Updated ACIP Statement on the Prevention of Measles, Rubella, Congenital Rubella Syndrome (CRS), and Mumps

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Outline

- Overview of the Updated (2013) ACIP MMR Statement
- Review of WG deliberations and recommendations
  - Use of a third dose of MMR vaccine for mumps outbreaks in certain settings
  - Acceptable evidence of immunity
  - Use of immune globulin for measles post exposure prophylaxis
  - Vaccination of persons with HIV infection

Overview of the 2013 ACIP MMR Statement

Rationale for Updating MMR Statement

- Full ACIP MMR statement last published in 1998[1]
- Epidemiology of diseases have changed
  - Elimination of measles (2000) and rubella (2004)
  - Large mumps outbreaks among highly vaccinated populations
- Monovalent vaccines no longer available in the US, MMRV vaccine licensed
- Revisions to recommendations
  - Interval for avoiding pregnancy after receiving rubella-containing vaccines (2001)[2]
  - Adequate mumps vaccination for school-aged children and adults at high risk* (2006)[3]
  - Evidence of immunity for health-care personnel and recommendations for personnel born before 1957 (2011)[4]

*i.e., health-care personnel, international travelers, and students at post-high school educational institutions.

[1]*MMWR* May 22 1998;47(RR-8):1-57. [2]*MMWR* Dec 14 2001;50(49):1117. [3]*MMWR* Jun 9 2006;55(22):629-630. [4]*MMWR* Nov 25 2011;60(RR-7):1-45

2013 MMR Statement Background Information

- Updated epidemiology
- Information regarding MMRV vaccine and immune globulin products
- Expanded section on vaccines (i.e., immune response, vaccine effectiveness, duration of immunity)
- Summary of Institute of Medicine (IOM) reports on MMR vaccine safety
- Summary of studies of a third dose of MMR vaccine for mumps outbreak control
- Link to CDC's Manual for the Surveillance of Vaccine-Preventable Diseases

2013 MMR Statement Recommendations

- Clarifies policy language
- Incorporates more recent recommendations
- Includes proposed revised recommendations
  - Evidence of immunity
  - Use of immune globulin products for measles prevention
  - Vaccination for persons with HIV infection

Review of WG Deliberations and Recommendations

- Use of a third dose of MMR vaccine for mumps outbreaks in certain settings
- Acceptable evidence of immunity
- Use of immune globulin products for post exposure prophylaxis for measles
- Vaccination of persons with HIV infection

Use of a Third Dose of MMR Vaccine during Mumps Outbreaks

Previously presented during the February 2012 ACIP Meeting
by Dr Preeta Kutty and Ms Amy Parker Fiebelkorn, CDC/NCIRD

Mumps in the United States

- Mumps vaccine (Jeryl Lynn strain) licensed in 1967, recommended for routine use in 1977
- 2 doses of MMR vaccine recommended for children for measles prevention in 1989
- By the early 2000s, <300 cases reported annually
- Large outbreaks among highly 2-dose vaccinated populations occurred in 2006 and 2009-2010

Epidemiology of Mumps Outbreaks United States, <2006

- **Pre-Vaccine Era**
  - Outbreaks common in crowded settings and in populations with build up of susceptible persons (prisons, orphanages, schools, military)
- **Late 1980s**
  - Outbreaks among cohorts of unvaccinated older children[1]
  - Outbreaks associated with 1 dose vaccine failure reported[2-4]

[1]Cochi SL, et al. *Am J Dis Child.* May 1988;142(5):499-507. [2]Hersh BS, et al. *J Pediatr.* Aug 1991;119(2):187-193. [3]Cheek JE, et al. *Arch Pediatr Adolesc Med.* Jul 1995;149(7):774-778. [4]Briss PA, et al. *J Infect Dis.* Jan 1994;169(1):77-82.

Epidemiology of Mumps Outbreaks United States, 2006

- 6584 cases (incidence = 2.2 cases per 100,000)[1]
- Outbreaks on college campuses with 2 dose vaccine coverage of 95%-99%[2-3]
  - Cohort: one and two dose VE ~80%
  - Roommate contact: one dose 65% (0-94%), two doses 88% (65%-96%)
- Risk factors for vaccine failure[3]
  - Younger age or college freshman
  - On versus off campus housing
  - Female
  - ≥10 years since 2nd mumps vaccine dose compared with <10 years

[1]Dayan GH, et al. *N Engl J Med.* Apr 10 2008;358(15):1580-1589. [2]Marin M, et al. *Vaccine.* Jul 4 2008;26(29-30):3601-3607. [3]Cortese MM, et al. *Clin Infect Dis.* Apr 15 2008;46(8):1172-1180.

