The Elimination of Congenital Rubella Syndrome

Stanley A. Plotkin

Current Manufacturers of Rubella Vaccines

Manufacturer	Virus Strain	Cell Substrate
Merck (United States)	RA27/3	HDCS
Glaxo SmithKline-RIT (Belgium)	RA27/3	HDCS
Crucell (Switzerland)	RA27/3	HDCS
Sanofi Pasteur (France)	RA27/3	HDCS
Novartis (Italy)	RA27/3	HDCS
Institute of Immunology (Yugoslavia)	RA27/3	HDCS
Serum Institute of India	RA27/3	HDCS
Kitasato Institute (Japan)	Takahashi	Rabbit kidney
Biken (Japan)	Matsuura	Quail embryo fibroblast
Takeda Chemical Industries (Japan)	TO-336	Rabbit kidney
	BRD-2 (China)	HDCS

HDCS, human diploid cell strain.

Modified from Perkins FT. Licensed vaccines. Rev Infect Dis 7:S73–S76, 1985.

Origin of RA/27/3 Rubella Vaccine

In 1964, many women in US infected during pregnancy.

My laboratory diagnosed many cases, and received aborted fetuses for study

One of those was selected for isolation of viruses for attenuation

Choice of Substrate

Rubella virus will grow in human, monkey and rabbit cells.

However, I wished to avoid contaminants.

I chose to use the WI-38 human fetal fibroblast cell strains developed at The Wistar Inst.

This cell was cultured from one fetus, from which cells were expanded exponentially by passage *in vitro*.

Cells stored frozen at 12th passage can be expanded to 30th passage, after which they become senescent.

Attenuation of RA 27/3

- ✓ **Isolated from fetal kidney explant**
- ✓ **Grown in WI-38 Human fetal fibroblasts**
- ✓ **Passaged in WI-38 4X by cell to cell contact at 35°C**
- ✓ **Passage of supernatant virus 4 X at 35°C**
- ✓ **Subsequent passages at 33°C, then 30°C with 4 terminal dilutions until passage 25**
- ✓ **Changes in *in vitro* markers**

Changes in Markers with Passage of RA27/3

Passage level	rct 30°C	BHK plaques	Markers Nt Ab induction	Rash induction	Pharyng Excr.
<8	–	–	+++	?	?
8-14	–	–	++	++	++
15-20	+/-	+	+	+	+
>20	+	+	+	–	+/-

Rubella Vaccine, Live

RA 27/3 Strain

- ✓ Isolated from rubella-infected fetus
- ✓ Attenuated in human fibroblast cells
- ✓ Cold-adapted mutant
- ✓ Immunogenic by the subcutaneous, intramuscular, intranasal and aerosol routes
- ✓ Used since 1960s
- ✓ Administered with measles and mumps vaccines 9-15 months of age

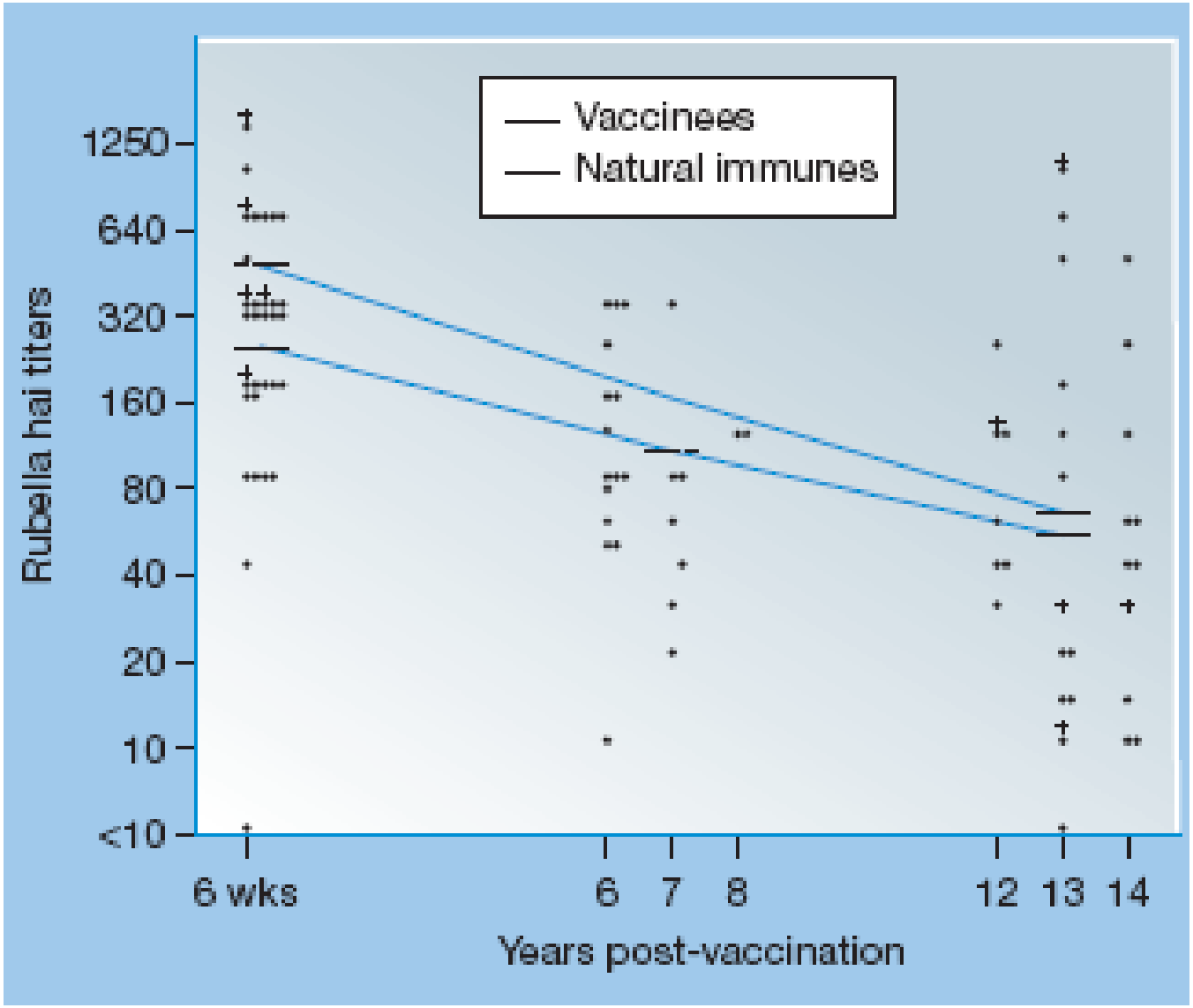
Viremia and Virus Excretion in Volunteers After Subcutaneous or Intranasal Challenge with RA27/3 Rubella Virus Vaccine

