

Review of Maternal Rubella Antibody Decay in Infants

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3 September 2015

Question 1

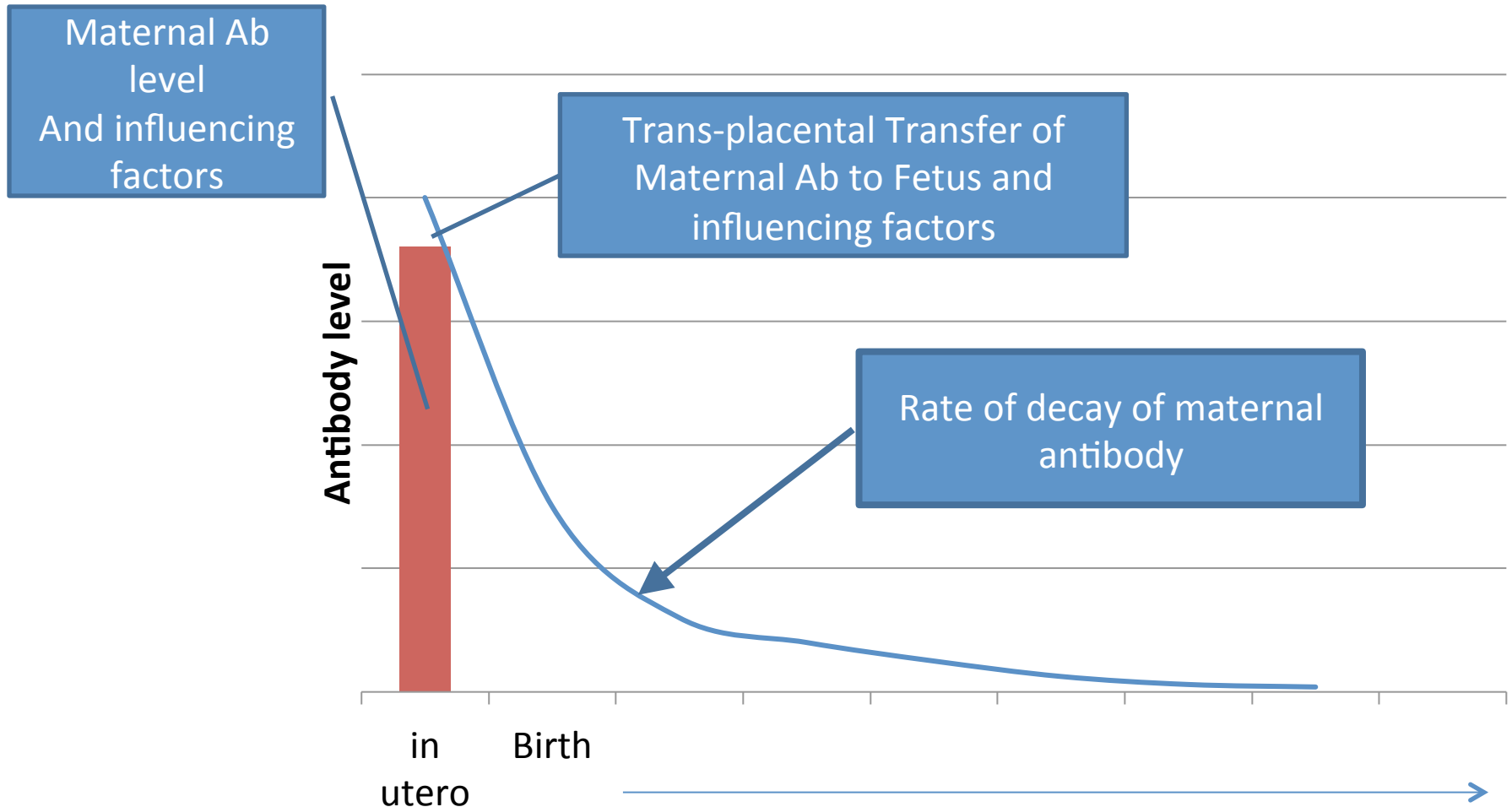
- Under what epidemiological circumstances is it recommended to provide a zero dose of MCV to infants <9 months of age?
 - (b)What is the rate of ***decay of maternal antibodies against measles and rubella*** in infants born to mothers with vaccine-induced immunity compared to mothers with immunity acquired from disease?

