

Measles Post-exposure Prophylaxis with Immune Globulin Products

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Advisory Committee on Immunization Practices Meeting

Atlanta, Georgia

June 21, 2012



Current Immune Globulin Products in U.S.

- Human Immune Globulins (IG) are blood products used to provide antibodies for the short term prevention of some infectious diseases, including measles.
 - **Immunoglobulin products** are prepared from plasma pools derived from thousands of donors.
 - **Pre-exposure prophylaxis** against measles and other diseases is provided to persons with immunodeficiency via frequent administration of immune globulin given intravenously (IGIV) or subcutaneously (IGSC).
 - **Post-exposure prophylaxis** with immune globulin given intramuscularly (IGIM) is recommended by ACIP for persons exposed to measles or at high risk of exposure for whom vaccine is either contraindicated or was not given within 3 days of exposure.

Specific Issues for Consideration

1. Multiple IG products are licensed in the U.S., (IGIM, IGIV and IGSC). The role of each in post-exposure measles prevention needs to be defined.
2. Measles antibody concentrations have decreased in immune globulin (IG) donor populations; Post-exposure prophylaxis (PEP) IG doses may need to be revised.
3. Susceptibility to measles among infants born in the US has increased; recommendations for PEP in early infancy may need to be revised.
4. Recommendations regarding the type of exposure for which IG PEP is indicated may need to be clarified.

Pre-Exposure Prophylaxis with IGIV

- IGIV available since 1981, 9 products currently licensed.
- Major indication: prevention of common infectious diseases in ~50,000 U.S. patients with primary immunodeficiency disorders. Many off-label uses.
- Dose ranges from 200-800 mg/kg, every 3-4 weeks.
- IGIV label recommends measles PEP in patients with primary humoral immunodeficiency (400 mg/kg).
- Average cost in 2007 of 6 products was about \$55 per gram.* **Cost estimates for a 400 mg/kg dose:**
10 kg child (\$220), 70 kg adult (\$1540).

*Sorenson R, et al. Expert Opinion Regarding Clinical and Other Outcome Considerations in the Formulary Review of Immune Globulin JMCP April 2007 Vol. 13, No. 3

+Leong H, et al Unlabeled uses of Immune Globulin. AM J Health System Pharm 65:1815-1824 2008

Pre-Exposure Prophylaxis with IGSC

- IGSC available since 2006, 4 products currently licensed
- Major indication is same as IGIV. IGSC infusion avoids need for venous access.
- IGSC administration requires a pump, advanced training.
- Recommended dosage ranges from 100-200 mg/kg, given weekly by subcutaneous infusion at 15 mL/hr with separate sites for volumes > 15 mL.
- Multiple, consecutive weekly doses are needed to establish steady-state, protective antibody levels.
- IGSC is recommended only for patients already on IGIV.

Current ACIP MMR Recommendations Immunocompromised - IGIV and IGSC

- 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.
- **IGIV is not specifically recommended by ACIP for PEP in patients not already on IGIV therapy.**
- Anecdotal reports suggest IGIV is used when IGIM is not readily available, for immunocompetent as well as immunocompromised patients.
- **IGSC is not mentioned in ACIP recommendations.**

Current ACIP MMR Recommendations

Post-exposure Immune Globulin

- Administration of IGIM to susceptible **household** contacts who are not vaccinated within 72 hours of initial exposure is recommended.
- The usual recommended dose of IGIM is **0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL)**. However, the recommended dose of IGIM for immunocompromised persons is **0.5 mL/kg of body weight (maximum dose = 15 mL)**.
- 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).

Current ACIP MMR Recommendations

Post-exposure Immune Globulin 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. IG prophylaxis is not indicated for household contacts who have received a dose of measles vaccine on or after the first birthday, unless they are immunocompromised.

IGIM Post-exposure Prophylaxis Studies in the US

- **(1990) IGIM PEP In a Neonatal ICU, Ohio***
 - Following exposure, 21 infants had pre-PEP measles antibody titers tested by ELISA, PEP with Gamastan 0.25 ml/kg and a second blood sample 48 hours later.
 - Of 15 infants seronegative initially, 2 were seropositive at 48hrs post-PEP, 2 with initial equivocal titers became seropositive.
- **1989-1991 Measles Resurgence, California+**
 - Retrospective secondary attack rate (AR) study of unvaccinated household contacts <1 month to 22 months of age.
 - AR 15/23 (66%) in children who did not receive IGIM.
 - AR 3/5 (60%) in children who received IGIM within 6 days post-exposure (PE 8%.) IGIM doses were not recorded.

*Subbarao EK, et al. Post-exposure prophylaxis for measles in a neonatal intensive care unit. J Pediatr. 1990 Nov;117(5):782-5.

+King GE, et al.. Clinical efficacy of measles vaccine during the 1990 measles epidemic. Pediatr Infect Dis J. 1991 Dec;10(12):883-8.

