

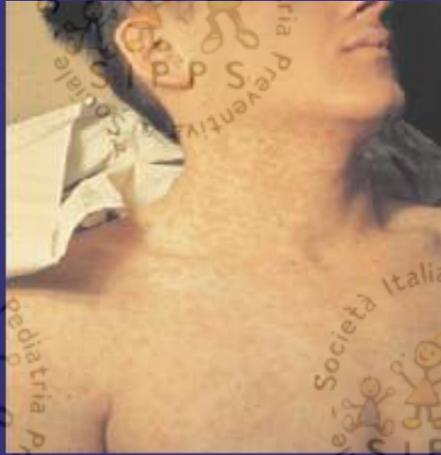
# IL CASO DEL TETRAVALENTE ANTI - MPRV

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# AGENDA

- Incidenza di morbillo, parotite, rosolia e varicella
- Coperture vaccinali insufficienti
- Complicanze di Morbillo, Parotite, Rosolia e Varicella
- Vaccinazioni disponibili



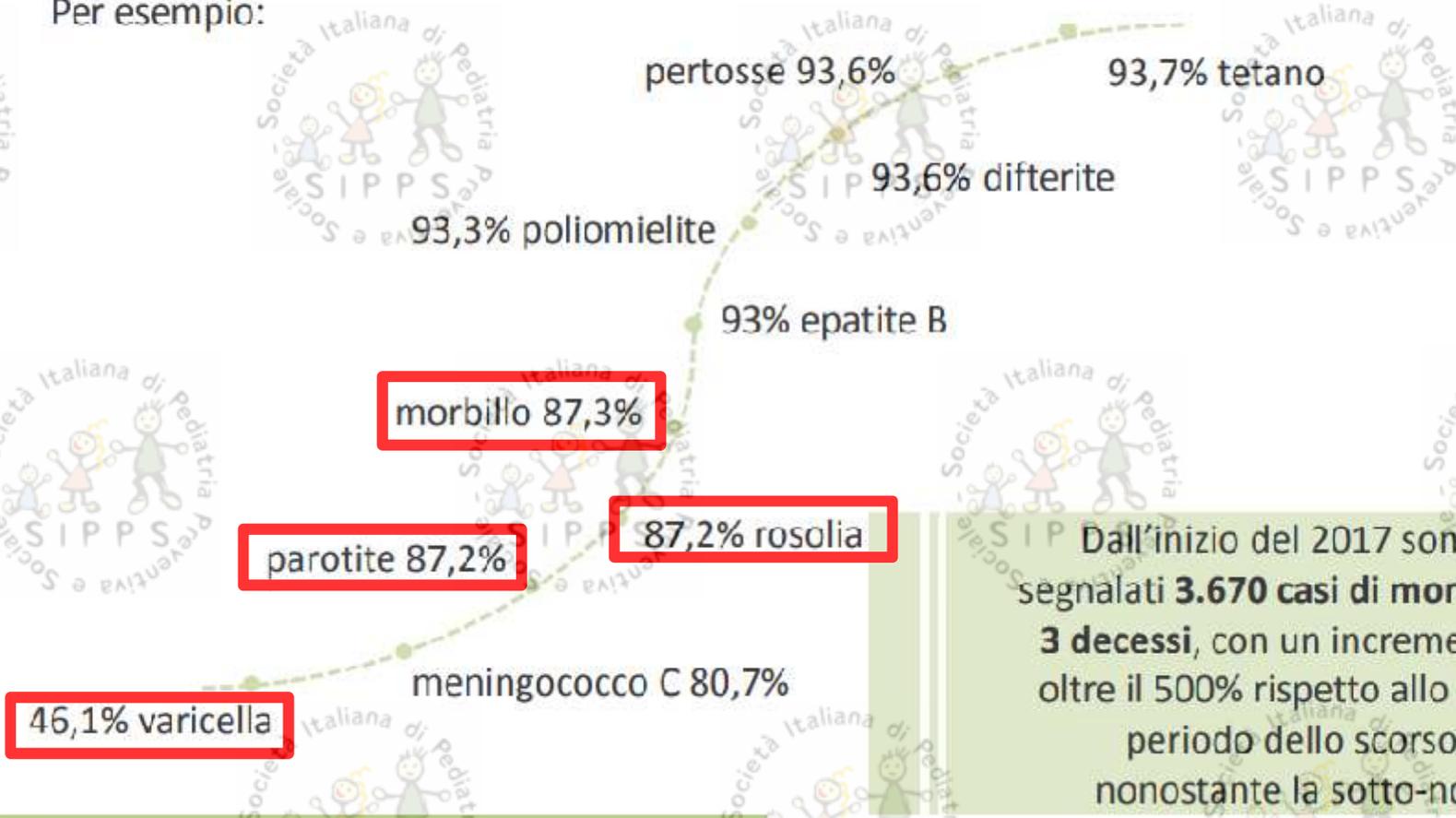
**IN ITALIA E IN MOLTI PAESI EUROPEI LA SITUAZIONE NON E' SOTTO CONTROLLO!**



## Le attuali coperture vaccinali

La copertura media nazionale delle vaccinazioni è oggi\* pericolosamente **sotto le soglie raccomandate dall'OMS.**

Per esempio:



Dall'inizio del 2017 sono stati segnalati **3.670 casi di morbilli e 3 decessi**, con un incremento di oltre il 500% rispetto allo stesso periodo dello scorso anno, nonostante la sotto-notifica.

\*dati coorte 2014 al 31/12/2016



Ministero della Salute

# MORBILLO





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## Update report 15/09/2017

Updates are provided for Italy and Romania. According to national public health authorities, measles has caused 43 deaths in EU countries in 2016 and 2017. In 2016, 12 deaths occurred in Romania and one in the UK. In 2017, 30 deaths were reported from Romania (22), Italy (3), Bulgaria (1), Germany (1), Portugal (1), France (1) and Spain (1). All EU/EEA countries have reported measles cases this year, except for Latvia, Liechtenstein, Malta and Norway.

Updates outside EU/EEA countries are provided for Switzerland, Ukraine, DR Congo, Liberia, Nigeria, Somalia, South Africa, South Sudan, Syria, Thailand, Australia and the US.

Epidemiological summary for EU/EEA countries, with updates since last week

**Italy** has reported 43 cases since the previous report on 8 September 2017. In 2017, as of 13 September, Italy has reported 4 487 cases, including three deaths. Of these cases, 297 are healthcare workers. The median age is 27 years; 88% of the cases were not vaccinated, and 7% received only one dose of vaccine. In 2016, Italy reported 861 cases.

**Romania** has reported 122 cases and one additional death since the previous report on 8 September 2017. Since 1 January 2016 and as of 8 September 2017, Romania has reported 9 104 cases, including 34 deaths. Of these, 1 969 cases were reported in 2016, and 7 135 cases were reported in 2017.



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## Update report 15/09/2017

### Epidemiological summary for countries outside EU/EEA since last month

**Switzerland**: In 2017, as of 4 September, Switzerland has reported 76 cases of measles. In the same period in 2016, 42 cases were reported.

**Ukraine**: In 2017, as of the end of July, Ukraine has reported 1 386 cases of measles, compared to 10 cases in the same period in 2016. Most cases of measles were reported in the Ivano-Frankivsk (837) and Odessa regions (528).

**DR Congo**: In 2017, as of 22 August, DR Congo has reported 30 211 suspected measles cases, including 370 deaths. This is an increase of 5 388 since the previous report on 25 August. The incidence has declined since the peak of the current outbreak in early 2017.

**Liberia**: In 2017, as of 27 August, Liberia has reported 1 048 suspected measles cases, an increase of 21 cases since the previous report on 25 August. Of the suspected cases, 884 were tested with 147 positive, 691 negative and 46 equivocal. One hundred sixty-four of the suspected cases were compatible with measles and had an epidemiological link. Of the 737 equivocal and negative cases, 708 samples have been tested for rubella, 312 of which were positive.

**Nigeria**: In 2017, as of 20 August, Nigeria has reported 16 833 suspected measles cases, including 101 deaths. During the same time period in 2016, 21 604 suspected cases and 86 deaths were reported.

**Somalia**: In 2017, as of 31 August, Somalia has reported almost 16 000 suspected cases. This is almost three times the number of cases reported in 2016 (5 657 cases).

**South Africa**: In 2017, as of 18 August, South Africa has reported 133 cases of measles. Most cases were reported from an ongoing outbreak in Gauteng province (68 cases) and from an outbreak in Western Cape province (31 cases). In KwaZulu-Natal Province, a measles outbreak has been declared with 19 confirmed or probable cases in three districts: Ethekwini (12), Umgungundlovu (5), and Ilembe (2).



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## Update report 15/09/2017

**South Sudan** : In August 2017, South Sudan reported six additional cases of measles. In 2017, as of 31 August, South Sudan has reported 1 025 measles cases and 24 deaths.

**Syria** : Between 30 July and 5 August 2017, Syria has reported 45 suspected measles cases, with most cases reported from Dar'a (8), Damascus (8) and Ar-Raqqa (8). In 2017, as of end of June, Syria has reported 352 confirmed measles cases. Most of the cases were reported in April (92 cases).

**Thailand** : In 2017, as of 2 September, Thailand has reported 2 231 cases from 72 provinces. No deaths were reported.

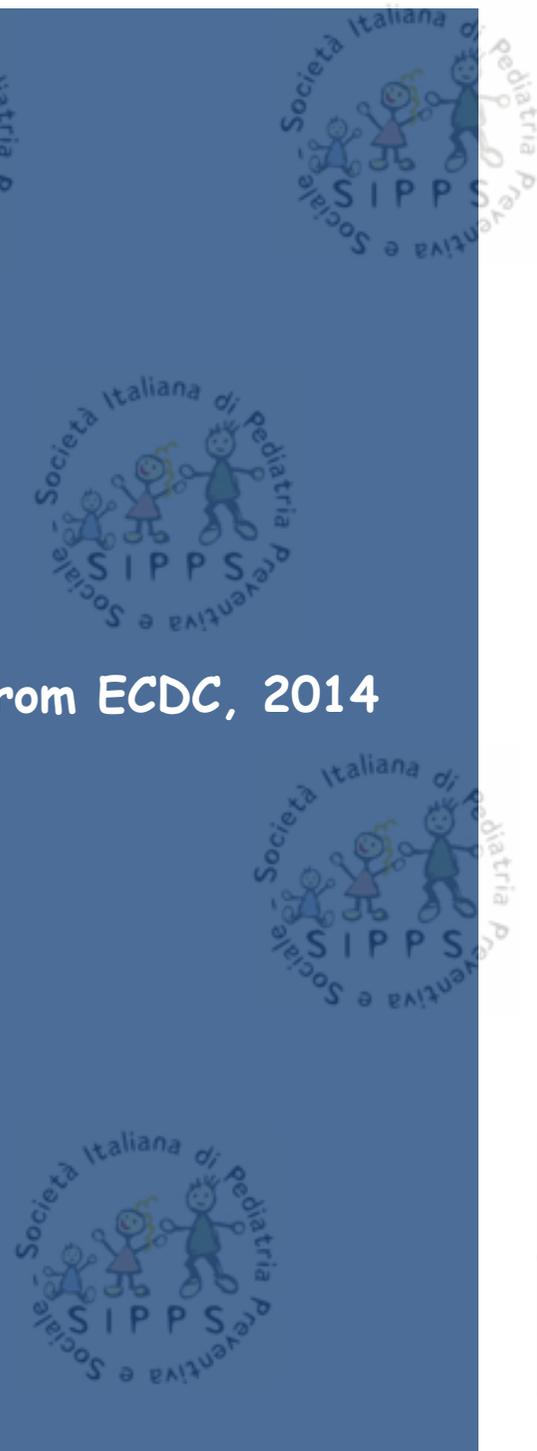
**Australia** : On 30 August 2017, Australia reported one additional case since the previous report on 25 August. Since the beginning of August 2017 and as of 30 August, Australia has reported four measles cases in a **school in Perth**, in Western Australia. In 2017, as of end of August, Australia has reported 58 cases. In the same time period in 2016, 63 cases were reported.

**USA** : In 2017, as of 12 August, 118 cases were reported from 14 states (California, Florida, Kansas, Maine, Maryland, Michigan, Minnesota, Nebraska, New Jersey, New York, Pennsylvania, Utah, and Washington). In 2016, 70 measles cases were reported from 16 states.

Number of measles cases by month and notification rate (cases per million) by country, July 2013–June 2014, EU/EEA countries

Country	2013	2013	2013	2013	2013	2013	2014	2014	2014	2014	2014	2014	Total cases	Cases per million	Total lab-positive cases
	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun			
Austria	0	6	6	9	3	5	33	11	8	5	8	17	110	13.0	76
Belgium	2	11	4	3	2	1	2	8	7	29	26	0	85	7.6	53
Bulgaria	1	0	0	0	0	0	0	0	0	0	0	0	1	0.1	1
Croatia	0	1	0	0	0	0	0	1	0	1	0	0	3	0.7	1
Cyprus	0	0	0	0	0	0	0	0	4	6	0	0	10	11.6	8
Czech Republic	0	0	0	0	0	1	0	2	34	57	25	11	130	12.4	178
Denmark	0	0	0	0	0	0	0	5	8	6	1	0	20	3.6	10
Estonia	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Finland	0	0	0	0	0	0	2	0	0	0	0	1	3	0.6	0
France	25	13	13	15	11	11	41	38	26	34	44	39	306	4.7	121
Germany	306	127	108	76	47	20	22	26	37	45	22	33	869	10.6	450
Greece	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Hungary	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Iceland	0	0	0	0	0	0	0	0	1	0	0	0	1	3.1	1
Ireland	2	3	0	16	6	1	2	6	15	11	1	0	63	13.7	40
Italy	198	74	42	35	177	265	317	204	309	274	195	95	2185	36.6	1097
Latvia	0	0	0	0	0	0	0	0	0	25	9	0	34	16.8	33
Lithuania	0	0	1	0	0	0	0	0	2	0	2	NR	5	1.7	2
Luxembourg	0	0	0	0	0	0	0	0	0	0	1	0	2	3.2	0
Malta	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Netherlands	700	407	444	473	177	106	46	24	42	21	5	1	2446	145.8	882
Norway	0	0	0	0	0	0	0	0	0	2	0	1	3	0.6	3
Poland	10	3	1	1	1	1	15	27	27	19	7	2	114	3.0	85
Portugal	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Romania	83	27	11	23	22	12	25	17	5	1	5	0	231	11.5	172
Slovakia	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Slovenia	1	0	0	0	0	0	0	0	0	0	1	0	2	1.0	2
Spain	31	8	4	4	0	3	10	26	78	27	8	1	200	4.3	182
Sweden	6	0	0	0	0	0	2	7	0	0	2	2	20	2.1	20
United Kingdom	81	22	15	28	13	4	39	27	26	13	2	3	273	4.3	270
Total	1446	692	648	683	459	426	557	429	629	576	365	206	7116	13.9	3688

From ECDC, 2014



**Table. Number of measles cases by month and notification rate (cases per million) by country, June 2016 to May 2017, EU/EEA countries**