Presentation Overview

- Overview of aspects of maternal decay
- Methodology of narrative review
- Review of rubella literature

Maternal Antibody Decay-

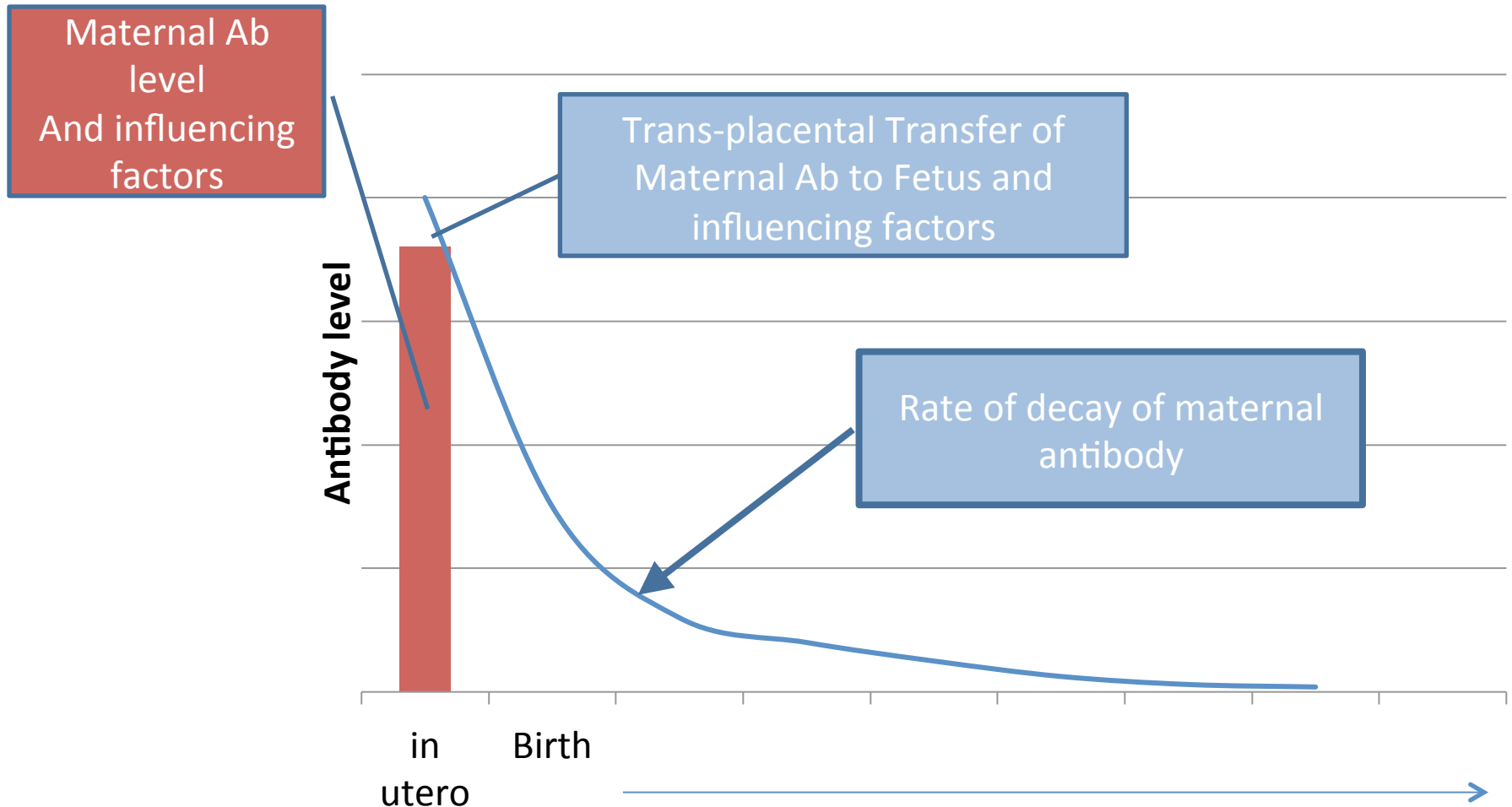
Areas evaluated



Methodology

- Literature review of existing evidence
 - Previously reviewed by Carceras (2000)
 - Update measles and review rubella
- Focus on field data, human data
- Literature reviewed identified 138 manuscripts (abstracts reviewed)
 - Antibody levels: 16 papers, 3 relevant
 - Transplacental transfer: 13 papers, 10 relevant
 - Decay: 26 papers reviewed, 4 relevant

Maternal Antibody Level



Maternal Rubella Antibody Levels

Vaccination Status

Study	N (vac/unvac)	Vaccinated	Unvaccinated
Gonclavs (2006)	122/109	“no sig difference” (66.6 vs. 80.9 IU/mL)	
Leuridin (2011)	213	26.6 IU/mL (“no sig difference”)	
Waijenborg (2013)	6351/1517	94.00 IU/mL (“no sig difference”)	