Epidemiology of Mumps Outbreaks United States and Guam, 2009-2010

Northeastern US[1]

- >3500
- 71% male
- 27% aged 13-17 years
- 97% occurred among Orthodox Jewish persons
- 76% had received 2 doses of MMR vaccine*

Guam[2]

- 505 cases
- 50% male
- 34% aged 9-14 years
- 34% Chamorro ethnicity
- 94% of school-aged children had received 2 doses of MMR vaccine

*Among the 72% of case-patient with vaccination status reported.

[1]Barskey AE, et al. *N Engl J Med* 2012;367:1704-13. [2]Nelson GE, et al. J *Pediatr Infect Dis J.* Oct 24 2012.

Key Issues

- Large mumps outbreaks have occurred despite high 2-dose MMR vaccine coverage
- Standard control measures have not been completely effective in some situations
- Mumps endemic in many parts of the world

Third Dose Studies for Mumps Control

- **Anamnestic response following a third dose[1]**
  - 14/17 (82%) of seronegative subjects who received a third dose of MMR vaccine had seropositive results within 7-10 days after vaccination.
- **Evaluated impact of a third dose of MMR vaccine during mumps outbreaks in two highly vaccinated populations (2010)**

[1]Date AA, et al. *J Infect Dis.* Jun 15 2008;197(12):1662-1668.

Orange County, New York: Third Dose MMR Vaccine Intervention Study

- 3 schools selected for the intervention
  - Children aged 11-17 years
  - High 2-dose MMR vaccine coverage: 94%
  - Ongoing mumps transmission in preceding 2 weeks
- 1755 (81%) eligible students received a third dose of MMR vaccine

Ogbuanu, I. U., et al. *Pediatrics. 2012 (In Press)*

Population-level Age-specific Mumps Attack Rates in the Village, Orange County, NY, 2009-2010

Age Group (years)	Pre-intervention period† AR (%)	Post-intervention phase 2¶ AR (%)	Relative percent decline
All	0.9	0.2	76 (66, 83)
< 5	0.2	0.1	27 (-126, 77)
5 – 10	1.4	0.4	73 (52, 84)
11 – 17	2.4	0.1	96 (87, 99)
18 – 24	0.7	0.3	53 (-11, 79)
≥25	0.2	0.2	11 (-123, 63)

†Pre-intervention period: 21 days prior to the third dose MMR vaccine intervention period (January 19-Feb 2, 2010)
¶Post-intervention phase 2: Days 22 to Day 42 after the intervention period

Slide courtesy of Dr Preeta Kutty, CDC/NCIRD

Orange County, NY: Limitations

- Outbreak on the decline when the intervention was conducted
- Did not have a large comparison group
- Small number of cases post intervention

Guam: Third Dose MMR Vaccine Intervention Study

- 7 schools selected for intervention
  - Children aged 9-14 years
  - Highest attack rates (8.4-31.5/1000)
  - High 2-dose vaccination coverage (99-100%)
- 1067 (33%) eligible students received a third dose of MMR vaccine

Nelson GE, et al. *Pediatr Infect Dis J.* Oct 24 2012.

Mumps Attack Rates among Students Aged 9-14 Years in 7 Schools Following the Third Dose MMR Vaccine Intervention, Guam 2010

	>1 incubation period post-vaccination			Comparison of ARs between students with 3 versus 2 MMR doses >1 incubation period post-vaccination¶	
	No. of cases	N	AR (per 1000)	RR (95% CI)	P-value
Students who had 2 doses of MMR vaccine	5	2106	2.4	Reference	
Students who had 3 doses of MMR vaccine	1	1067	0.9	0.4 (0.05, 3.4)	0.67

¶Value calucated using Fischer's exact test

Nelson GE, et al. *Pediatr Infect Dis J.* Oct 24 2012.

Slide courtesy of Ms Amy Parker Fiebelkorn, CDC/NCIRD

Guam: Limitations

- Intervention occurred after the peak of the outbreak
- Small numbers of mumps cases post-intervention
- Under-reporting of cases

Adverse Events following MMR Vaccination

	2nd dose summary*† (n= 6 studies)	Orange County† (3rd dose)	Guam§ (3rd dose)
Study Characteristics			
No. vaccinated	18 - 2216	1597	533
Age of subjects	4 years – College-age	9-21 years	9-14 years
Follow-up period (days)	14-42	14	14
Symptoms (%)			
Pain, Redness, or Swelling	17.4 (2.0 - 33.3)	3.6	2.4
Arthralgia or joint pain	3.0 (0.4 - 12.0)	1.8	2.6
Dizziness or lightheadedness	5.1 (1.6 - 8.6)	1.7	2.4
Fever	8.7 (4.0 - 16.2)	1.3	1.0
Difficulty Breathing	NA	0.2	0
Rash or hives	3.6 (0.0 - 7.0)	0.4	0
Syncope	0.7	0.2	0

*median percent and range

†Abedi, G. R., et al. *Vaccine.* Oct 3 2012.

