Morbillo
storia di un'incompiuta

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DIBIC L:Sacco, UNIMI

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Measles cases have continued to climb into 2019. Preliminary global data shows that reported cases rose by 300 percent in the first three months of 2019, compared to the same period in 2018. This follows consecutive increases over the past two years.

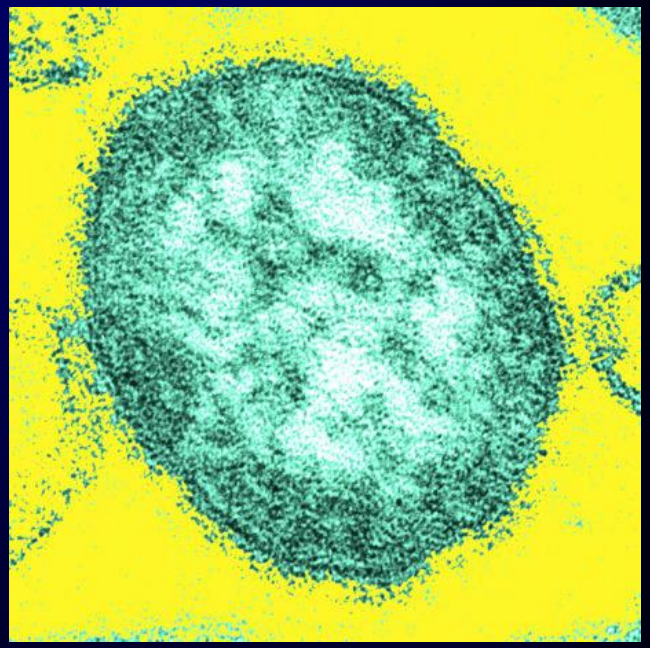
The disease is almost entirely preventable through two doses of a safe and effective vaccine. For several years, however, global coverage with the first dose of measles vaccine has stalled at 85 percent. This is still short of the 95 percent needed to prevent outbreaks, and leaves many people, in many communities, at risk. Second dose coverage, while increasing, stands at 67 percent.

CDC
Health Information for Travelers to Italy

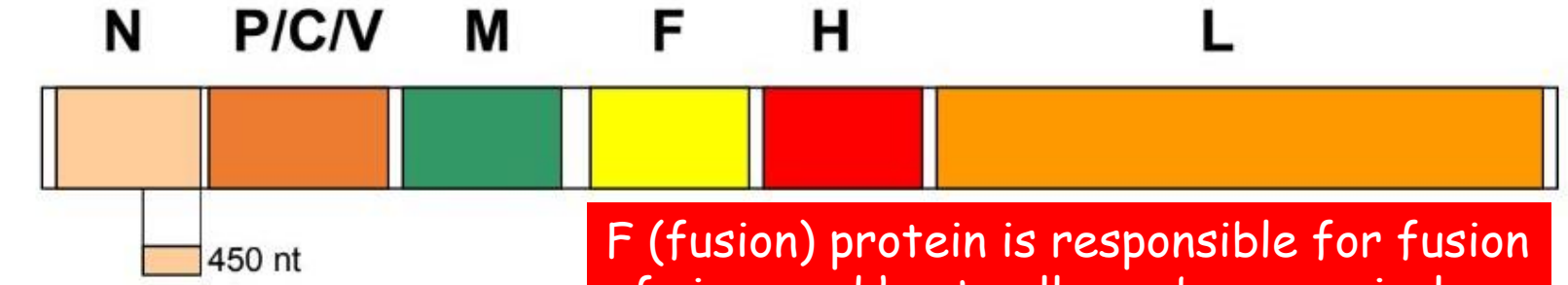
Outbreak alert: *There is an outbreak of measles in Italy. Travelers to Italy should be vaccinated against measles*

Measles virus

- Measles virus is a paramyxovirus belonging to the genus Morbillivirus.
- It is a pleomorphic virus ranging in diameter from 100 to 300 nm having a single, non-segmented, negative-sense RNA genome with a linear arrangement of genes that are separated by an intergenic trinucleotide, GAA.

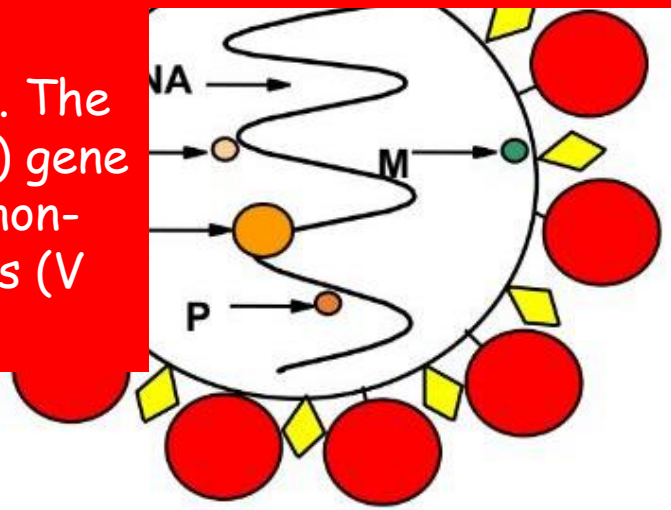


Structure of Measles Virus



F (fusion) protein is responsible for fusion of virus and host cell membranes, viral penetration, and haemolysis.
H (haemagglutinin) protein is responsible for binding of virus to cells.

The genome consists of six genes, each encoding a single structural protein. The phosphoprotein (P) gene also encodes two non-structural proteins (V and C)



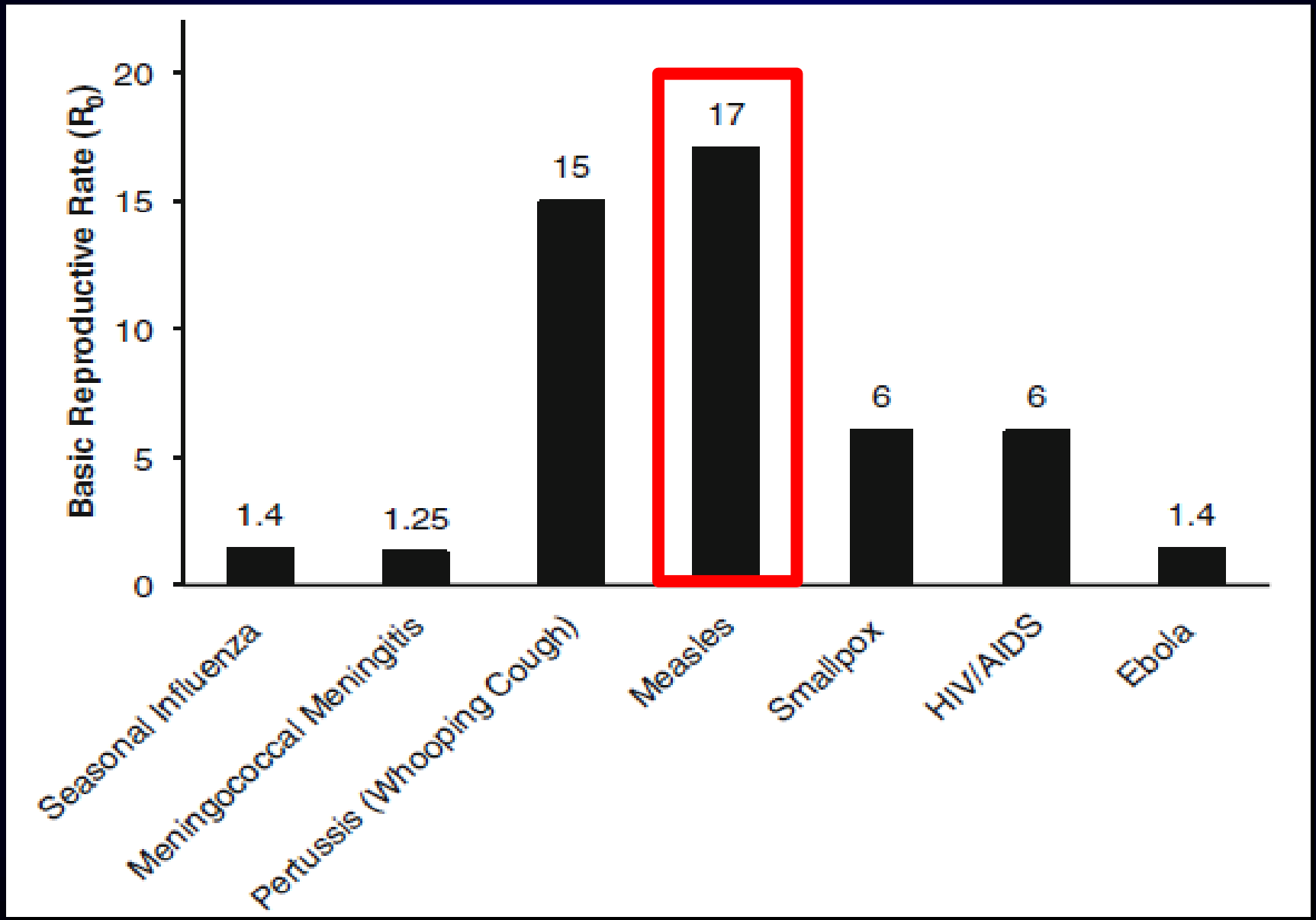
N, Nucleocapsid
P, Phosphoprotein
M, Matrix protein
F, Fusion protein
H, Hemagglutinin
L, Large protein

Circulation of measles genotypes 2005-2017

- As of 2015, there are 24 genotypes of measles virus with reference strains recognized by WHO.
- Clades A, E and F have continued to consist of only a single genotype. All of the recognized genotypes have one reference strain, except for B3, C2, D5 and D7, which have two reference strains.
- During 2005-2015, 11 wild-type genotypes were detected, and in 2017 only five genotypes in three clades (B3, D4, D8, D9, and H1) were detected/ reported to MeaNS.