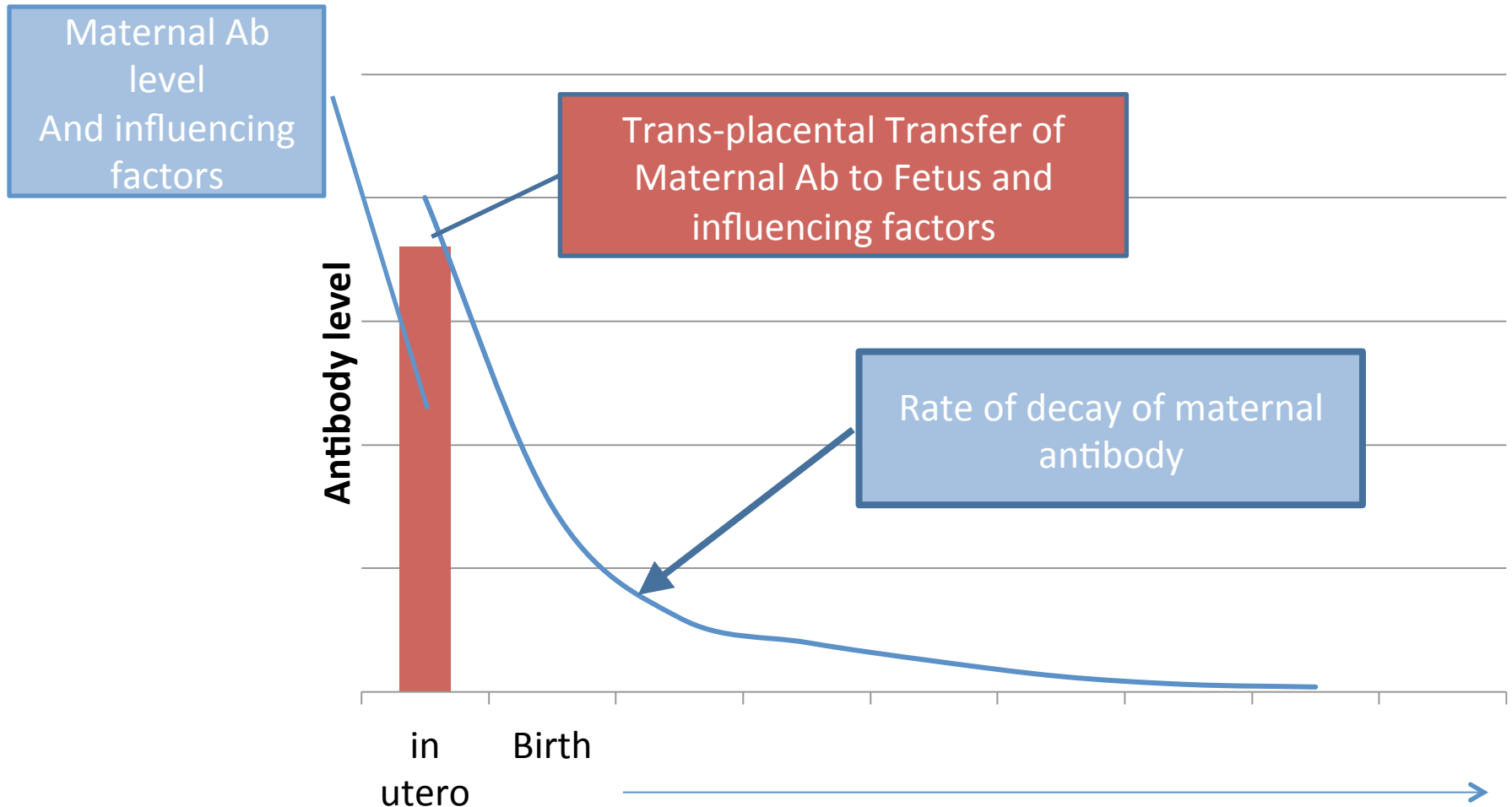
Gonclavs + Leuridin

-compared antibody titers by documented vaccination status

Waijenborg

- study compared vaccinated and unvaccinated by population groups with high and low vaccination coverage, not actual vaccination status

Trans-placental Transfer



Trans-placental Transfer

- Antibodies are transferred from mother to child through ACTIVE transport
 - Antibody levels in fetus may be higher than mother
- Measured by comparison of Ab level in cord blood with maternal blood

$$\text{Ratio} = \frac{\text{Cord Blood Ab}}{\text{Maternal Ab}}$$

Trans-placental Transfer Ratio

Study	n	Ratio	Assay
Leuridan (2011)	213	1.27	ELISA
Sato (1979)	28	1.2 (± 1.0)	Neut Assay
Dennin (1986)	59	1.3-1.5	
Gotlieb-Stematsky (1983)	258	1.4	HI
Griffith (1982)	93	1.09	HI

Antibody levels are greater in infants than their mothers,

Trans-placental Transfer - Prematurity

Study	Sub-group	n	Ratio	Assay
Berg (2014)	Pre-term (<32w)	97	.87 (.75-87)	Multiplex
	Full-term (>37w)	42	1.62 (1.39-1.65)	
Linder (1999)	Pre-term (<35w)	90	0.76	Neut Assay
	Full term (>37w)	69	1.01	
Leinweber (2004)	Pre-term	39	“>1” at 32-36 weeks	ELISA
	Full term	59		

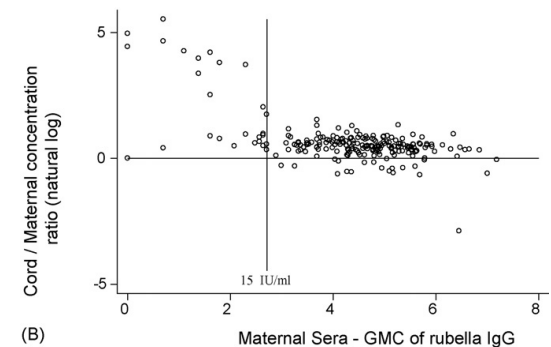
Active transport occurs late in pregnancy, resulting in lower antibody levels among pre-term infants