Antibody Status Before Vaccination	No. of Vaccinees	Viremia	Virus Excretion
Seronegative	21	15	12 (6–14)*
Seropositive (>15 IU)	10	0	1 (7)
Low titer (£15 IU)			
Natural infection	12	0	0
Previous vaccination			
RA27/3	7	0	0
Other strains	12	1 (12)	3 (6–9)

*

Numbers in parentheses indicate days after vaccination on which findings were positive.

Adapted from O'Shea S, Best J, Banatvala JE. Viremia, virus excretion, and antibody responses after challenge to volunteers with low levels of antibody to rubella virus. J Infect Dis 148:639–647, 1983.

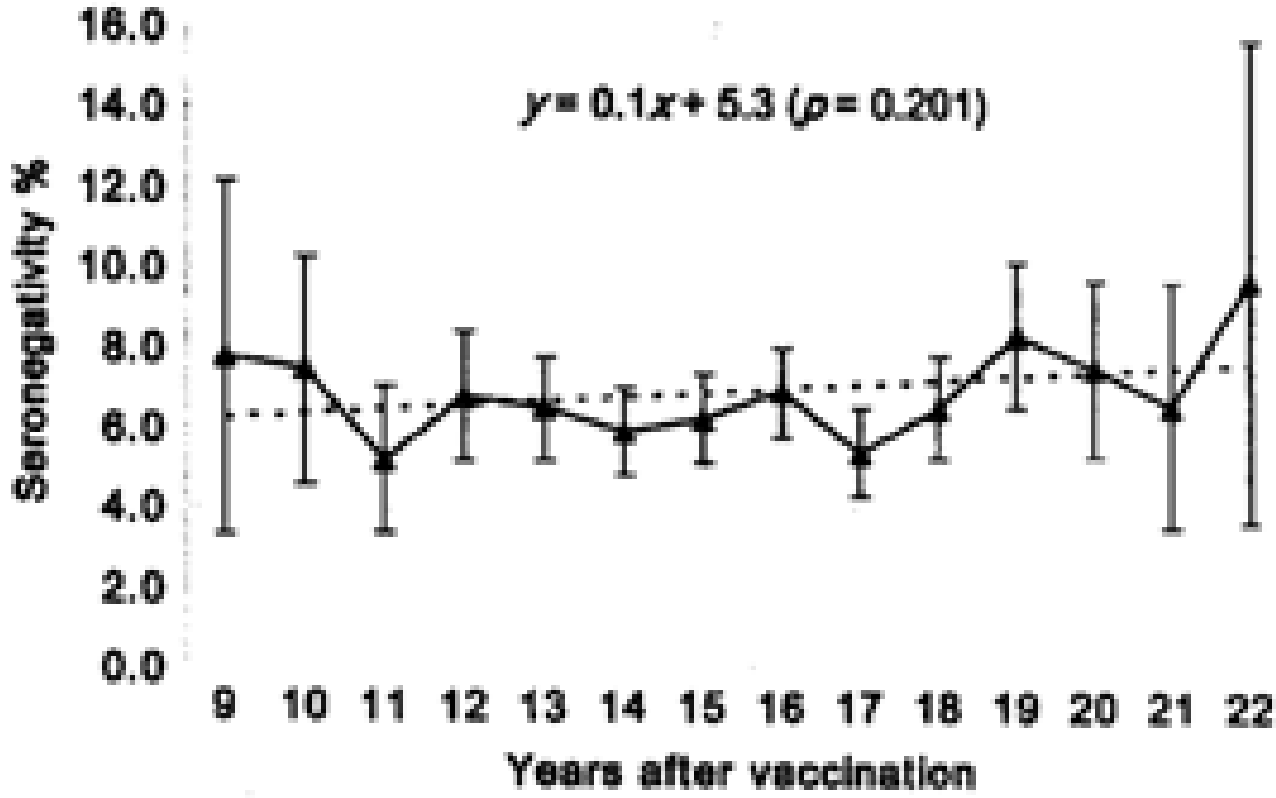


Plotkin SA, et al. Rev Infect Dis 7(suppl):S77-S89, 1985

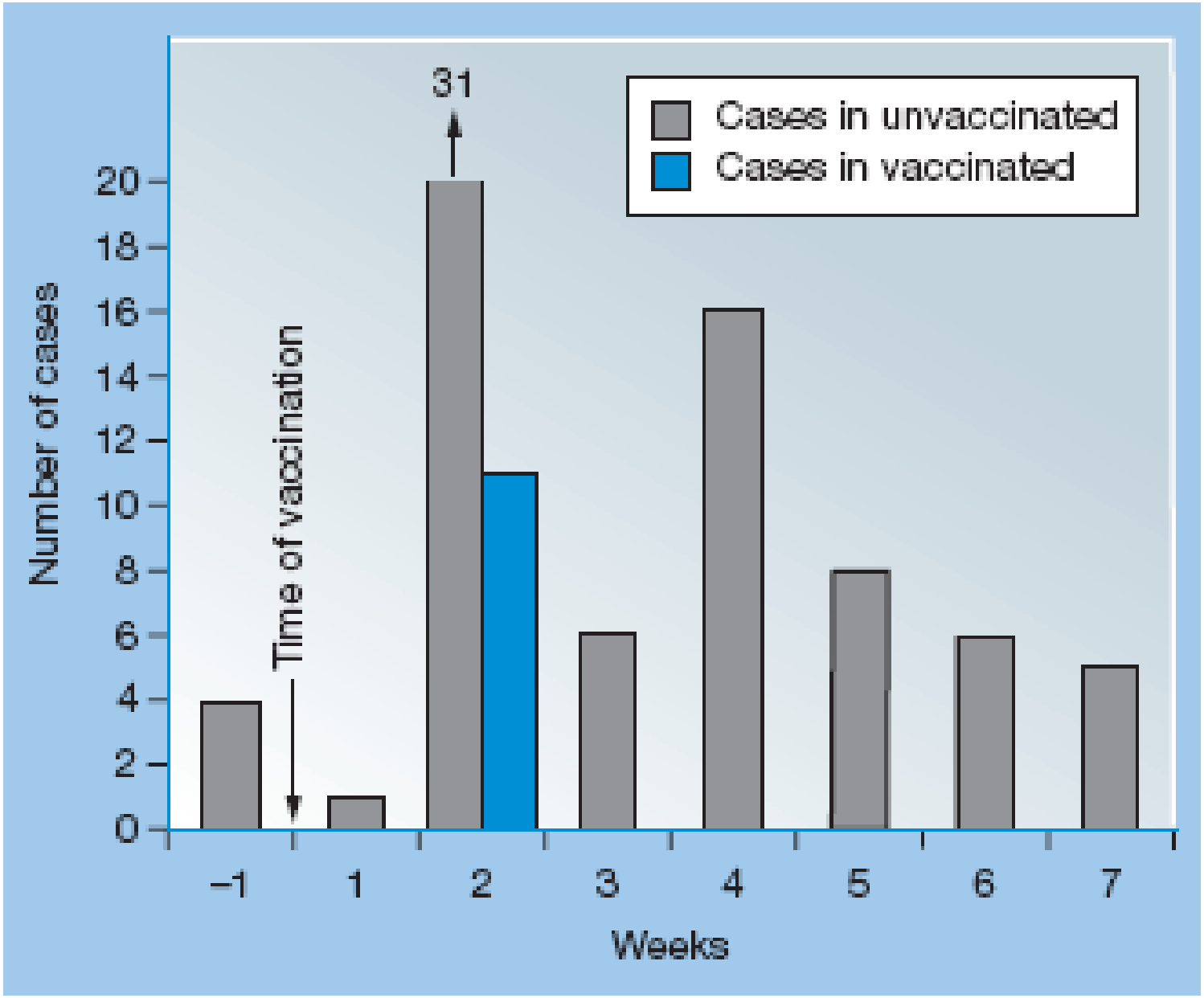
Long-term persistence of rubella antibodies after vaccination with the RA27/3 strain.

References	Country where study carried out	Years after vaccination (number of doses)	No. Sero-positive/no. tested (%)	Serological method used
Christenson & Bottiger, 1994	Sweden	16 (1)	184/190 (96.8%)	HI
Enders & Nickerl, 1988	Germany	14 (1)	115/115 (100%)	HI
Hillary & Griffith, 1988	Ireland	15 (1)	20/21 (93.3%)	HI
Horstmann et al. 1985	USA	11-12 (1)	35/35 (100%) 33/35 (95%)	NT HI
O'Shea et al. 1988	UK	10-21 (1)	47/48 (97.9%)	SRH, EIA, latex aggl.
Zeally & Edmond	UK	12 (1)	93/94 (99%)	SSRH
Plotkin & Buser, 1985	USA	12-14 (1)	29/29 (100%)	HI
Johnson et al. 1996	USA	10-12 (1)	36/57 (63%)	NT
Kremer et al, 2000	Luxemburg	7(1)	1224 (92%)	EIA
Vandermeulen et al, 2007	Netherlands	8 (2)	119/119 (100%)	EIA
Davidikin et al, 2008	Finland	20 (2)	275/275 (100%)	EIA
LeBaron et al, 2009	USA	7-12 (2)	521/613 (85%)	NT
Kakowliden et al, 2010	Sweden	22 (2)	1707/1870 (91%)	EIA

Rubella seronegative rates with 95% CI for primiparous women, 9 to 22 years after vaccination in the third grade of junior high school (at 15 years of age) in Taiwan



Lin CC, et al. Clin Vacc Immunol, 2012; 19(1):1-4