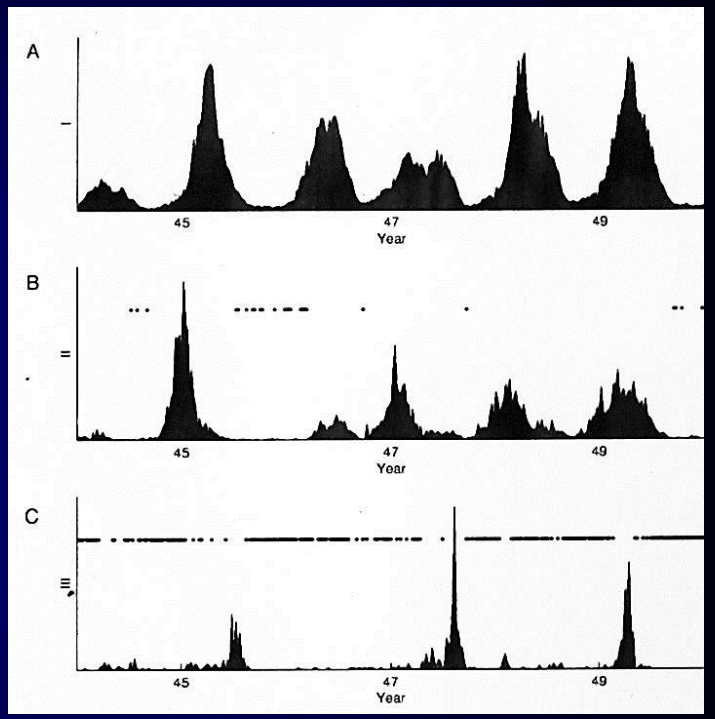
- Measles virus is viable for less than 2 hours at ambient temperatures on surfaces and objects, while the aerosolized virus remains infectious for 30 minutes or more.
- It is heat-labile and is inactivated after 30 minutes at 56°C.
- However, the virus appears to survive freeze-drying relatively well and, when freeze-dried with a protein stabilizer, can survive storage for decades at -70°C.
- The virus is inactivated by solvents, such as ether and chloroform, by acids (pH less than 5), alkalis (pH greater than 10), and by UV and visible light.
- It is also susceptible to many disinfectants, including 1% sodium hypochlorite, 70% alcohol and formalin.

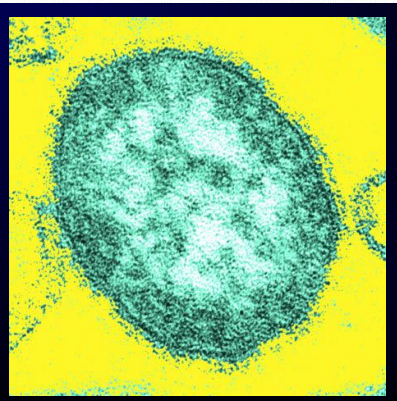
Dinamiche di popolazione e infezioni



Modalità epidemiche in funzione della numerosità delle popolazioni interessate: il caso del morbillo

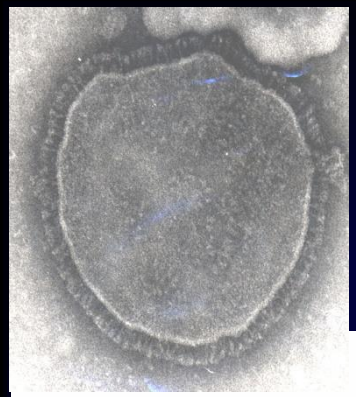
- ✓ **Tipo I:**
  - popolazione >300.000
  - casi/anno 7000-10000
  - serie regolare di picchi epidemici
  - andamento endemo-epidemico (consentito dal permanere di un numero congruo di suscettibili)
- ✓ **Tipo II:**
  - popolazione minima 10.000 (≤300.000)
  - picchi epidemici regolari
  - catena epidemica interrotta (la disponibilità di suscettibili non consente stabilizzazione di endemia)
- ✓ **Tipo III**
  - popolazione <10.000
  - picchi irregolari, lunghi intervalli (R_0<<1, la malattia deve essere reintrodotta)



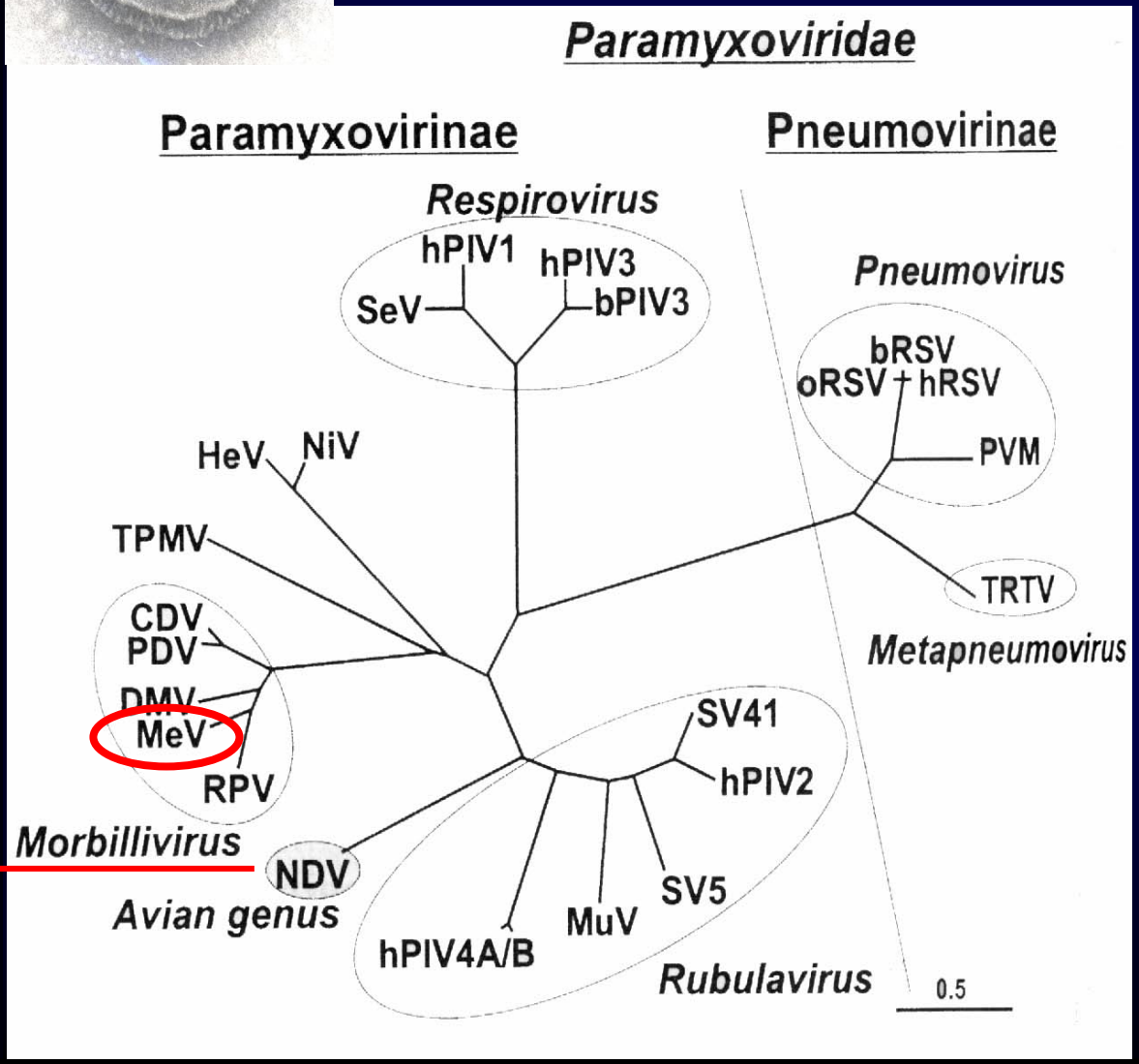


Timeline of epidemics in modern age

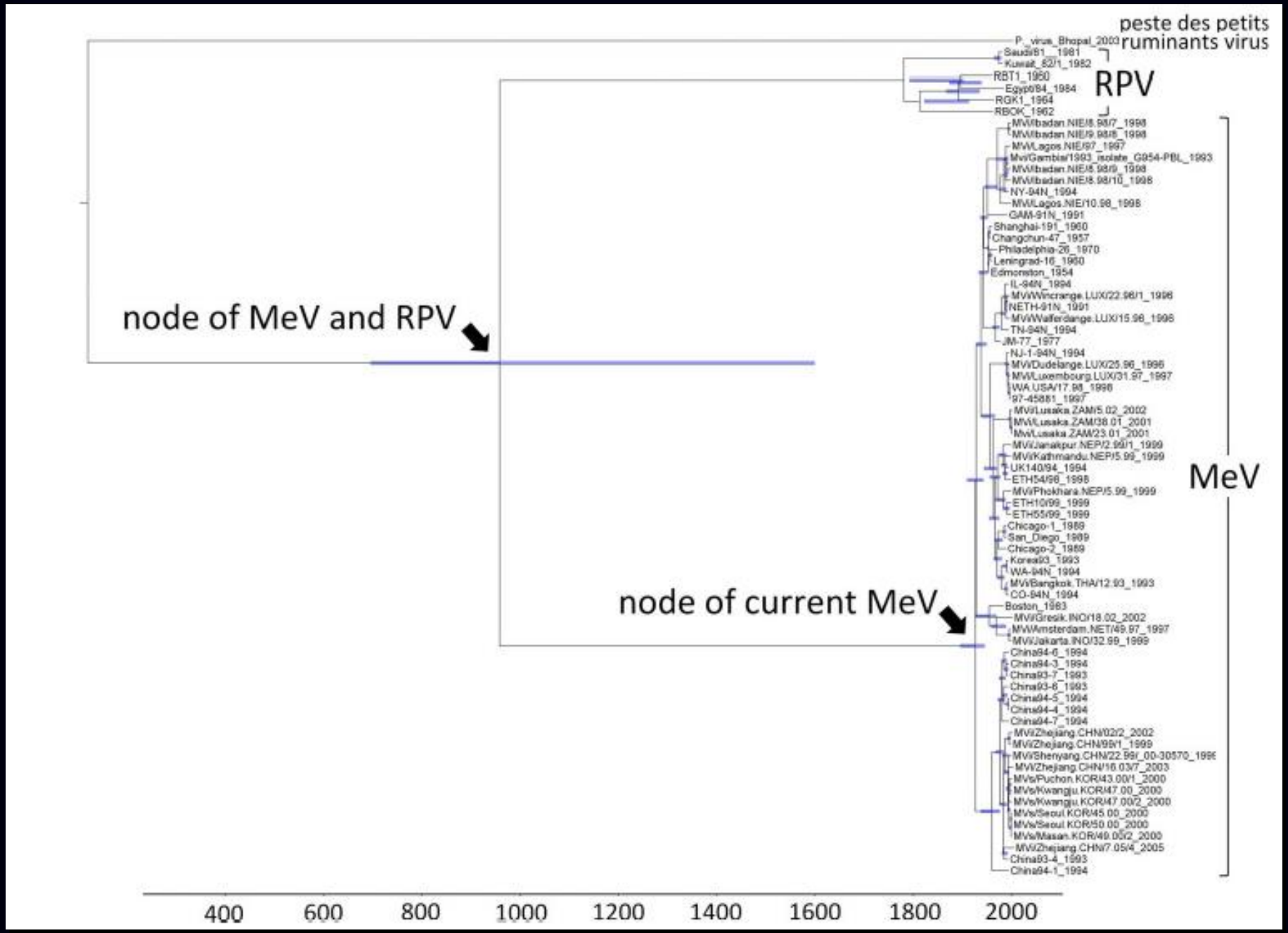
1529	**The Spanish introduce measles to Cuba, killing two out of three natives.**
1533	Measles epidemic breaks out in Nicaragua soon after Francisco Pizarro's third expedition to Peru.[9]
1657	The earliest recorded measles epidemic breaks out in Colonial America.
1850–1859	Measles kills one fifth of Hawaii's population within a decade.[7]
1870–1879	Measles kills about one fifth of Fiji's indigenous population within a decade.
1911	First Introduction of measles virus to the Polynesian island of Rotuma. Most residents of a population of approximately 2,600 are exposed to the virus for the first time. The official mortality register documents 491 deaths (19% of the total population).
1951	A traveler from Denmark first introduces measles virus into the Inuit population of southern Greenland. Only five out of 4,262 people escape the disease, with a final attack rate of 99.9%. 1.8% of the population died during this epidemic.[16]