Trans-placental Rubella Ab Transfer Rate

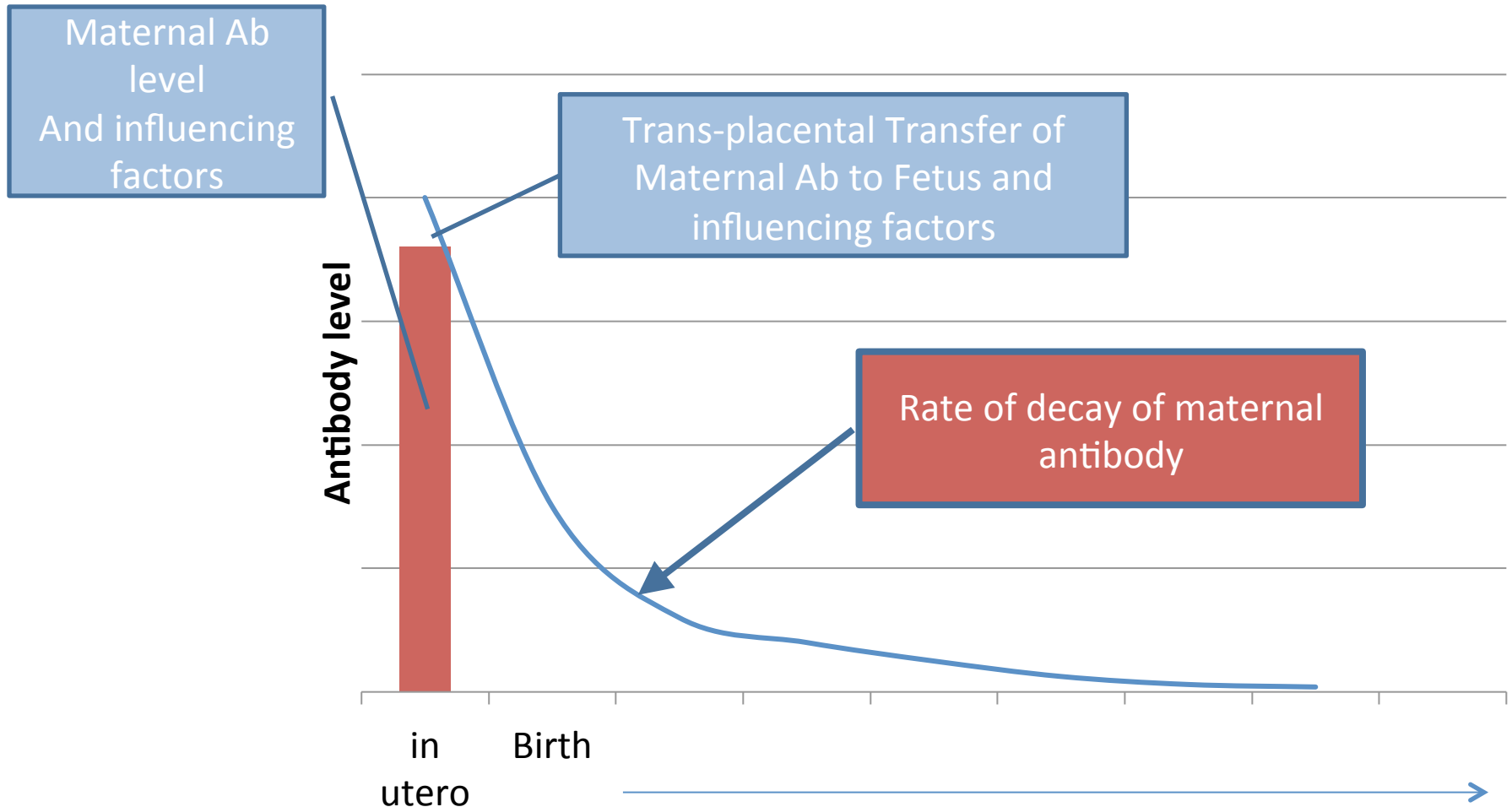
Vaccination Status

Study	Maternal Sub-group	n	Ratio	Absolute Diff (IU/mL)
Gonclav (2006)	<i>Antibody <15IU/ml</i>			
	Unvaccinated	20	5.1	46.9
	Vaccinated	18	15.1	112.8
	<i>Antibody >15IU/ml</i>			
	Unvaccinated	89	1.44	78.1
	Vaccinated	104	1.63	79.5

- In mothers with antibody levels <15, transfer ratio is high
- In mothers with antibody levels >15 transfer ratio is lower
 - similar between vaccinated and unvaccinated