Furukawa T,. et al. JAMA 213:987-990, 1970

Protective Efficacy against Rubella Disease Afforded by Rubella Vaccines RA27/3 During Rubella Outbreaks (adapted from Plotkin & Reef 2004)

Reference	Population studied	No. Vaccinees exposed	Protective efficacy
Beasley et al. 1969	Primary schools, China	198	99.5%
Furukawa et al. 1969	Boys' school, Japan	24	100%
de Valk & Rebiere, 1998	Primary school, France	119	95%
Greaves et al. 1983	High school children, USA	>600	90%
Davis et al. 1971	Institution USA	22	100%

Target Groups for Rubella Vaccination

Infants 12 mo (could be down to 6 mo)
Older unvaccinated children and adolescents
College students
Childcare personnel
Health care workers
Military personnel
Adult women before pregnancy
Adult seronegative women postpartum
Adult men in contact with pregnant women
All of the above as part of a two-dose elimination strategy

Symptoms and Signs Caused by MMR Vaccination and Day of Peak Occurrence in Finnish Twin Study

Symptoms and Signs	Maximum Difference in Rate*	95% CI	Peak Frequency (Days After Vaccination)
Local erythema (>2 cm)	0.8	0.1–1.4	2
Other local reaction	0.4	0–1.4	2
Mild fever (£38.5°C rectal)	2.7	0–6.1	10
Moderate fever (38.6–39.5°C)	2.9	1.6–4.3	9
High fever (³39.5°C)	**1.4**	**0.7–2.1**	**10**
Irritability	4.1	2.1–6.1	10
Drowsiness	2.5	1.4–3.6	11
Willingness to stay in bed	1.4	0.5–2.3	11
Generalized rash	**1.6**	**0–3.0**	**11**
Conjunctivitis	2.1	0.9–3.2	10
Arthropathy	**0.8**	**0.2–1.3**	**7–9**
Peripheral tremor	0.4	0–0.9	9
Cough and/or coryza	-1.5†	-4.6–1.6	9
Nausea and/or vomiting	-0.8†	-1.6–0	7–8
Diarrhea	0.7	0–1.7	11

*Between MMR group and placebo group.
†More in placebo-injected children.
From Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine: a double-blind placebo-controlled trial in twins. Lancet 1:939–942, 1986, with permission.