Albero filogenetico dei Paramyxoviridae



Il virus umano del morbillo (MeV) è geneticamente vicino al virus della peste bovina (RPV)


peste des petits ruminants virus
P_virus_Bhopal_2003
Saudi/81_1981
Kuwait_82/1_1982
RBT1_1960
Egypt/84_1984
RGK1_1964
RBOK_1962
RPV
MVi/Ibadan.NIE/8.98/7_1998
MVi/Ibadan.NIE/9.98/8_1998
MVi/Lagos.NIE/97_1997
MVi/Gambia/1993_isolate_G954-PBL_1993
MVi/Ibadan.NIE/8.98/9_1998
MVi/Ibadan.NIE/8.98/10_1998
NY-94N_1994
MVi/Lagos.NIE/10.98_1998
GAM-91N_1991
Shanghai-191_1960
Changchun-47_1957
Philadelphia-26_1970
Leningrad-16_1960
Edmonston_1954
IL-94N_1994
MVi/Wincrange.LUX/22.98/1_1998
NETH-91N_1991
MVi/Walferdange.LUX/15.98_1998
TN-94N_1994
JM-77_1977
NJ-1-94N_1994
MVi/Dudelange.LUX/25.96_1996
MVi/Luxembourg.LUX/31.97_1997
WA.USA/17.98_1998
97-45881_1997
MVi/Lusaka.ZAM/5.02_2002
MVi/Lusaka.ZAM/38.01_2001
MVi/Lusaka.ZAM/23.01_2001
MVi/Janakpur.NEP/2.99/1_1999
MVi/Kathmandu.NEP/5.99_1999
UK140/94_1994
ETH54/96_1996
MVi/Phokhara.NEP/5.99_1999
ETH10/99_1999
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Chicago-1_1989
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Korea93_1993
WA-94N_1994
MVi/Bangkok.THA/12.93_1993
CO-94N_1994
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MVi/Gresik.INO/18.02_2002
MVi/Amsterdam.NET/49.97_1997
MVi/Jakarta.INO/32.99_1999
China94-6_1994
China94-3_1994
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China93-6_1993
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China94-7_1994
MVi/Zhejiang.CHN/02/2_2002
MVi/Zhejiang.CHN/99/1_1999
MVi/Shenyang.CHN/22.99/_00-30570_199
MVi/Zhejiang.CHN/16.03/7_2003
MVs/Puchon.KOR/43.00/1_2000
MVs/Kwangju.KOR/47.00_2000
MVs/Kwangju.KOR/47.00/2_2000
MVs/Seoul.KOR/45.00_2000
MVs/Seoul.KOR/50.00_2000
MVs/Masan.KOR/49.00/2_2000
MVi/Zhejiang.CHN/7.05/4_2005
China93-4_1993
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OPEN

Molecu haema measle

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Hirokazu Kimura
Daisuke Kurai[4], H
Kunihisa Kozawa
Hisanori Minakar

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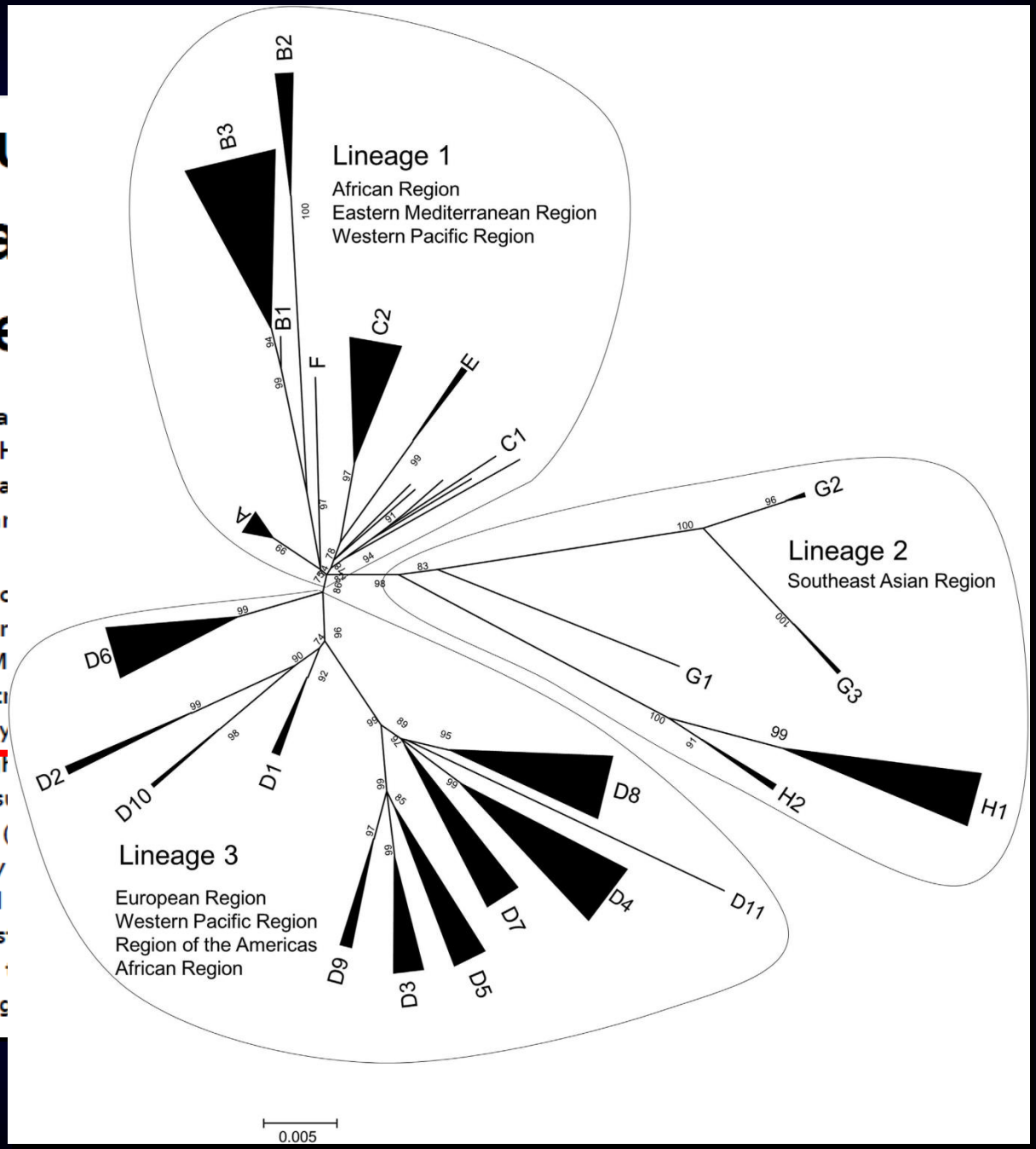


Storia 'antica' del morbillo in Europa

- ✓ Possibile penetrazione in Europa nel II-III secolo dC.
- ✓ Possibile epidemia di morbillo descritta in Roma nel 189 dC. Cassio Dione riporta fino a duemila morti al giorno.
- ✓ Possibile epidemia di morbillo nel 455-56, nell'area dell'attuale Vienna (*Orae Favianae*) con sintomi respiratori , congiuntivite, esantema generalizzato.
- ✓ Acquisizione delle caratteristiche di malattia dell'infanzia in Europa e Asia già in periodo alto medioevale ?

Epidemie in età Imperiale

	Fonte	Sintomi	Compatibilità con vaiolo	Compatibilità con morbillo
Peste Antonina 164-180	Galeno	Viso rosso/livido	+	+
		Febbre	+	+
		Esantema ->pustole (9 gg)	+	-/+
		Vomito/diarrea	+/-	+
		Ricorrenza (stagionale)	+	+
Peste del 189	Galeno	Esantema	-/+	+
		Febbre	+	+
		Diarrea	-/+	+
		Ricorrenza	+/-	+
Peste di San Cipriano 250-266	San Cipriano	Febbre	+	+
		Diarrea	-/+	+
		Angina ulcerosa	-/+	+/-
		Vomito	-/+	-
		Congiuntivite	-/+	+
		(esantema??)	(?)	(?)
		Gangrena mani/piedi	-	-
		Ricorrenza	+/-	+/-

Le prime osservazioni: confusione/commistione col vaiolo

- ✓ Rhazes (865-925) lo descrive nel nel 910, senza distinguerlo dal vaiolo.
- ✓ Costantino l'Africano (dec. 1087) intoduce il termine *morbillus* (piccolo morbo)
- ✓ In Inghilterra, il termine *mezils* appare nel XIII secolo, riferito alla lebbra, per poi essere trasferito a eruzioni cutanee di vario tipo.
- ✓ Nel 1546, Fracastoro attribuisce la diffusione tra persona e persona ai *seminaria*
- ✓ Sydenham descrive con precisione l'epidemia di morbillo di Londra del 1670, ma attribuisce diffusione a *miasms*