Decay Rate



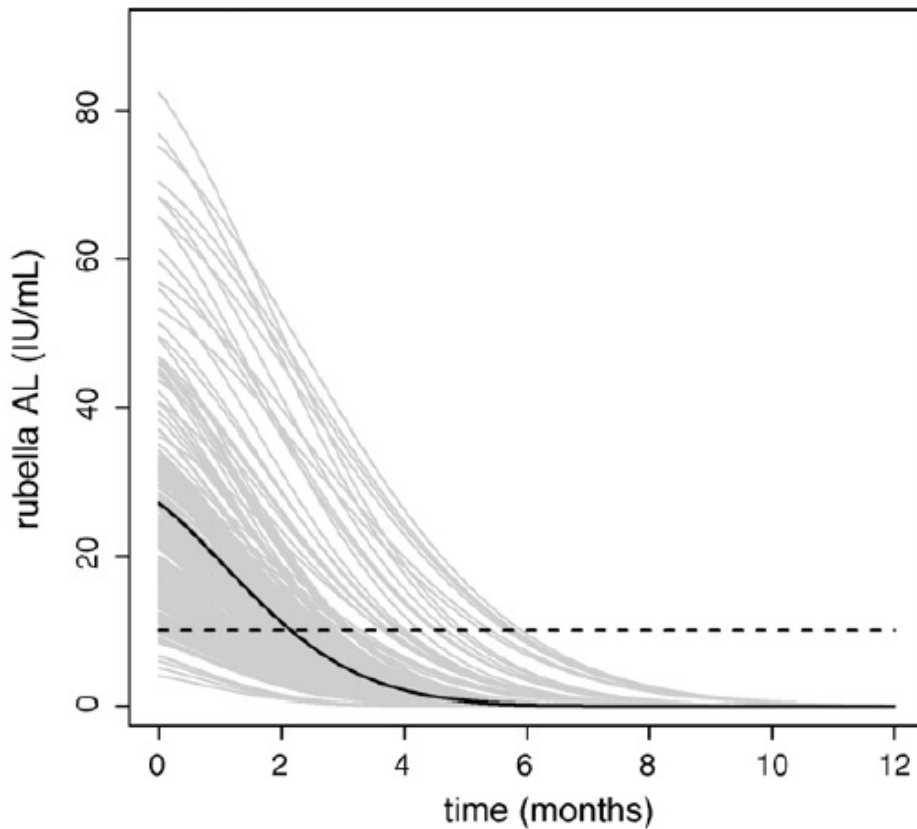
Decay Rate of Maternal Rubella Antibody

- Three studies (a) looked at exponential rates of decay, estimated half-lives 30-43 days
 - Wide variability between subjects in terms of decay
 - Done in setting of low vaccination
 - Utilized HIT or Neut testing
- One study (b) looked at decay as non-exponential function (n=221 pairs)

(a) Cloonan (1970), Herrmann (1971), Sato (1979)

(b) Leuridan (2011)

Leuridan 2011



- Decay rate decreases over time
- $n=221$
- Mean period of immunity is 2.1 months (range 0-6)
- High variability between subjects

Limitations

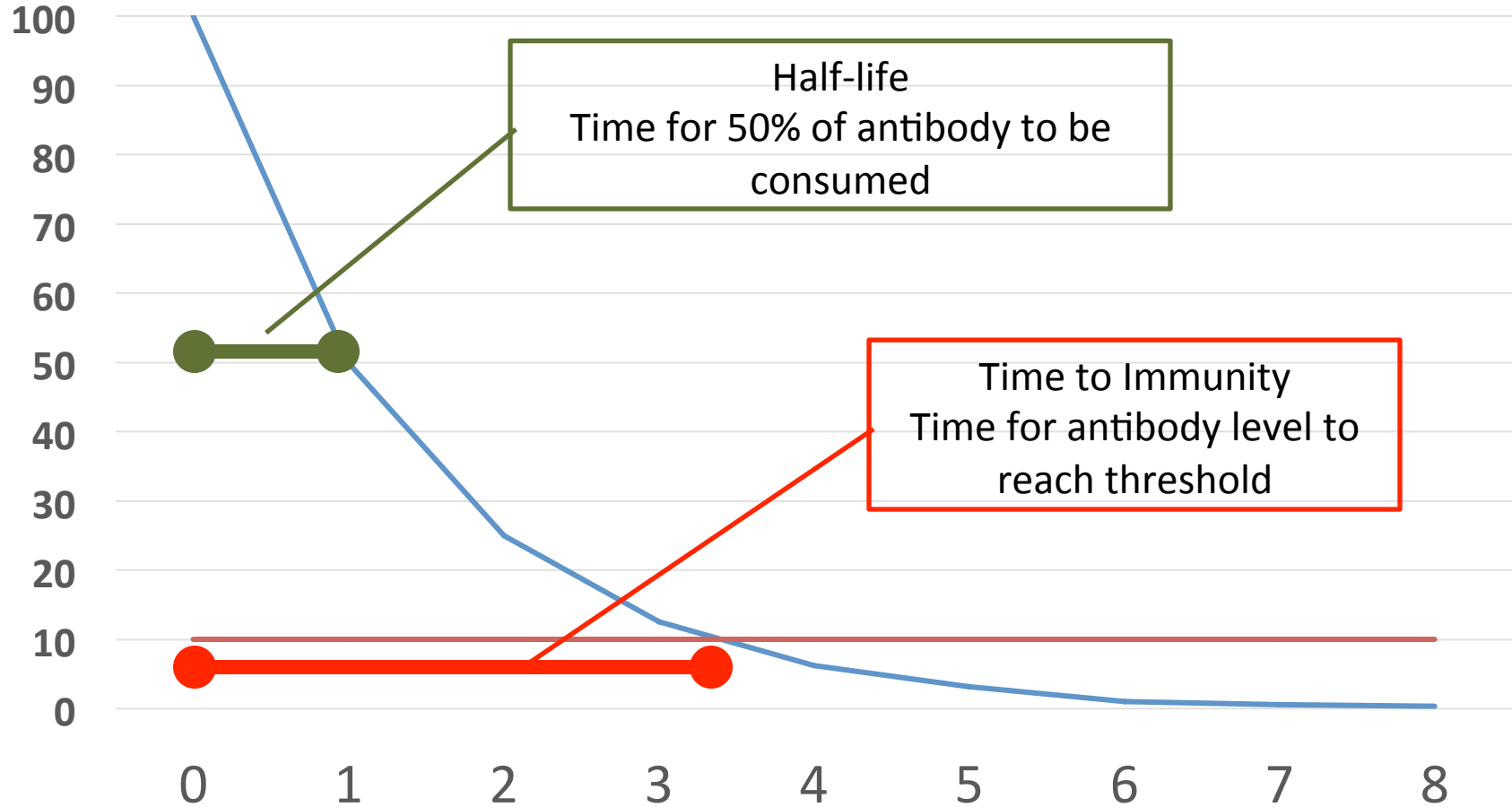
- Impact of passive antibodies on immunity in young,
 - Impact of non-seroprotective antibody levels on immunity following vaccination
 - Level of cell mediated immunity following vaccination is unknown in infants
- Not able to differentiate “vaccine induced” immunity from “vaccine and natural” induced immunity

