The relative clinical safety of different mumps vaccine strains

A review for the
Global Advisory Committee on Vaccine Safety
W.H.O.

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Objectives

Review published data on the safety profiles of the different mumps vaccine strains used worldwide:

- Rates of aseptic meningitis (AM)
- Overall adverse event rates
- Critical review of strengths and limitations of studies reporting mumps AEFI
- Include vaccine-specific information that might enable linkage of clinical safety data with laboratory studies of genetic stability and strain characterization

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Mumps Disease

Pathology relevant to aseptic meningitis:

- “Asymptomatic” CSF pleocytosis in 50% of mumps cases

Clinical manifestations:

- Up to 1/3 of mumps infections are subclinical, with children under two years old more often experiencing subclinical infections
- low grade fever, headache, malaise, myalgia, anorexia
- parotitis (60-70%)
- orchitis (25% in postpubertal men)
- mastitis (31% in women over 14 years)
- oophritis (5%)
- Aseptic meningitis (10-15%)
- Encephalitis (0.02% - 0.3%)
- Deafness (4% transient; 0.005% permanent)

Methods

- 40 articles identified by CDC review of mumps aseptic meningitis (2002 – K. Fullerton)
  - PubMed (Ovid) search with MESH terms:
    - Mumps vaccine /adverse effects
    - Mumps /complications
- 17 articles were provided by WHO
- 6 articles identified through updated search (to 2003 week 19) using Embase and Ovid
- 18 articles in Russian (I. Mikheeva)
- 4 articles in Spanish or Portuguese including PAHO country reports (C. Silveira)
- 4 articles in Japanese (A. Kato)

Total 89 articles

Number of reviewed studies* within 89 identified articles relevant to mumps vaccine strains in current use

Vaccination cohort size	Jeryl Lynn	Leningrad-3	L-Zagreb	Urabe	RIT 4385	Total
> 1 million vaccinees	3	2	1	4	1	11
100,000 – 1 million	2		6	8		16
5,000 – 30,000	1		1	3		5
1,000 – 5,000	2	4	1	2	2	11
< 1,000	11	9	1	7	1	29
Other	Jeryl Lynn	Leningrad-3	L-Zagreb	Urabe	RIT 4385	
Case report / case series	1	1	1	6		9
AM not mentioned	1	1	2	5		9
Other			1	5		6
Totals	21	17	14	40	4	96

* From a total of 77 published articles, 3 reports and 1 unpublished work.

Mumps Vaccine Virus Strains

Strain	Country Developed	Manufacturer(s)*
Jeryl Lynn	USA (1967)	Merck Sharpe and Dohme
Urabe Am9	Japan (late 1960s)	SmithKline Beecham, Pasteur Merieux, Biken
Leningrad-3	Former USSR (1970s)	Bacterial Medicine Institute, Moscow
RIT 4385	Germany 1997	GlaxoSmithKline
L-Zagreb	Yugoslavia (Croatia) (1970s)	Serum Institute of India

* The list of manufacturers for each strain is not necessarily complete, but represents the manufacturers relevant to the publications reviewed.

Mumps Vaccine Virus Strains of limited or no use

Strain	Country Developed	Manufacturer
Hoshino	Japan 1970s	Kitasato Institute
Torii	Japan 1970s	Takeda Chemicals
Sofia 6	Bulgaria 1965	Center for Infectious and Parasitic Diseases, Sofia
Rubini	Switzerland 1985	Swiss Serum Institute

Common features of case definitions: Mumps Vaccine-Associated Aseptic Meningitis

- Mumps vaccine-associated aseptic meningitis commonly occurs between 15-35 days post vaccination
- Signs and symptoms of meningitis, which often include meningism
- Physician or discharge diagnosis of meningitis, aseptic, or viral meningitis on hospital record
- CSF pleocytosis with lymphocyte predominance (>5 lymphocytes /ml), and bacteria absent
- Lab-confirmation (LC) includes one of the following:
    - Mumps virus isolated from CSF, or
    - Mumps virus isolated from CSF and identified as vaccine-type by sequencing