Decessi per morbillo in Europa nel 1887-88

	N	o/ooo	N	o/ooo
Italia	23768	8.03	20961	7.04
Francia (195 città)	5517	6.43	3519	4.10
Inghilterra	16765	5.94	9784	3.42
Scozia	681	1.72	1548	4.00
Irlanda	1307	2.70	1933	4.05
Impero Germanico (città 15.000 abitanti)	3678	3.66	2789	2.71
Prussia	11470	4.00	8240	2.83
Austria	14209	6.16	14073	6.04
Svizzera	451	1.54	2490	8.49
Belgio	3233	5.41	2933	4.87
Olanda	1541	3.50	1655	3.67
Svezia	1280	2.71	1383	2.91

da G. Fabbri, Guida alla profilassi delle Malattie Infettive, Milano 1892

Morbillo: cronologia delle scoperte scientifiche

1757 F. Home dimostra infettività del morbillo

1790 J.Lucas descrive encefalomielite postmorbillosa

1908 C.F.Von Pirquet descrive l'anergia postmorbillosa

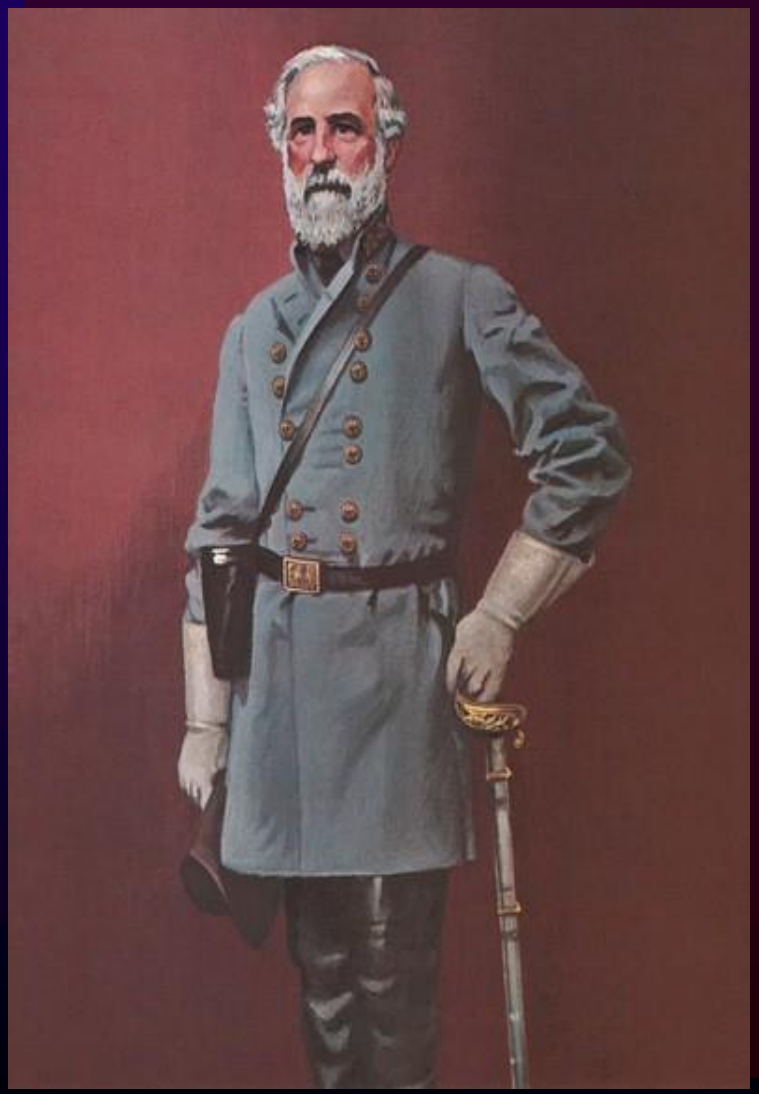
1933 Dawson descrive la PESS

1954 JF Enders e T Peebles isolano il virus da pazienti con macchie di Koplik

1961 Enders mette a punto il vaccino

C.F.Von Pirquet

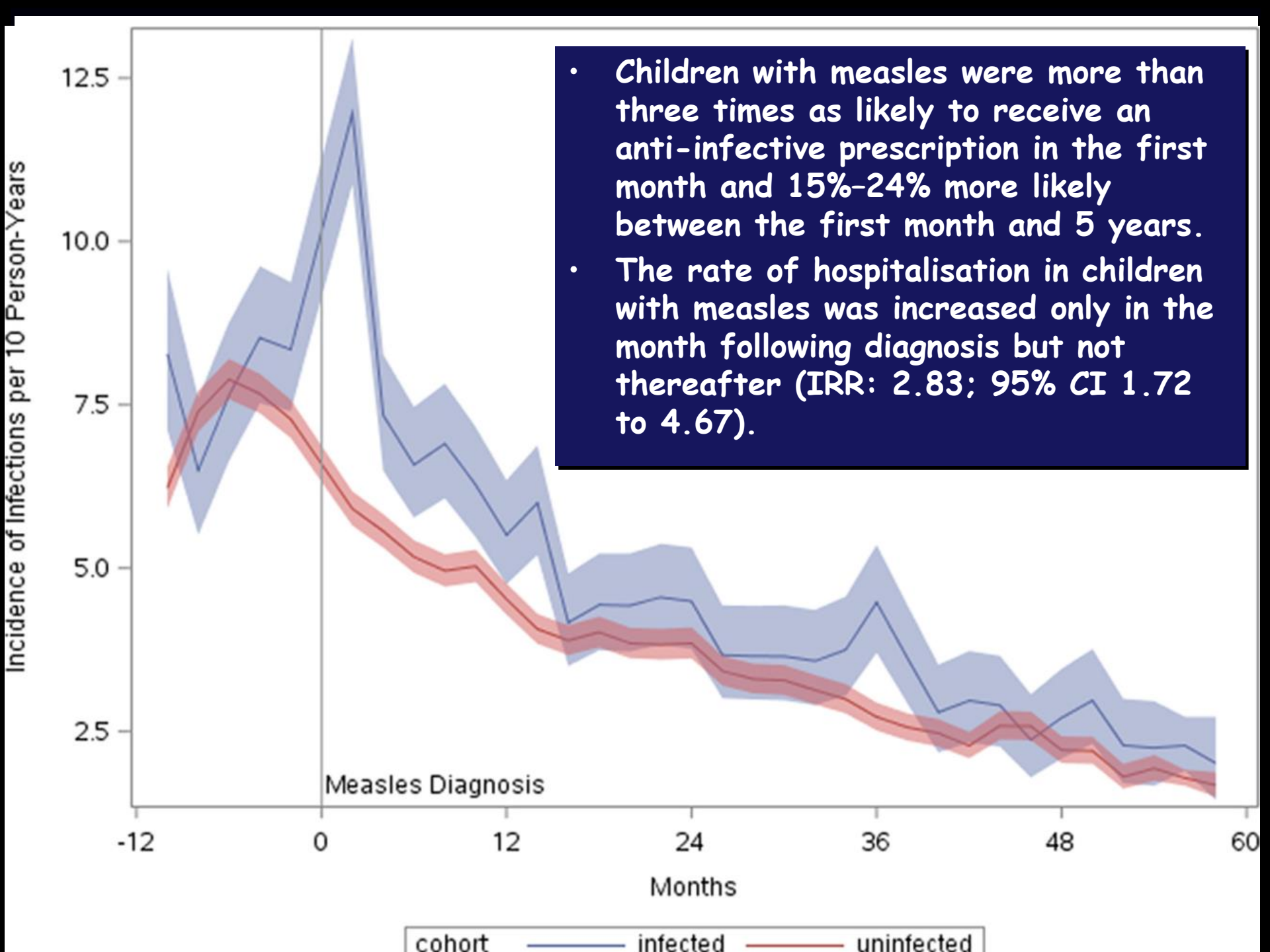
Morbillo, soldati contadini e anergia durante la guerra di secessione americana



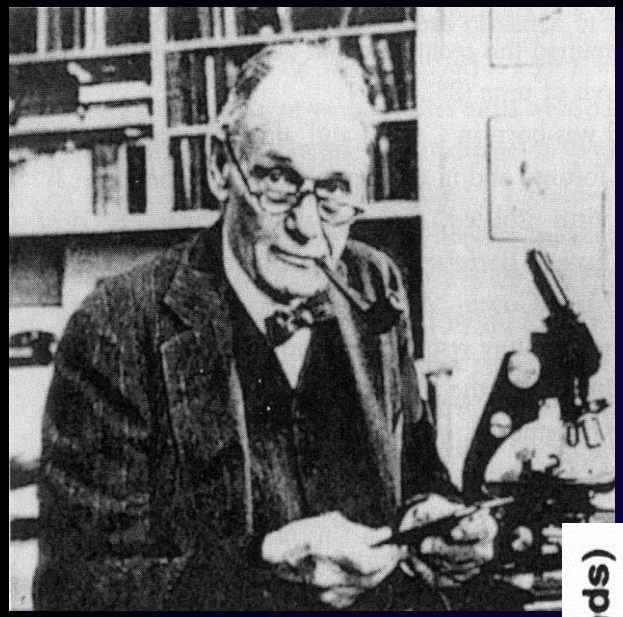
- 67.000 casi di morbillo con 4000 morti tra le truppe unioniste durante la guerra di secessione

- *'... but it is a disease which though light in childhood is severe in manhood, and prepares the system for other attacks...'*