Country	2016					2017							Total cases	Cases per million	Total lab pos cases
	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul			
Austria	3	4	3	1	4	28	34	8	2	6	1	2	96	11,05	83
Belgium	0	2	2	2	3	27	79	147	35	23	33	15	368	32,53	239
Bulgaria	0	0	0	0	0	0	0	19	41	57	44	5	166	23,2	86
Croatia	0	1	0	0	0	2	5	0	0	0	0	0	8	1,91	8
Cyprus	0	0	0	0	0	0	0	0	0	1	2	0	3	3,54	3
Czech Republic	0	1	0	1	0	0	0	20	63	43	7	1	136	12,89	129
Denmark	1	0	0	0	1	0	0	1	0	0	0	0	3	0,53	3
Estonia	0	0	0	0	0	0	0	0	0	1	0	0	1	0,76	1
Finland	0	0	0	0	3	0	0	0	0	0	1	4	8	1,46	8
France	4	7	2	2	4	34	52	49	61	112	42	0	369	5,53	241
Germany	28	31	11	25	22	47	157	212	175	134	73	NR	915	11,13	616
Greece	0	0	0	0	0	0	0	0	0	3	1	7	11	1,02	8
Hungary	0	0	0	0	0	1	11	3	0	0	0	8	23	2,34	23
Iceland	1	0	0	0	0	0	0	2	0	0	0	0	3	9,02	3
Ireland	5	1	0	0	0	0	1	2	2	1	1	5	18	3,81	8
Italy	34	54	80	83	89	287	460	897	799	725	571	465	4544	74,9	3477
Latvia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lithuania	0	0	0	0	0	0	0	0	1	0	0	1	2	0,69	2
Luxembourg	0	0	0	0	0	0	0	3	0	0	0	0	3	5,21	3
Malta	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	2	0	0	0	4	0	0	0	2	6	2	1	17	1	15
Norway	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Poland	39	40	24	13	4	6	6	5	4	2	4	6	153	4,03	94
Portugal	0	0	0	0	0	0	2	10	18	4	0	0	34	3,29	29
Romania	185	219	426	614	506	484	843	1334	100	156	100	100	5067	256,42	2098
Slovakia	0	0	0	0	0	0	0	0	1	0	0	0	1	0,18	1
Slovenia	0	0	0	0	0	2	4	0	0	0	0	0	6	2,91	6
Spain	2	3	2	6	2	10	29	22	9	40	32	NR	157	3,38	148
Sweden	2	0	0	0	0	2	8	7	3	4	0	0	26	2,64	26
United Kingdom	108	29	37	14	1	10	1	8	17	34	23	19	301	4,6	301
<b>Total</b>	<b>414</b>	<b>392</b>	<b>587</b>	<b>761</b>	<b>643</b>	<b>940</b>	<b>1692</b>	<b>2749</b>	<b>1333</b>	<b>1352</b>	<b>937</b>	<b>639</b>	<b>12439</b>	<b>24,1</b>	<b>7659</b>

From ECDC, 2017

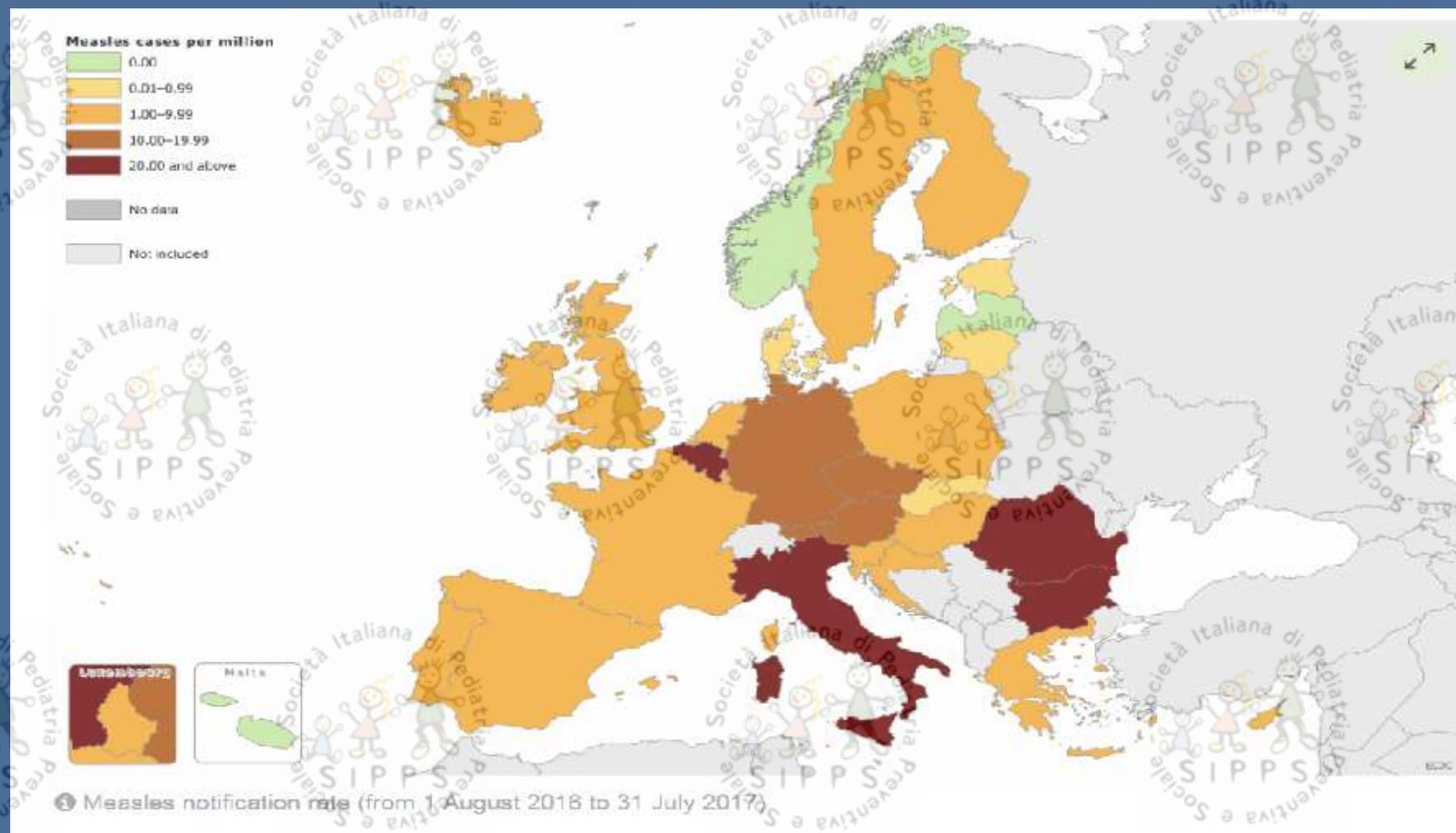
3670 casi by OMS



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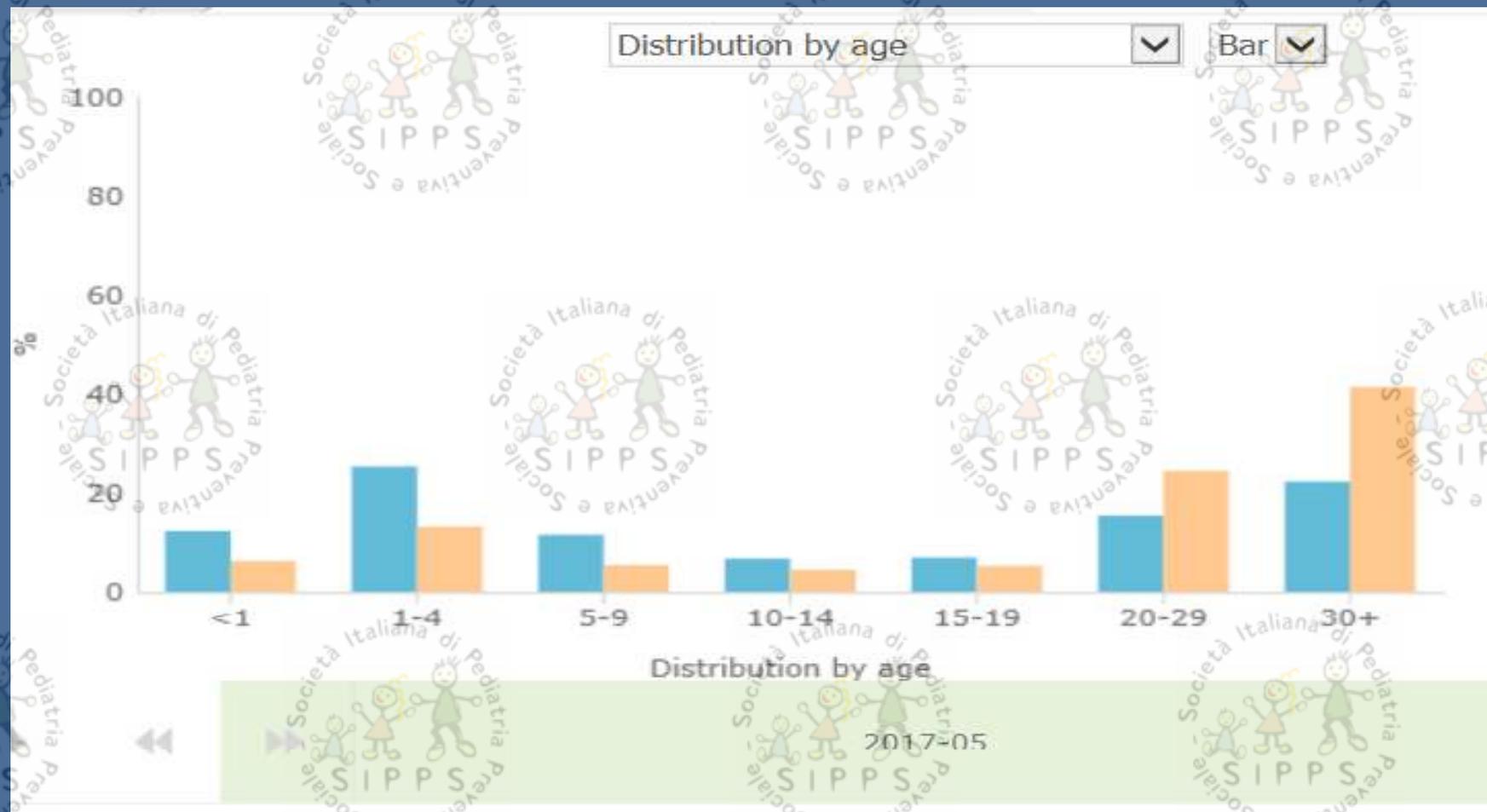


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Measles reported cases

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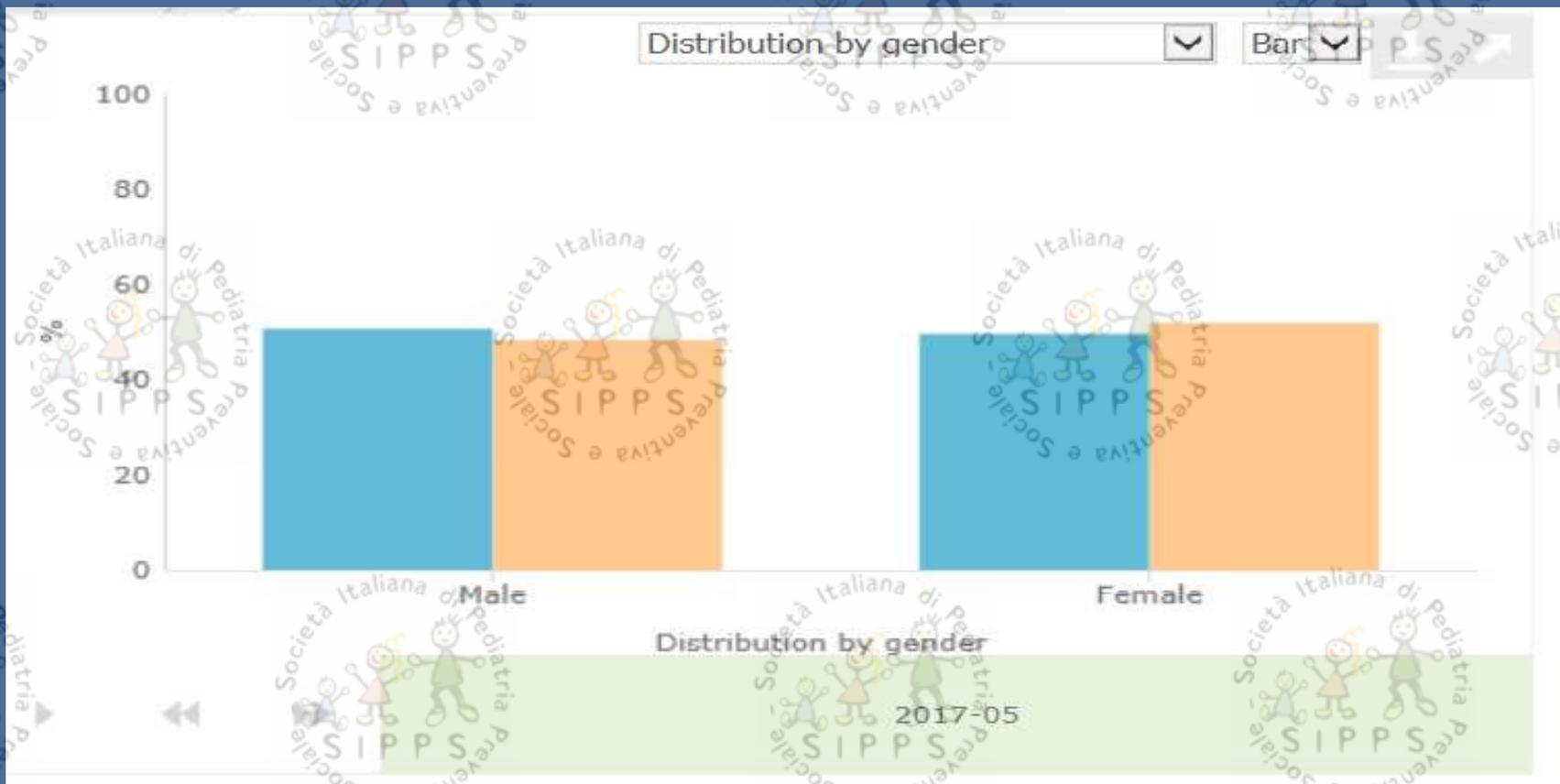