§Data courtesy of Ms Amy Parker Fiebelkorn, CDC/NCIRD

Summary of Third Dose Intervention Studies

- Impact in targeted group
  - Orange County: 96% decline among those aged 11-17 years
  - Guam: Lower attack rates among 3 dose versus 2 dose recipients
  - Limitations include timing of intervention
- Very few mild and no serious adverse events reported
- Do not provide conclusive evidence on impact of a third dose for outbreak control but consistent with potential impact

WG Deliberation: Use of a Third Dose of MMR Vaccine for Mumps Outbreaks

- Data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps control
- Provide link to CDC's Manual for the Surveillance of Vaccine-Preventable Diseases Mumps Chapter with CDC guidance

Proposed Language for Link to CDC Guidance

"Currently, data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps outbreak control.

CDC has issued guidance for considerations for use of a third dose in specifically identified target populations along with criteria for public health departments to consider for decision making (link to CDC website and/or CDC's Manual for the Surveillance of Vaccine-Preventable Diseases Mumps Chapter)"

Language for CDC Guidance for Use of a Third Dose of MMR Vaccine for Mumps Outbreaks (1)

"During mumps outbreaks, public health authorities may administer a third dose of MMR vaccine for specifically identified target populations.

Criteria to consider prior to administering a third dose in a target population for mumps outbreak control include:

- high two-dose vaccination coverage (i.e., vaccination coverage >90%);
- intense exposure settings likely to facilitate transmission (e.g., schools, colleges, correctional facilities, congregate living facilities) or healthcare settings;
- high attack rates (i.e., >5 cases per 1,000 population); and
- evidence of ongoing transmission for at least two weeks in the target population (i.e., population with the high attack rates)."

Language for CDC Guidance for Use of a Third Dose of MMR Vaccine for Mumps Outbreaks (2)

"Additional data on the effectiveness and impact of a third dose of MMR vaccine for mumps outbreak control are needed to guide control strategies in future outbreaks.

Authorities who decide to administer a third dose as part of mumps outbreak control are encouraged to collect data to evaluate the impact of the intervention.

The following data should be collected:

- incidence of mumps in target population (before and after the intervention, by vaccination status),
- incidence of adverse events following vaccination with a third dose, and
- costs associated with the intervention (vaccine, personnel)."

Acceptable Evidence of Immunity

Previously presented during the June 2012 ACIP Meeting

Acceptable Evidence of Immunity

- Developed to guide vaccination assessment and administration
- Criteria provide presumptive evidence of immunity to measles, rubella, and mumps
- Persons who meet the criteria have a very high likelihood of immunity

Acceptable Evidence of Immunity Proposed Changes and Rationale

- **Proposed changes**
  - Include "laboratory confirmation of disease"
  - Remove "physician diagnoses of disease" for measles and mumps
- **Rationale**
  - Validity of history low, especially over last 30 years
  - Challenges with documenting history from physician records for adults
  - For consistency with recommendations for health-care personnel
    - Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1-45

Acceptable Evidence of Immunity - Routine

	Current	Proposed
Measles	(1) documentation of adequate vaccination: - preschool-aged children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed measles~~	(1) documentation of age-appropriate vaccination with a live measles virus-containing vaccine[§]: -preschool-aged children: 1 dose -school-aged children (grades K-12): 2 doses -adults not at high risk[¶¶]: 1 dose, or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease,** or (4) born before 1957 (except women of childbearing age who could become pregnant[§§])
Mumps	(1) documentation of adequate vaccination with live mumps virus vaccine: - preschool-aged children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed mumps~~	(1) documentation of age-appropriate vaccination with a live mumps virus-containing vaccine:[§] -preschool-aged children: 1 dose -school-aged children (grades K-12): 2 doses -adults not at high risk[¶¶]: 1 dose, or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957

[§]The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.

[¶]Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.

[§§]Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

[¶¶]Adults at high risk include students in post-high school educational institutions, healthcare personnel, and international travelers

Acceptable Evidence of Immunity
Students at Post-High School Educational Institutions

	Current	Proposed
Measles	(1) documented administration of 2 doses of live measles virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed measles~~	(1) documentation of vaccination with 2 doses of live measles virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus, vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957 (except women of childbearing age who could become pregnant[§§])
Mumps	(1) documented administration of two doses of live mumps virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed mumps~~	(1) documentation of vaccination with 2 doses of live mumps virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957

[§]The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.
[¶]Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.
[§§]Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

Acceptable Evidence of Immunity
International Travelers

	Current	Proposed
Measles	(1) documented administration of 2 doses of live measles virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed measles~~	(1) documentation of age-appropriate vaccination with live measles virus-containing vaccine: -infants age 6-11 months[††]: 1 dose -persons age ≥12 months[§]: 2 doses, or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus, vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957 (except women of childbearing age who could become pregnant[§§])
Mumps	(1) documented administration of two doses of live mumps virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or ~~(4) documentation of physician diagnosed mumps~~	(1) documentation of vaccination with 2 doses of live mumps virus-containing vaccine[§], or (2) laboratory evidence of immunity[¶], or (3) **laboratory confirmation of disease**, or (4) born before 1957

[§]The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.