Conclusions

- No strong evidence that maternal antibody levels are different between vaccinated vs. naturally immune mothers
- Transplacental transfer of antibodies is higher in women with low antibody levels
 - vaccinated women may have enhanced transport
 - pre-maturity decreases opportunity for active transport
- Decay of maternal rubella antibodies is variable, range from 30-45 days
- Seroconversion studies can provide insight to the practical implications of maternal rubella antibodies on infant's seroconversion following vaccination

THANK YOU

Half-life vs. Time to Immunity

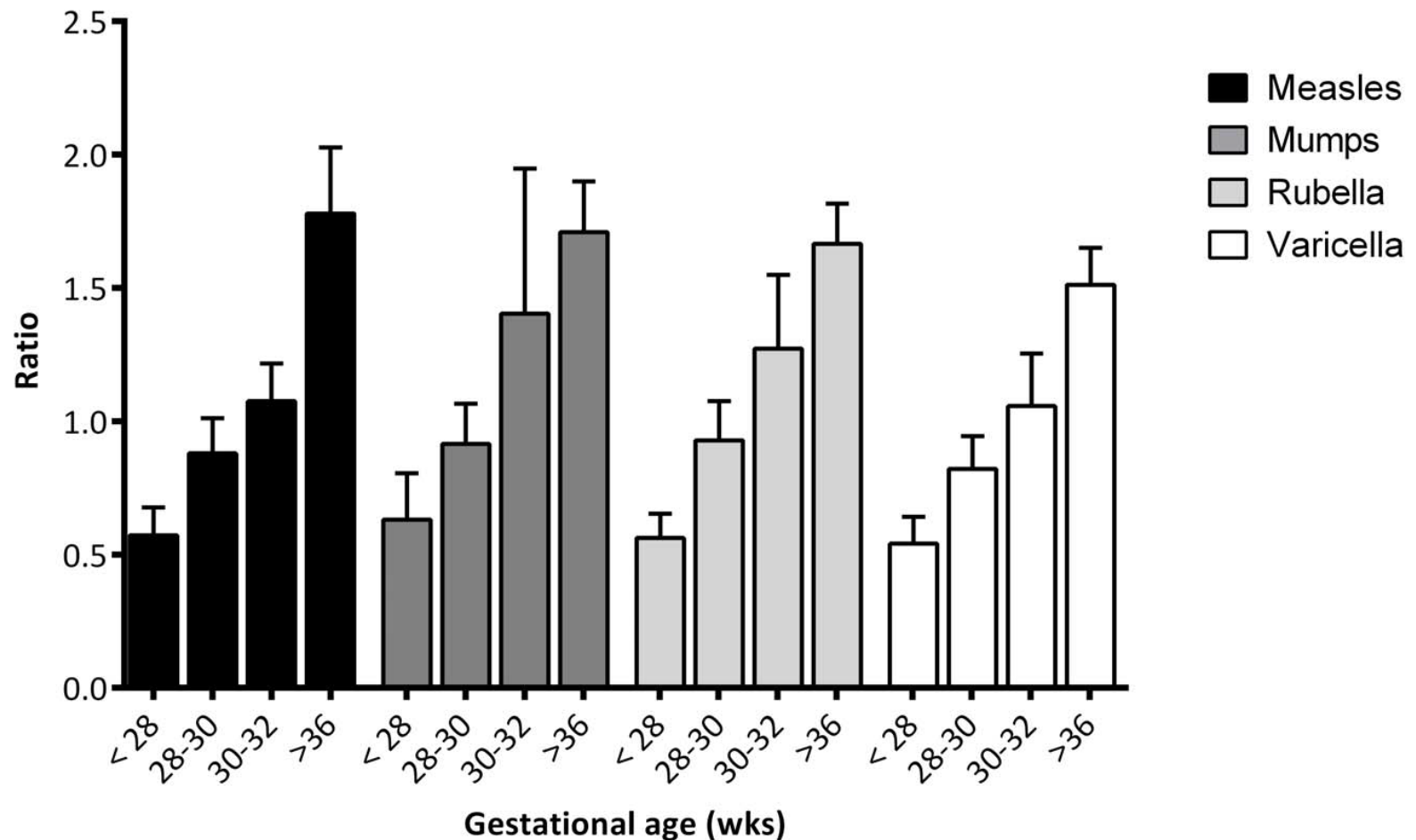


Annex: Search Terms and Databases

Database	Strategy
Medline	<p>((maternal rubella antibody) OR (maternal antibody AND rubella) OR (passive immunity AND rubella AND infant*)) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust*).ti,ab</p> <p>OR</p> <p>(Immunity, Maternally-Acquired/OR Maternal Fetal Exchange/ OR placental transfer.ti,ab. OR transplacental* OR passive immunity.ti,ab. OR acquired immunity.ti,ab. OR maternally acquired.ti,ab. OR maternally derived.ti,ab.) AND (Rubella/ OR Rubella Virus/ OR rubella.ti,ab) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust* OR loss OR absence OR degrad* OR protection).ti,ab. AND (Antibodies/ OR antibod*.ti,ab.)</p> <p>Limit 1967-</p>
Embase	<p>((maternal rubella antibody) OR (maternal antibody AND rubella) OR (passive immunity AND rubella AND infant*)) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust*).ti,ab</p> <p>OR</p> <p>(Immunity, Maternally-Acquired/OR Maternal Fetal Exchange/ OR placental transfer.ti,ab. OR transplacental* OR passive immunity.ti,ab. OR acquired immunity.ti,ab. OR maternally acquired.ti,ab. OR maternally derived.ti,ab.) AND (Rubella/ OR Rubella Virus/ OR rubella.ti,ab) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust* OR loss OR absence OR degrad* OR protection).ti,ab. AND (Antibodies/ OR antibod*.ti,ab.)</p> <p>Limit 1967-</p>