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Measles reported cases

Update report 15/09/2017

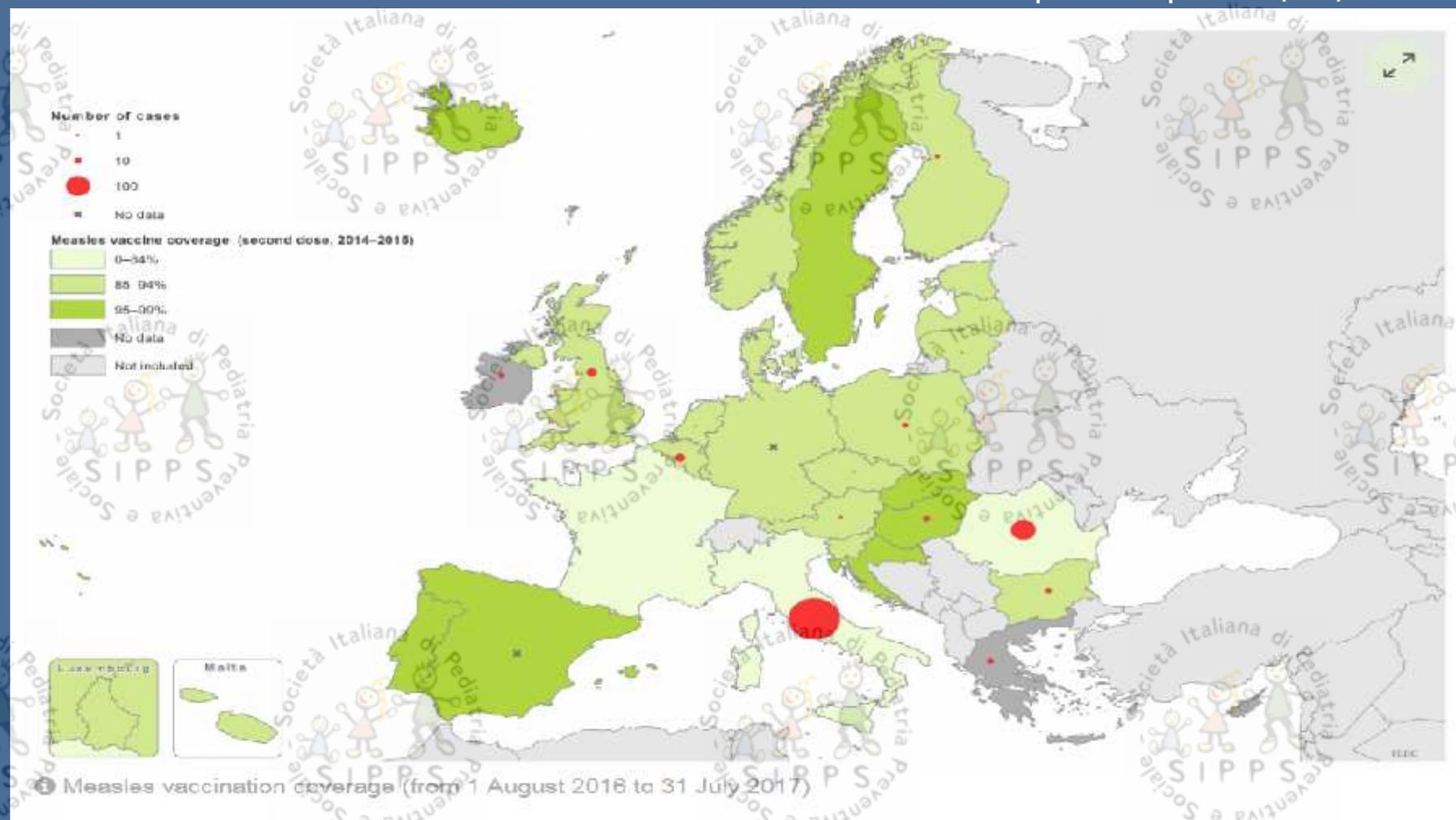




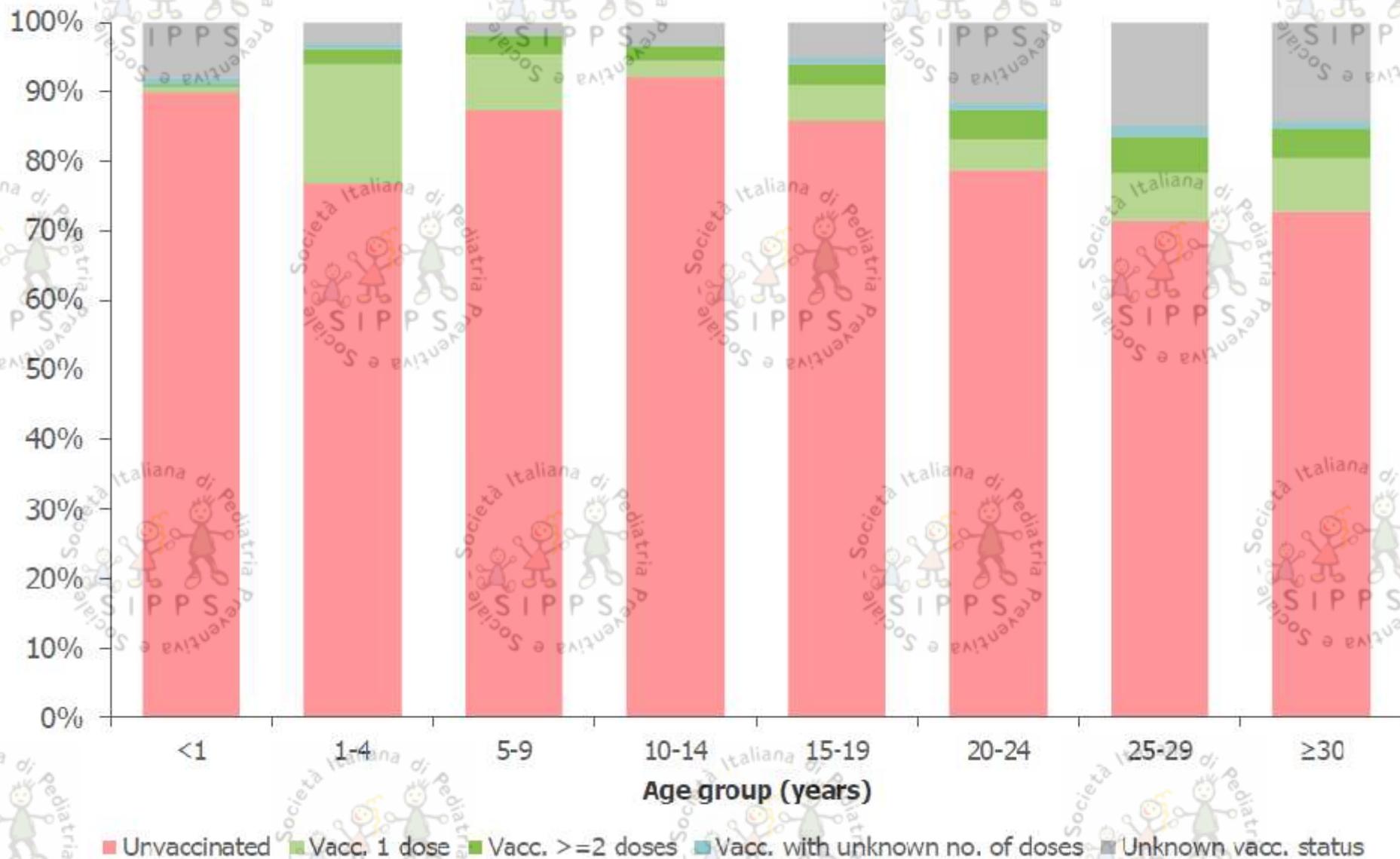
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**Percentage distribution of vaccination status among measles cases by age group, July 2013 – June 2014, EU/EEA countries (n=7 114, cases with known age)**



From ECDC, 2014

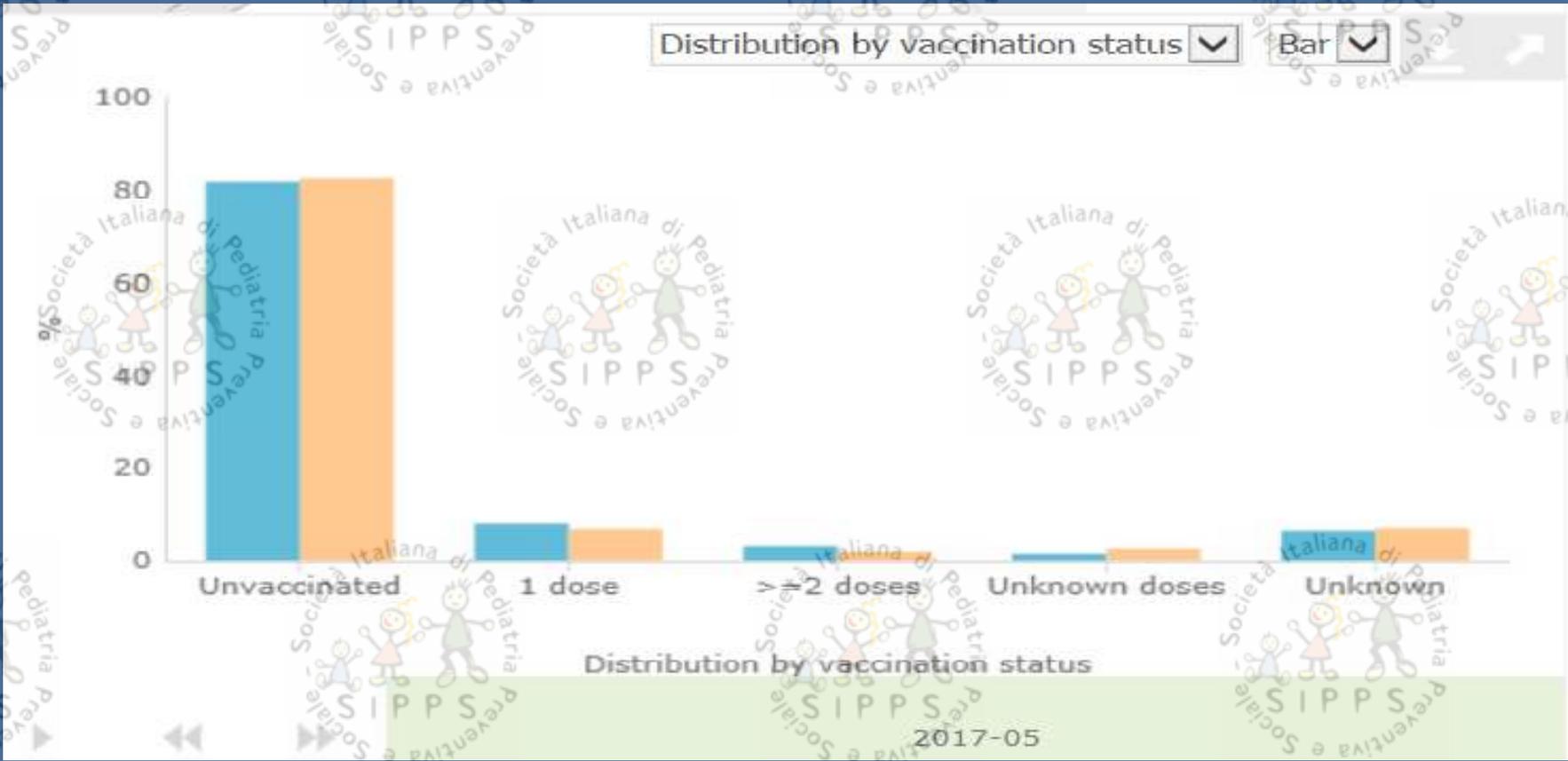


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# Complications of typical measles infection

Complication	Rate per 100,000 cases	Cases, %
Ortis Media	8500-15,000	7-9
Pneumonia	3800-7300	1-6
Seizures	500-1000	1-2
Encephalitis	50-400	0.10-0.01
Systemic side effects	0.5-2.0	0.0001*
Deaths	10-10,000	0.001-10

\* Prevacine era

# ROSOLIA



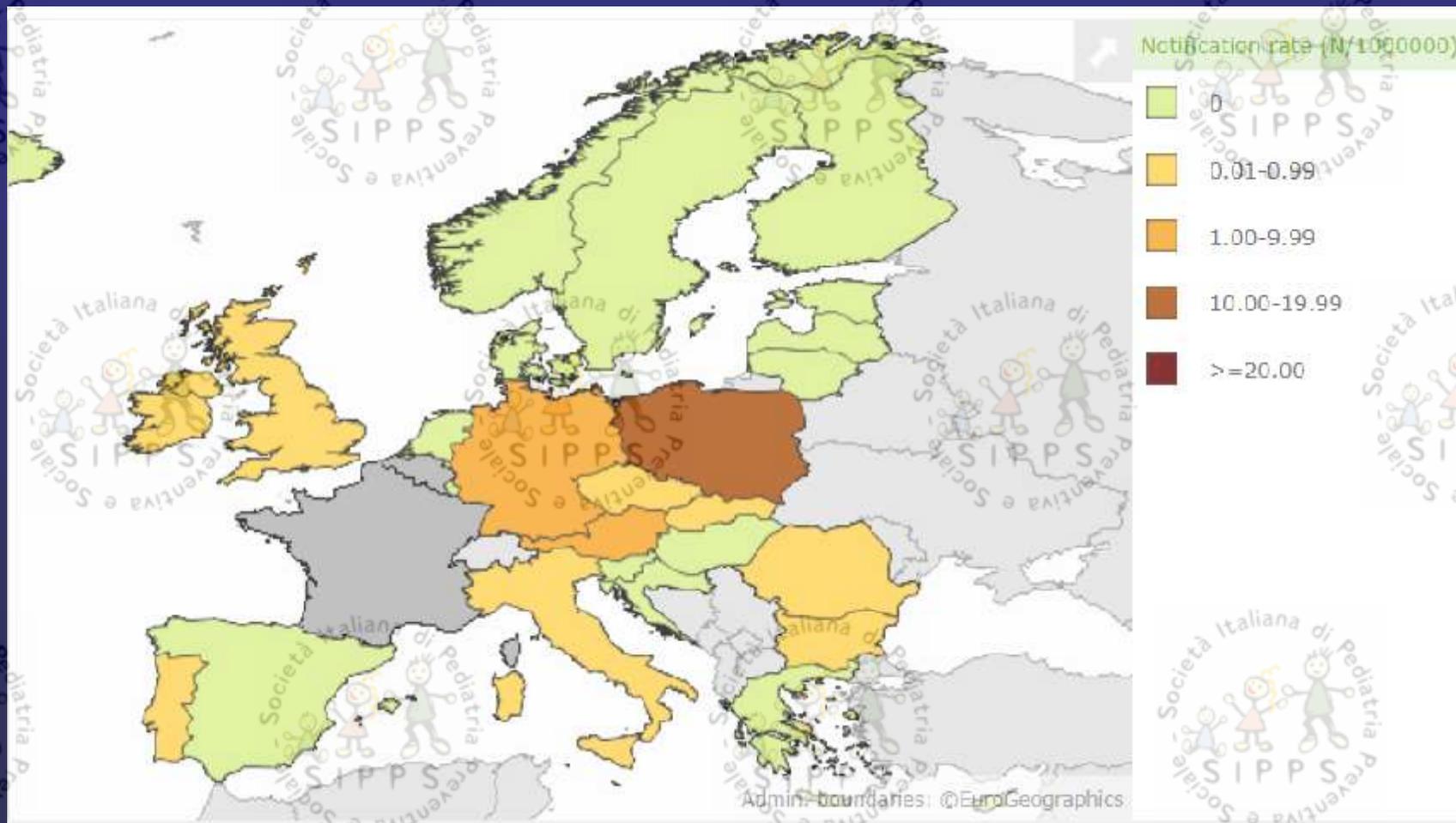


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Rubella reported cases

Update report 15/09/2017



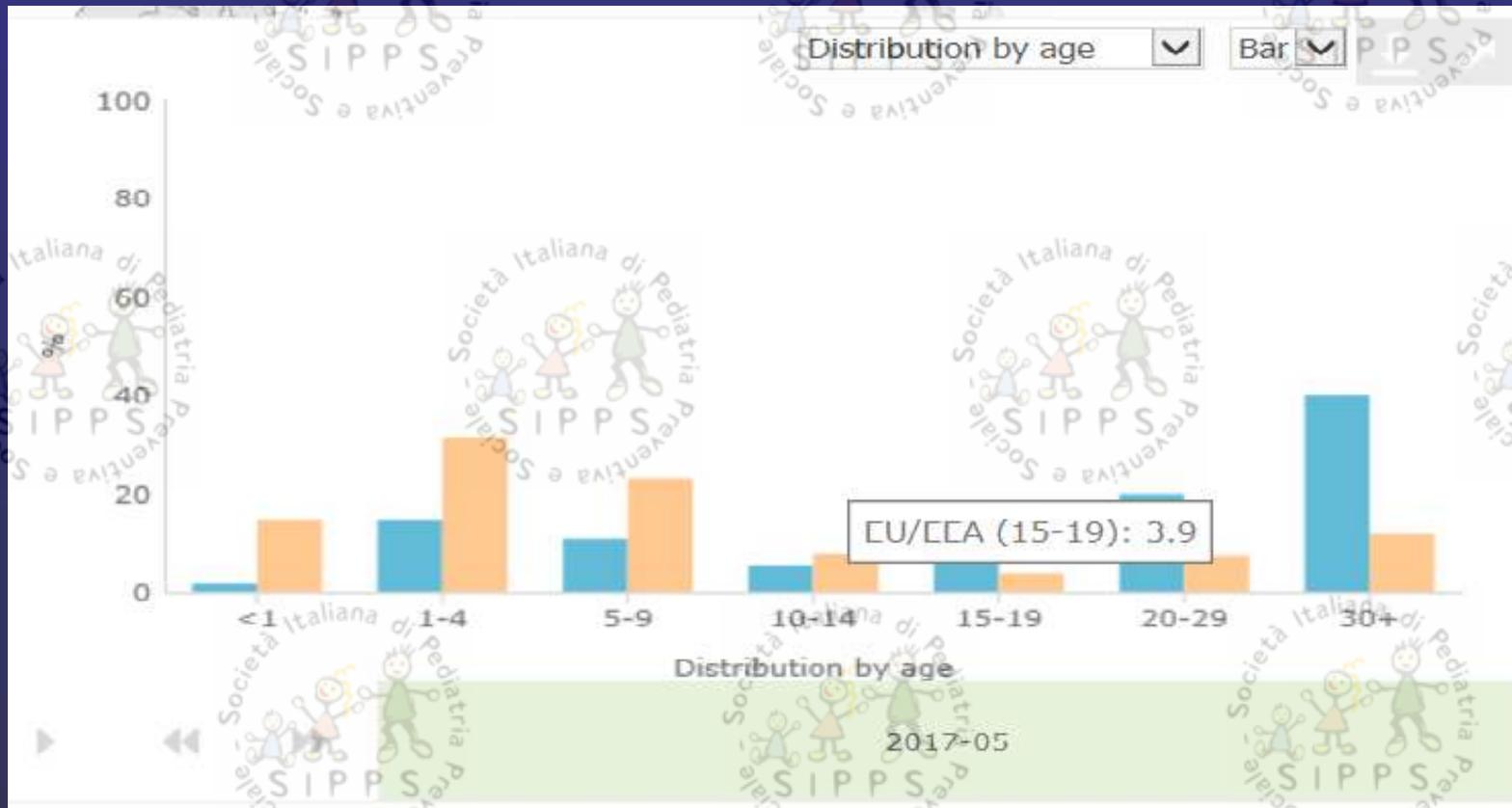


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Rubella reported cases

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Rubella reported cases

Update report 15/09/2017





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**Table 2. Year of introduction of surveillance systems for rubella, rubella in pregnancy and congenital rubella, by country**