Mumps vaccine-associated Aseptic Meningitis (Urabe)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
U.K.	Maguire (1991) N=1.65 million distributed	1990-91	1 /69,000 (1 /236,000 LC)	Retrospective /Passive
	Colville (1992)	1988-91	1/3,800 (1 /11,500 LC)	Retrospective (6 cases)
	Miller (1993)	1988-92	1 /11,000 (1 /37,000 LC)	Retrospective (13 cases)
	Farrington (1995)	1988-93	1 /15,000	Retrospective

Mumps vaccine-associated Aseptic Meningitis (Urabe)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Japan	Fujinaga (1991) N=11,750	1989	1 /336 (1 /904 LC)	Retro /Passive
	Sugiura (1991) N=630,000	1989	1 /2041 (1 /6250 LC)	Retro /Passive
	Kimura (1996) N=4832	1991-93	1 /402 (1 /602 LC)	Prospective /Active

Mumps vaccine-associated Aseptic Meningitis (Urabe)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Canada	Hockin (1988)	1986-87	(1 /62,000) (Lab- confirmed)	Retro/Passive (8 cases)
France	Rebiere (1995)	1991-93	1 /26,300* * (1 /66,000)	Retro/Passive
	Jonville-Bera (1996)	1983-92	1 /122,000	Retro/Passive (4/54 cases LC)

* The rate of 1 /26,300 is based on the estimate of 116 clinical cases estimated by capture-recapture methodology. The actual number of clinical cases observed was 46 and no virus isolation was performed. Otherwise, calculation based on the number of cases observed would be 1 /65,750.

Mumps vaccine-associated Aseptic Meningitis (Urabe)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Brazil **(Salvador)** N=450,000	Dourado (2000)	1997	1/14,000	MIC /Passive
Saudi Arabia N=1,800,000	Al-Mazrou (2002)	2000	1 /295,000 (1 /1,800,000 LC)	Retro /Active

Mumps vaccine-associated Aseptic Meningitis (L-Zagreb)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Yugoslavia (Slovenia)	Cizman (1989)	1979-86	1 /1,000 * (1 /8846 Lab confirmed)	Retro /Passive (115 cases: interval 30 days)
Yugoslavia (Slovenia)	Kraigher (1990)	1979-85	1 /5000	Passive
Croatia	Tesovic (1993)	1988-92	1 /1,111	Retro /Passive (50 cases)
Bahamas	Country report (1999)	1997-98	1 /103,000 **	Retro /Passive