[¶]Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.

[§§]Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

[††]Children who receive a dose of MMR vaccine before age 12 months should be revaccinated with 2 doses of MMR vaccine, the first of which should be administered when the child is aged 12 through 15 months (12 months if the child remains in a high-risk area) and the second at least 28 days later.

Measles Post Exposure Prophylaxis (PEP) with Immune Globulin (IG)

Previously presented during the June 2012 ACIP Meeting
by Dr Mark Papania, CDC/NCIRD

Immune Globulin (IG)

- Blood product used to provide antibodies for short term prevention of some infectious diseases, including measles
- Prepared from plasma pools derived from 1000s of donors

IG Products

- **IGIM – IG given intramuscularly**
  - Historically been the blood product of choice for measles PEP
  - Dose and volume restrictions may limit usefulness as PEP in certain populations
- **IGIV – IG given intravenously**
  - Available since 1981
  - Primarily used for patients with primary immunodeficiency disorders
  - High cost* and administration requires observation by skilled professional, and hospital admission
- **IGSC – IG given subcutaneously**
  - Available since 2006
  - Same major indications as IGIV
  - Administration requires a pump and advance training
  - Multiple, weekly doses are needed

*The average cost in 2007 was $55 per gram = $220 for a 10 kg child and $1540 for a 70 kg adult for a 400 mg/kg dose (Sorenson R, et al. JMCP 2007)

Effectiveness of IGIM for Measles PEP

- 1940s: IGIM can reduce the risk of measles or modify disease if given within 6 days of exposure[1,2]
- Few studies of PEP effectiveness in the vaccine era
  - PE = 8% among household contacts in 1990 (US)[3]
  - PE = 76% among "susceptible contacts" in 2006 (New South Wales)[4]
  - 2/15 (13%) seronegative infants became seropositive 48 hours after PEP with IGIM (following exposure in NICU in 1990)[5]
- Optimal IGIM dose needed for protection unknown
  - A 1999-2000 study showed higher anti-measles titer provided greater protection[6]
    - Protected children received a mean dose of 10.9 IU/kg (SD 3.4) compared to 5.7 IU/kg (SD 1.6) for whom PEP failed

[1]Janeway CA. *Bull N Y Acad Med* 1945;21(4):202-222. [2]Ordman CW, et al. *J Clin Invest.* Jul 1944;23(4):541-549. [3]King GE, et al. *Pediatr Infect Dis J.* Dec 1991;10(12):883-888. [4]Sheppeard V, et al. *N S W Public Health Bull.* May-Jun 2009;20(5-6):81-85. [5]Subbarao EK, et al. *J Pediatr.* Nov 1990;117(5):782-785. [6]Endo A, et al. *J Pediatr.* Jun 2001;138(6):926-928.

Current Recommendations
Use of IG for Post Exposure Prophylaxis

- Administration of IGIM to susceptible household contacts who are not vaccinated within 72 hours of initial exposure is recommended.
- IGIM is indicated for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged ≤12 months, pregnant women, or immunocompromised persons).
- The usual recommended dose of IGIM is 0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL).

MMWR 1998;47(RR-8):1-57

Current Recommendations
Use of PEP IG for Infants

- Infants <6 months of age are usually immune because of passively acquired maternal antibodies. However, if measles is diagnosed in a mother, unvaccinated children of all ages in the household who lack other evidence of measles immunity should receive IG.

MMWR 1998;47(RR-8):1-57

Current Recommendations
Use of PEP IG for Immunocompromised Patients

- Severely immunocompromised patients and other symptomatic HIV-infected patients who are exposed to measles should receive IG prophylaxis regardless of vaccination status because they may not be protected by the vaccine.
- For patients receiving IGIV therapy, a standard dose of 100-400 mg/kg should be sufficient to prevent measles infection after exposures occurring within 3 weeks after administration of IGIV; for patients exposed to measles >3 weeks after receiving a standard IGIV dose, an additional dose should be considered.