Gen R.E. Lee,
comandante delle truppe confederate

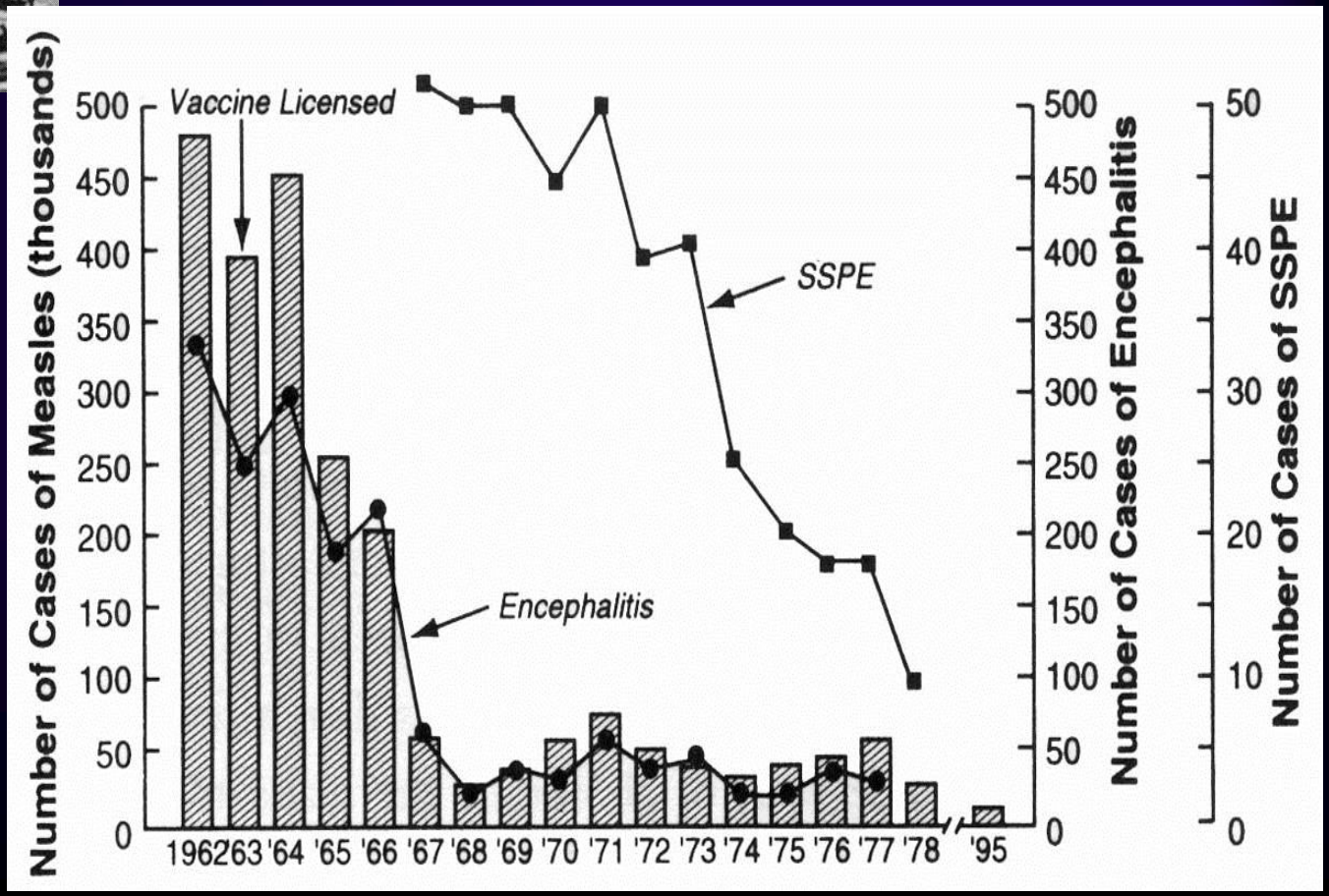


- Children with measles were more than three times as likely to receive an anti-infective prescription in the first month and 15%–24% more likely between the first month and 5 years.
- The rate of hospitalisation in children with measles was increased only in the month following diagnosis but not thereafter (IRR: 2.83; 95% CI 1.72 to 4.67).



Ruolo del vaccino con virus attenuato nel controllo del morbillo

John Enders



Subacute sclerosing panencephalitis

- The diagnosis is clinical, supported by periodic complexes on electroencephalography, brain imaging suggestive of demyelination, and immunological evidence of measles infection.
- Management of the disease includes seizure control and avoidance of secondary complications associated with the progressive disability.
- Trials of treatment with interferon, ribavirin, and isoprinosine using different methodologies have reported beneficial results.
- However, the disease shows relentless progression; only 5% of individuals with SSPE undergo spontaneous remission, with the remaining 95% dying within 5 years of diagnosis

Gutierrez et al. Developmental Medicine & Child Neurology 2010, 52: 901-907

Clinical Infectious Diseases 2017; 65: 226-32

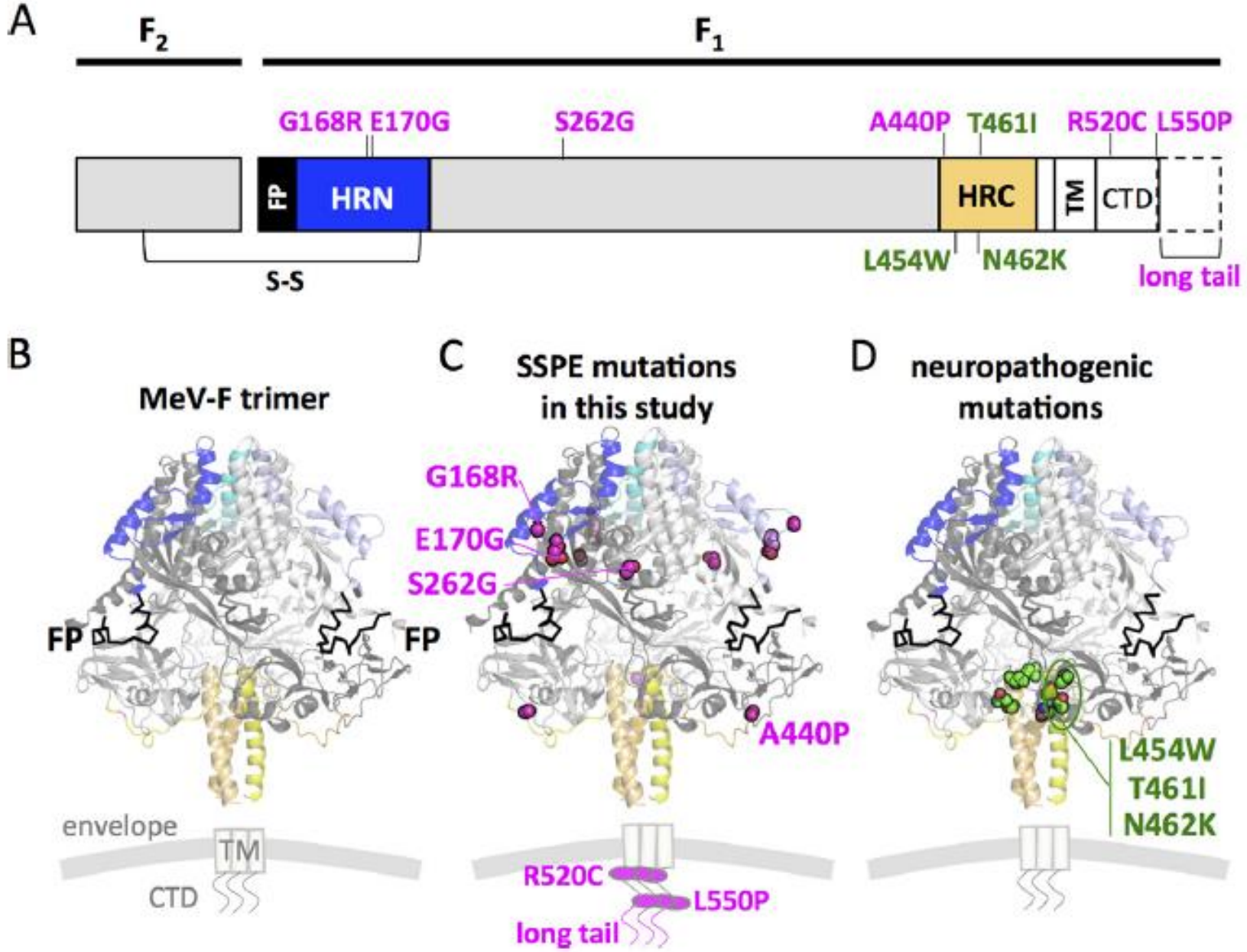
MAJOR ARTICLE

Subacute Sclerosing Panencephalitis: The Devastating Measles Complication That Might Be More Common Than Previously Estimated

Kristen A. Wendorf,[1] Kathleen Winter,[1] Jennifer Zipprich,[1] Rob Schechter,[1] Jill K. Hacker,[2] Chris Preas,[2] James D. Cherry,[3] Carol Glaser,[4] and Kathleen Harriman[1]

[1]Immunization Branch and [2]Viral and Rickettsial Disease Laboratory, California Department of Public Health, Richmond; [3]David Geffen School of Medicine, University of California, Los Angeles; and [4]Kaiser Permanente, Infectious Diseases, Oakland, California

- Seventeen SSPE cases were identified.
- Males outnumbered females 2.4:1.
- Twelve (71%) cases had a history of measles-like illness and had illness prior to 15 months of age.
- SSPE was diagnosed at a median age of 12 years (3–35 years), with a latency period of 9.5 years (2.5–34 years).
- Among measles cases reported during 1988–1991, the incidence of SSPE was 1:1367 for children <5 years, and 1:609 for children <12 months at time of measles disease.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Measles after vaccination

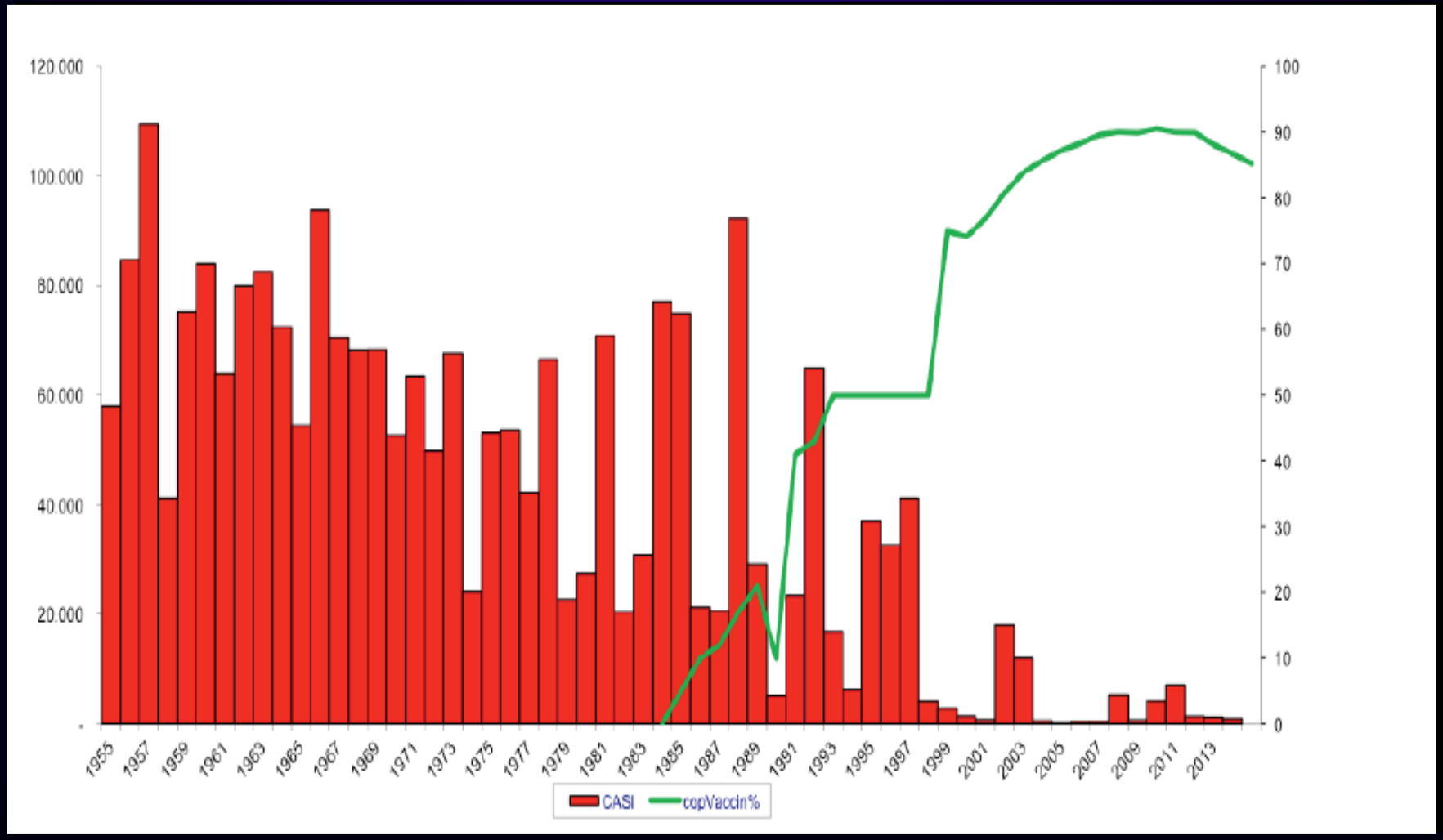
1963 (Pre-vaccine Era)	**Seven to eight million children died from measles each year.** **Epidemic cycles occur every 2 to 3 years** **Lifelong immunity is provided by natural infection.**	*Goodson, JL. Et al. J Infect Dis. 2011; **204** (s1): S205-14.* *Ludlow M, et al. J Pathol 2012; **235** : 253-65.*
1963 onward	Major measles control programs result in a dramatic decline in incidence of the disease	
2000–2015	Prevented an estimated 20.3 million deaths. In 2015, about 85% of the world's children received one dose of vaccine	*"Measles - Key facts". WHO.*