Country	Rubella	Rubella in pregnancy	Congenital Rubella
Austria (AT)	2007	2007	2007
Belgium (BE)			2006
Bulgaria (BG)	1970		2001
Cyprus (CY)	1984	1984	2004
Czech republic (CZ)	1961	1961	1961
Germany (DE)	2001		1961
Denmark (DK)		1994	1994
Estonia (EE)	1979	1979	1979
Spain (ES)	1981	1981	1987
Finland (FI)	1995	1969	1969
France (FR)		1976	1976
Greece (GR)	1998	2004	1998
Hungary (HU)	1973	1976	1976
Ireland (IE)	1948	1948	1948
Iceland (IS)	1977	1977	1977
Italy (IT)	1934	2005	2005
Lithuania (LT)	2003	2003	2003
Luxembourg (LU)	2004		
Latvia (LV)	1999	1999	1999
Malta (MT)	2004	2004	1997
Netherlands (NL)	1950	2004	2004
Norway (NO)	1975	1994	1977
Poland (PL)	1966	1966	1966
Portugal (PT)	1987	1987	1987
Romania (RO)	2010	2010	2000
Sweden (SE)	1996	1996	1996
Slovenia (SI)	1977	1977	1977
Slovakia (SK)	1976	1976	1976
United Kingdom (UK)	1995	1971	1971
Total	26	25	28

Legend: ■ < 1970    ■ 1970–1999    ■ ≥ 2000

DE: Rubella surveillance system; the five 'New Länder' introduced rubella surveillance at different dates (2001–2009)

## TECHNICAL REPORT

Survey on rubella, rubella in pregnancy and congenital rubella surveillance systems in EU/EEA countries

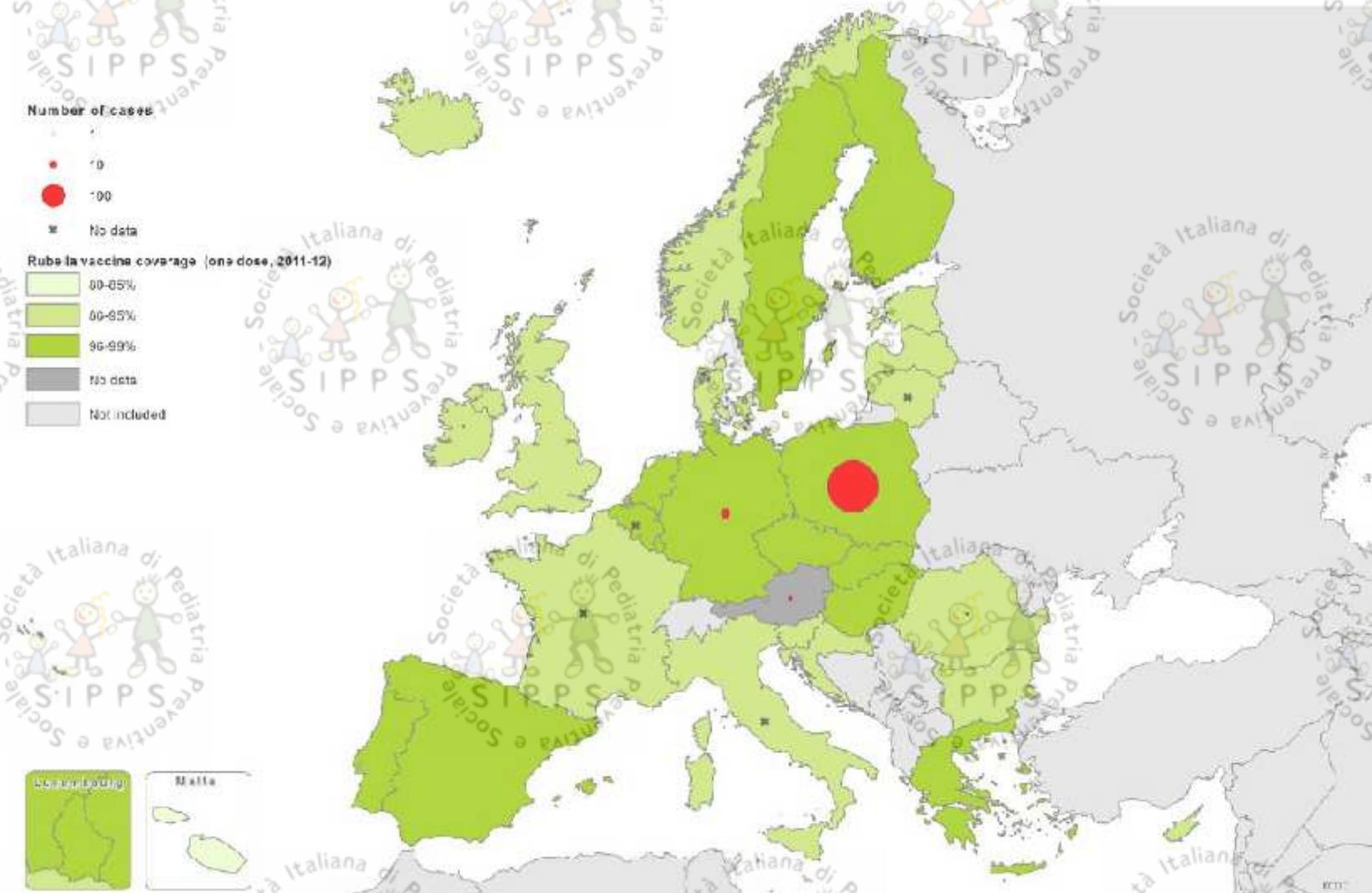
[www.ecdc.europa.eu](http://www.ecdc.europa.eu)

**Table. Number of rubella cases by month and notification rate (cases per million) by country, June 2016 to May 2017, EU/EEA countries**

ECDC 2017

Country	2016					2017					Total cases	Cases per million	Total lab-positive cases			
	2016	2016	2016	2016	2016	2016	2016	2016	2016	2016						
	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May				
Austria	0	0	1	0	0	0	0	0	0	0	24	1	1	27	3,11	23
Bulgaria	0	1	0	0	0	0	1	1	0	0	0	0	0	3	0,42	0
Croatia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cyprus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Czech Republic	0	0	0	0	0	0	0	0	0	0	0	1 NR	1	0,09	1	
Denmark	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estonia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Finland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Germany	15	15	3	4	3	7	5	5	4	8	7	9	85	1,03	20	
Greece	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hungary	0	0	0	0	0	0	0	0 NR	NR	NR	NR	NR	0	0	0	0
Iceland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ireland	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0,21	0
Italy	6	1	1	0	3	4	2	3	6	10	10	9	55	0,91	24	
Latvia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lithuania	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Luxembourg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malta	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Netherlands	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Norway	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Poland	113	52	47	46	78	57	70	50	39	49	51	64	716	18,86	9	
Portugal	2	0	0	0	0	1	0	0	0	1	0 NR	4	0,39	0		
Romania	1	0	3	0	1	2	2	1	0	0	0 NR	10	0,51	10		
Slovakia	0	0	0	0	0	0	0	0	0	0	1	0	1	0,18	0	
Slovenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Spain	0	0	0	0	0	0	0	0	0	0	0 NR	0	0	0	0	
Sweden	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
United Kingdom	0	0	0	0	0	1	0	0	0	0	1	0	2	0,03	2	
<b>Total</b>	<b>137</b>	<b>69</b>	<b>55</b>	<b>50</b>	<b>85</b>	<b>73</b>	<b>80</b>	<b>59</b>	<b>49</b>	<b>93</b>	<b>72</b>	<b>83</b>	<b>905</b>	<b>2,1</b>	<b>89</b>	

**Number of rubella cases by country, June 2014 (n=511), and rubella vaccine coverage (one dose, 2011-12, WHO\*), EU/EEA countries**



\* Coverage figures (%) are official national figures reported via the annual WHO/UNICEF Joint Reporting Form. See notes at the end of this report for further explanations.

From ECDC, 2014

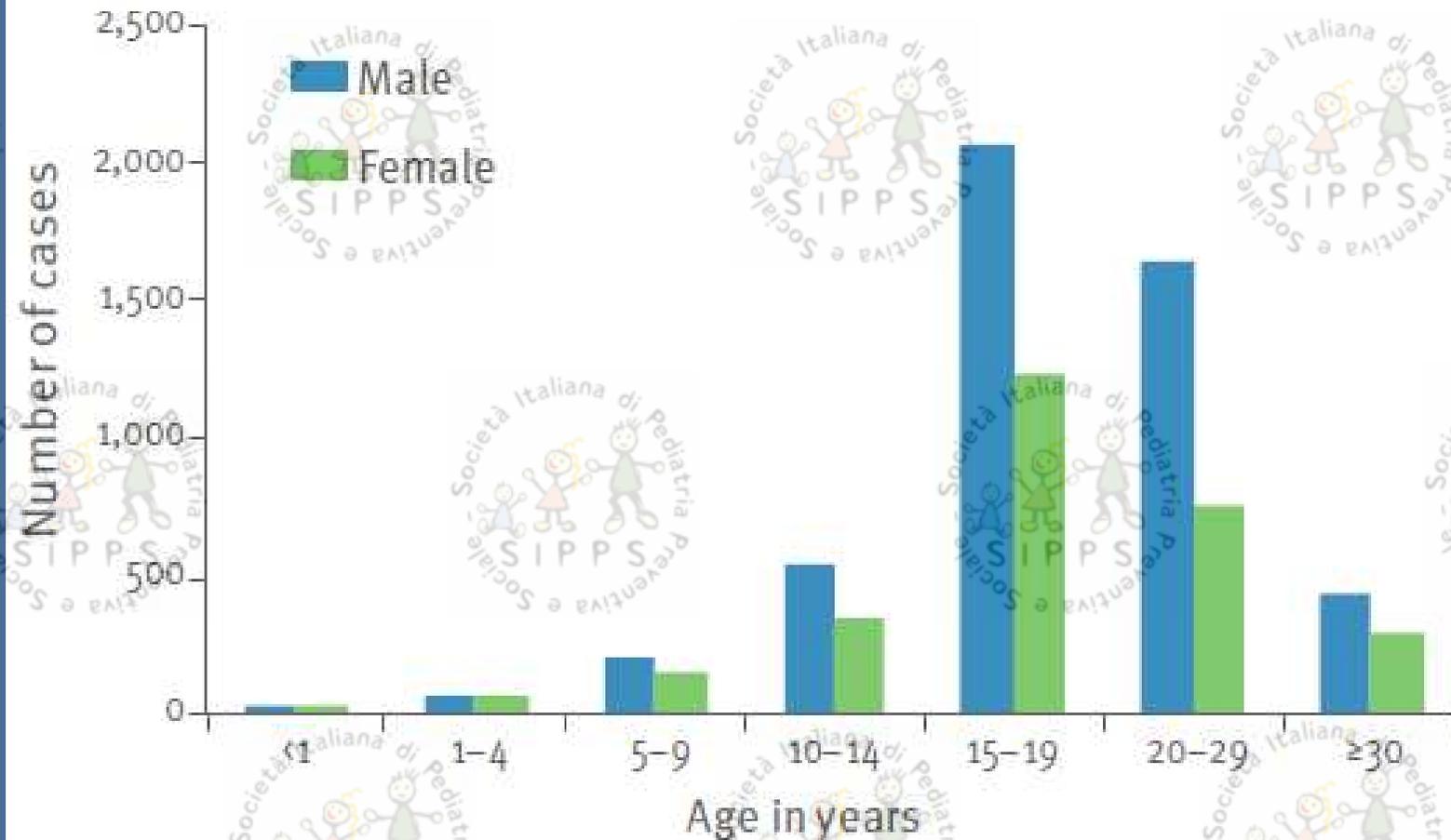
# CONGENITAL RUBELLA SYNDROME (CRS)

- CRS prevention is the objective of rubella immunization
- Rubella can be a most dangerous disease, particularly when rubella in pregnant women is occurring early in pregnancy (first trimester); after 4th month of pregnancy defects are rare
- CRS may lead to fetal death, spontaneous abortion, stillbirths
- CRS can affect all organ systems, most common is deafness
- Other manifestations: e.g., eye defects (cataracts, glaucoma, retinopathy), cardiac defects (septal defects, pulmonic stenosis), microcephaly, mental retardation, bone lesions

# PAROTITE



# Number of mumps cases by age and sex in an outbreak in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, December 2010–September 2012 (n=7,895)



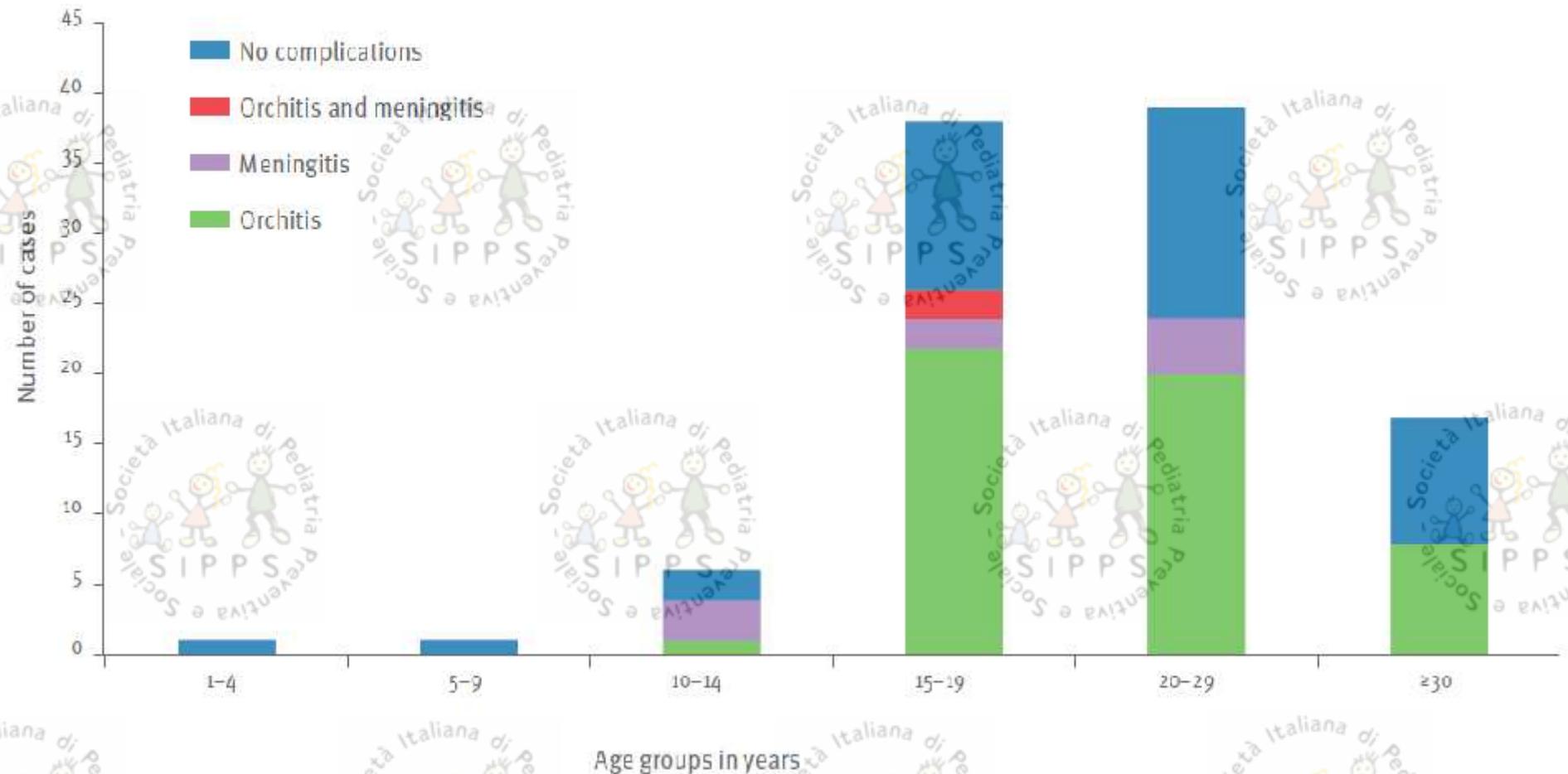
From Hukic M et al., Euro Surveill 2014

Characteristics of mumps patients hospitalised at the Clinical Centre of the University of Sarajevo during a mumps outbreak in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, December 2010–September 2012 (n=105)