MMWR 1998;47(RR-8):1-57

IG for Measles Post Exposure Prophylaxis (PEP) Specific Issues Considered

- Recommendations regarding the type of exposure for which IG PEP is indicated may need to be clarified
- Measles antibody concentrations may be lower in IG products due to the change in donor demographics
  - Dose/volumes recommended for PEP may need to be revised
- Susceptibility to measles among infants born in the US has increased
  - Recommendations for PEP in early infancy may need to be revised
- Multiple IG preparations licensed in the US
  - The role of each product in measles prevention needs to be defined

Measles Antibody Titers in IG Products

- All US licensed IG products must contain a measles antibody level of adequate potency [1]
- Lower measles antibody concentrations from donor populations with predominately vaccine-induced immunity[2]
- Much higher volumes can be given with IGIV and IGSC compared to IGIM

[1]DHHS, FDA. Additional Standards for Human Blood and Blood Products (21 CFR Part 640 Subpart J-Immune Globulin (Human). Code of Federal Regulations, Title 21, Volume 7, Revised April 1, 2005. Online at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=640&showFR=1&subpartNode=21:7.0.1.1.7.10

[2]Audet S, et al. J Infect Dis. 2006 Sep 15;194(6):781-9.

Estimates of US Minimum Measles Antibody Dose for Various IG Products

IG Product	Minimum Measles Antibody Potency / mL	Measles Antibody Dose	Measles Antibody Dose, 70kg person
IGIM (0.25 ml/kg)	25.2 IU/mL	6.3 IU/kg	5.4 IU/kg
IGIM (0.5 ml/kg)	25.2 IU/mL	12.6 IU/kg	5.4 IU/kg
IGIV (100 mg/kg)	12.3 IU/mL	12 IU/kg	12 IU/kg
IGIV (200 mg/kg)	12.3 IU/mL	24 IU/kg	24 IU/kg
IGIV (400 mg/kg)	12.3 IU/mL	48 IU/kg	48 IU/kg

Slide courtesy of Dr Mark Papania, CDC/NCIRD

Calculated Serum Measles Antibody Concentration following IG Post Exposure Prophylaxis

IG Product (Dose)	Minimum[1] Measles Antibody Dose IU/KG	Calculated Serum Measles Antibody Concentration		
		Peak 4-6 hours mIU/mL	Equilibrium 4-5 days mIU/mL	Trough 28-30 days mIU/mL
IGIM (0.25 ml/kg)	6.3	[158]	63	32
IGIM (0.50 ml/kg)	12.6	[315]	126	63
IGIV (100 mg/kg)	12	300	120	60
IGIV (200 mg/kg)	24	600	240	120
IGIV (400 mg/kg)	48	1200	480	240

Estimated protective level of measles antibody concentration ≥120 mIU/mL (PRN)[2]

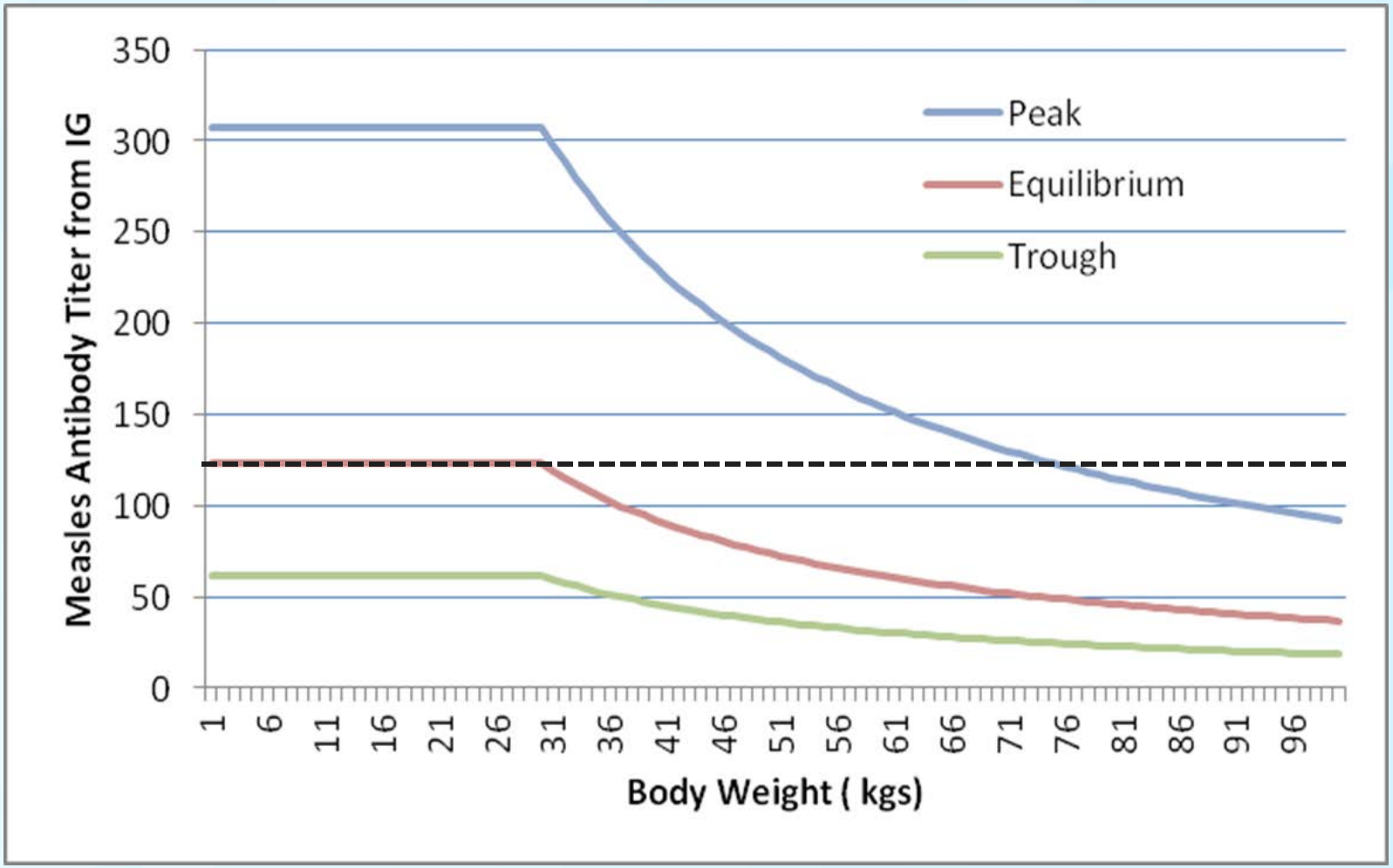
[1]At FDA minimum titer using 30 kg body weight as an example. Maximum volume of 15 ml for IGIM is reached at 60 kg for 0.25 ml/kg and at 30kg for 0.5 ml/kg. Above these weights IU/kg dose decreases with increasing body weight.

