1 dosis < 13 yrs
 - 2 dosis $\geq$ 13 yrs
(4-8 semanas)
- Régimen NUEVO:
2 dosis para
TODOS

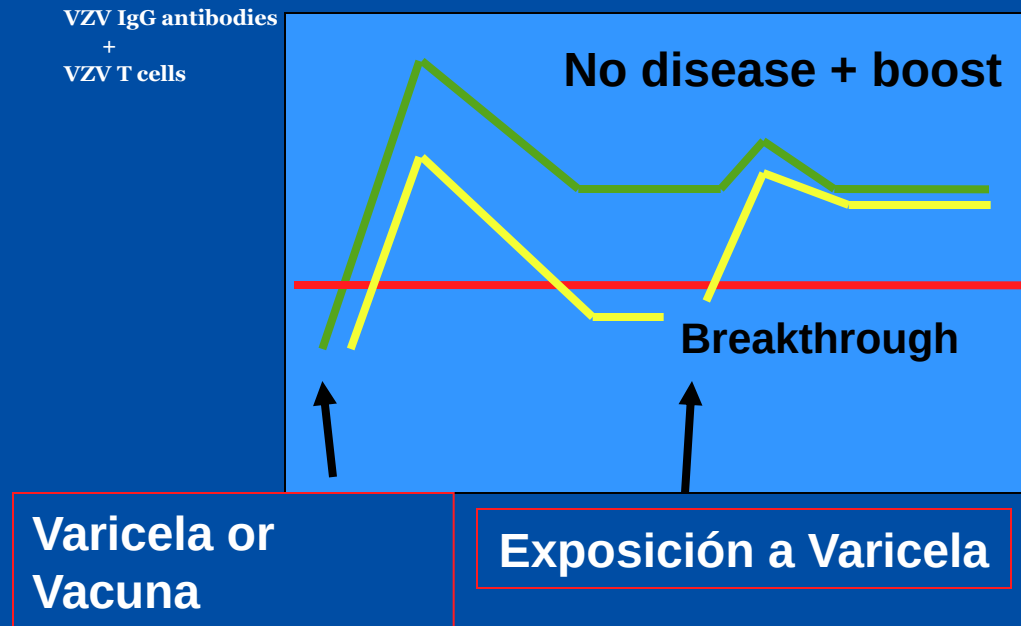




¿Dos o sólo una?



Dos Dosis de Vacuna de Varicela Daría Impulso (immunologic Boost)



- Concepto inmunológico:
 - Importancia de un “boost” o impulso inicial de la respuesta para establecer inmunidad a largo plazo contra el virus



Ten year follow-up of healthy children who received one or two injections of varicella vaccine

BARBARA KUTER, PHD, HOLLY MATTHEWS, MS, HENRY SHINEFIELD, MD, STEVE BLACK, MD, PENELOPE DENNEHY, MD, BARBARA WATSON, MD,* KEITH REISINGER, MD, LEE LIAN KIM, PHD, LISA LUPINACCI, PHD, JONATHAN HARTZEL, PHD, IVAN CHAN, PHD AND THE STUDY GROUP FOR VARIVAX

TABLE 2. Clinical characteristics of varicella cases occurring >42 days postvaccination during 10 years of follow-up*

Variable	1-Dose Regimen	2-Dose Regimen (0 and 3 mo)
No. of varicella cases	60	17
Median days duration of rash (range)	4 (1–18)	5 (1–14)
Median of the daily maximum number of lesions (range)	26 (2–272)	20 (2–100)
% with >50 lesions (no./total)	22.8 (13/57)	18.8 (3/16)
% with 1 or more vesicles (no./total)	77.2 (44/57)	68.8 (11/16)
Median of the daily maximum no. of vesicles (range)	13 (1–272)	5 (1–80)
% with temperature $\geq 102^{\circ}\text{F}$, oral equivalent†	2.4 (1/42)	0 (1/12)

* Rash and temperature information available on the number of subjects shown.

† Excludes subjects with temperatures reported as abnormal (2 subjects in each group) without numerical temperature values.