Vaccinazioni: infezioni prevenute in Italia

Vaccine-preventable diseases	Pre-vaccination period	Post-vaccination period	Pre-vaccination morbidity rates (per 100,000)	Post-vaccination morbidity rates (per 100,000)	Reported cases	Prevented cases (95% C.I.)	Vaccine coverage 2015 (24 months) (%)
Diphtheria	1901–1938	1939–2015	53.03	11.42	403,712	1,832,142 (1,540,355–2,167,723)	93.3
Tetanus	1955–1962	1963–2015	1.45	0.39	10,673	30,818 (29,905–32,824)	93.6
Poliomyelitis	1925–1963	1964–2015	5.23	0.06	1,651	198,279 (162,693–241,572)	93.4
Hepatitis B	1987–1990	1991–2015	5.52	2.53	34,880	41,675 (39,092–51,341)	93.2
Pertussis	1925–1994	1995–2015	42.79	3.97	47,751	234,958 (82,466–566,026)	93.3
Measles	1901–1998	1999–2015	183.16	5.93	58,376	277,417 (187,579–400,312)	85.3
Mumps	1936–1998	1999–2015	60.45	13.11	127,357	1,026,714 (634,083–1,624,411)	85.2
Rubella	1970–1998	1999–2015	35.94	2.61	25,529	226,478 (158,679–319,240)	85.2
Chickenpox	1925–2002	2003–2015	86.91	124.65	949,504	679,512 (617,171–744,353)	30.7
Meningococcus	1976–2004	2005–2015	0.84	0.27	1,734	1,563 (1,235–1,936)	76.6

Pezzotti et al. Vaccine 2018; 36: 1435–1443

Morbillo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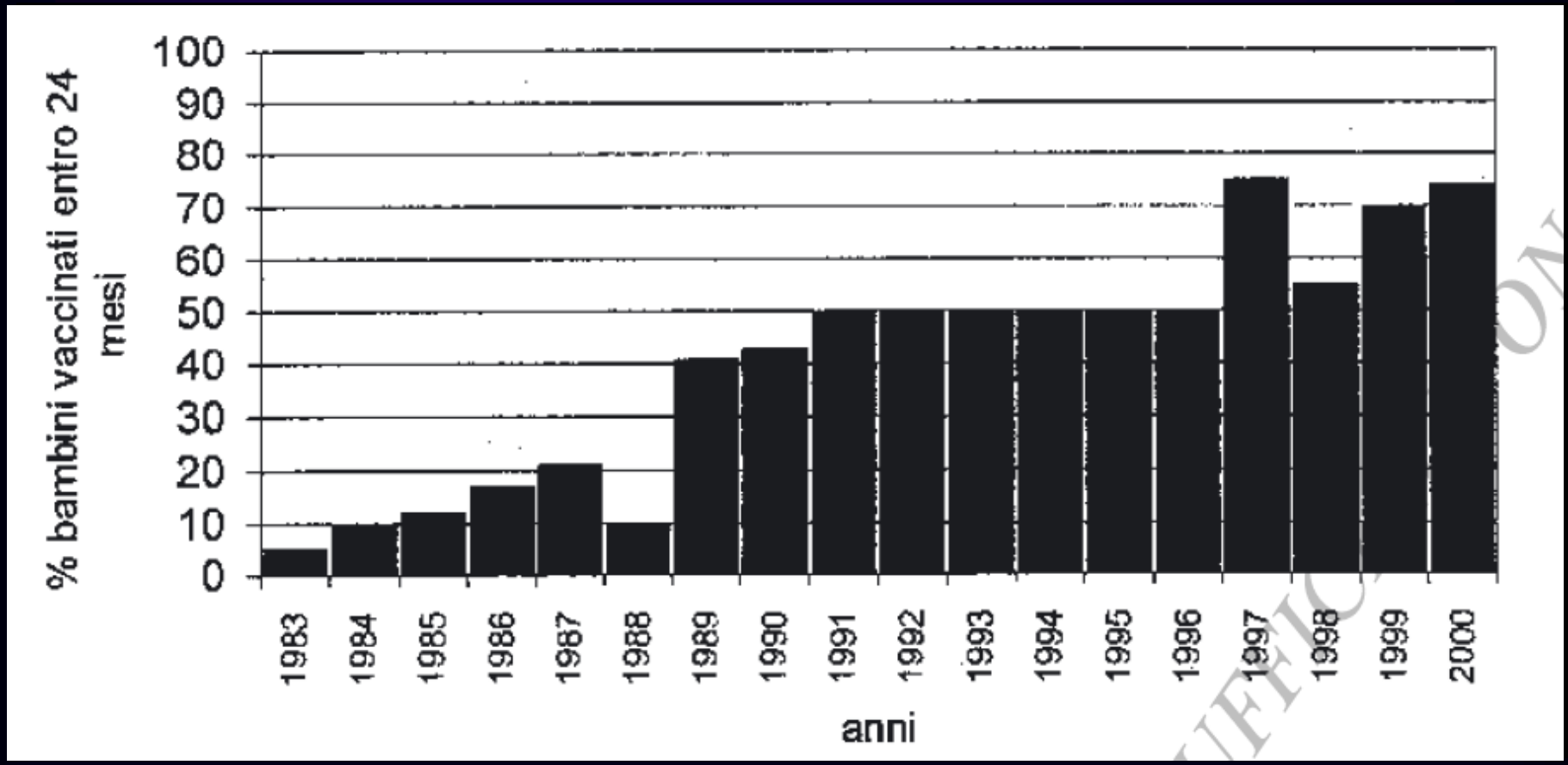
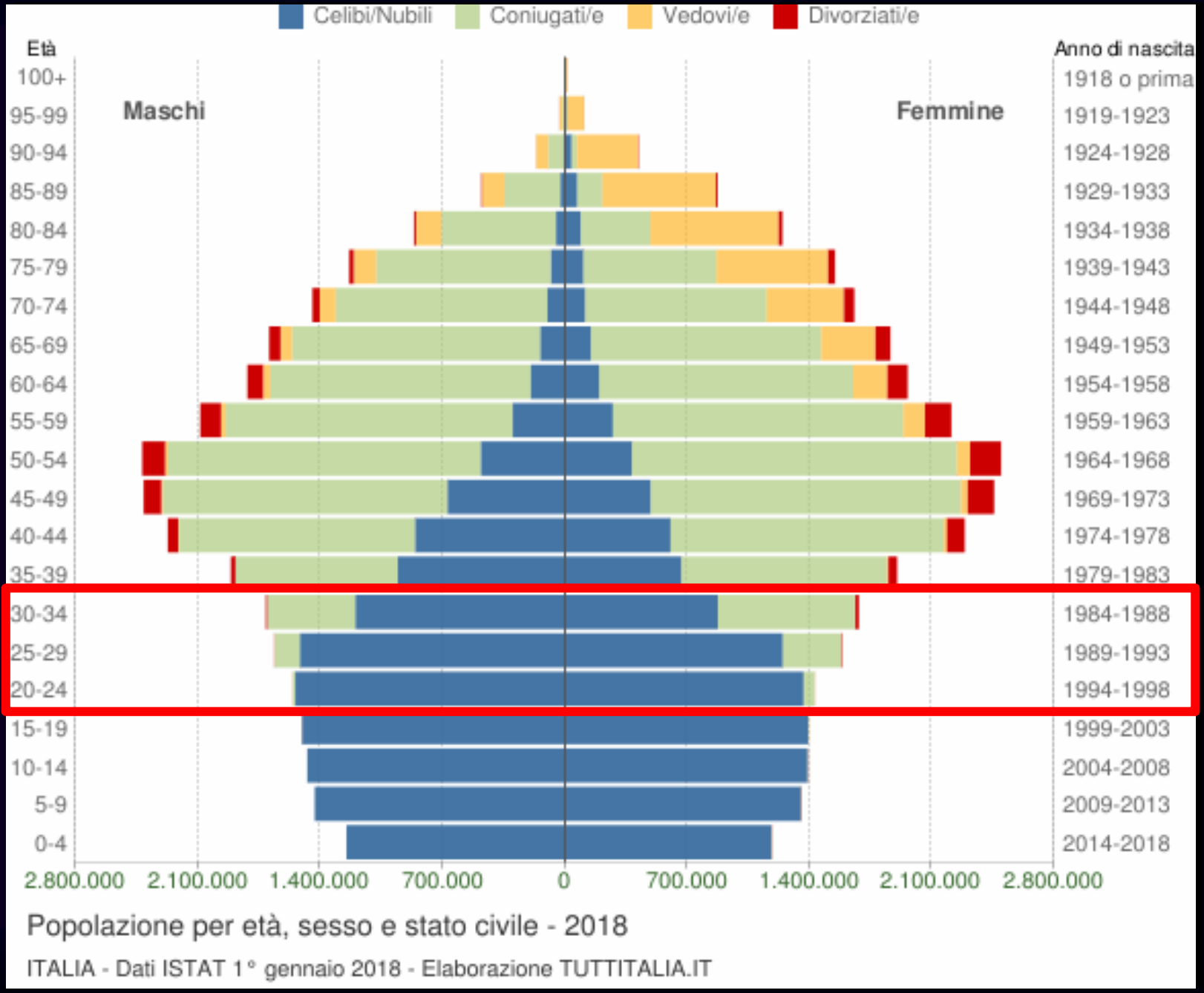
Percentuale di bambini vaccinati contro il morbillo entro i 24 mesi di età. Italia, 1983-2000