Frequencies of Acute and Chronic Reactions to Rubella Vaccine or Placebo in Adult Women

	Group (%)		
	Placebo (*N* = 275)	Vaccine (*N* = 268)	Odds Ratio (95% CI)
Acute Reactions			
Sore throat	32	34	1.09 (0.75–1.59)
Lymphadenopathy	10	19	2.21 (1.31–3.76)
Rash	**11**	**25**	**2.57 (1.58–4.21)**
Myalgia	16	21	1.36 (0.88–2.10)
Paresthesias	7	7	1.09 (0.57–2.09)
Arthralgia	16	21	1.42 (0.92–2.19)
Arthritis	4	9	2.36 (1.13–4.92)
Arthralgia or arthritis	**20**	**30**	**1.73 (1.17–2.57)**

Adapted from Tingle A, Mitchell L, Grace M, et al. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. Lancet 349:1277–1281, 1996.

Summary of Data on Accidental Vaccination Before Pregnancy and During Early Pregnancy of Women in the United States and Germany Vaccination of Unknowingly Pregnant Rubella Susceptible Women

Country	Live births to women receiving rubella immunization		
	Within 3 months before conception or during pregnancy	Laboratory Evidence of Infection	Abnormalities compatible with CRS ¶
USA	324 +	6/222 (2.7%)	0/324
Germany (West BRD)	280 +	3/69 (4.3%)	0/279
Sweden	5 +	NK	0/5
U.K.	71 +	4/52 (7.7%)	0/71
Brazil	1647 *	67/1647 (4.1%)	0/1647
Ecuador	43 *	2/43 (5%)	0/43
El Salvador	59 *	1/59 (1.6%)	0/59
Paraguay	119 *	0/119	0/119
Iran	117 ¥		0/117
Costa Rica	93 *	0/93 (0%)	0/93
Mexico	175€	0/174	0/174
Total	**2933#**	**83/2478 (3.3 %)**	**0/2931**

#Confirmed susceptibles; actual number much higher.

Contraindications and Precautions for MMR

Prior allergic reaction to vaccine

Severe immunodeficiency or immunosuppression

Prior thrombocytopenia

Pregnancy

Status of Rubella and Vaccination

Elimination Achieved:

Scandinavia
USA, Canada
Caribbean
Latin America

Elimination set as goal:

Western Europe

Control Starting:

Eastern Europe
Middle East
Japan, Malaysia, Korea, Thailand

US Strategy for Rubella Elimination

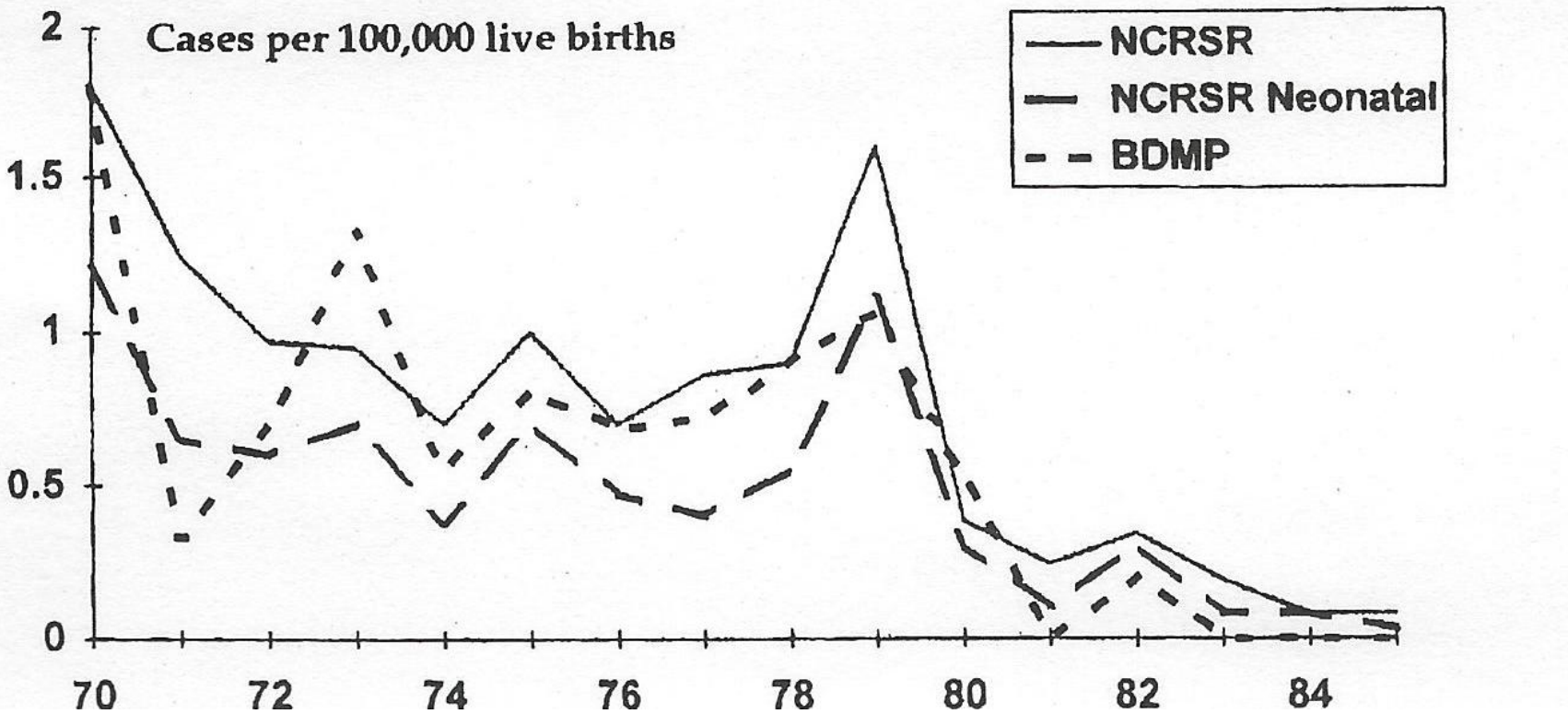
Universal vaccination with MMR at 12 - 15 months