Global Health	<p>((maternal rubella antibody) OR (maternal antibody AND rubella) OR (passive immunity AND rubella AND infant*)) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust*)</p> <p>OR</p> <p>((MH Immunity, Maternally-Acquired) OR (MH Maternal Fetal Exchange) OR placental transfer OR transplacental* OR passive immunity OR acquired immunity OR maternally acquired OR maternally derived) AND ((MH Rubella) OR (MH Rubella Virus) OR rubella) AND (decay* OR waning OR prevalence OR duration OR persist* OR robust* OR loss OR absence OR degrad* OR protection) AND ((MH Antibodies) OR antibod*)</p> <p>Limit to 1967-</p>

Berg 2014

Figure 1. Transplacental transport ratio of measles, mumps, rubella and varicella with 95% confidence intervals.



Waaijenborg, 2013

Compare Measles and Rubella

all (IU/mL)	Measles		Rubella	
	MLE	95% CI	MLE	95% CI
Mean Ab level	1.61	1.47, 1.74	94.00	87.26, 100.74
Rate of decay (/yr)	7.77	7.27, 8.27	7.01	6.73, 7.29
Std Dev of Ab level	1.11	1.07, 1.16	0.97	0.93, 1.01
Diff in Ab level b/w newborn and adult	0		0	
Diff mean Ab b/w groups	4.13	1.82, 6.43	0	
Diff in decay bw groups	0		0	

- Mean Ab level
- Decay, 7/yr is half life of ~1month
- Difference between communities with high and low coverage
- Estimates are modeling estimates

Summary: Antibody Decay Rate

Reference	n	Half-life estimate (days)	Maternal Vaccination Level(a)	Methodology	Lab Methodology	Comments
Cloonan (1970) (2)	95	43	Limited vaccine availability	Serial serum regular intervals 2-12 months	HIT(b)	High variability between subjects
Herrmann (1971) (3)	10	30	Limited vaccine availability	Serial monthly serum collection of infants	HIT(b)	Impact on seroconversion
Sato (1979)(4)	30	35-40	Not reported	Serial bimonthly serum collection of infants	Plaque Neutralization	
Leuridan (2011) (5)	213	35-45	High vaccine availability	Serial serum at 0, 1,3,6,9,and 12 months of age, mathematical model fit of decay	ELISA	High variability between subjects