Vaccination status	Number of patients	Complications			
		Orchitis n(%)	Meningitis n (%)	Orchitis and meningitis n(%)	No complications n(%)
Vaccinated (2 doses)	29	16 (55)	4 (14)	1 (3)	8 (28)
Vaccinated (1 dose)	2	1 (50)	0 (0)	0 (0)	1 (50)
Unvaccinated	36	20 (56)	1 (3)	1 (3)	14 (39)
Unknown	38	14 (37)	4 (11)	0 (0)	20 (53)
<b>Total</b>	<b>105</b>	<b>51 (49)</b>	<b>9 (9)</b>	<b>2 (2)</b>	<b>43 (41)</b>

From Hukic M et al., Euro Surveill 2014

Complications observed among mumps patients hospitalised at the Clinical Centre of the University of Sarajevo according to age, mumps outbreak in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, December 2010–September 2012 (n=105)



From Hukic M et al., Euro Surveill 2014

# VARICELLA



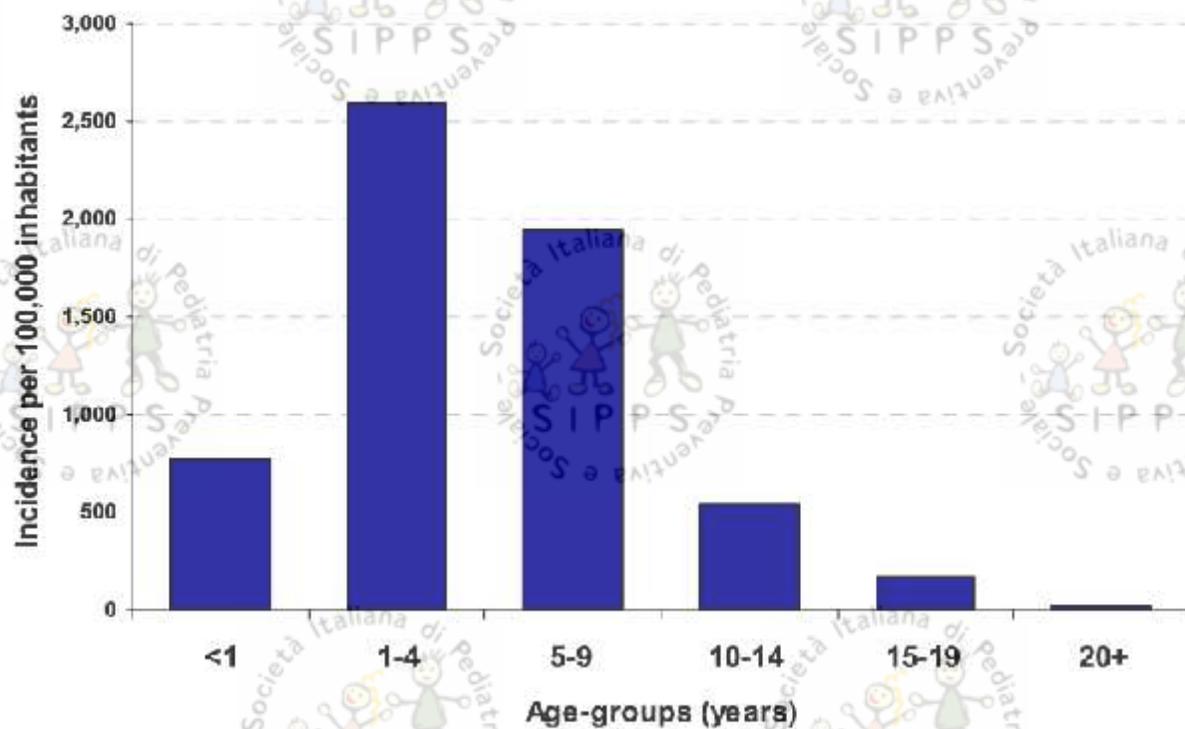




# European Centre for Disease Prevention and Control

An agency of the European Union

Figure 2. Average age-specific incidence of varicella cases, 9 countries, 2000-07





# European Centre for Disease Prevention and Control

An agency of the European Union

*Table 1. Vaccination policies for varicella in European countries (last update through EUVAC.NET gatekeepers on November 2010). Recommendation implies recommendation by the National Health Authority*

Universal varicella vaccination (year of start of the programme)	Only recommended vaccination for susceptible individuals and/or high risk groups	No policy on varicella vaccination
Germany (2004)	Austria	Bulgaria
Greece (2006)	Belgium	Croatia
Italy ( 4 regions Sicilia, Veneto, Puglia, Toscana ) (2003,2007, 2010, 2010)	Cyprus	Czech Republic
Latvia (2008)	Estonia	Denmark
Spain (4 Autonomous regions, Madrid, Navarra, Ceuta and Melilla ) (2006-2009)	Finland	Hungary
	France	Netherlands
	Iceland	Norway
	Ireland	Portugal
	Italy (national)	Romania
	Lithuania	Slovakia
	Luxemburg	Sweden
	Malta	Turkey
	Poland*	
	Slovenia	
	Spain (national)	
	Switzerland	
	United Kingdom	

**Table 1.** Year of introduction, number of doses and age of varicella vaccination in EU and EEA/EFTA countries with childhood universal vaccination, 2012

	Year of introduction	First dose	Second dose
Germany	2004 <sup>1</sup>	11-14m	15-23m
Latvia	2008	12-15m	
Greece	2006	12-15m	4-6y
Cyprus	2010	13-18m	4-6y
Luxemburg	2010	12m	15-23m
Italy			
Sicily	2003	2y	-
Veneto	2005	15m	3y
Puglia	2010		
Toscana	2010		
Spain			
Madrid <sup>2</sup>	2006	15m	-
Navarre	2007	15m	3y
Ceuta	2009	18m	24m
Melilla	2009	15m	24m

<sup>1</sup> Universal vaccination of infants with one dose was recommended in Germany in 2004, and universal vaccination with a second dose in 2009.

<sup>2</sup> Programme withdrawn in 2013.

From ECDC, 2014

# Varicella incidence rates based on mandatory notifications (x 1.000) and hospitalization rates (x100.000) due to varicella in 8 Italian Regions (2003-2012)



- Annual incidence rate 3.0 (2003) → 0.4 (2012)
- Hospitalization rate 3.2 (2003) → 0.8 (2012)

- Annual incidence rate 3.9 (2003) → 3.7 (2012)
- Hospitalization rate 2.3 (2003) → 2.1 (2012)

- Annual incidence rate 1.0 (2003) → 0.1 (2012)
- Hospitalization rate 3.4 (2003) → 0.5 (2012)

- Annual incidence rate 3.2 (2004) → 0.4 (2012)
- Hospitalization rate 5.3 (2004) → 1.2 (2012)

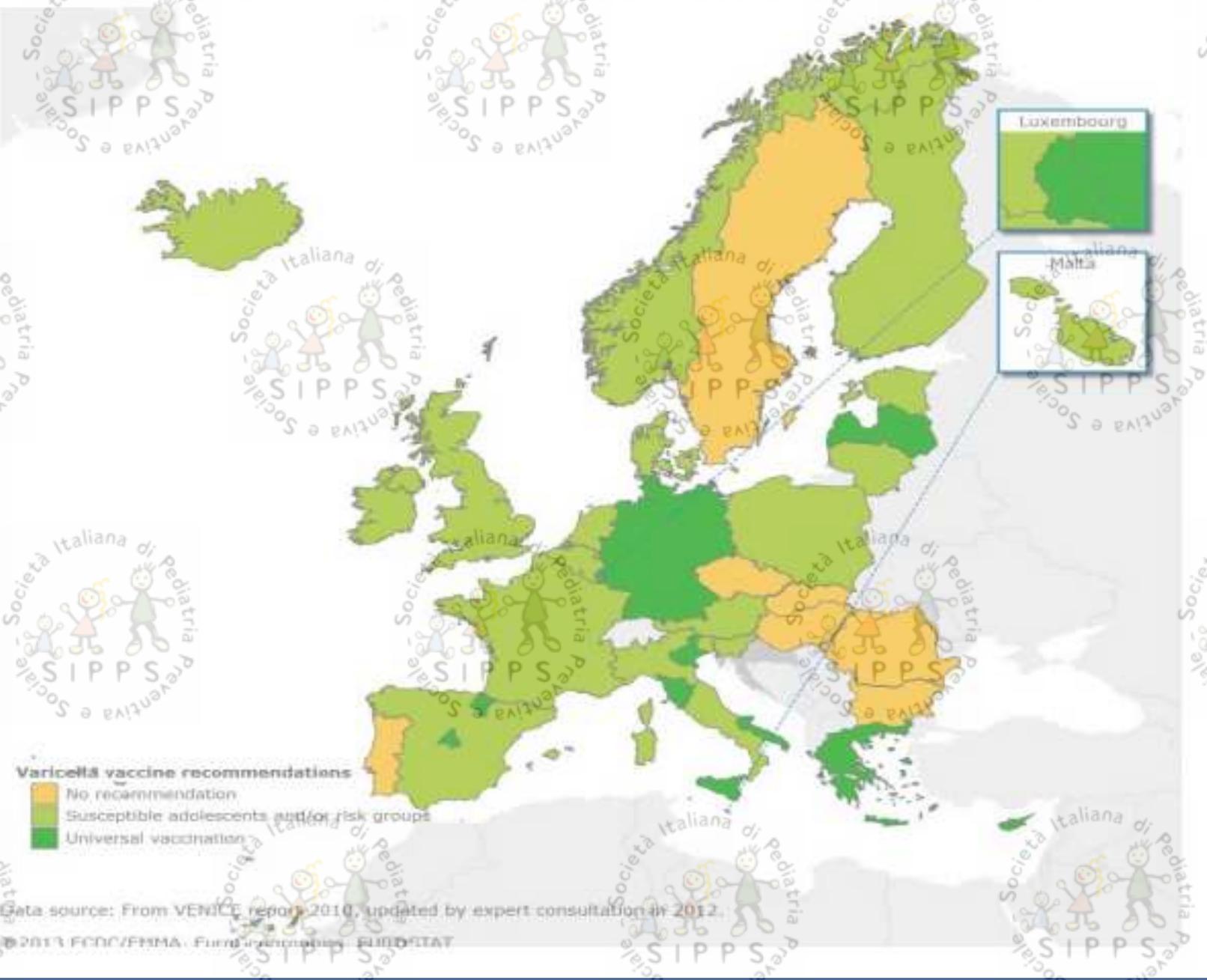
- Annual incidence rate 1.4 (2003) → 0.3 (2012)
- Hospitalization rate 1.8 (2003) → 0.5 (2012)

- Annual incidence rate 1.1 (2003) → 0.6 (2012)
- Hospitalization rate 3.8 (2003) → 1.8 (2012)

- Annual incidence rate 1.1 (2003) → 0.1 (2009)
- Hospitalization rate 4.8 (2003) → 0.8 (2012)

- Annual incidence rate 0.8 (2003) → 0.2 (2012)
- Hospitalization rate 3.3 (2005) → 1.1 (2012)

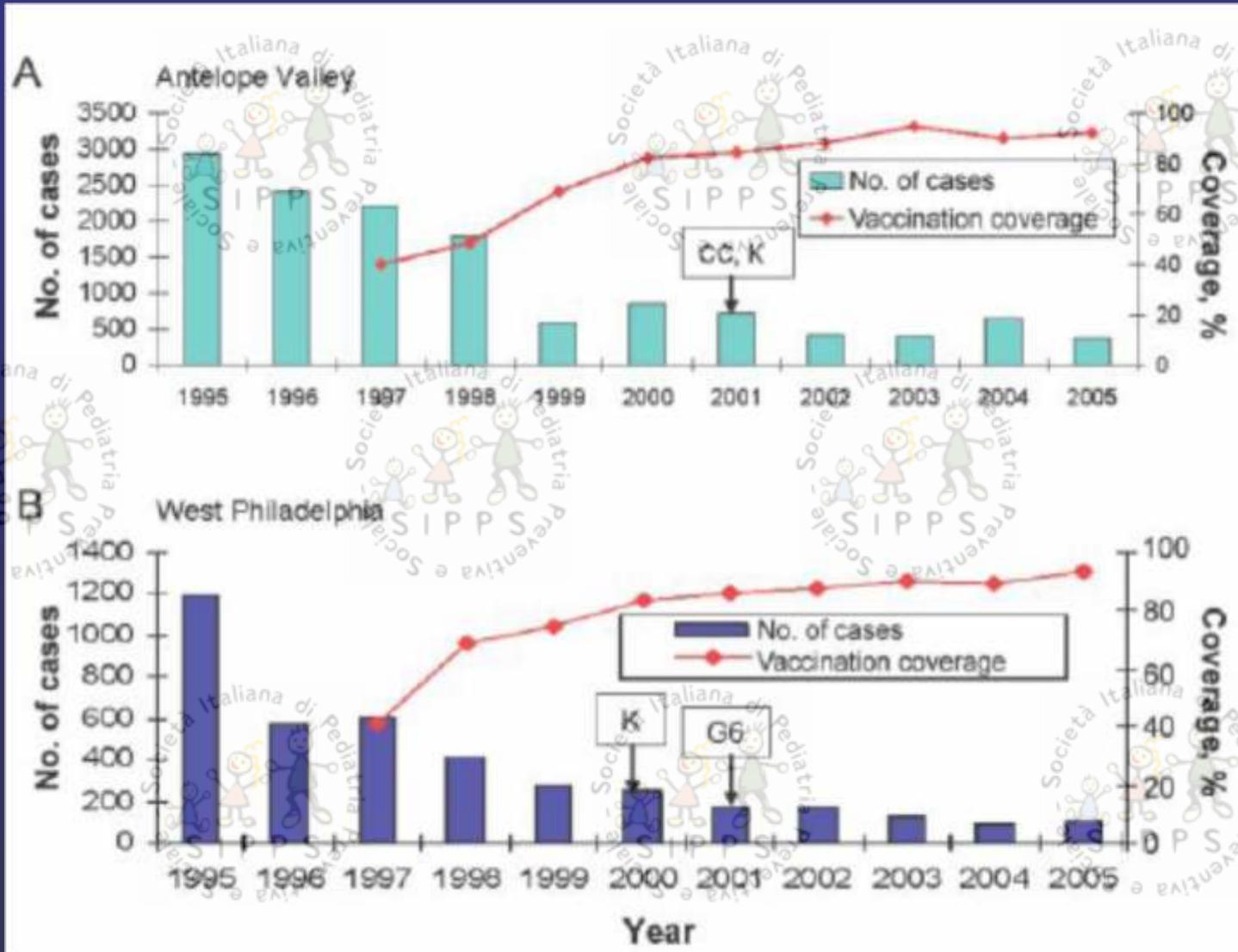
# Varicella vaccination recommendations in EU/EEA countries, 2012



From ECDC, 2014

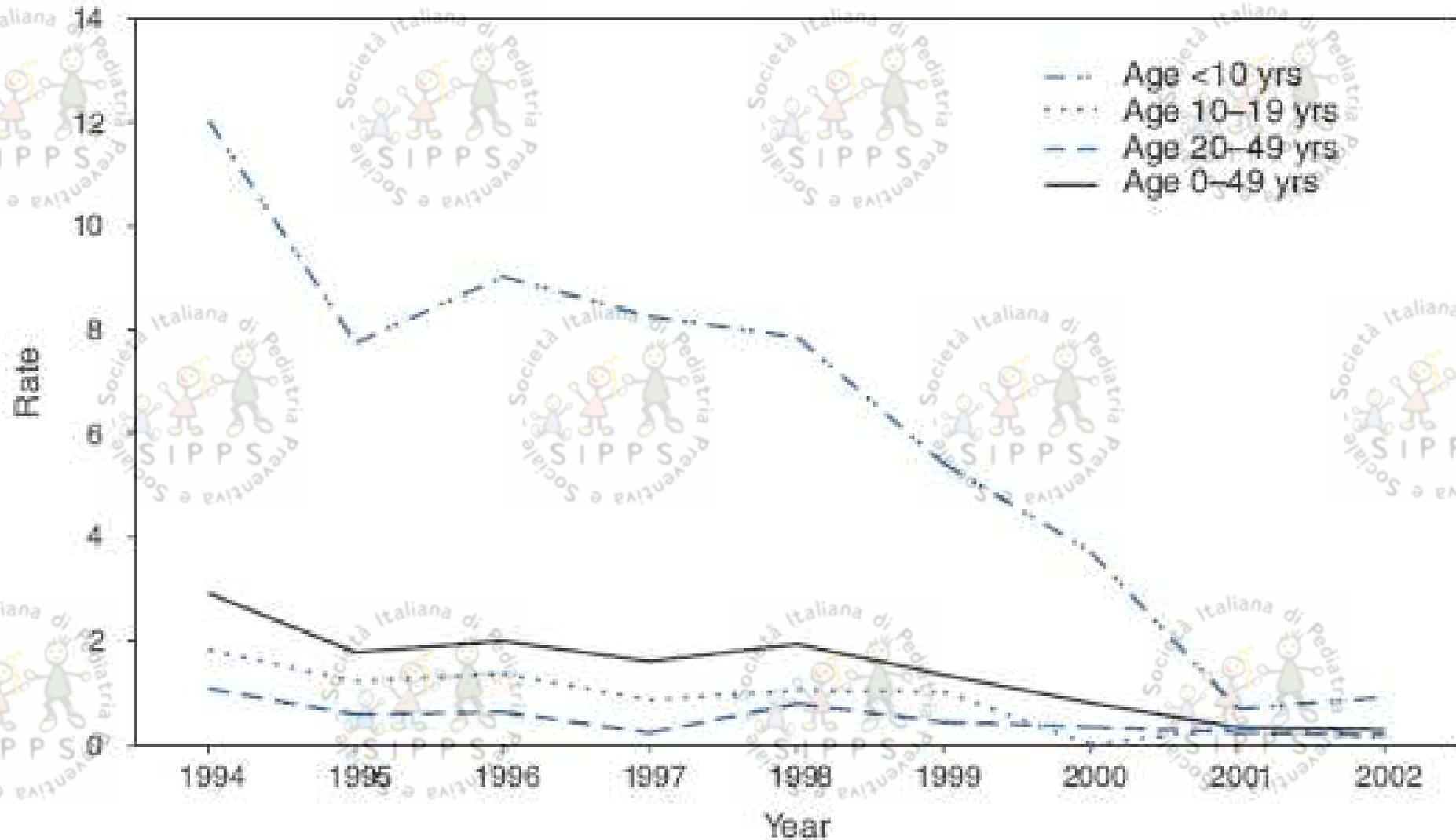
# INCIDENZA DI VARICELLA E COPERTURA VACCINALE IN 2 AREE DEGLI U.S.A.