Catch-up vaccination of adolescents

Vaccination of adult women at gynecological visits or post-partum

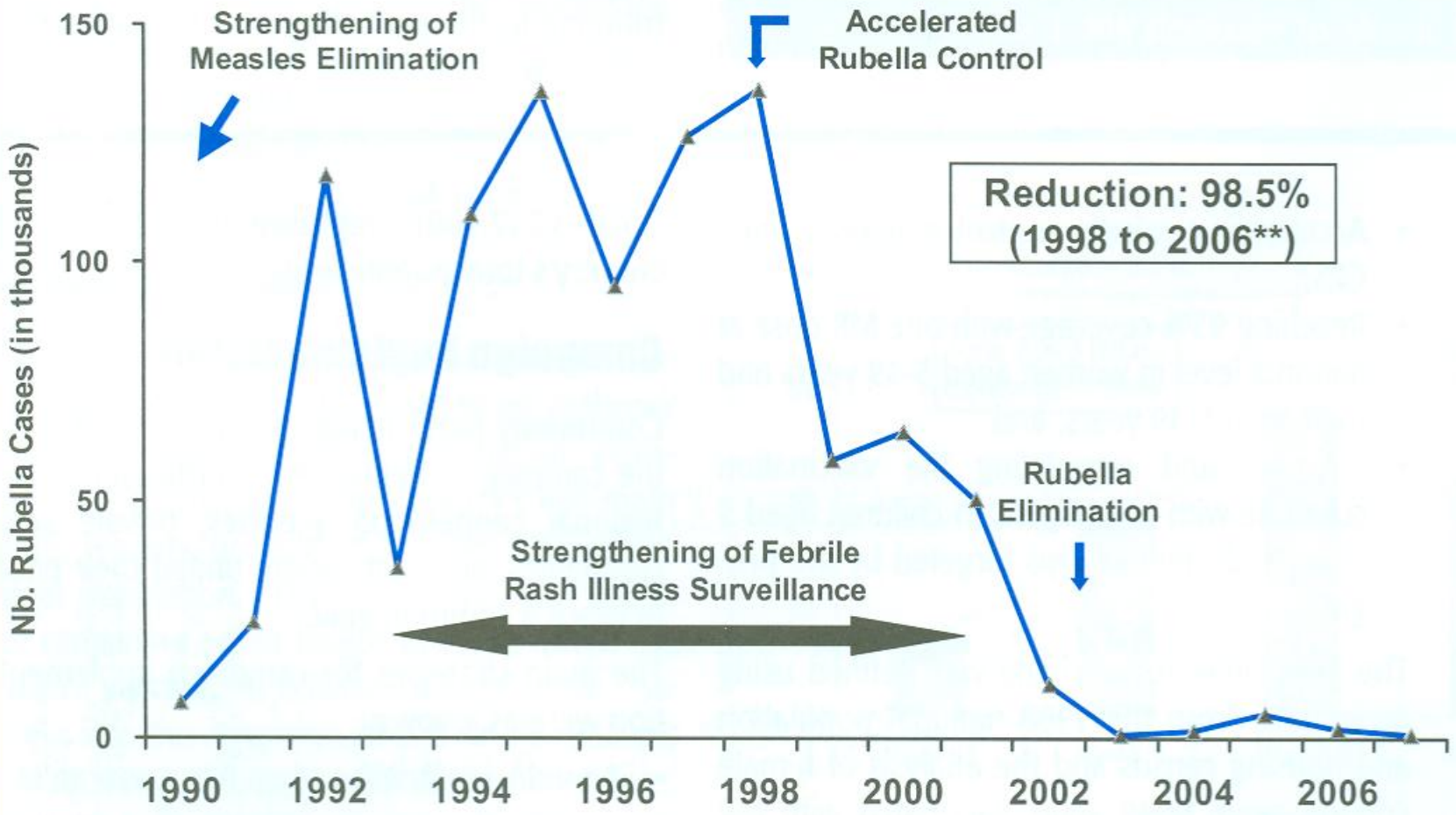
Reported congenital rubella syndrome, United States, 1970-1985

S.A. Plotkin



History of Vaccine Development, Plotkin SA, ed. Springer, 2011:228

Figure 1. Impact of Rubella Control and Elimination Strategies, The Americas, 1990–2007*