* 5000 recipients received the Jeryl Lynn strain

** 3 cases with Echoviruses and 7 “virulent” mumps virus cases were included. The lab-

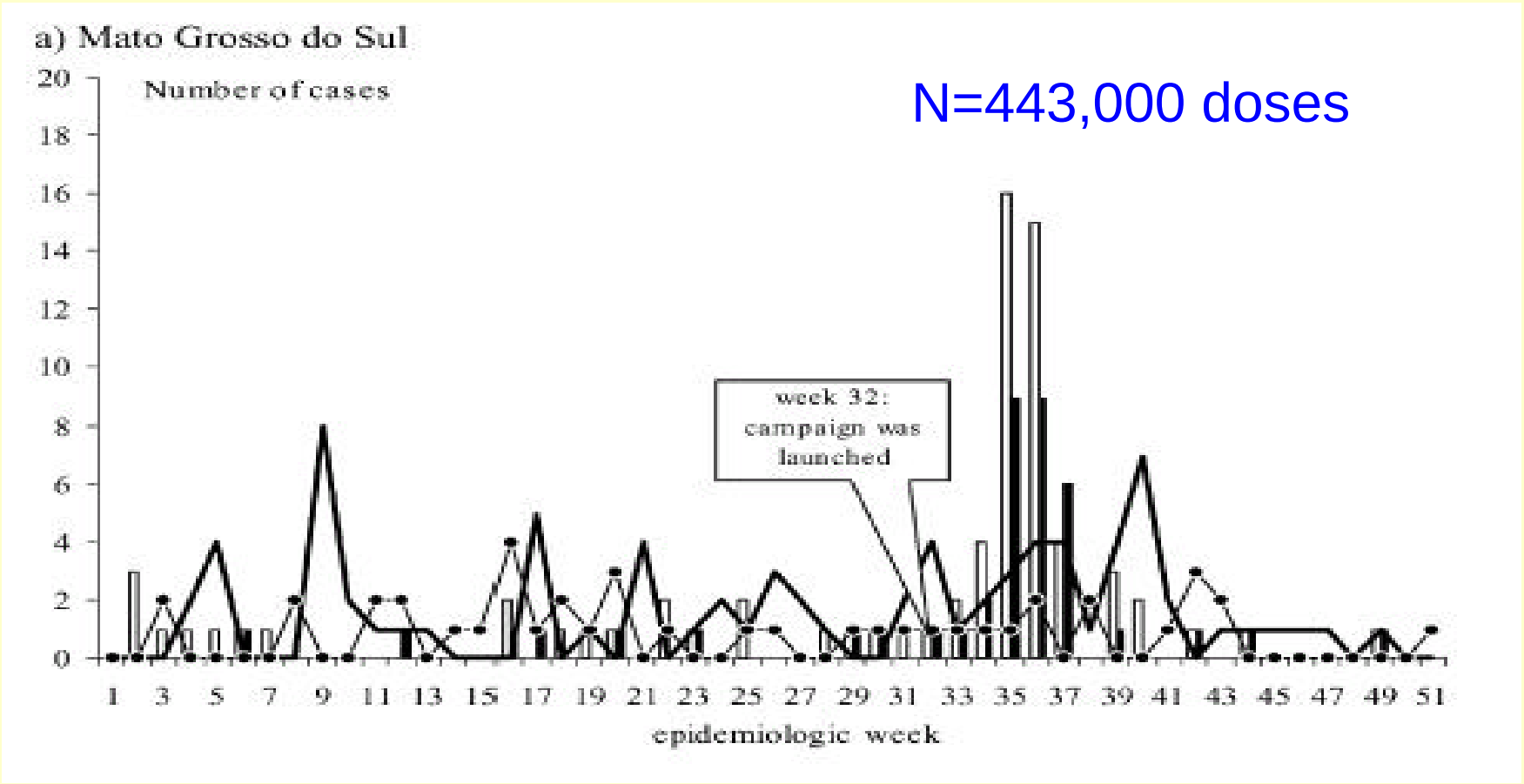
Mumps Vaccine-associated Aseptic Meningitis (L-Zagreb)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Brazil RS	Souza Cunha (1998) N=1,900,000	1997	1 /3,293	MIC /Passive
Brazil RS	Silveira (2002) N=105,000	1997	1 /3,390	MIC /Passive
Brazil Parana	Parana Dept. of Health N=900,000	1998	1 /10,000	MIC /Passive
Brazil Curitiba, Parana	Arruda W (2001) N=600,000	1998	1 /5,882	MIC /Passive

Mumps vaccine-associated Aseptic Meningitis (L-Zagreb)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Brazil Mato Grosso	Martins R (2001)	1992-99	1 /15,500	Retro /Passive
	Souza Cuhna (2002) N=403,000	1998	1 /9,518	MIC /Passive
Brazil Mato Grosso do Sul	Martins R (2001)	1992-99	1 /55,000	Retro /Passive
	Souza Cuhna (2002) N=443,000	1998	1 /19,738	MIC /Passive

Aseptic meningitis and mumps after mass vaccination using the Leningrad-Zagreb mumps strain*



* Souza da Cunha et al. Vaccine 2002; 20:1106-12.