- Casos (1,2 dosis) en su mayoría leves
- Riesgo de varicella 3.3 veces menor en aquellos que reciben 2 dosis
- VE 1 dosis 94.4%
- VE 2 dosis 98.3%
- Anticuerpos persistían 9 años



Safety of a second dose of varicella vaccine administered at 4 to 6 years of age in healthy children in Argentina

Diego Fridman,¹ Andrea Monti,¹ Marie-Claude Bonnet,^{2,*} Judith Armoni³ and Daniel Stambouliau¹

¹Centros de Estudios Infectológicos; Buenos Aires, Argentina; ²sanofi pasteur; Lyon, France; ³sanofi pasteur; Buenos Aires, Argentina

Seguridad



MAJOR ARTICLE

Effectiveness of 2 Doses of Varicella Vaccine in Children

Eugene D. Shapiro,^{1,3,4} Marietta Vazquez,¹ Daina Esposito,¹ Nancy Holabird,¹ Sharon P. Steinberg,⁵ James Dziura,^{1,2} Philip S. LaRussa,⁵ and Anne A. Gershon⁵

¹Department of Pediatrics; ²Department of Medicine; ³Department of Epidemiology; ⁴Department of Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, Connecticut; and ⁵Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York

Control de Varicela, Versión 2.0

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Effectiveness of 2 Doses of Varicella Vaccine in Children

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¹Department of Pediatrics; ²Department of Medicine; ³Department of Epidemiology; ⁴Department of Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, Connecticut; and ⁵Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York

Table 1. Characteristics of the Subjects

	Case Subjects n = 71 (%)	Controls n = 140 (%)	P value
Age, years			.905
Mean $\pm$ SD	10.7 $\pm$ 2.7	10.7 $\pm$ 2.7	
Median	11	11	
Range	4–18	4–18	
Male sex	40 (56.3)	77 (55.0)	.853
Caucasian race	62 (87.3)	126 (90.0)	.556
Parent education			.185
High school or less	22 (31.9)	48 (34.3)	
Some college	18 (25.4)	21 (15.0)	
College/postgraduate degree	31 (43.7)	71 (50.7)	
Weekday location			.015
Home	3 (4.2)	22 (15.7)	
School or day-care	68 (95.8)	118 (84.3)	
Diagnosis of asthma	4 (5.6)	17 (12.1)	.136





Effectiveness of 2 Doses of Varicella Vaccine in Children

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¹Department of Pediatrics; ²Department of Medicine; ³Department of Epidemiology; ⁴Department of Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, Connecticut; and ⁵Department of Pediatrics, Columbia University College of

Table 2. Vaccination Status of Subjects

	Case Subjects n = 71 (%)	Controls n = 140 (%)	P value
Varicella vaccine			<.001
0 doses	5 (7.0)	1 (0.7)	
1 dose	66 (93.0)	117 (83.6)	
2 doses	0 (0.0)	22 (15.7)	
Months since dose 1			.151
Mean ± SD	103.2 ± 24.1	97.4 ± 28.2	
Median	106	101	
Range	35–139	17–161	
Months since dose 2			N/A
Mean ± SD	–	14.8 ± 13.3	
Median	–	12	
Range	–	0–50	
Received MMR ^a >1 dose	71 (100.0)	139 (99.3)	1.000
Received MMR 2 doses	70 (98.6)	137 (97.9)	1.000

NOTE. ^a MMR, Measles, mumps, and rubella vaccine; N/A, not applicable.



Table 3. Receipt of Varicella Vaccine by Dose and Matched Groups

Doses Received by Case Subject	Doses Received by Matched Control Subjects					
	Neither Control Received Vaccine	One Control Received 1 Dose	One Control Received 2 Doses ^a	Both Controls Received 1 Dose	One Control Received 1 Dose, One 2 Doses	Both Controls Received 2 Doses
0	0	0	1	3	1	0
1	0	1	1	48	13	3
2	0	0	0	0	0	0

NOTE. Matched odds ratio, 1 dose vs 0 dose of vaccine: 0.14 (95% CI: 0.003–1.445; $P = .124$)

Matched odds ratio, 2 doses vs 0 dose of vaccine: 0.017 (95% CI: 0–0.165) $P < .001$

Matched odds ratio, 2 doses vs 1 dose of vaccine: 0.053 (95% CI: 0.002–0.320; $P < .001$)

^a Both cases in this category had only one control.

- 0 dosis vs. 1 dosis VE 86%
- 2 dosis vs. 2 dosis VE 99%
- 1 dosis vs. 2 dosis VE 94.7%

• La probabilidad de desarrollar varicella es 94.7% más baja en aquéllos que recibieron 2 dosis comparados con 1 dosis de varicela.

Varicella: Efficacy of Two-Dose Vaccination in Childhood

Peter Wutzler, Markus Knuf, Johannes Liese

BOX

A two-dose vaccination schedule improves protection against varicella*¹

- All children aged 11 to 23 months receive two doses of varicella vaccine:
a first dose usually at the age of 11 to 14 months,
a second dose usually at the age of 15 to 23 months.
The interval between the two doses should be no less than 4 to 6 weeks.
- Supplementation of vaccination with a second dose for all persons who have not yet reached their 18th birthday, who have not had varicella, and who have received only a single dose of vaccine to date (or none at all). If possible, this should be performed before the child begins school or group child care. The interval between the two doses should be no less than 4 to 6 weeks.
- Post-exposure vaccination of all susceptible persons*² in varicella outbreaks.