(Guris D et al. J Infect Dis 2008)

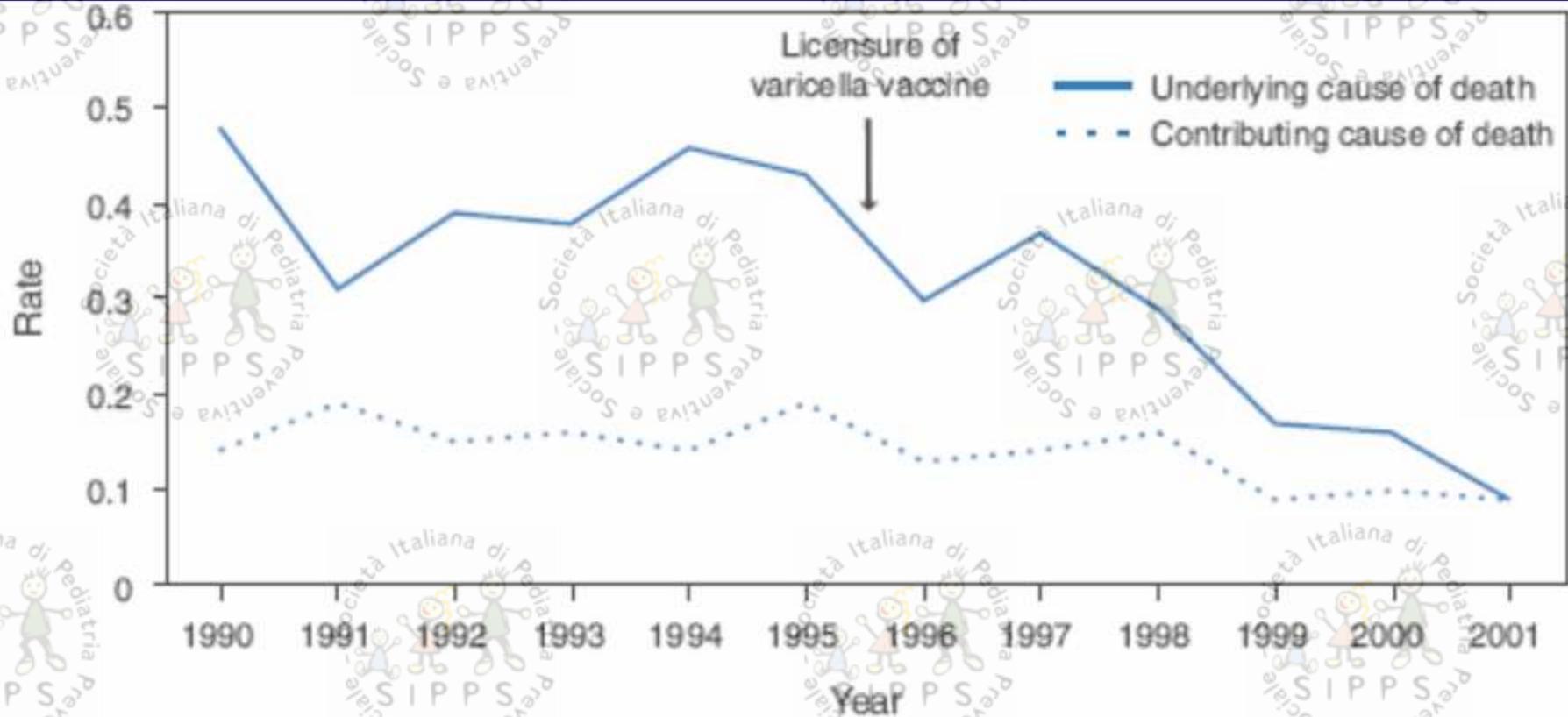


# OSPEDALIZZAZIONE PER VARICELLA NEGLI U.S.A. (casi/100.000)

(Zhou F et al. JAMA 2005)



# MORTALITA' DA VARICELLA NEGLI U.S.A. (casi/milione di popolazione) (MMWR 2007)



# Obiettivi della vaccinazione estensiva per Varicella?

**Obiettivo primario di sanità pubblica:**

- riduzione del numero di casi di varicella con complicanze e ospedalizzazioni,
- contenimento della morbosità della malattia.

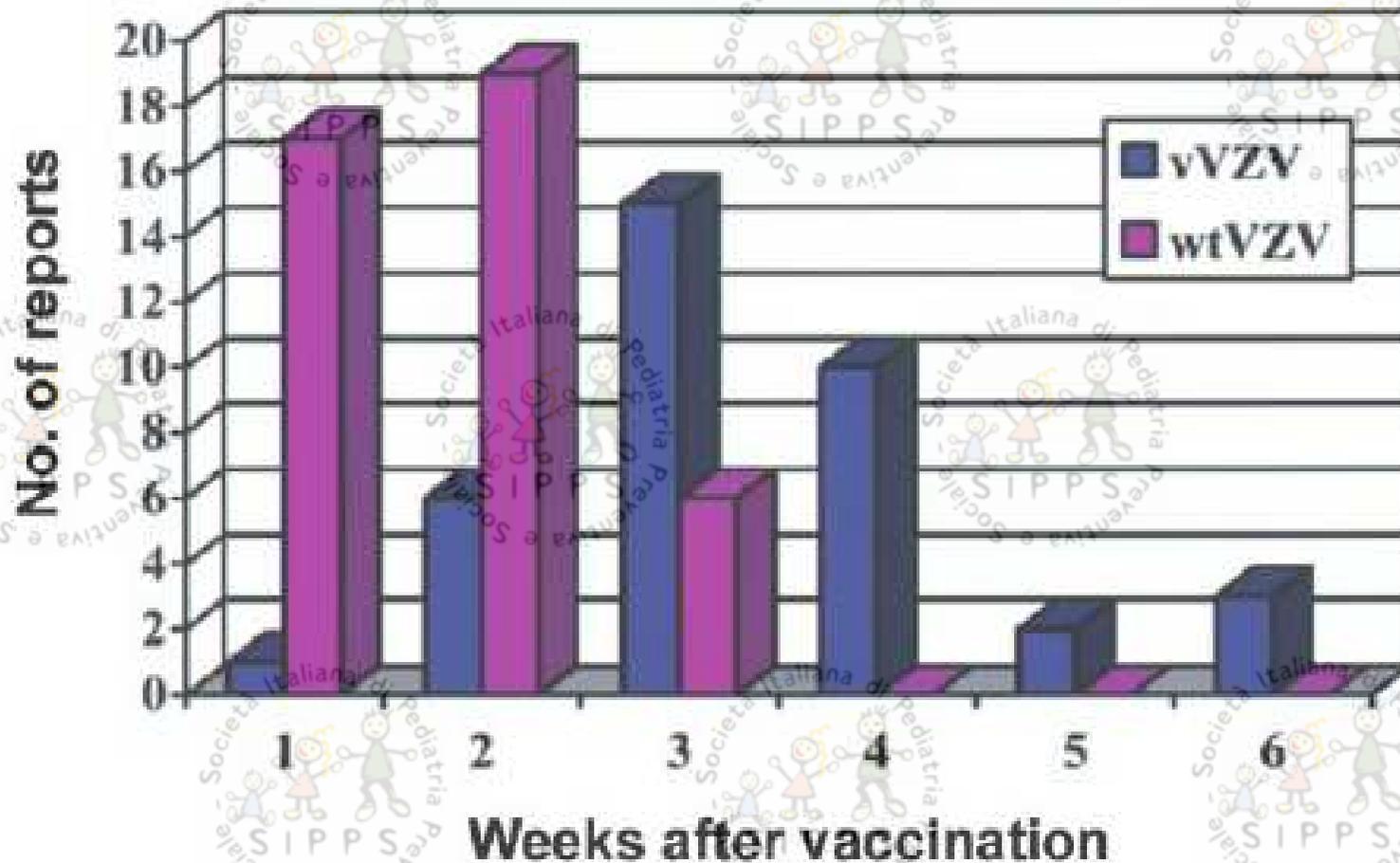
# CARATTERISTICHE DELLA VARICELLA NEI SOGGETTI CON O SENZA VACCINAZIONE

(Da Chaves SS et al. J Infect Dis 2008)

Clinical characteristic	No. (%) of case patients		aOR (95% CI) <sup>a</sup>
	Vaccinated	Unvaccinated	
Fever			
Temperature >38°C	564 (34)	3715 (65)	0.28 (0.25–0.31)
Duration >2 days	99 (18)	604 (16)	0.53 (0.43–0.66)
≥50 lesions <sup>b</sup>	417 (25)	3679 (65)	0.19 (0.17–0.21)
Rash			
Duration >5 days	499 (50)	376 (68)	0.50 (0.39–0.63)
Mostly maculopapular	695 (70)	240 (44)	2.96 (2.35–3.73)
Mostly vesicular	303 (31)	319 (58)	0.32 (0.25–0.41)
Described as itchy	1115 (80)	1343 (88)	0.63 (0.51–0.77)
Moderate to severe illness	635 (38)	5063 (89)	0.07 (0.06–0.08)
Patient seen by a health care provider	589 (63)	1811 (38)	2.82 (2.50–3.17)
Presence of complication	83 (5)	652 (12)	0.44 (0.35–0.56)
Use of acyclovir	38 (3)	275 (5)	0.56 (0.39–0.79)
Use of other antibiotics	73 (5)	376 (7)	0.80 (0.62–1.04)
Use of antipyretic or analgesics	454 (36)	1130 (46)	0.67 (0.58–0.77)

# CASI DI RASH DA VACCINO O DA VIRUS SELVAGGIO REGISTRATI DOPO VACCINAZIONE CON VZV

(da Galea SA, J Infect Dis 2008)



# COSTO ANNUO COMPLESSIVO A LIVELLO NAZIONALE DELLA VARICELLA IN ITALIA

	COSTO MEDIO(€)		NUMERO EVENTI		COSTI ANNUALI (€)	
	BB	Adulto	BB	Adulto	BB	Adulto
<b>TRATTAMENTO DOMICILIARE</b>	34,20	39,70	493.337	50.475	16.872.125	2.003.857
<b>OSPEDALIZZAZIONE</b>	1.951,00 <sup>1</sup>		1.079*		2.105.129	
<b>TOTALE COSTI SSN</b>					<b>20.981.111</b>	
<b>COSTI INDIRETTI</b>	76,80	704,00	493.337	50.475	37.888.828	35.534.400
<b>TOTALE COSTI INDIRETTI</b>					<b>73.423.228</b>	
<b>TOTALE COSTI PER LA SOCIETÀ</b>					<b>94.404.339 €</b>	

Note: <sup>1</sup> Valore medio ponderato calcolato in base al numero delle ospedalizzazioni del triennio 2003-2005 e alle tariffe di rimborso dei DRG 421 e 422. \* Fonte SDO Min Sal anno 2005.

# PIANO PER LA PREVENZIONE VACCINALE 2016-2018

Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	↳	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni
DTPa**		DTPa		DTPa			DTPa				DTPa***	dTpaIPV	1 dose dTpa**** ogni 10 anni		
IPV		IPV		IPV			IPV			IPV					
Epatite B	EpB-EpB*	Ep B		Ep B*			Ep B						3 Dosi: <i>Pre Esposizione</i> (0, 1, 6 mesi) 4 Dosi: <i>Post Esposizione</i> (0, 2, 6 sett. + booster a 1 anno) o <i>Pre Esposizione immediata</i> (0, 1, 2, 12)		
Hib		Hib		Hib			Hib								
Pneumococco		PCV		PCV			PCV		PCV		PCV/PPV23 (vedi note)				PCV
MPRV								MPRV			MPRV				
MPR								MPR			oppure MPR	MPR	oppure MPR	2 dosi MPR***** + V <sup>h</sup> (0-4/8 settimane)	
Varicella									V						
Meningococco C								Men C o MenACWY coniugato	Men C o MenACWY coniugato						
Meningococco B**		Men B	Men B			Men B		Men B	Men B						
HPV												HPV*: 2-3 dosi (in funzione di età e vaccino); fino a età massima in scheda tecnica			
Influenza								Influenza <sup>oo</sup>				Influenza <sup>oo</sup>		1 dose all'anno	
Herpes Zoster															1 dose#
Rotavirus		Rotavirus##													
Epatite A									EpA###			EpA###	2 dosi (0-6-12 mesi)		

TABLE 1. Humoral and Cellular Immune Response to 1 and 2 Doses of Varicella Vaccines Among Children Aged 12 Months to 12 Years

Immune Response	6 wk After Dose 1		6 wk After Dose 2 and 3 mo Between Doses		6 wk After Dose 2 at Age 4–6 y	
	Varicella Vaccine	MMRV	Varicella Vaccine	MMRV	Varicella Vaccine	MMRV
VZV IgG gpELISA $\geq 5$ U/mL	85.7% <sup>44</sup>	91.2% <sup>47</sup>	99.6% <sup>44</sup>	99.2% <sup>67</sup>	99.4% <sup>66</sup>	98.9% <sup>66b</sup>
GMT VZV IgG gpELISA U/mL	12.5 <sup>44</sup>	13.0 <sup>67</sup>	142.6 <sup>44</sup>	583 <sup>67</sup>	212.4 <sup>66</sup>	317 <sup>66</sup>
Mean stimulation index	28.6 $\pm$ 6.2 <sup>65</sup>		36.9 $\pm$ 9.1 <sup>65</sup>		58.6 $\pm$ 6.5 <sup>69</sup>	

Mean stimulation indices from different laboratories and from different studies should not be compared directly.