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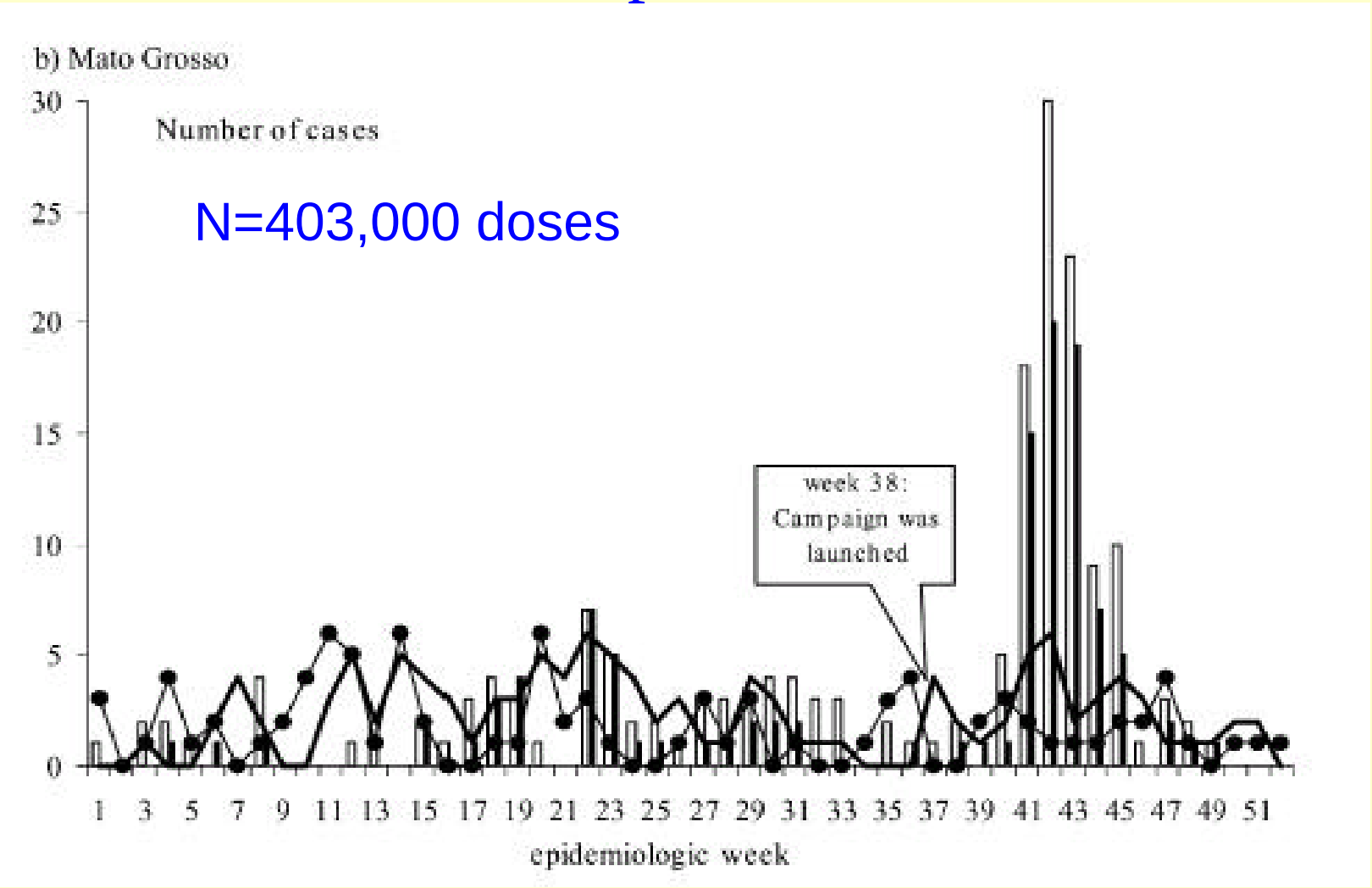


* Souza da Cunha et al., Vaccine 2002; 20:1106-12

Mumps vaccine-associated Aseptic Meningitis (Leningrad -3)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Russia	Popov (1997)	1987-97	1 /1,587,301	Retro /Passive
	Maximova (2001)	1980-98	1 /5,555,555	Retro /Passive