- a. Coverage- represents the general vaccination coverage of the population at the time of the study. Two studies are conducted soon after vaccine availability, and high levels of rubella natural immunity could be expected. Sato did not report the coverage and source of immunity of the population study, and Leuridan reported high vaccine coverage, though it is not possible to determine level of natural immunity of the population.
- b. HIT- Hemagglutination Inhibition Test; ELISA- Enzyme Linked Immunosorbant Assay;

Berg (2014)

- Study
 - Transfer ratios and pregnancy
- Population
 - Mother and pre (<32 weeks or <1500g) or full term infants (dutch)
 - n=96 preterm vs. n=42 term
- Blood specimen
 - Collected
 - Flourecent bead immunosorbent assay

Cloonan (1970)

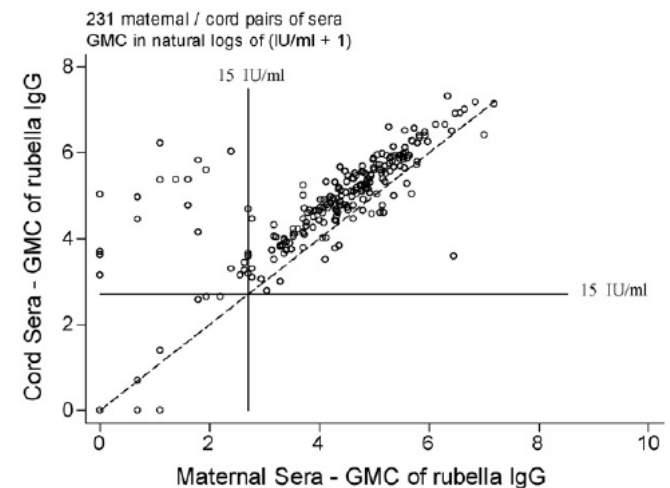
- Study
 - Focus on decay
- Population
 - 95 infants, Australia
- Blood sample
 - Serum, regular intervals 2-12 months
 - Hemagglutination inhibition titer

Dennin (1986)

- Study
 - Compare titers in mother and infant
- Population
 - 59 pairs, at birth
- Blood specimen
 - Enzyme immune test

Gonclavs (2006)

- Study
 - Cross-sectional
- Population
 - Stored specimens Portugal
 - n=231 Maternal-cord paired specimens
 - Banked serum from previous study
 - Documented vaccination hx
- Blood specimen
 - Immunoassay (ELFA)
 - Positive $\geq 15\text{IU/mL}$



Gotlieb-Stematsky (1983)

- Study
 - Consecutive deliveries, maternal-infant titers
- Population
 - n=258
 - Israel
- Blood specimen
 - Mother-infant pairs
 - Hemagglutination inhibition (dilutions)

Hermann (1971)

- Study
 - Recruit mothers from Houston Tx hospital
 - Vaccinated 6-12 months of age (random month)
- Population
 - Recruitment 137 infants at birth
- Assay
 - Hemagglutinin Assay
- Saw a delayed immune response in younger infants (6-7m of age)

Lai (2015)

- Study
 - Collected prenatal serum
- Population
 - Prenatal screen from first pregnancy in Alberta, Canada 2009-2012
- Blood Specimen
 - Architect system
 - Immunity >15 immune, (10-≤15 intermediate)

Leuridan(2011)

- Study
 - Cross-section study of recruited women
- Population
 - Mother-infant pairs n=211
 - Belgium, 2008
 - Mothers 18-40 years of age
- Blood specimen
 - Mother, cord, m1, m3, m12 + (m6 or m9, random)
 - ELISA assay
- Immunity cut-off was 10IU/ml

Leinweber (2004)

- Study
 - Maternal-fetal titers, and decay
 - Difference of prenatal and full term
- Population
 - Basel, Switzerland- 1999-2000
 - 71 full- vs. 101 pre-term (96 mothers)
- Blood specimen
 - Collected birth, 6-9 month, and one more
 - ELISA assay, >15IU/mL

Linder (1999)

- Study
- Population
 - Israeli Mothers
 - 90 pre-term (<35 weeks)/ 69 full-term (>37 weeks)
- Blood specimen
 - paired
 - Hemagglutination and neutralization assays

Sato (1979)

- Study
 - Impact on passive antibodies on seroconversion
- Population
 - 42 maternal-infant pairs, recruited for another study
- Blood specimen
 - Cord blood, and 2-4 month intervals, MMR at 12m
 - Enhanced neutralizing assay
- Found that seroconversion occurs, but lower titers if Ab present at 12 months.

Waijenborg (2013)

- Study
 - Cross-sectional
 - National Dutch serosurvey, cluster
- Population
 - General population (65.6% R coverage), n=1243
 - Orthodox community (17.2% R coverage), n=55
 - Vaccination history documented sources
- Blood Specimens
 - Collected 2006-7
 - Luminex based assay , immunity was 10IU/mL
- Unvaccinated mothers had 55.2x greater Rubella Ab levels than vaccinated mothers
- Calculated half-life based on population data, 1 month