## Perché 2 dosi?

- per completare il ciclo di immunizzazione
- ridurre il rischio di insuccessi vaccinali

# VACCINI ANTIVARICELLA

- **Attualmente sono disponibili due tipi di vaccini:**
  - **un vaccino a singolo antigene**
  - **un vaccino tetravalente nel quale il virus VZ è combinato con quello del morbillo, rosolia e parotite (MMRV)**
- **In entrambi i casi il virus VZ è quello Oka attenuato attraverso numerosi passaggi su colture cellulari**

# Priorix-Tetra™ vs Proquad: Composizione

			
Schwarz measles*	10 <sup>3.0</sup> CCID <sub>50</sub>	Enders Edmonston	10 <sup>3.0</sup> CCID <sub>50</sub>
RIT 4385 (Jeryl Lynn-derived) mumps*	10 <sup>4.4</sup> CCID <sub>50</sub>	Jeryl Lynn-derived	10 <sup>4.3</sup> CCID <sub>50</sub>
Wistar RA 27/3 rubella†	10 <sup>3.0</sup> CCID <sub>50</sub>	Wistar RA 27/3	10 <sup>3.0</sup> CCID <sub>50</sub>
Oka varicella†	10 <sup>3.3</sup> pfu	Oka/Merck	10 <sup>3.99</sup> pfu

CCID<sub>50</sub> = median cell culture infective dose;

pfu = plaque forming unit

\* Propagated in chick embryo tissue cultures

† Propagated in MRC-5 human diploid cells

# CARATTERISTICHE DEL VACCINO VZV OKA/Merck

- Il vaccino è liofilizzato
- Quando ricostituito secondo le istruzioni della casa produttrice e mantenuto a temperatura ambiente per un massimo di 30 minuti contiene un minimo di 1.350 PFU di VZV in ciascuna dose di 0,5 mL
- Ciascuna dose contiene anche 12,5 mg di gelatina idrolizzata, tracce di neomicina e di siero di feto di bovino, 25 mg di saccarosio e tracce di cellule diploidi umane, incluso DNA e proteine
- Nel vaccino tetravalente (MMRV), la concentrazione di VZV è significativamente più elevata rispetto a quella del vaccino monovalente ( $3,99 \log_{10}$  PFU in confronto a  $3,13 \log_{10}$  PFU)

# CARATTERISTICHE DEL VACCINO VZV OKA/GSK

- Il vaccino è liofilizzato
- Quando ricostituito secondo le istruzioni della casa produttrice e mantenuto a temperatura ambiente per un massimo di 30 minuti contiene un minimo di  $10^{3.3}$  PFU di VZV in ciascuna dose di 0,5 mL
- Ciascuna dose contiene anche 12,5 mg di gelatina idrolizzata, tracce di neomicina e di siero di feto di bovino, 25 mg di saccarosio e tracce di cellule diploidi umane, incluso DNA e proteine
- Nel vaccino tetravalente (MMRV), la concentrazione di VZV è sostanzialmente sovrapponibile a quella presente nella preparazione con il solo VZV

# Benefici derivanti dall'impiego di vaccini combinati

- Praticità grazie a un numero inferiore di iniezioni
- Minori preoccupazioni in merito al fatto di causare dolore e ansia nei soggetti
- Tempo ridotto di assistenza medica/infermieristica richiesto per l'iniezione
- Minore spreco del vaccino
- Tempi più rapidi di avvicendamento dei soggetti vaccinati
- Logistica semplificata (es. inventari ridotti)
- Costi ridotti della vaccinazione

## Notice to Readers: Licensure of a Combined Live Attenuated Measles, Mumps, Rubella, and Varicella Vaccine

*Please note:* An erratum has been published for this article. To view the erratum, please click [here](#).

On September 6, 2005, the Food and Drug Administration licensed a combined live attenuated measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad<sup>®</sup>, Merck & Co., Inc., Whitehouse Station, New Jersey) for use in children aged 12 months--12 years. The attenuated measles, mumps, and rubella vaccine viruses in ProQuad are identical and of equal titer to those in the measles, mumps, and rubella (MMR) vaccine, MMRII<sup>®</sup> (Merck). The titer of Oka/Merck varicella-zoster virus is higher in MMRV vaccine than in single antigen varicella vaccine, VARIVAX<sup>®</sup> (Merck), a minimum of 3.13 log<sub>10</sub> plaque-forming units (pfu) versus 1,350 pfu (approximately 1.13 log<sub>10</sub>), respectively.

Advisory Committee on Immunization Practices (ACIP) current recommendations are that children aged 12 months--12 years receive 2 doses of MMR vaccine at least 1 month apart and 1 dose of varicella vaccine (1). \* MMRV vaccine can decrease the number of injections received by children when all of the component antigens are indicated for administration. One dose of MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination (2).

MMRV vaccine was licensed on the basis of equivalence of immunogenicity of the antigenic components rather than clinical efficacy; the efficacy of the individual components of MMRV has been established previously (3,4). Clinical studies of 7,484 healthy children aged 12--23 months (of whom 5,446 received MMRV vaccine) indicated that those who received 1 dose of MMRV vaccine developed levels of antibody to measles, mumps, rubella, and varicella similar to those of children who received 1 dose of MMR and 1 dose of varicella vaccines concomitantly at separate injection sites. The respective prevalences of detectable antibody (i.e., positive serologic response) using defined cutoff levels among MMRV vaccine recipients were 97.4% (95% confidence interval [CI] = 96.9%--97.9%) for measles ( $\geq 255$  mIU/mL when compared with the WHO II [66/202] reference immunoglobulin for measles), 95.8% (CI = 95.1%--96.4%) for mumps ( $\geq 10$  enzyme-linked immunosorbent assay [ELISA] units/mL), 98.5% (CI = 98.1%--98.8%) for rubella ( $\geq 10$  IU rubella antibody/mL when compared with the WHO international reference serum for rubella), and 91.2% (CI = 90.3%--92.0%) for varicella ( $\geq 5$  gpELISA units/mL [a response rate highly correlated with long-term protection]) (5).



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## MMRV Vaccine

**MMRV vaccine** may be given to children from 1 through 12 years of age to protect them from these four diseases.

Two doses of MMRV vaccine are recommended:

- The first dose at **12 through 15 months of age**
- The second dose at **4 through 6 years of age**

These are *recommended* ages. But children can get the second dose up through 12 years as long as it is at least 3 months after the first dose.

Children may also get these vaccines as 2 separate shots: **MMR** (measles, mumps and rubella) and **varicella** vaccines.

### 1 Shot (MMRV) or 2 Shots (MMR & Varicella)?

- Both options give the same protection.
- One less shot with MMRV.
- Children who got the first dose as MMRV have had more fevers and fever-related seizures (about 1 in 1,250) than children who got the first dose as separate shots of MMR and varicella vaccines on the same day (about 1 in 2,500).

Your doctor can give you more information, including the Vaccine Information Statements for MMR and Varicella vaccines.

Anyone 13 or older who needs protection from these diseases should get MMR and varicella vaccines as separate shots.

MMRV may be given at the same time as other vaccines.



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## Some children should not get MMRV vaccine or should wait.

### Children should not get MMRV vaccine if they:

- I have ever had a life-threatening allergic reaction to a previous dose of MMRV vaccine, or to either MMR or varicella vaccine.
- Have ever had a life-threatening allergic reaction to any *component* of the vaccine, including gelatin or the antibiotic neomycin. Tell the doctor if your child has any severe allergies.
- Have HIV/AIDS, or another disease that affects the immune system.
- Are being treated with drugs that affect the immune system, including high doses of oral steroids for 2 weeks or longer.
- Have any kind of cancer
- Are being treated for cancer with radiation or drugs

### Check with your doctor if the child:

- Has a history of seizures, or has a parent, brother or sister with a history of seizures.
- Has a parent, brother or sister with a history of immune system problems.
- Has ever had a low platelet count, or another blood disorder.
- Recently had a transfusion or received other blood products.
- Might be pregnant.

Children who are moderately or severely ill at the time the shot is scheduled should usually wait until they recover before getting MMRV vaccine. Children who are only mildly ill may usually get the vaccine.

Ask your doctor for more information.



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## What are the risks from MMRV vaccine?

A vaccine, like any medicine, is capable of causing serious problems, such as severe allergic reactions. The risk of MMRV vaccine causing serious harm, or death, is extremely small.

Getting MMRV vaccine is much safer than getting measles, mumps, rubella, or chickenpox.

Most children who get MMRV vaccine do not have any problems with it.

### Mild problems

- Fever (about 1 child out of 5).
- Mild rash (about 1 child out of 20).
- Swelling of glands in the cheeks or neck (rare).

If these problems happen, it is usually within 5-12 days after the first dose. They happen less often after the second dose.

### Moderate problems

- Seizure caused by fever (about 1 child in 1,250 who get MMRV), usually 5-12 days after the first dose. *They happen less often when MMR and varicella vaccines are given at the same visit as separate shots (about 1 child in 2,500 who get these two vaccines), and rarely after a 2nd dose of MMRV.*
- Temporary low platelet count, which can cause a bleeding disorder (about 1 child out of 40,000).

### Severe problems (very rare)

Several severe problems have been reported following MMR vaccine, and might also happen after MMRV. These include severe allergic reactions (fewer than 4 per million), and problems such as:

- Deafness.
- Long-term seizures, coma, lowered consciousness.
- Permanent brain damage.

# IMMUNOGENICITA' DI MMRV (GSK)

(Da Knuf et al. *Pediatr Infect Dis J* 2006)

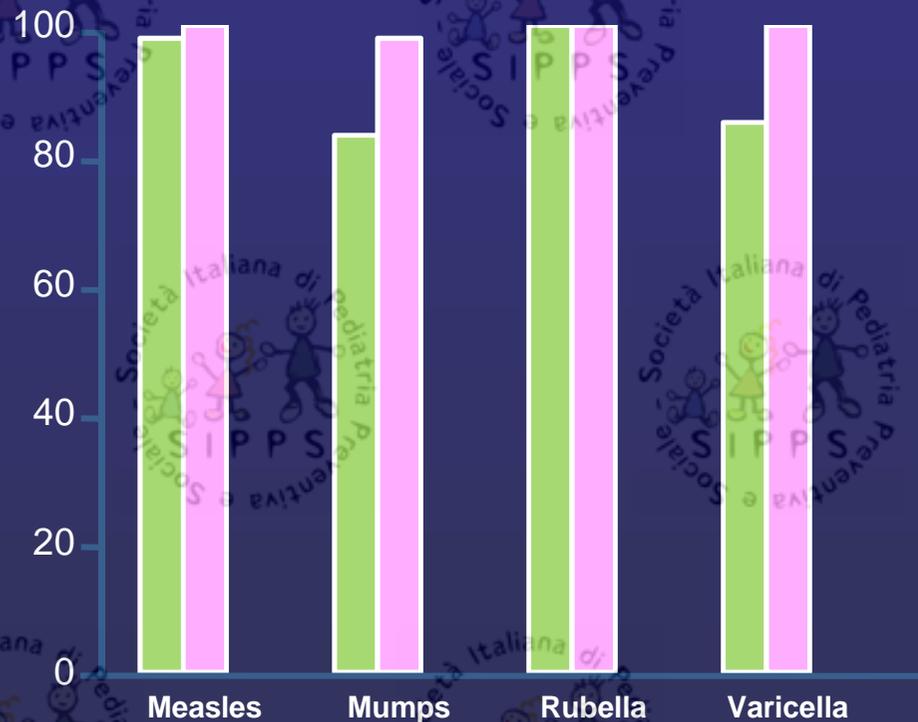
Vaccine	Seroconversion*		GMTs					
	N	n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
<b>Measles</b>								
MMRV	307	307	100	98.8	100	6103.9	5639.6	6606.4
MMR+V	108	108	100	96.6	100	3719.2	3183.7	4344.7
<b>Mumps</b>								
MMRV	307	301	98.0	95.8	99.3	1465.4	1343.8	1598.0
MMR+V	108	107	99.1	94.9	100	1667.8	1441.7	1929.3
<b>Rubella</b>								
MMRV	307	307	100	98.8	100	101.5	94.6	108.8
MMR+V	108	108	100	96.6	100	107.0	95.3	120.2
<b>Varicella</b>								
MMRV	306	306	100	98.8	100	4932.1	4215.1	5771.0
MMR+V	108	108	100	96.6	100	155.2	126.2	190.5

\*Titer  $\geq$  assay cutoff in initially seronegative subjects.

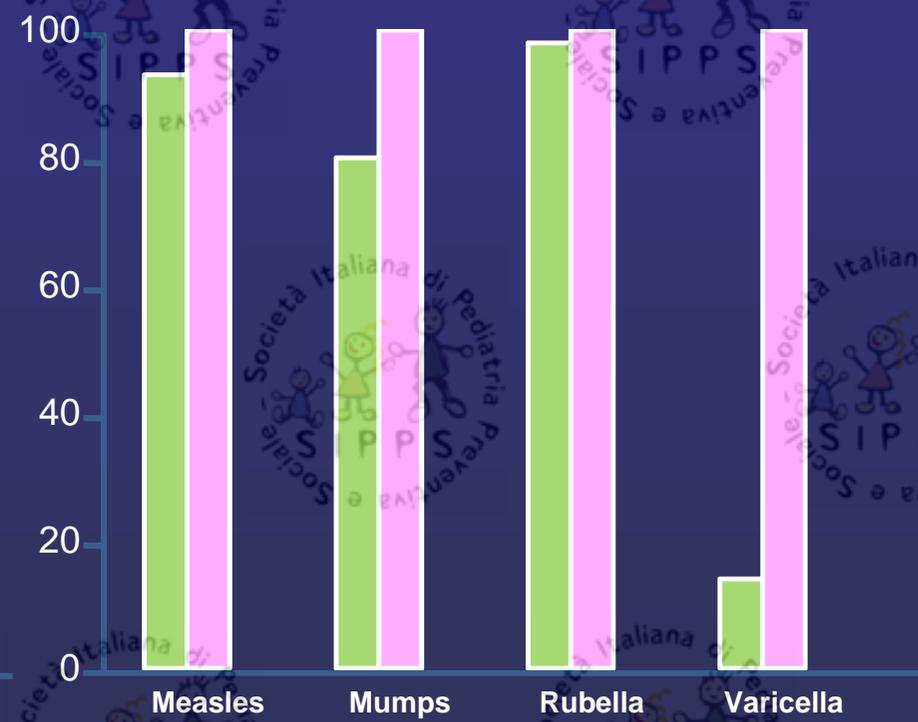
N indicates number of subjects with available results; n, number of seropositive subjects at a given time point; %, percent of subjects with titer for antimeasles  $\geq 150$  mIU/mL, antimumps  $\geq 231$  units/mL, antirubella  $\geq 4$  IU/mL and antivariella  $\geq 4$  dilution<sup>-1</sup>; u/UL, lower/upper limit of 95% CI.

# Seropositivity Rates Before and 42 Days After Administr. of MMRV as a Second Vaccine Dose at 5 to 6 Years of Age

## Pre-vaccinated with MMR-V



## Pre-vaccinated with MMRV



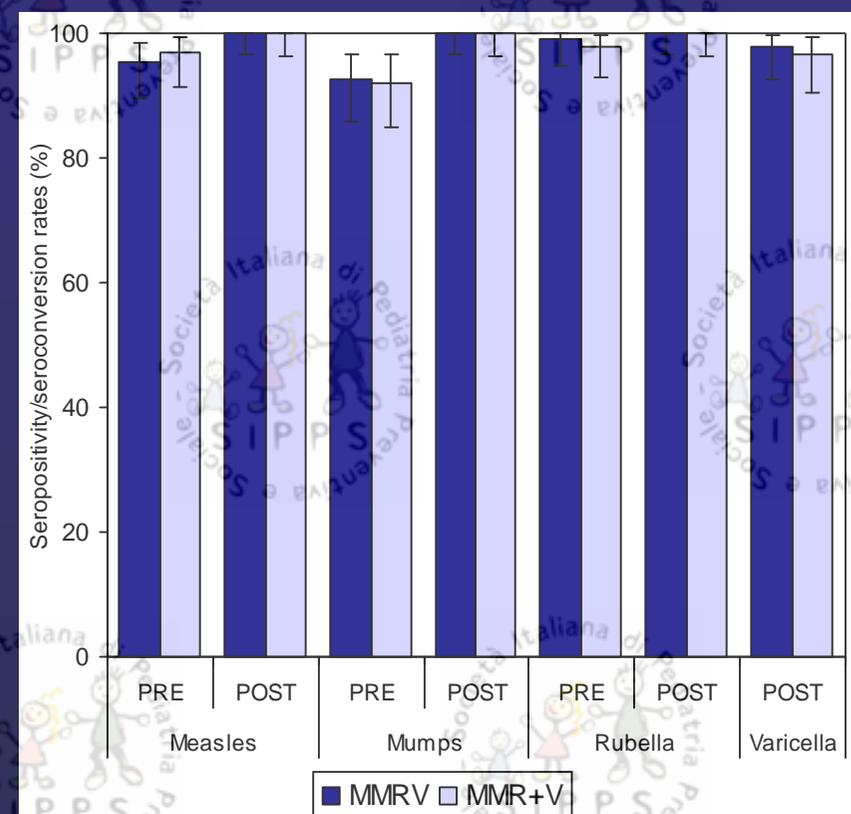
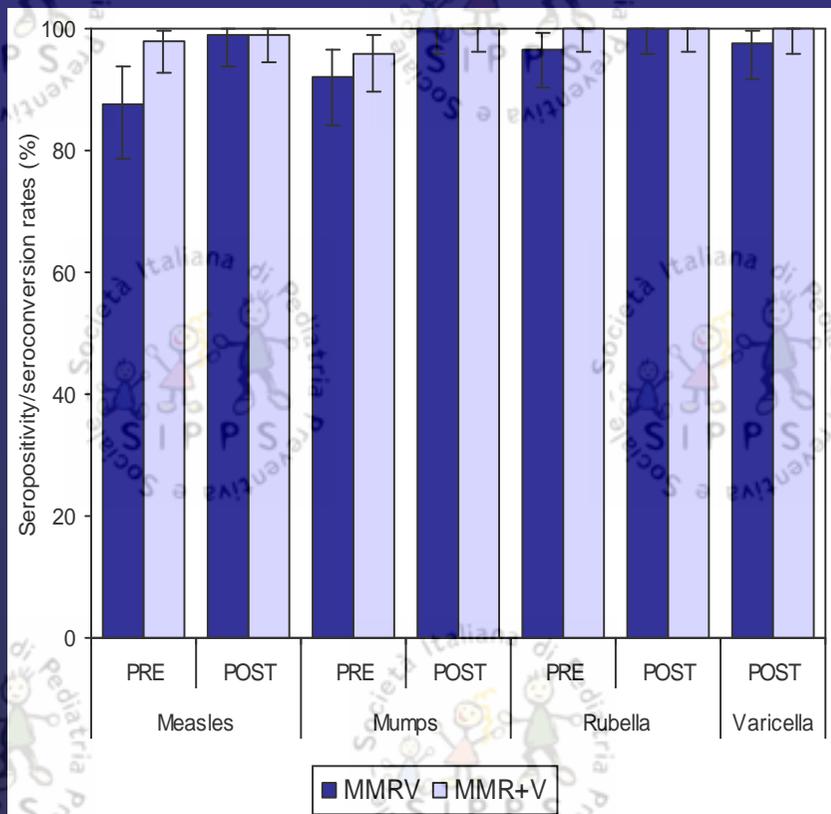
■ Value Pre 2nd Dose  
■ Value Post 2nd Dose