[2]Chen RT, et al. *JInfect Dis.* Nov 1990;162(5):1036-1042.

Slide courtesy of Dr Mark Papania, CDC/NCIRD

Calculated Measles Antibody Titers

IGIM Administration Dose 0.5 mL/kg (15 mL maximum dose)



Slide courtesy of Dr Mark Papania, CDC/NCIRD

Increasing Susceptibility to Measles among Infants in the United States

- **High measles incidence among US infants aged <12 m**
  - 2001-2008: 63 cases (0.2/million for 0-5 m; 3.5/million for infants 6-11m)[1]
  - 2011: 27 cases (1.4/million for 0-5 m; 5.6/million for infants 6-11 m)
- **Infants of vaccinated mothers are more likely to be susceptible at a younger age**
  - 30% of infants of vaccinated mothers had measles antibody titers <300 mIU/mL at birth; 97% by age 6 months (Belgium 2006-2009) [2]
  - 48% (14/29) of 6-month-old infants had undetectable transplacentally derived measles neutralizing antibodies (US 2004)[3]
- **Most women giving birth in the US were born after 1963, the year measles vaccination began in the US**

[1]Parker Fiebelkorn A, et al. *J Infect Dis.* Nov 15 2010;202(10):1520-1528. [2]Leuridan E, et al. BMJ. 2010 May 18;340:c1626. [3]Gans HA, et al. J Infect Dis. 2004 Jul 1;190(1):83-90.

Measles Post Exposure Prophylaxis with IG Proposed Changes

- Remove wording that limits use to household exposure settings
- Increase the recommended dose of IGIM
- Include use of IGIV
- Expand recommendation for use of IGIM to infants aged 0-5 months

Proposed Recommendations
Use of IG for Post Exposure Prophylaxis

"The following patient groups are at risk for severe disease and complications from measles and should receive IG:

- Infants aged <12 months,
- Pregnant women without evidence of measles immunity, and
- Immunocompromised persons.

IGIM can be given to other persons who do not have evidence of measles immunity, but priority should be given to persons exposed in settings with intense, prolonged, close contact (e.g., household, daycare, classroom, etc.)."

Proposed Recommendations
Dose of IG for Post Exposure Prophylaxis

"The recommended dose of IG given intramuscularly (IGIM) is 0.5 mL/kg of body weight (maximum dose = 15 mL) and the recommended dose of IG given intravenously (IGIV) is 400 mg/kg."

Proposed Recommendations
Use of IG for Post Exposure Prophylaxis
Infants aged <12 months

"Because infants are at higher risk for severe measles and complications and infants are susceptible to measles if their mother is nonimmune or their maternal antibodies to measles has waned, IGIM should be given to infants aged <12 months who have been exposed to measles.

For infants aged 6 through 11 months, MMR vaccine can be given in place of IGIM, if administered within 72 hours of initial exposure."

Proposed Recommendations
Use of IG for Post Exposure Prophylaxis
Pregnant Women Without Evidence of Immunity

"Because pregnant women might be at risk for severe measles complications, IGIV should be given to pregnant women without evidence of measles immunity who have been exposed to measles."