*¹ Recommendations of an expert group (2).

*² Persons considered susceptible are those who were not vaccinated, or were vaccinated only once, and have no history of varicella (either clinically evident or laboratory-documented).

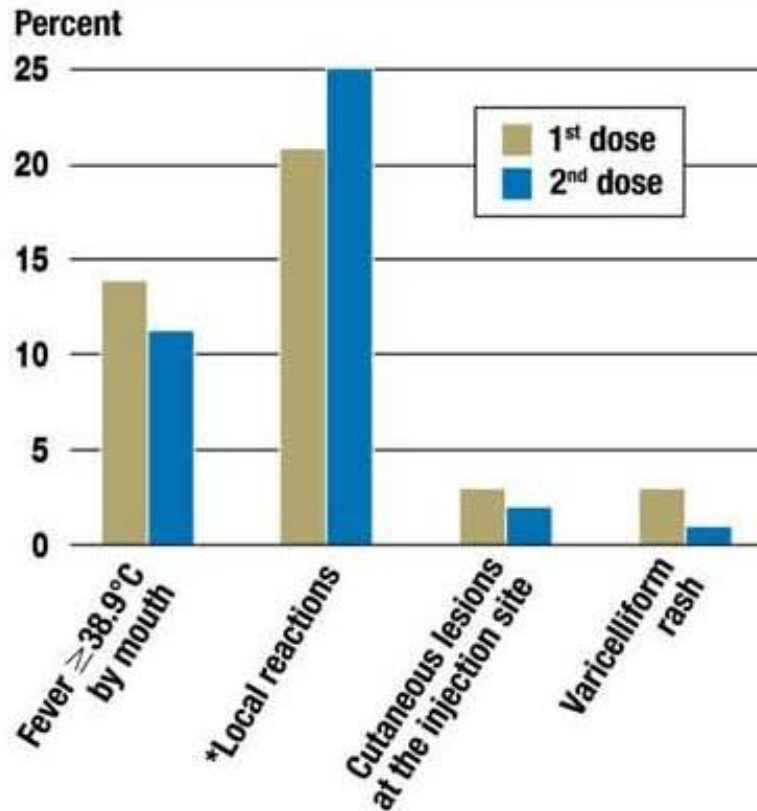


Varicella: Efficacy of Two-Dose Vaccination in Childhood

Peter Wutzler, Markus Knuf, Johannes Liese

The frequency of vaccination reactions in healthy children aged 12 months to 12 years (mean age 4.4 years) after the administration of the first and second doses of a mono-valent varicella vaccine. Period of observation, 42 days. * Redness, swelling, pain on days 0–3 (from [21]).

FIGURE 2



Conclusiones

- ❖ Existe controversia a cerca de la razón por la cual sólo 1 dosis de vacuna puede ser subóptima—fallo vacunal? versus merma de anticuerpos? Ambas?
- ❖ Cualquiera que sea la causa, nuestra data indica que 2 dosis son altamente efectivas en prevenir varicela; ninguno de los 71 casos confirmados (PCR) han sido en niños luego de haber recibido 2 dosis.
- ❖ A 3 años después de la recomendación universal de 2 dosis en los EU, la probabilidad de desarrollar varicella es 94.7% más baja en aquéllos que recibieron 2 dosis comparados con 1 dosis de varicela.
- ❖ **Una segunda dosis de vacuna de varicela es importante no sólo para prevenir la varicela postvacunal y la transmisión del virus, sino para potencialmente disminuir el riesgo de desarrollar herpes zoster-- al disminuir probabilidad de desarrollar infección latente (latent infection) con la cepa tipo salvaje de VZV.**



Herpes Zoster in Children in the Era of Varicella Vaccine

Marietta Vázquez, MD¹, Anne A. Gershon, MD², Alexandra P. Grizas, MPH¹, Phil LaRussa, MD², Nancy Holabird¹, Sharon P. Steinberg² and Eugene D. Shapiro, MD¹

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²Columbia University, College of Physicians and Surgeons School of Medicine, New York, NY.



Objective

- To characterize features of Herpes Zoster in children due to wild-type (WT) and vaccine-type (OKA) varicella-zoster virus (VZV).