Mumps vaccine-associated Aseptic Meningitis (Jeryl Lynn B)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Germany	Fescharek (1990)	1976-89	1 /1,000,000	Retro / Case series (1/5 cases in 15-35 day interval)
USA	Black (1997)	1984-93	1 /150,000	Retro /Passive (2 cases: interval 15-30 days)
	Davis (1997)	1991-94	0 /18,036; 0 /8514	Retro /Passive

Mumps vaccine-associated Aseptic Meningitis (Jeryl Lynn B)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Finland	Patja A (2000)	1982-96	0 /1,800,000	Retro /Passive
	Makela A (2002)	1982-86	~ 0 /535,000	Retro /Passive
Germany	Schlipkoter (2002)	1998-2000	1 /950,000	Retro /Active (2 cases: interval 15-35days)

Mumps vaccine-associated Aseptic Meningitis (RIT 4385)

Country	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Germany	Schlipkoter (2002)	1998-2000	0/ 1,575,000	Retro /Active

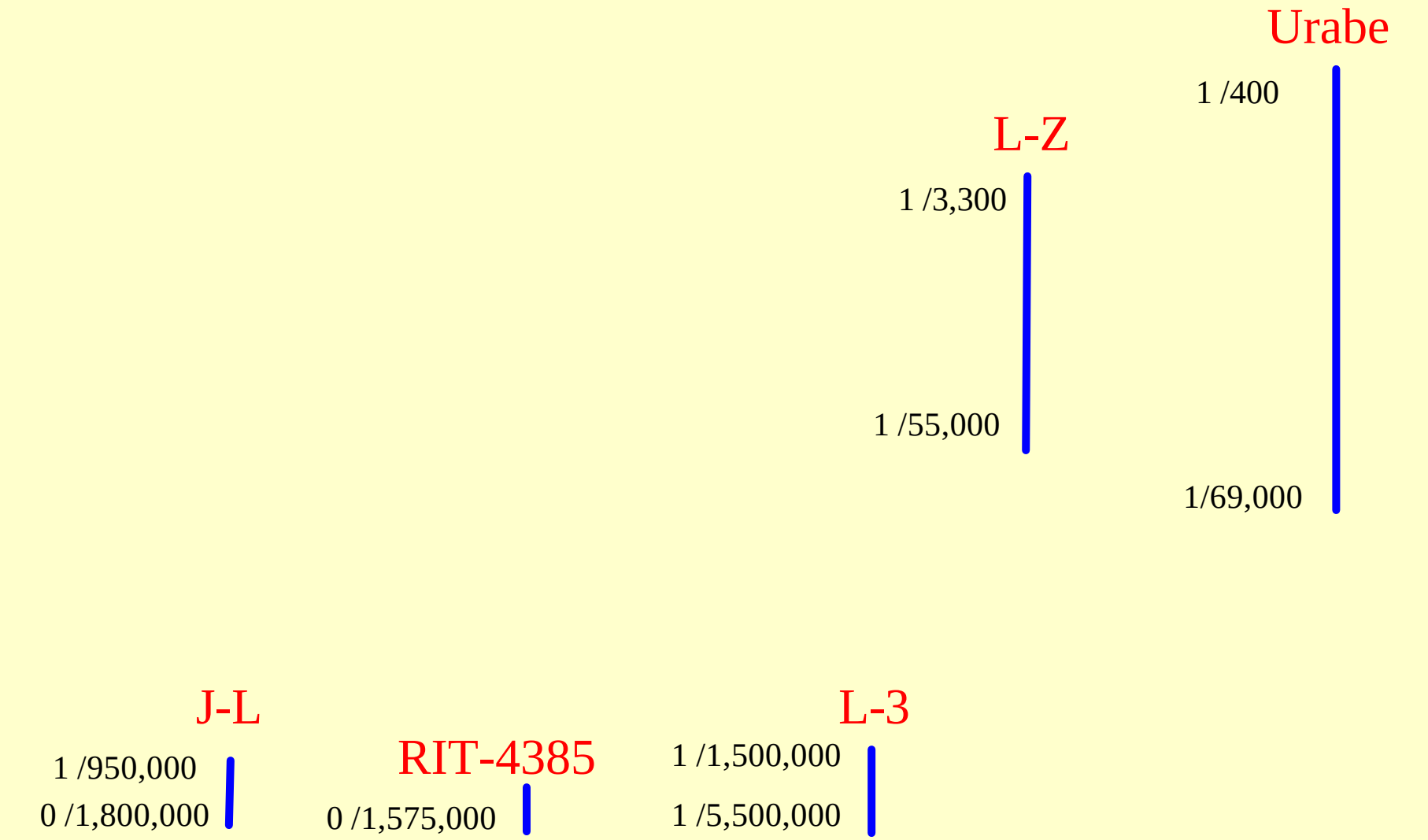
Mumps vaccine-associated Aseptic Meningitis (Sofia - 6)