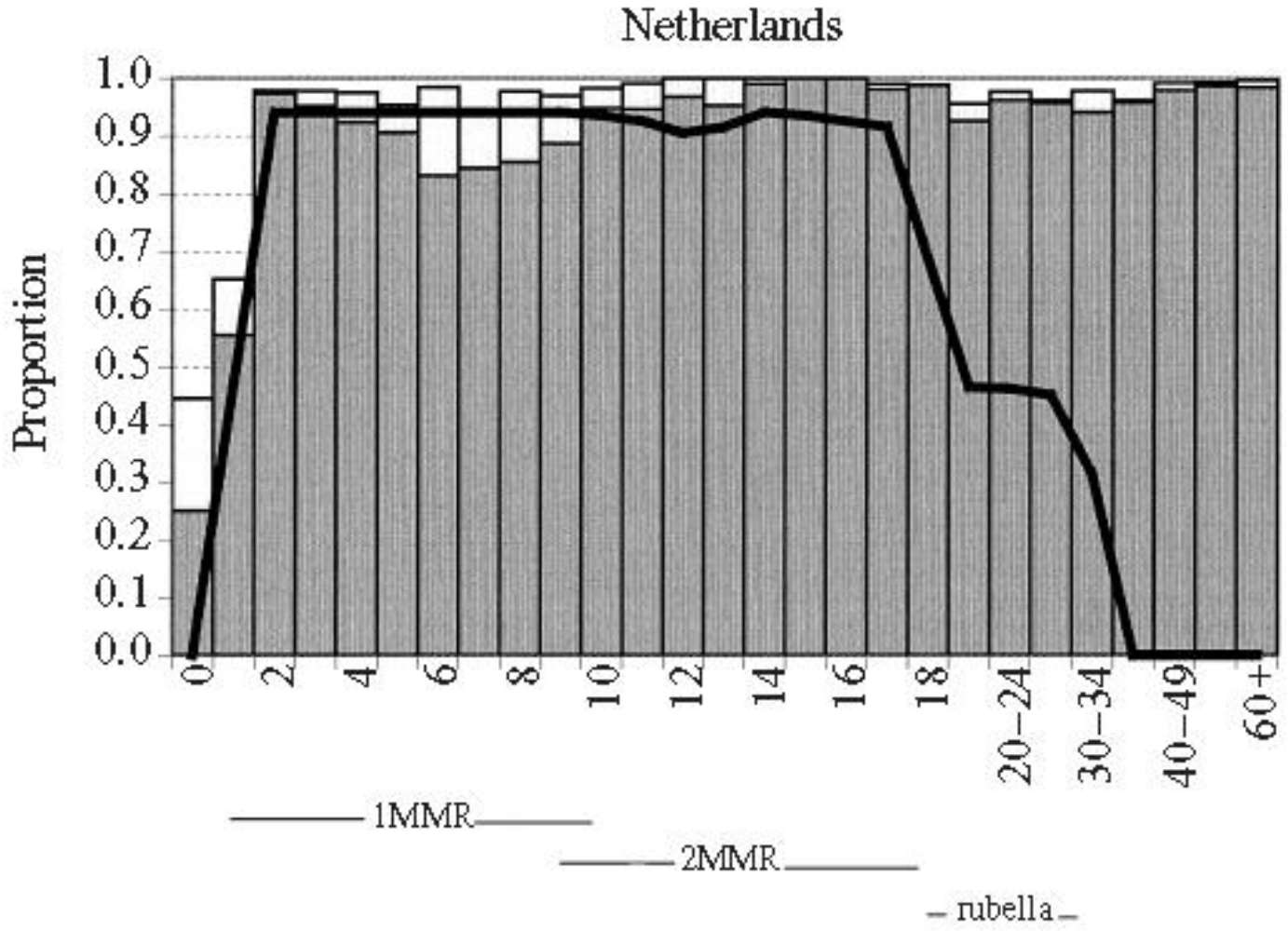


* Includes rubella cases reported to PAHO as of Epidemiological Week 19/2007.
** Provisional data.

Source: Country Reports to Immunization Unit, PAHO.

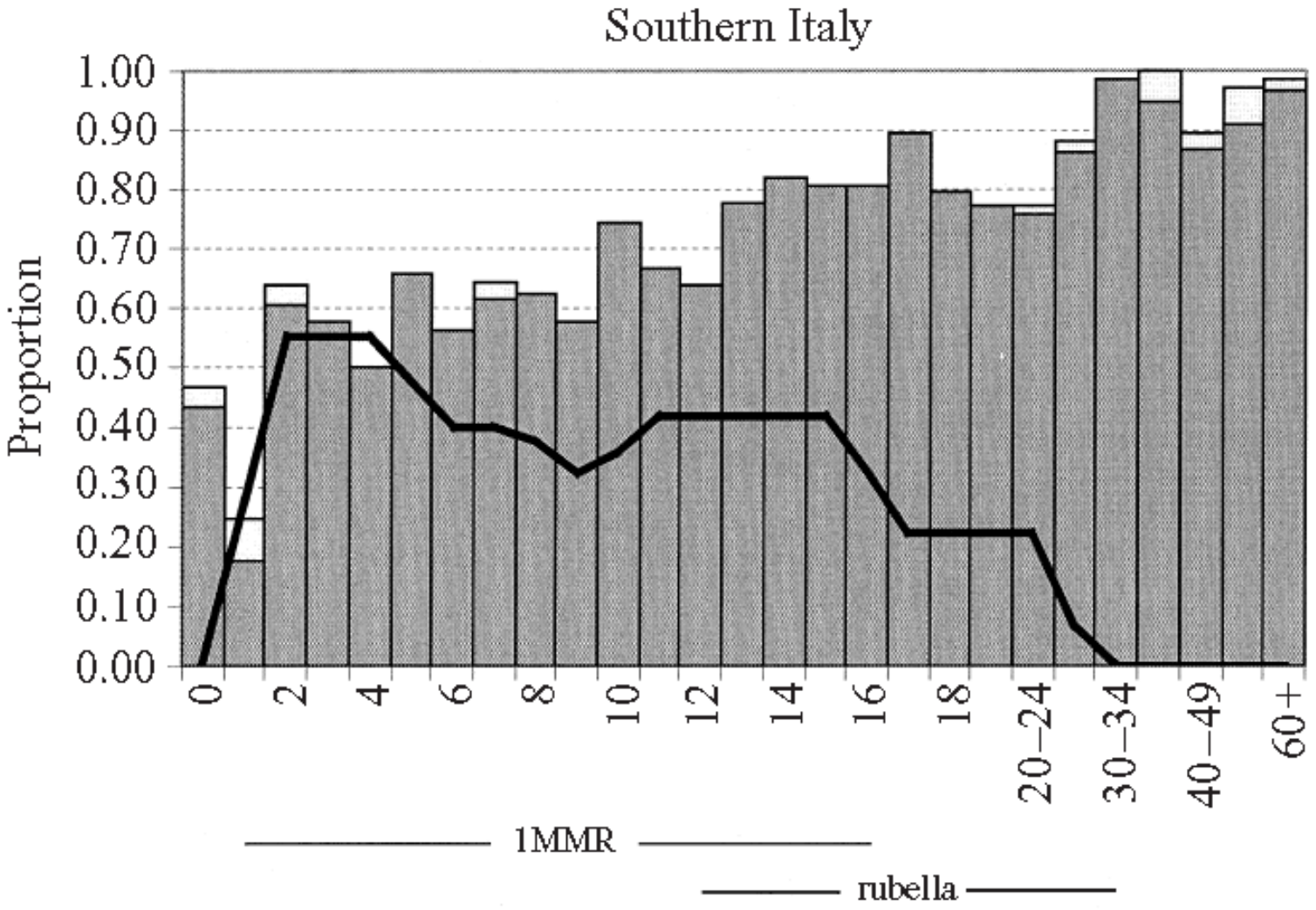
Immunization Newsletter PAHO Vol. XXIX, no. 3, June 2007, page 1.