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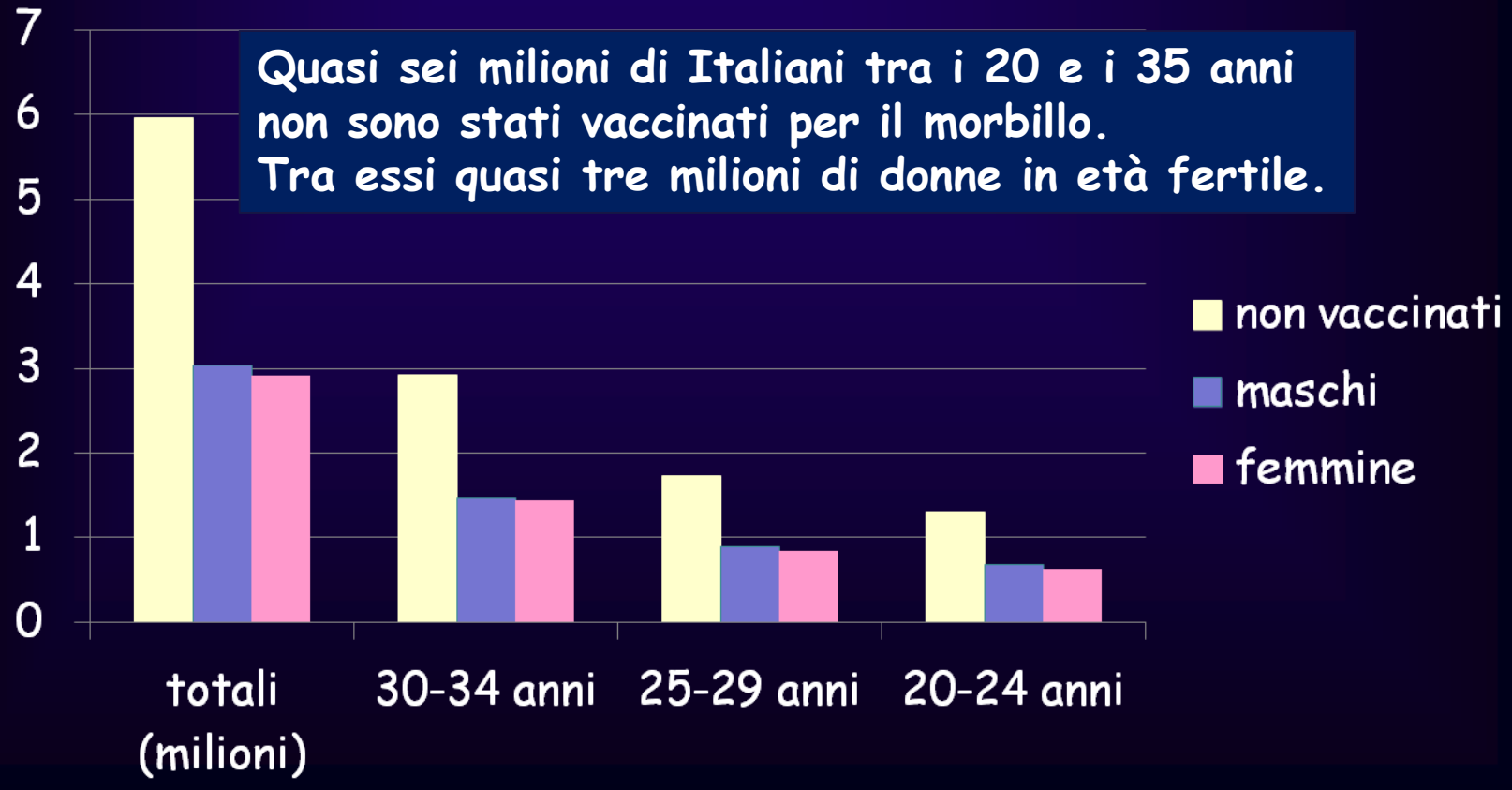
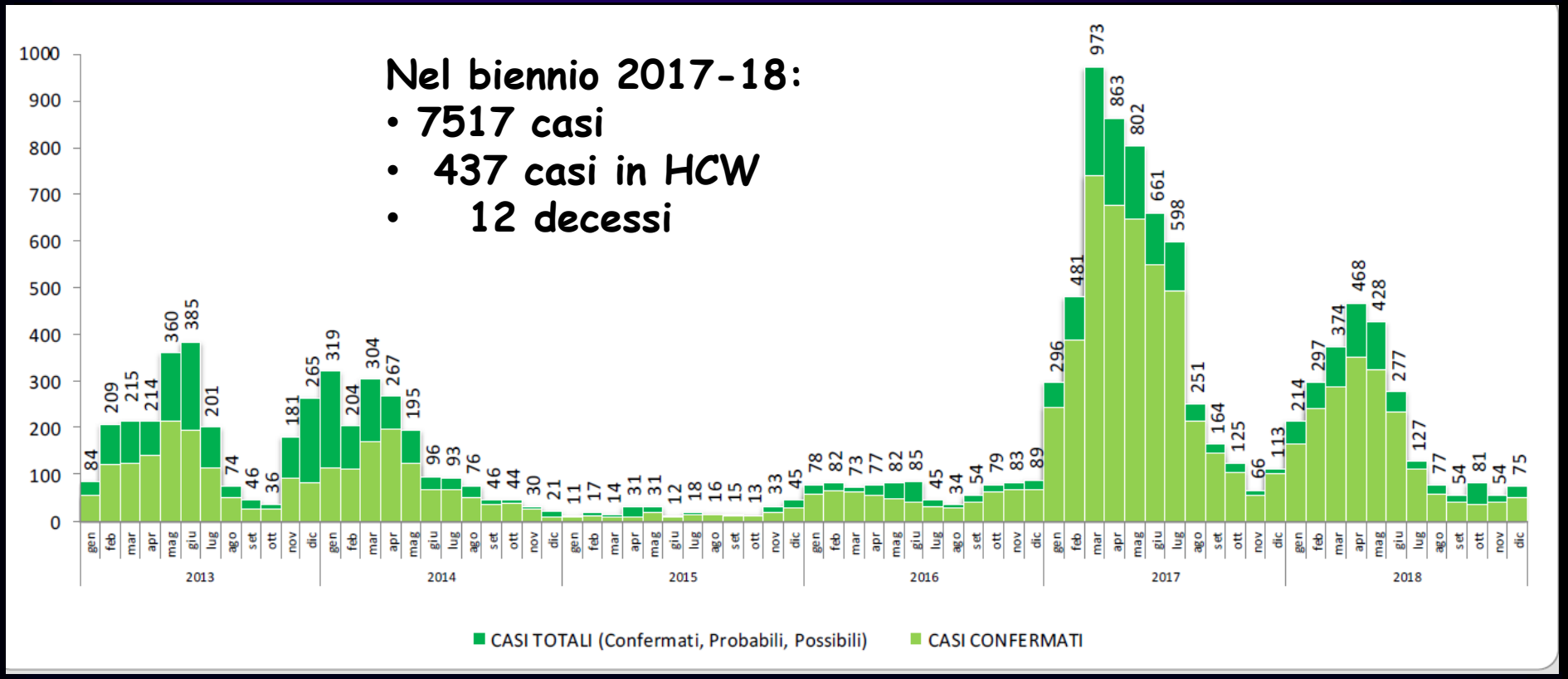
Popolazione per età, sesso e stato civile - 2018
ITALIA - Dati ISTAT 1° gennaio 2018 - Elaborazione TUTTITALIA.IT

Da conti fatti in casa un sabato mattina …

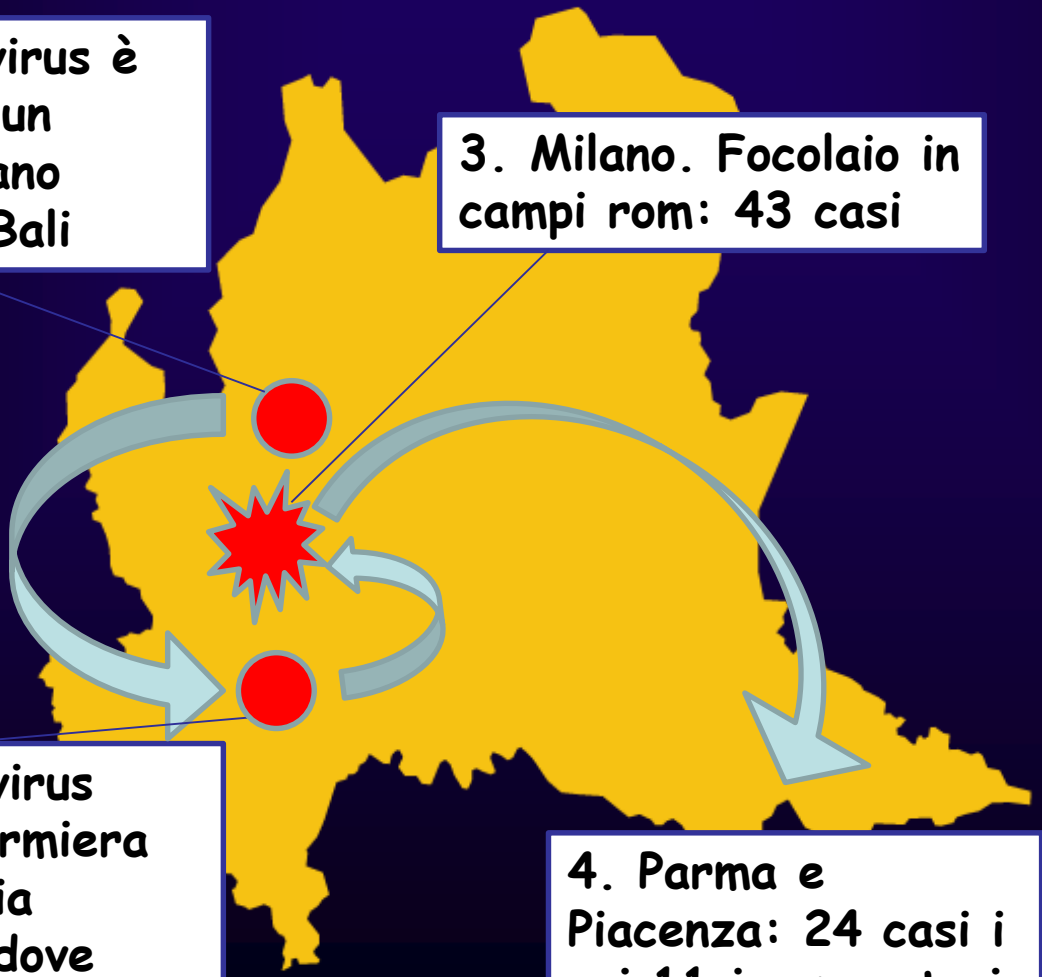


Casi di morbillo per mese di insorgenza dei sintomi. Italia: gennaio 2013-dicembre 2018