Country (Strain)	Author (Year)	Study period	Rate of AM by dose	Type of Study/ Surveillance
Bulgaria (Sofia-6)	Odisseev H (1994)	1972 - 1982; revaccination in 1982	1/5,286 upon revaccination of 4-12 year olds; 1/22,000 for 1-3 year olds – 1st dose	Retro /Passive

Summary

Strain	High AM rate	Low AM rate
Jeryl Lynn	1 /950,000 (Schlipkoter, Germany, 2002) N = 1.9 Million	0 /1,800,000 (Patja, Finland, 2000) N = 1.8 million
RIT 4385	0 /1,500,000 (Schlipkoter, Germany, 2002) N = 1.5 million	
Leningrad-3	1 /1,500,000 (Popov, Russia, 1997) N ~ 50 million	1 /5,500,000 (Maximova, Russia, 2001) N ~ 100 million
L-Zagreb	1 /3,300 (Souza Cuhna, Brazil, 1998) N=105,000	1 /55,000 (Martins, Brazil, 2001) N = ~ 3.6 million
Urabe	1 /400 (Kimura, Japan, 1996) N = 4830	1/69,000 (Maguire, U.K., 1991) N = ~ 1.65 million

Summary of rate ranges*

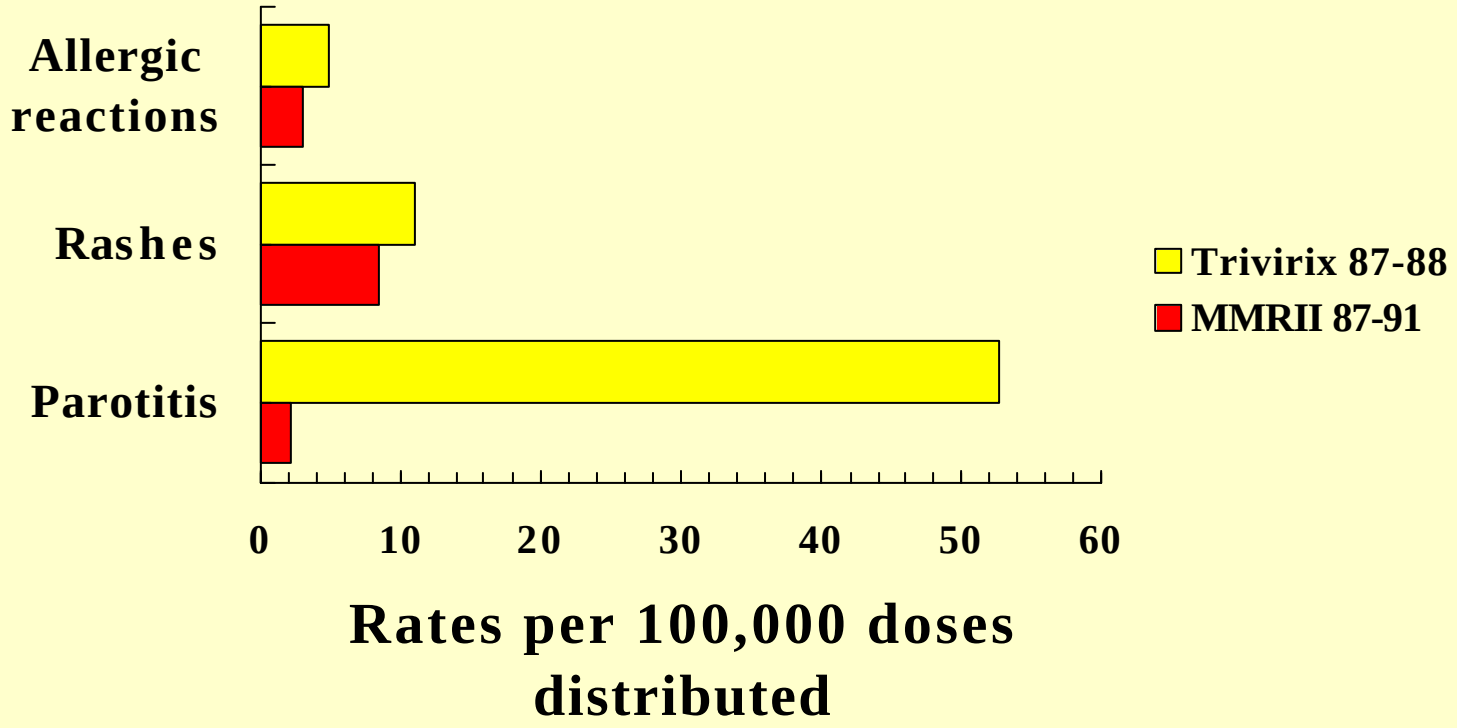