Seropositivity and Vaccine Coverage



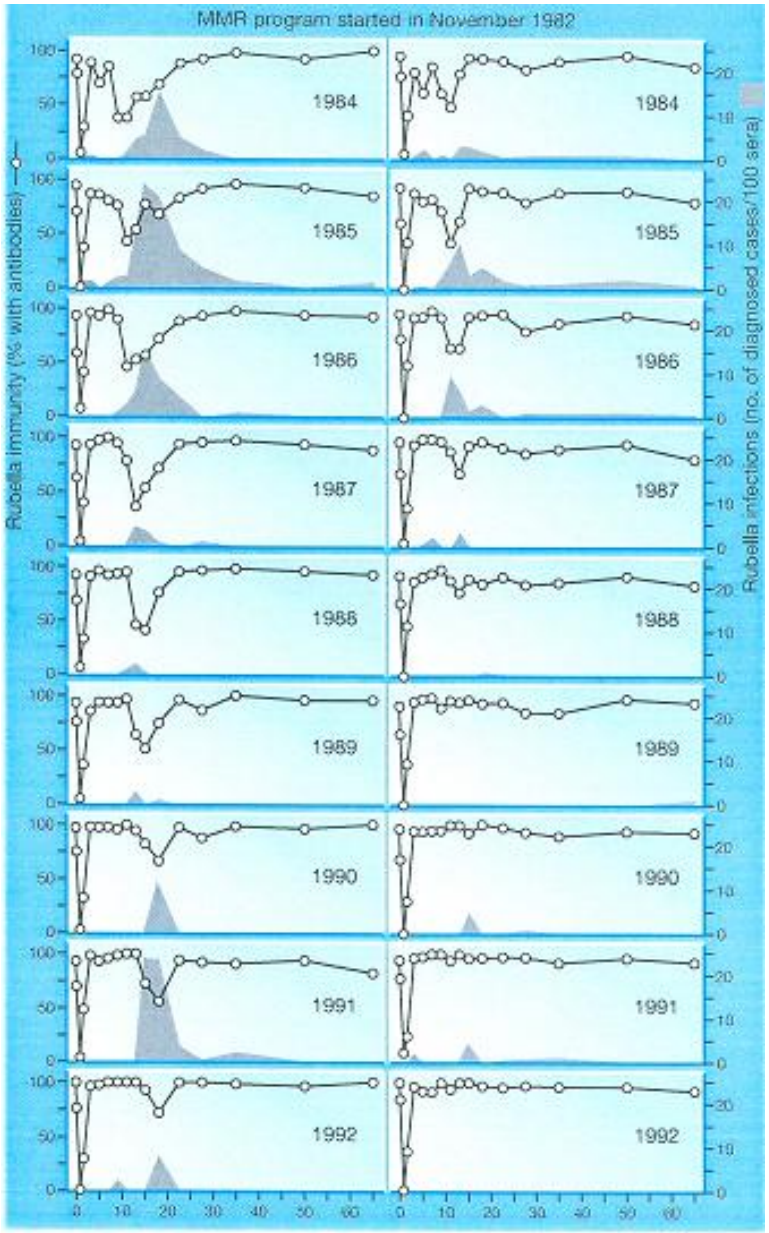
Pebody RG et al. Epidemiol Infect. 125:347-357, 2000