Le rotte del Morbillo: sviluppo di un'epidemia

1. Lecco. Il virus è importato da un manager italiano rientrato da Bali



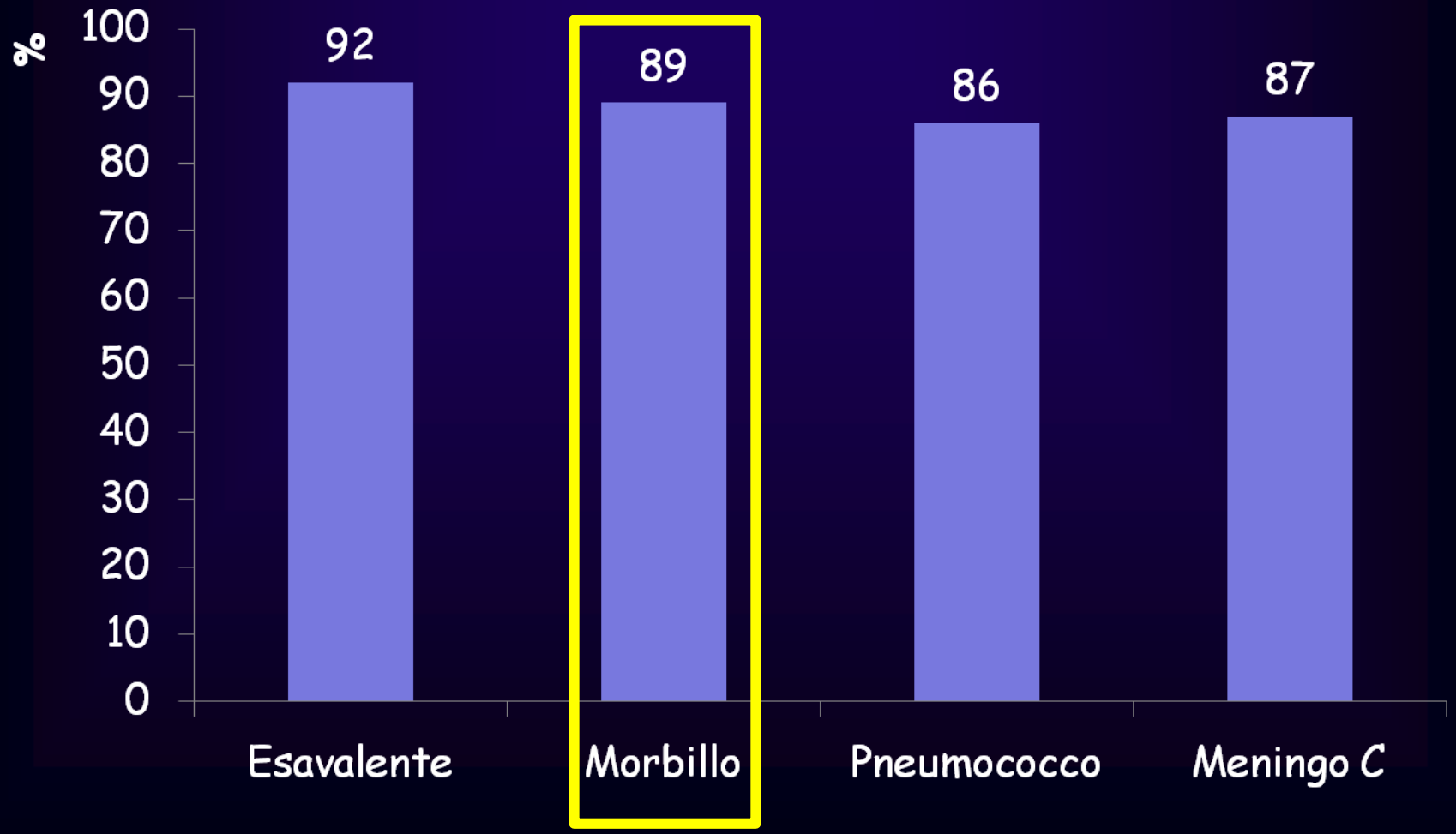
3. Milano. Focolaio in campi rom: 43 casi

2. Pavia. Il virus contagia infermiera della pediatria Ospedaliera dove avviene il contatto con i Rom di Milano

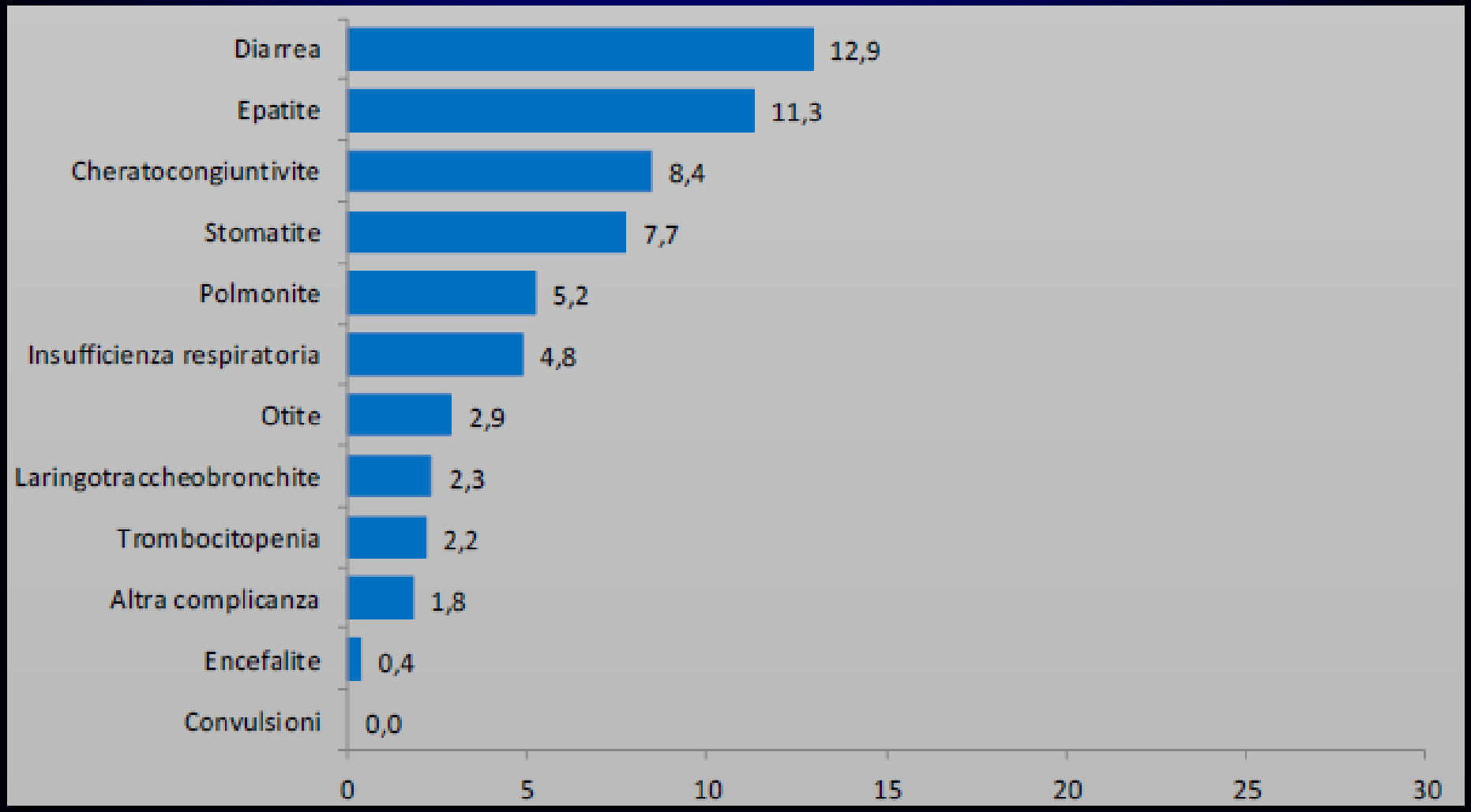
4. Parma e Piacenza: 24 casi i cui 11 in operatori sanitari

Courtesy M.Faccini

Coperture vaccinali Milano 2016- Bambini di 2 anni di età



Morbillo in Italia al 31.3 19



Frequenza delle reazioni avverse al vaccino

febbre	5-10%	da comune a molto comune
rash	5%	comune
reazione nel sito di iniezione	17-30%	molto comune
convulsioni febbrili	1/2.000-3.000	raro
encefalomielite	$1/10^6$	molto raro
trombocitopenia	1/30.000	molto raro
anafilassi	$1-3,5/\ 10^6$	molto raro

Frequenza delle complicanze

Otite media	7-9%
Polmonite	1-6%
Diarrea	6%
Encefalite	0,05-1% *
PESS	0,001%
Letalità	0,01- 0,1%

* Il 15% muore e nel 25% sequele cerebrali permanenti

Compiere l'incompiuta

- Implementare politiche di educazione sanitaria a favore della vaccinazione e a contrasto delle fake news
- Mantenere l'obbligo vaccinare fino allo stabile conseguimento della copertura conferente l'immunita di gregge (e oltre).
- Promuovere la vaccinazione degli adulti, con particolare riguardo per i giovani adulti nati dopo il 1980.
- Vaccinare gli operatori sanitari e gli operatori scolastici

Grazie pre l'attenzione