Proposed Recommendations
Use of IG for Post Exposure Prophylaxis
Severely Immunocompromised Persons (1)

"Severely immunocompromised patients [including HIV-infected persons with CD4 percentages <15% (all ages) or CD4 <200 cells/mm^3 (age >5 years) and those who have not received MMR vaccine since receiving effective ART; some experts would include all HIV-infected persons, regardless of immunologic status or MMR vaccine status] who are exposed to measles should receive IGIV prophylaxis regardless of immunologic or vaccination status because they may not be protected by the vaccine."

Proposed Recommendations
Use of IG for Post Exposure Prophylaxis
Severely Immunocompromised Persons (2)

"For persons already receiving IGIV therapy, administration of at least 400 mg/kg within 3 weeks before measles exposure should be sufficient to prevent measles infection.

For patients receiving subcutaneous immune globulin (IGSC) therapy, administration of at least 200 mg/kg body weight for two consecutive weeks before measles exposure should be sufficient."

Vaccination of Persons with HIV Infection

Previously presented during the October 2011 ACIP Meeting
by Dr George Siberry, NIH

Persons with HIV Infection Current Recommendations

- Recommended for all **asymptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)
  - HIV-infected infants without severe immunosuppression should routinely receive MMR vaccine *as soon as possible upon reaching the first birthday*
  - Consideration should be given to administering the second dose of MMR vaccine *as soon as 28 days after the first dose*
- Consider for all **symptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)
- Not recommended for persons with severe immunosuppression

MMWR 1998;47(RR-8):1-57.

Vaccination of Persons with HIV Infection Specific Issues Considered

- **Availability of effective antiretroviral therapy (ART) has improved immune status of patients**
  - Revaccination of persons vaccinated prior to receiving effective ART
  - Recommendations based on symptomatic staging
  - Recommended timing of vaccine doses

Serious Adverse Events (SAEs) Reported for Measles Vaccine in HIV-Infected Persons

Age	Country /Year	CD4	ART	Clinical Manifestation	Outcome	Ref
21y	USA 1993	Very low	No	Giant-cell pneumonitis 10 months after MMR. Measles vaccine virus - lung	Death 5 months after onset	MMWR 1996

- No SAEs reported after small studies of administering MMR to children on ART with <u>past history</u> of immunosuppression[1-4]
- No additional SAEs reported in the United States
- No additional SAEs reported worldwide despite immunization of millions of HIV-infected children

[1]Melvin AJ, Mohan KM.. *Pediatrics*. Jun 2003;111(6 Pt 1):e641-644. [2]Aurpibul L, et al. *HIV Med*. 2006;7(7):467-470. [3]Farquar C. et al. *Pediatr Infect Dis J*. 2009;28(4):295-299. [4]Abzug MJ, et al. *J Infect Dis*. 2012.

Vaccine Immunogenicity – Pre Effective ART

- **Suboptimal response following measles vaccination**
  - Lower antibody titer responses (Nair JID 2009)
  - Faster antibody decay (Moss JID 2007)
- **Factors associated with poorer response**
  - Low CD4 counts, high viral loads, and HIV stage
  - *Not consistent* across studies
- **Concern about the quality and duration of the antibody response of infants not receiving ART**

Moss WJ, et al.. *Bull World Health Organ.* 2003;81(1):61-70.

ART after Vaccination: Does Immunity Reappear?

Typical sequence for most US perinatally HIV-infected Youth

- Routine immunizations in infancy/early childhood (no ART)
- Primary failure; loss of immunity
- Variable degree of immunosuppression
- ART initiated
- Recovery from immunosuppression

Does measles-specific immunity "recover" with ART-related reversal of immunosuppression?

Slide courtesy of Dr George Siberry, NIH

Effective ART Does Not Reliably "Restore" Immunity to Previous Vaccinations

Country	N	Age (years)	ART duration (months)	% detectable measles antibody	Comments
US[1]	18	3-14	median 20 (range 8-37)	6% (EIA IgG)	-Vaccinated with 1-3 doses prior to ART
Thailand[2]	93	≥5	average 42	42% measles immune (EIA IgG ≥320 mIU/mL)	-Vaccinated as infants -immunity not predicted by any variables tested
Kenya[3]	62	5 (median)	>6	42% (ELISA IgG)	-Vaccinated as infants -Pre-ART: 31% measles IgG+
US[4]	193	2-18	≥6	83% detectable; 52% PRN≥120 mIU/mL	-≥1 prior MMR vaccination

[1]Melvin AJ, Mohan KM. *Pediatrics.* Jun 2003;111(6 Pt 1):e641-644. [2]Aurpibul L, et al. *HIV Med.* Oct 2006;7(7):467-470.
[3]Farquhar C, et al. *Pediatr Infect Dis J.* Apr 2009;28(4):295-299. [4]Abzug MJ, et al. *J Infect Dis.* Jun 12 2012.