Results

- 32 potential cases of Herpes Zoster were identified from 2004-2011:
 - 22 (69%) were positive for VZV
 - 6 (19%) were negative for VZV
 - 4 (12%) had an inadequate sample
- Of the 22 VZV positive cases
 - 8 (36%) were Wild Type VZV
 - 14 (64%) were OKA strain (vaccine strain) VZV.

Results

Table 1. Characteristics of Subjects by Varicella Zoster Virus Type

	Zoster Virus Type		P-value
	Wild 8 (36%)	OKA 14 (64%)	
Age at FT (years)*			0.024
> 7	7 (88%)	5 (36%)	
≤ 7	1 (12%)	9 (64%)	
Mean Age (years)*	10.6 ± 3.7	6.3 ± 2.5	0.004
Median Age (years)*	11.5	6.1	0.013
Gender			0.787
Female	3 (38%)	5 (36%)	
Male	5 (63%)	9 (64%)	
Race/Ethnicity [†]			0.257
Other	0 (0%)	3 (21%)	
White	8 (100%)	11 (79%)	

* Statistically significant at the $\alpha = 0.05$ level for chi-square test for categorical variables and t-test or Wilcoxon Rank Sum test for continuous variables.

[†] Other includes Black race and subjects reporting Other race.

Results

Table 2. Characteristics of Subjects by Zoster Virus Type

	Zoster Virus Type		P-value
	Wild 8 (36%)	OKA 14 (64%)	
# Dermatomes			0.354
≥2	1 (14%)	5 (36%)	
1	6 (86%)	9 (64%)	
Side of Body Affected			0.605
Right	1 (17%)	5 (36%)	
Left	6 (83%)	9 (64%)	
Zoster on Vaccination Side			0.571
Yes	2 (100%)	6 (86%)	
No	0 (0%)	1 (14%)	
Antiviral Therapy			0.673
Yes	4 (50%)	6 (43%)	
No	4 (50%)	8 (57%)	

Results

Table 3. Characteristics of Subjects by Zoster Virus Type

	Zoster Virus Type^a		P-value
	Wild 8 (36%)	OKA 14 (64%)	
Varicella Vaccination*			0.003
Yes	3 (37%)	14 (100%)	
No	5 (63%)	0 (0%)	
# Doses			0.620
2	0 (0%)	2 (14%)	
1	3 (100%)	12 (86%)	
Mean Age at Vax (yrs)	1.1 ± 0.1	1.4 ± 1.1	0.674
Mean Time from Vax to FT (years)	6.0 ± 3.8	4.7 ± 2.6	0.473
History of Varicella disease*			0.003
Yes	5 (63%)	0 (0%)	
No	3 (37%)	14 (100%)	

^a Column values may not sum to 100% due to or missing data.

* Statistically significant at the $\alpha = 0.05$ level for chi-square test for categorical variables and t-test or Wilcoxon Rank Sum test for continuous variables.

Table 4: Severity of Disease by Zoster Virus Type

	OKA strain (n=13)	Wild Type (n=8)	<i>Total</i>
Mild	6 (46%)	2 (25%)	8
Moderate	6 (46%) (92%)	5 (63%) (88%)	11
Severe	1 (8%)	1 (12%)	2
	13	8	21

Herpes Zoster



Oka virus



Herpes Zoster



Wild type virus

Herpes Zoster



Oka virus

Herpes Zoster



Wild type virus

Herpes Zoster



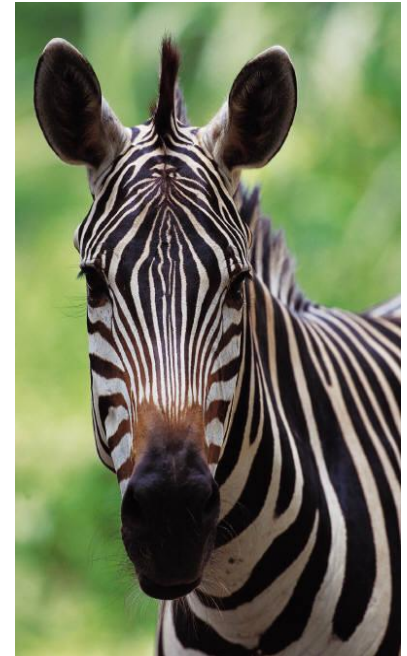
Oka virus

Conclusiones

- **En la edad pediátrica, la presentación de herpes zoster tipo vacunal (OKA) es similar a la de herpes zoster causado por wild-type.**
- **El riesgo de herpes zoster después de vacunación es menor que después de varicela**
- **Pacientes vacunados pueden desarrollar herpes zoster wild type sin haber tenido un historial de varicela.**

VARICELA

Fue de ser el pan nuestro de cada día a zebra



Gracias