Seropositivity and Vaccine Coverage



Pebody RG et al. Epidemiol Infect. 125:347-357, 2000

Incidence of Rubella and Coverage in Finland



Ukkonen P. Scand J Infect Dis 28:31-35, 1996

Impediments to Rubella/CRS Elimination

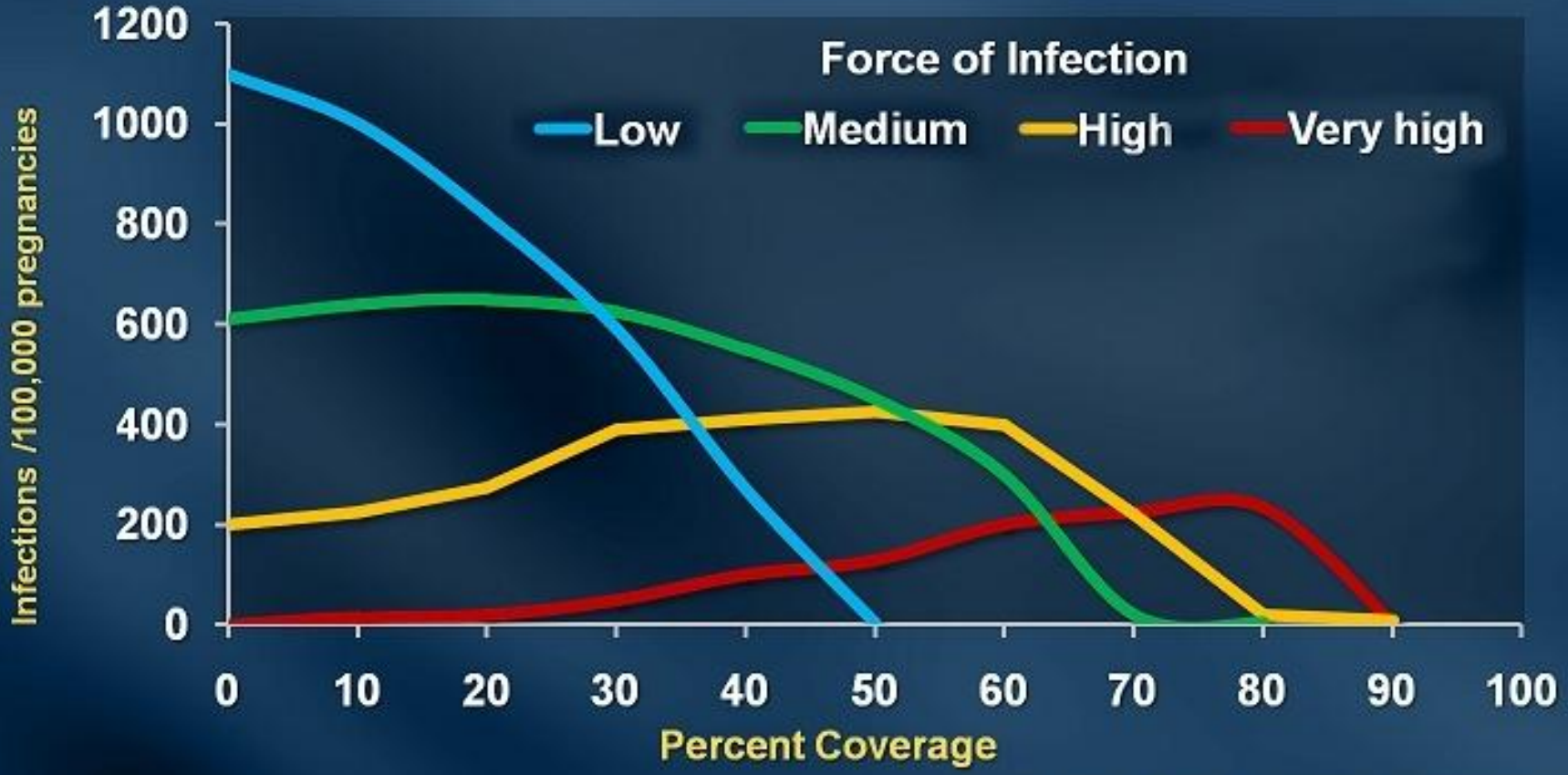
1) Cost of vaccine – $.25 -.50 per dose

2) Inapparent rubella – but rash present in 60-70%

3) Difficult surveillance of CRS –
but screen for neonatal cataracts

4) Concern regarding paradoxical enhancement of susceptibility of pregnant women.

Predicted long-term effect of infant vaccination on incidence of CRS

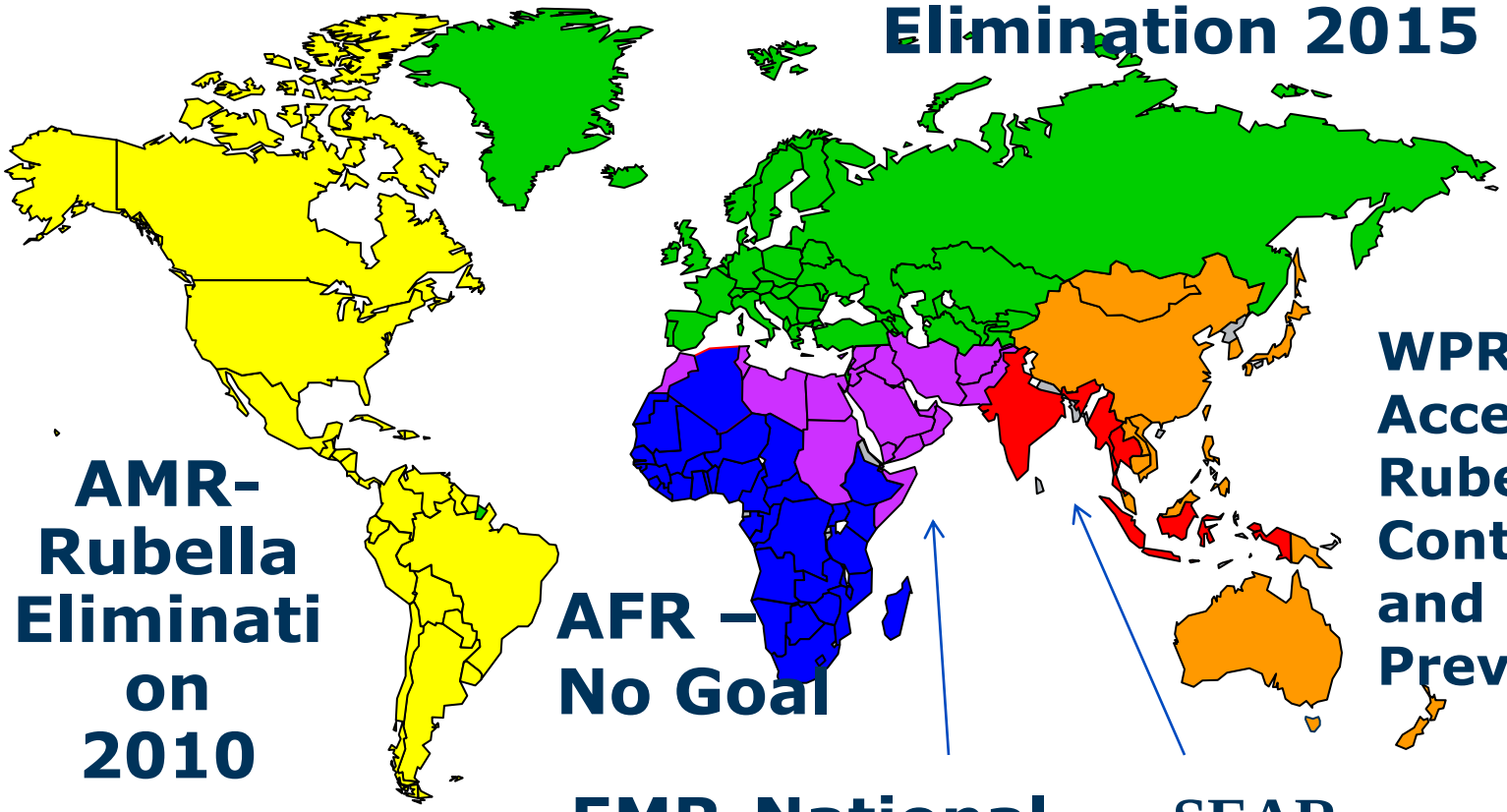


N. Gay, from Plotkin (Vaccines)

Rubella Vaccine Use by WHO Region, 1996 vs. 2009

Region	1996 No. of countries (%)	2009 No. of countries (%)
AFR	2 (4%)	2 (4%)
AMR	21 (60%)	35 (100%)
EMR	9 (43%)	AMR
EUR	39 (74%)	53 (100%)
SEAR	2 (20%)	4 (36%)
WPR	10 (37%)	21 (78%)
Global	83 (43%)	130 (67%)

WHO Regions by Rubella/CRS Control Target (2011)



Requirements for Eradication

	Polio	Measles	Rubella
Animal reservoir	**0**	**0**	**0**
Human reservoir	**+**	**0**	**0***
Clinically apparent	**±**	**+++**	**++**
Effective vaccine	**+/++/+++**	**+++**	**+++**
Coverage required	**?**	**95%**	**80%**
*Transient in CRS			