Other Studies of IGIM PEP

- (1999-2000) Japan (Endo et al)*
 - 33 unvaccinated infants (age 1.5+/- 1.4 years) given IGIM (0.33 mL/kg) within 5 days of measles exposure (>1 hour same room).
 - Neutralizing antibody concentrations determined in IGIM lots.
 - Measles attack rates were:
 - 8/14 (57%) among infants given IGIM from lots with 16 IU/mL, (5.28 IU/kg).
 - 1/6 (17%) among infants given IGIM with 33 IU/mL, (10.89 IU/kg).
 - 0/13 (0%) among those given IGIM with 40 or 45 IU/mL. (13.2 IU/kg).
 - 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.
- (2006) New South Wales Measles Outbreak (57 cases).+
 - 553 exposed (same room as case, up to 2 hrs later) defined as susceptible by Australian guidelines.
 - 0.2 ml/kg IGIM, estimated concentration 32 IU/kg = 6.4 IU/kg.
 - AR 13/288 (4.5%) without PEP.
 - AR 2/183 (0.8%) with IGIM. PE overall 76%, within 6 days 100%.

*Endo A, et al. Current efficacy of postexposure prophylaxis against measles with immunoglobulin. J Pediatr. 2001 Jun;138(6):926-8.

+Sheppard V, et al. The effectiveness of prophylaxis for measles contacts in NSW. N S W Public Health Bull. 2009 May-Jun;20(5-6):81-5.

Measles Antibody Titers in IG products

- The FDA requires that all US licensed IGs contain a measles antibody level (neutralizing or HAI) of adequate potency as compared with the US standard.*
- Plasma from donor populations with predominantly vaccine-induced immunity yields IG with lower measles antibody concentrations.+
- Lower antibody concentrations in donor plasma made minimum measles antibody concentration requirements difficult for IGIV and IGSC lots.
- Much higher volumes of IG can be given by IV and SC routes compared to IM.

*Department of Health and Human Services, Food and Drug Administration. 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>

+Audet S, , et al.. Measles-virus-neutralizing antibodies in intravenous immunoglobulins. J Infect Dis. 2006 Sep 15;194(6):781-9.

Measles Antibody Concentrations in IG products

FDA Minimum Requirements

- (2007) FDA Blood Products Advisory Committee lowered for IGIV and IGSC measles antibody concentration requirement.
- FDA calculations estimated that products released at minimum potency and given at minimum label recommended dose (200 mg/kg) would provide a measles antibody concentration of ≥ 120 mIU/mL for 28-30 days.*
- The IGIM minimum measles antibody concentration was not changed.
- We repeated the FDA pharmacokinetics calculations for IGIM at the currently recommended doses.

*Department of Health and Human Services, Food and Drug Administration, Blood Products Advisory Committee Meeting Minutes August 16, 2007. Measles Antibody Levels in U.S. Immune Globulin Products Online. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4317M.htm> Accessed April 28, 2011.