* This is a schematic diagram of the range of reported rates of vaccine-associated aseptic meningitis attributed to different mumps vaccine strains from the present review. The figure is not to scale and is not a representation of statistical difference between strains.

Reports of parotitis associated with different mumps vaccine strains

Strain	Reference	Data reported
Jeryl Lynn	Fescharek 1990	1 /90,000 within 5.5 million vaccinees; Onset 7 days – 1 month; 32M:19F
Leningrad-3	Melachenko 1974	1 /44 (1146 vaccinees)
	Ivanov 1985	1 /18 (497 vaccinees)
Urabe	Canada 1987-88	1 /3050 (500,000 doses distributed)
	Al-Mazrou 2002	1 /3255 (2.4 million vaccinees)
	Santos 2002	1 / 75 (2179 vaccinees) RR = 6.69 (CI95% 2.94, 15.26)
Sofia-6	Odisseev 1994	1 /167 (412,000 vaccinees)

Rates of Selected Reported MMR-Associated Adverse Events, Canada



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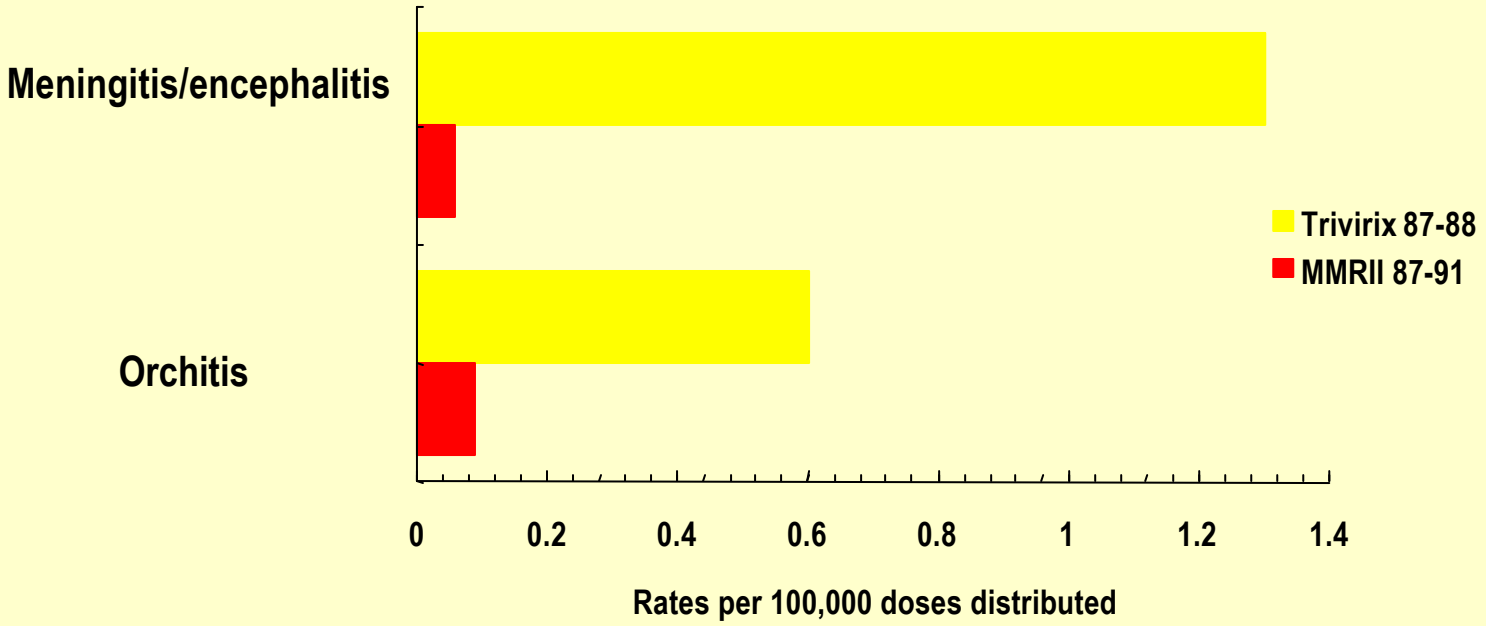