Measles and Rubella Seroprotection and Mumps Seropositivity Among Perinatally HIV-infected Children in the US

- **Pediatric HIV-AIDS Cohort Study**
  - Perinatally HIV-infected (HIV+) or HIV-exposed but uninfected (HEU)
  - Age 7 to <16 years at study entry
  - Complete medical history, including ART, lab results, and vaccinations

	HIV+ (n=428) % (95% CI)	HEU (n=221) % (95% CI)
Measles (PRN)	57 (52, 62)	99 (96, 100)
Rubella	65 (61, 70)	98 (95, 99)
Mumps	59 (55, 64)	97 (94, 99)

Siberry G, et al. Presented at the 4th International Workshop on HIV Pediatrics, July 2012.

Majority Respond with Re-Vaccination After Effective ART

Ref	N	Age (years)	ART duration (months)	% measles antibody	% rubella antibody	% mumps antibody
Melvin 2003[1]	18 15	3-14	Median 20	83 (4 w post) 73 (1y post)		
Aurpibul 2007[2]	51 49	≥5	Mean 32	90 (4w post) 80 (6m post)	100 (4w post) 94 (6m post)	78 (4w post) 61 (6m post)
Abzug 2012[3]	193 179	2-18	≥6m	89 (8w post) 80 (20m post) [PRN]		

[1]Melvin AJ, Mohan KM. *Pediatrics*. Jun 2003;111(6 Pt 1):e641-644. [2]Aurpibul L, et al. *Clin Infect Dis*. Sep 1 2007;45(5):637-642. [3]Abzug MJ, et al. *J Infect Dis*. Jun 12 2012.

Seroprotection/Seroprevalance According to number of MMR Doses on Effective ART

Number of doses received after on effective ART for ≥3 months	0 (n=188)	1 (n=141)	2* (n=99)
Measles (PRN), protected	84 (45%)	77 (55%)	83* (84%)
Rubella, protected	98 (52%)	97 (69%)	84 (85%)
Mumps, seropositive	99 (53%)	79 (56%)	76 (77%)

*includes one subject who received 3 MMRs after ≥3 months on ART

Siberry G, et al. Presented at the 4th International Workshop on HIV Pediatrics, July 2012

Current State of Immunity in Perinatally HIV-Infected Youth

- Lack of immunologic memory and protective immunity common
  - Vaccines given prior to effective ART
  - Despite current effective ART
- Increasing evidence to support MMR revaccination once stable, effective ART in place
  - Sutcliffe Lancet ID 2010;10: 630–42

Considerations Regarding Timing of Doses Persons with HIV Infection

- Few newly diagnosed infants in the US
  - Routinely started on ART right away
- Expect these infants/toddlers to have a response to MMR vaccine similar to that of HIV-uninfected children[1-2]

[1]Lima M, et al. *Pediatr Infect Dis J.* Jul 2004;23(7):604-607. [2]Pensieroso S, et al. *Proc Natl Acad Sci U S A.* May 12 2009;106(19):7939-7944.

Vaccination of Persons with HIV Infection Proposed Changes

- Include recommendation for revaccination of persons with perinatal HIV infection who were vaccinated prior to effective ART
- Remove the distinction between asymptomatic and symptomatic HIV infection
- Change timing of the two doses to 12 through 15 months and 4 through 6 years

Proposed Recommendations

Revaccination of Persons with Perinatal HIV Infection Who Do Not Have Current Evidence of Severe Immunosuppression

- Persons with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine prior to establishment of effective ART should receive two appropriately spaced doses of MMR vaccine once effective ART has been established [≥6 months with CD4 percentages ≥15% (all ages) and CD4 ≥200 cells/mm^3 (age >5 years)] unless they have other acceptable current evidence of measles, rubella, and mumps immunity.

Proposed Recommendations

Vaccination of Persons with HIV Infection Who Do Not Have Current Evidence of Severe Immunosuppression

- Two doses of MMR vaccine are recommended for all persons aged ≥12 months with HIV infection who do not have evidence of current severe immunosuppression [i.e., must have CD4 percentages ≥15% (all ages) and CD4 ≥200 cells/mm^3 (age >5 years) for ≥6 months] or other current evidence of measles, rubella, and mumps immunity.

Proposed Recommendations

Timing of Doses for Persons with HIV Infection

- The first dose of MMR vaccine should be administered at age 12 through 15 months and the second dose at age 4 through 6 years, or as early as 28 days after the first dose.

ACIP Vote

ACIP MMR Statement

Prevention of measles, rubella, congenital rubella syndrome, and mumps

Does ACIP approve the updated recommendations for the prevention of measles, rubella, CRS, and mumps, including revised recommendations for

1. Evidence of immunity,
2. Use of IG products for measles post exposure prophylaxis, and
3. Vaccination of persons with HIV infection?