Estimates of US Minimum Measles Antibody Dose for Various IG Products

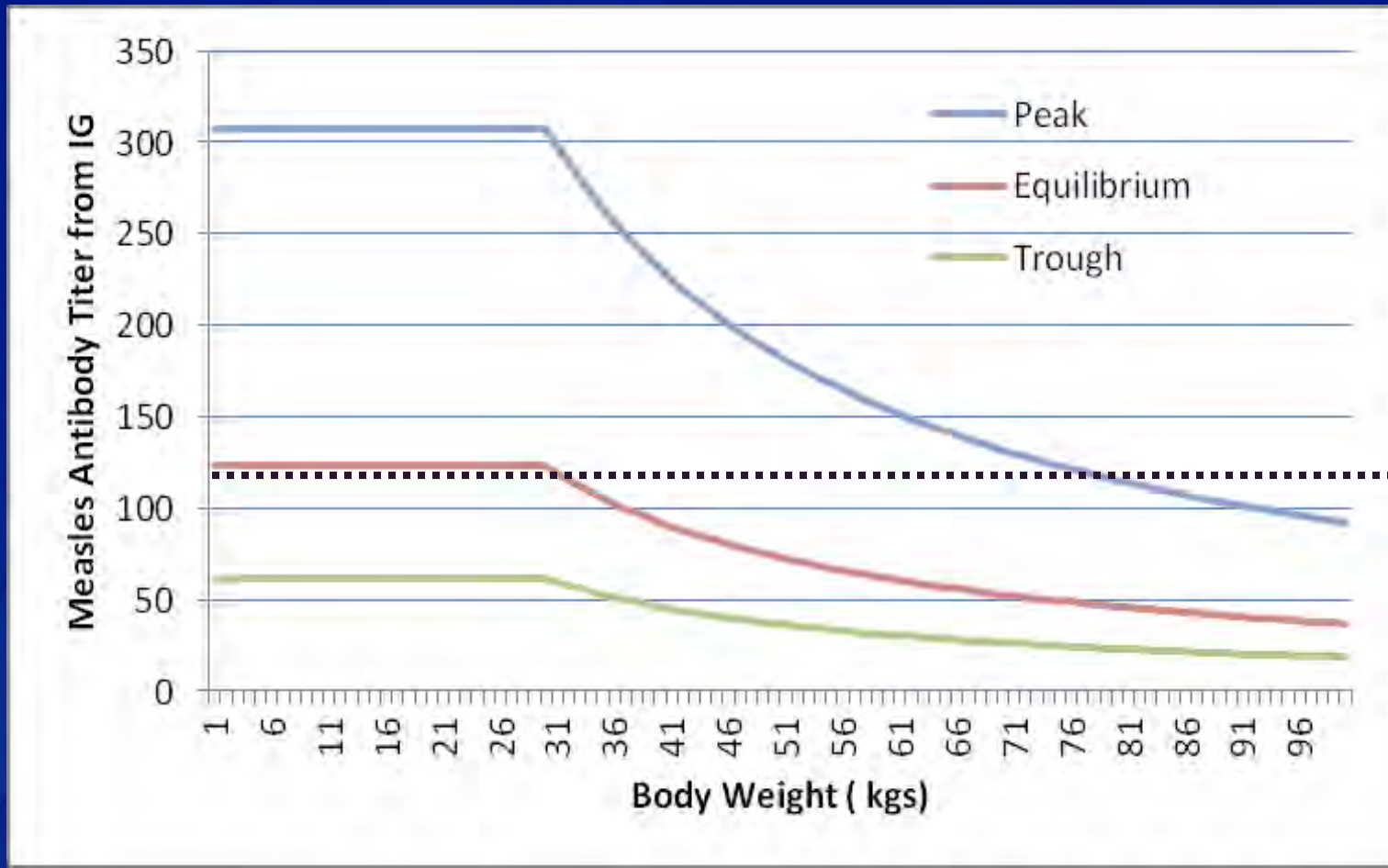
IG Product	Minimum Measles Antibody Potency / mL	Measles Antibody Dose Current Recommendation	Measles Antibody Dose 70kg person
IGIM (0.25 ml/kg)	25.2 IU/mL	6.3 IU/kg	5.4 IU/kg
IGIM (0.5 ml/kg)	25.2 IU/mL	12.6 IU/kg	5.4 IU/kg
IGIV (100 mg/kg)	12.3 IU/mL	12 IU/kg	12 IU/kg
IGIV (200 mg/kg)	12.3 IU/mL	24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

Calculated Serum Measles Antibody Concentration following IG Post-exposure Prophylaxis

Immune Globulin Product (Dose)	Minimum* 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 (0.25ml/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

*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.

Calculated Measles Antibody Titers from IGIM Administration Dose 0.5 ml/kg (15 ml maximum dose)



Increasing Susceptibility to Measles among Infants in the United States

- **(2001-2008)** Infants < 12 months had the highest incidence of measles among US residents (59 cases, 3.5 cases/million)
- **(2011)** 29 (13%) of US measles cases were in infants < 12 months of age, 3 were in infants < 6 months of age.
- **(2009)** 99.9% of women giving birth in the U.S. were born after 1963, the year measles vaccination began in the US.
- **(2006-2008)** Among infants of vaccinated mothers In Belgium, Leuridan found measles antibody titers < 300 mIU/ml in 30% at birth, increasing to 97% < 300mIU by 6 months of age. *
- **(2004)** Gans et al., detected transplacentally derived measles neutralizing antibodies in 52% (15/29) of 6-month-old, 19% (4/21) of 9-month-old, and no 12-month-old (0/83) infants.+

*Leuridan E, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ. 2010 May 18;340:c1626.

+Gans HA, et al. Humoral and cell-mediated immune responses to an early 2-dose measles vaccination regimen in the United States. J Infect Dis. 2004 Jul 1;190(1):83-90.

Quick Survey of State Immunization Programs on IGIM PEP

- State immunization programs have variable roles in IGIM PEP.
- Estimated IGIM measles PEP doses in 2011 was less than 5 for all states except PA, (93 doses) and NYC (74 doses.)
- PA spent roughly \$30,000, had many doses remaining.
- PA reported no problem in IGIM supply, other states say it's generally available with difficulties in distribution.
- IGIM back order, no doses were expected for the rest 2011.
- States are not involved in pre-exposure prophylaxis (IGIV/IGSC), do not recommend IGIV in place of IGIM.
- All states give IGIM to exposed infants < 6 months of age, some attempt to determine mother's immunity first.
- All states give IGIM to persons exposed in any setting, some assess the duration and setting to make a decision.

Convenience sample : California, New York, NYC, New Jersey, Pennsylvania, Utah, Florida, Virginia, Massachusetts, Texas , Washington. Surveyed 8/8-24/2012

State Immunization Programs

IGIM PEP Issues

- States asked for clarification on recommendations
 - For infants < 6 months of age
 - For infants 6-12 months- Preference for IG versus vaccine PEP?
 - For exposure other than household
- States asked for data on protective efficacy of PEP with IG or vaccine.