Reports of parotitis associated with mumps vaccine strains

Strain	Reference	Data reported
L-Zagreb	Kraigher 1990	1 /444 (210,000 vaccinees)
	Santa Catarina, Brazil Dept. Health – 1996	1 /4462 (1.1 million vaccinees)
	Bhargava – 1995	1 /433 (866 vaccinees)
	Bahamas – 1997-98	1 /833 (103,000 vaccinees*) * 4.9% of vaccinees received Jeryl Lynn vaccine
	Santos 2002	1 /32 (2226 vaccinees) RR = 15.6 (CI95% 7.2; 33.9)
	Cizman 1993	Within 112 AM cases, 32 parotitis also observed
	Tesovic 1993	Within 50 AM cases, 4 parotitis also observed
	Souza Cuhna 1998	"Outbreak" associated with MIC in Ceara, Brazil 1997 - but no rates available
	Parana, Brazil –1998 Dept. Health	"Outbreak" associated with MIC – Parana, 1998 - no rates available
	Baker 2001	Higher rate of parotitis among vaccinated vs. controls (RR=3.2)

Factors for further consideration:

Population immunity:

Age-specific immunity is an important under-recognized factor with potential to cause rate differences among populations receiving the same strain.

Persons without immunity to mumps may have a much greater risk of VAAM, and immunity to mumps usually increases rapidly through childhood and also varies among populations.

Therefore, knowledge about a populations' immunity may be important in risk – benefit assessments of a particular mumps vaccine strain, especially in the context of other health system expenditures.

Factors for further consideration:

Possible high prevalence rate of CSF pleocytosis, and its impact on rates:

Since is possible that a substantial proportion of mumps vaccinees exhibit CSF pleocytosis, measured VAAM rates may be strongly influenced by rates of presentation to health services and rates of lumbar puncture.

Heightened public awareness and health care provider awareness may lead to increased presentation rates and lumbar puncture rates, respectively. These biases may interact during times of heightened awareness resulting in increased rates.

Factors for further consideration:

Background rates of aseptic meningitis:

Any difference in background rates of AM among communities may cause differences in detected excess AM cases after vaccination.

Factors for further consideration:

Vaccine-associated parotitis:

Documentation of parotitis rates in populations affected by increased VAAM rates is poor. The available data suggest a potential correlation between vaccine-associated parotitis and vaccine-associated aseptic meningitis.

Factors for further consideration:

Case definition of aseptic meningitis:

The lack of a standardized clinical case definition complicates interpretation of available data, and may increase the probability of higher “case” ascertainment influenced by non-strain factors.

End