# Study 046 - immunogenicity

Seroconversion/seropositivity rates

Age group: 15 months – 2 years

Age group: 2 – 6 years



## Profilo di tollerabilità e reattogenicità sull'intero database

- Oltre 6.700 dosi di Priorix Tetra sono state somministrate a più di 4.000 bambini con un'età compresa tra i 9 e i 27 mesi. Gli eventi sono stati registrati fino a 42 giorni dopo la vaccinazione
- Priorix-Tetra™ ha evidenziato un buon profilo di reattogenicità
- **Febbre**
  - di grado 3 (temperatura ascellare 39.5°C o rettale 39.0°C) comparabile tra la somministrazione di Priorix-Tetra™ and Priorix™ + Varilix™.
  - La comparsa di febbre dopo la 1a dose tende ad essere più frequente in Priorix-Tetra™ che in Priorix™ + Varilix™.
  - Dopo la seconda vaccinazione l'incidenza è sovrapponibile nei 2 gruppi.
- **Incidenza di rashes o altri eventi sistemici sono comparabili tra Priorix-Tetra™ e Priorix™ + Varilix™.**

# OSSERVAZIONI SU PRIORIX-TETRA

- **Priorix-Tetra è immunogeno, sicuro e ben tollerato**
- **La somministrazione di MMRV può dare risultati di prevenzione delle 4 malattie verso cui è rivolto non diversi da quelli che si possono ottenere con MMR e V somministrati separatamente**
- **MMRV offre ovvi vantaggi sul piano dell'accettazione delle vaccinazioni e della organizzazione dei programmi vaccinali**
- **MMRV può essere utilizzato per completare il ciclo vaccinale nei bambini che hanno già ricevuto MMR o MMR+V**

# Opzione 1

Vaccino	Nascita	3° mese	4° mese	5° mese	6° mese	11-12° mese	13° mese	14° mese	5aa	11-12aa	14-15aa
DTP		DTaP		DTaP		DTaP			DTaP	dTap	
IPV		IPV		IPV		IPV			IPV		
HBV	HB*	HB		HB		HB					
Hib		Hib		Hib		Hib					
MPR							MPR		MPR		
VZV							V	V*			

\* Rispettando l'intervallo minimo riportato in RCP (4 o 6 settimane in rapporto al vaccino utilizzato)

# Opzione 2

Vaccino	Nascita	3° mese	4° mese	5° mese	6° mese	11-12° mese	13° mese	14° mese	5aa	11-12aa	14-15aa
DTP		DTaP		DTaP		DTaP			DTaP	dTap	
IPV		IPV		IPV		IPV			IPV		
HBV	HB*	HB		HB		HB					
Hib		Hib		Hib		Hib					
MPR							MPRV		MPR		
VZV								V*			

\* Rispettando l'intervallo minimo riportato in RCP (4 o 6 settimane in rapporto al vaccino utilizzato)

# Opzione 3

Vaccino	Nascita	3°mese	4°mese	5°mese	6° mese	11-12° mese	13° mese	14-16° mese	5aa	11-12aa	14-15aa
DTP		DTaP		DTaP		DTaP			DTaP	dTap	
IPV		IPV		IPV		IPV			IPV		
HBV	HB*	HB		HB		HB					
Hib		Hib		Hib		Hib					
MPRV							MPRV	MPRV*			

- Rispettando l'intervallo minimo riportato in RCP (4 o 6 settimane in rapporto al vaccino utilizzato)

# Opzione 1 - 2 - 3

Queste schedule permetterebbero di ridurre il *rischio* di casi *breakthrough* a partire dai 5 anni successivi alla vaccinazione

**MA**

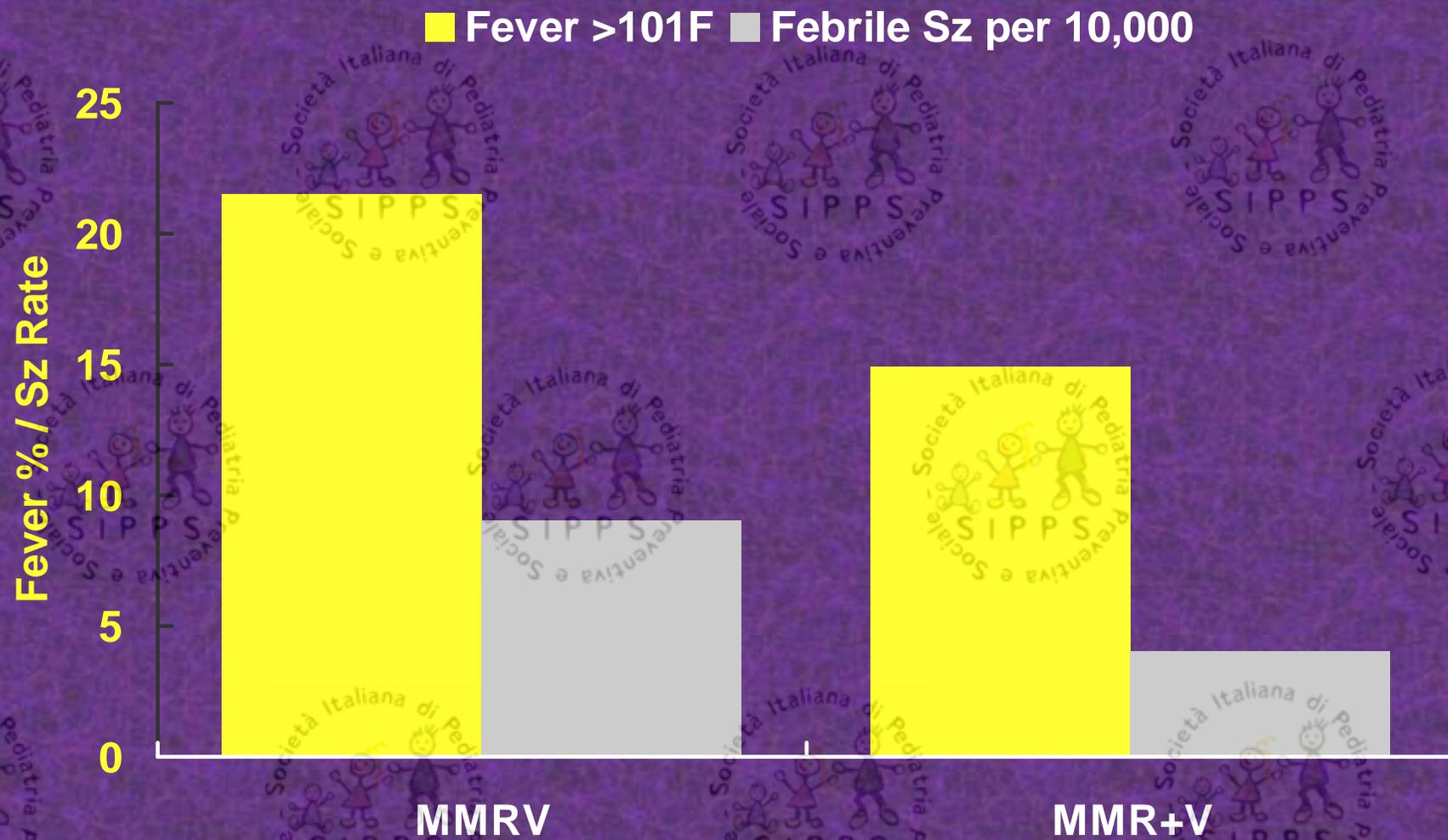
andrebbero a complicare il calendario vaccinale, imponendo una modifica rispetto alla schedula attualmente in uso per il vaccino combinato MPR

# Opzione 4

Vaccino	Nascita	3° mese	4° mese	5° mese	6° mese	11-12° mese	13° mese	14° mese	5aa	11-12aa	14-15aa
DTP		DTaP		DTaP		DTaP			DTaP	dTap	
IPV		IPV		IPV		IPV			IPV		
HBV	HB*	HB		HB		HB					
Hib		Hib		Hib		Hib					
MPRV							MPRV		MPRV		

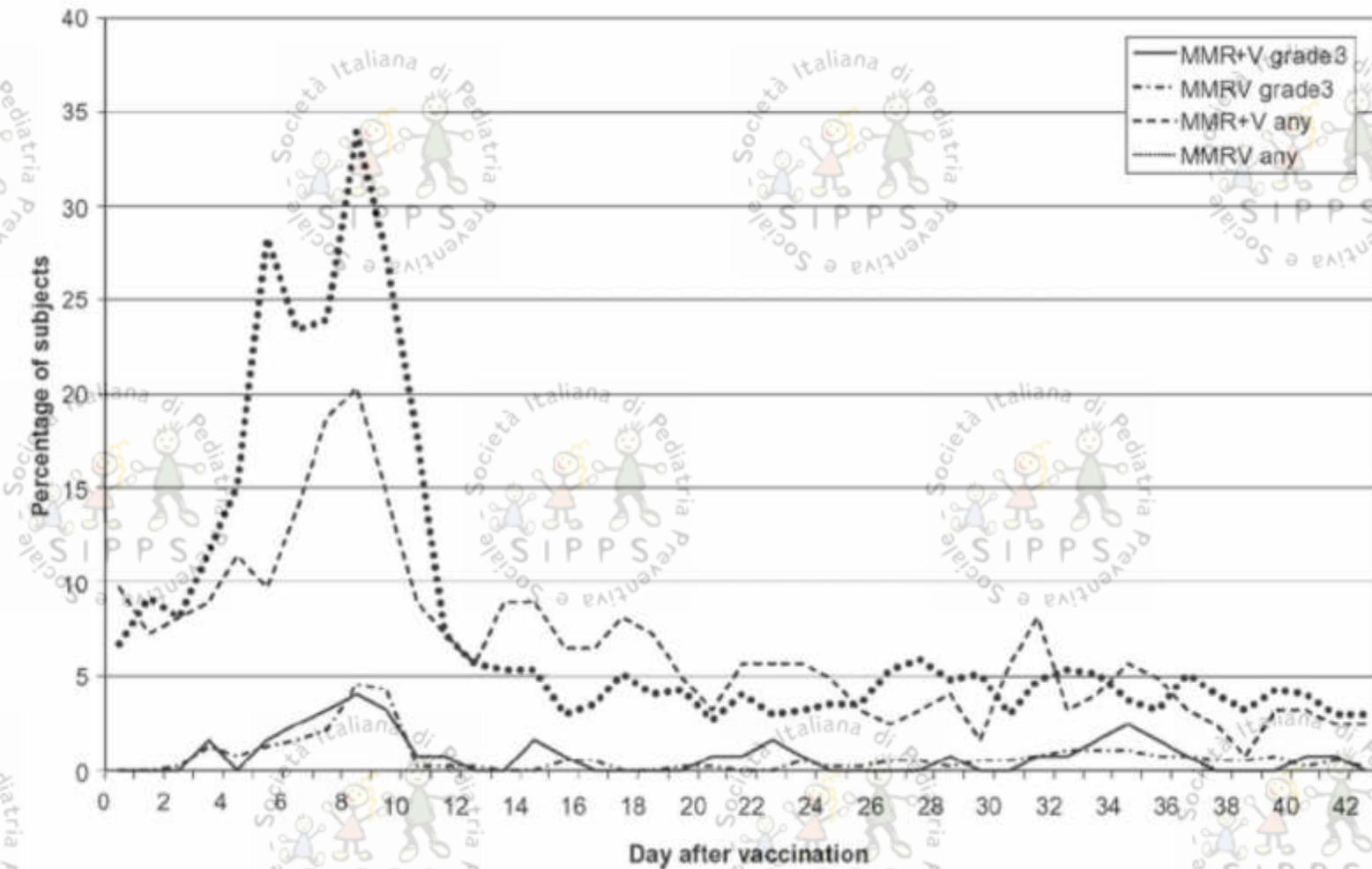
Questa schedula non comporta problemi organizzativi o di compliance.

# Adverse Reactions Following MMRV or MMR+V



Shinefield et al, PIDJ 2005; CDC unpublished data 2008

# Profilo Febbre dopo somministrazione di MPRV o MPR+V - Studio A



# Risultati: coorte MPRV-MPR

	MPRV N = 74,734	MPR N = 74,734
Sesso (uomini, %)	38,104 (51.0%)	38,104 (51.0%)
Età (media)	13.7 ± 4.7 mesi	13.8 ± 4.6 mesi
Storia di CF	578 (0.77%)	571 (0.76%)
Storia di epilessia	569 (0.76%)	567 (0.76%)
Infezioni prima della vaccinazione	127 (0.17%)	110 (0.15%)
<b>Casi di FC Narrow</b>	<b>14</b> 1.9/10,000 bambini	<b>3</b> 0.4/10,000 bambini
<b>Casi di FC Jacobsen</b>	<b>45</b> 6.0/10,000 bambini	<b>19</b> 2.6/10,000 bambini

# Stima delle convulsioni febbrili attese in Regione Veneto

BIPS

eventi aggiuntivi vs MMR/MMR+V

5-12 gg

Narrow:  $37.440 : 5882 = 6,3$  eventi /anno

Jacobsen :  $37.440 : 2747 = 13,6$  eventi /anno

0-30 gg

Narrow:  $37.440 : 8264 = 4,5$  eventi /anno

Jacobsen :  $37.440 : 2577 = 14,5$  eventi /anno

# Stima delle convulsioni febbrili attese in Regione Veneto

■ 48.000 nuovi nati x 78% coperture = 37.440 vaccinati/anno

■ RCP

— evento raro:  $> 0,01\%$  e  $< 0,1\%$  [dei soggetti vaccinati]

$37.440 \times 0,01\% = 3.74$  eventi /anno correlabili a MPRV

$37.440 \times 0,1\% = 37.44$  eventi /anno correlabili a MPRV

■ Canale Verde

$2,3/10.000 \rightarrow 8,6$  eventi /anno correlabili a MPRV

■ STORIA NATURALE

Convulsioni febbrili attese:  $48.000 \times 4-5\% = 1920 - 2400$  /anno/coorte

# CONCLUSIONI 1

- Inadeguata copertura vaccinale per morbillo, parotite, rosolia e varicella
- Morbillo può dare gravi complicanze
- Rilevanza rosolia congenita
- Impatto economico di varicella
- Recenti epidemia in est Europa di parotite

## CONCLUSIONI 2

- **Semplificazione del calendario vaccinale utilizzando MPRV**
- **Importanza informazione alle famiglie su eventi avversi: convulsioni febbrili**