Corso di Aggiornamento

LA MEDICINA DI GENERE IN REUMATOLOGIA:
APPROCCIO MULTIDISCIPLINARE PER LA SALUTE DELLA DONNA

Quando la mamma ha una malattia reumatica:

il punto di vista del pediatra

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Autoimmunità e Gravidanza

1. Mio figlio/a avrà la mia stessa malattia?
2. Mio figlio/a avrà uno sviluppo normale?
3. Potrò allattare mio figlio/a?
4. Mio figlio/a deve essere vaccinato regolarmente?

Lupus Eritematoso Neonatale

Modello di Autoimmunità Acquisita Passivamente

CIRCOLAZIONE MATERNA

PASSAGGIO PLACENTARE

CIRCOLAZIONE FETALE

IgG,11 settimane

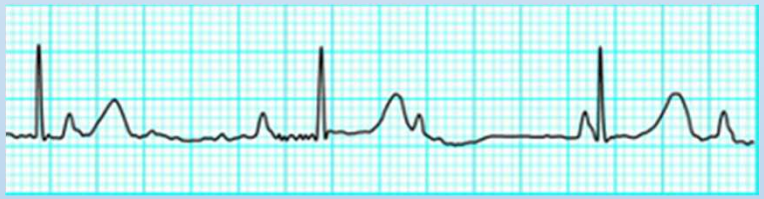
anti-52kD SSA/Ro

anti-60kD SSA/Ro

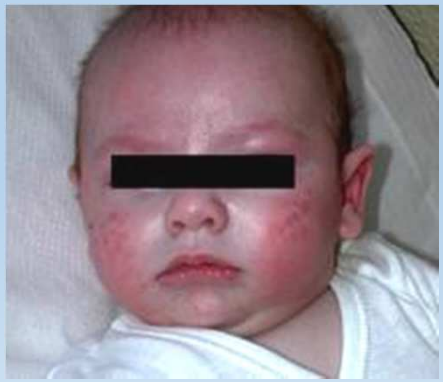
anti-48kD SSB/La

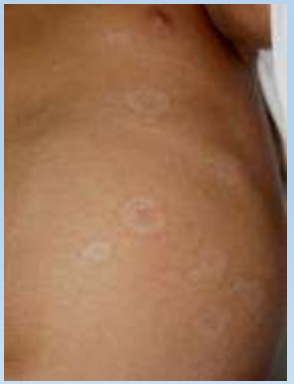
FcRIIb

Bolcco Cardiaco Congenito

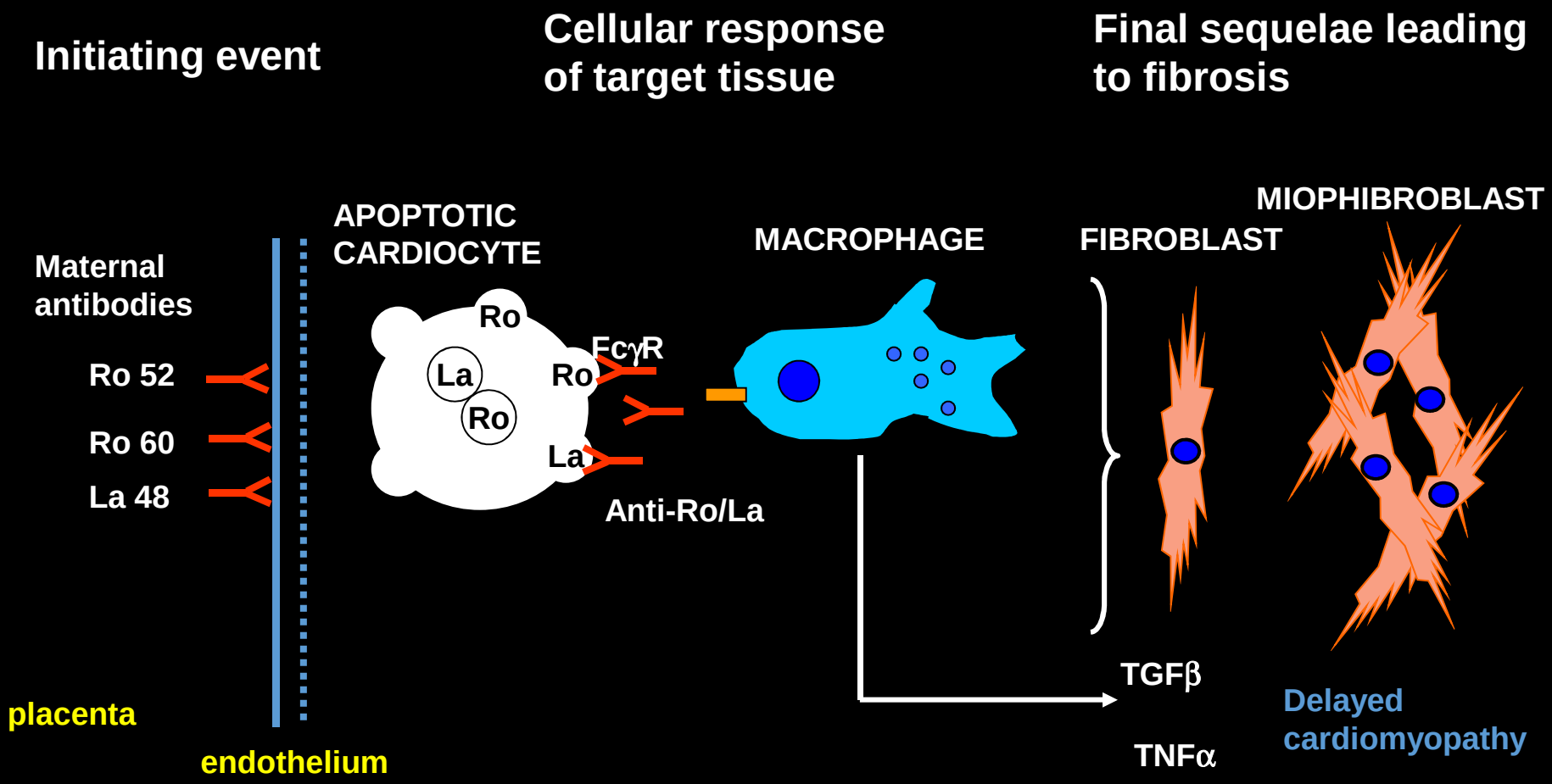


Rash Neonatale





Blocco Cardiaco Congenito, Patogenesi



Bujon JP, Neonatal Lupus Syndromes, Lupus 2004

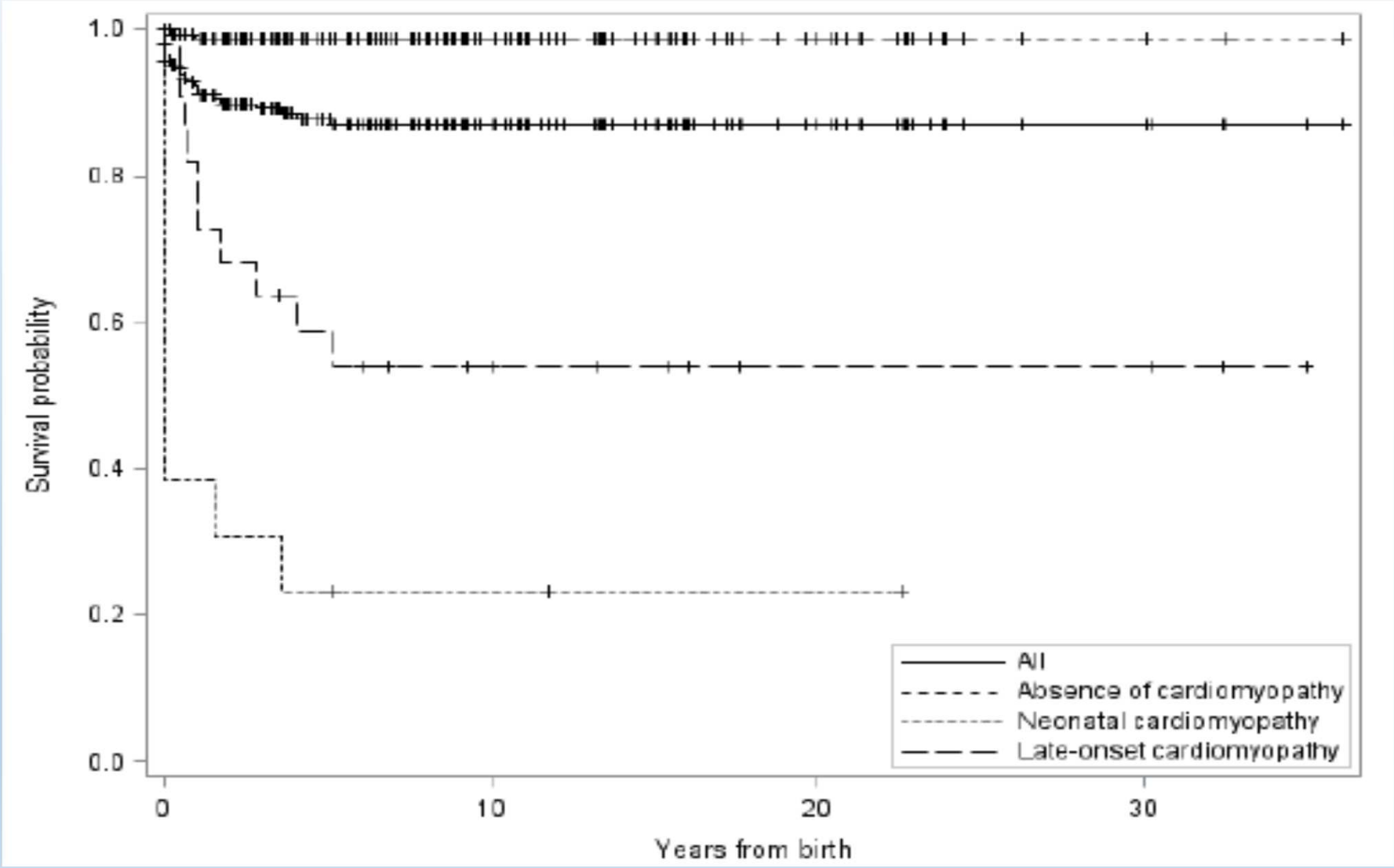
Lupus Neonatale: blocco AV congenito

- Rischio 1-2% in Ro/SSA+
- Fetale, 18-26 sett. Gestazione, in una settimana
- Blocco AV completo è permanente (CCHB)
- 60-80% pacemaker (entro 12 mesi)
- Cardiomiopatia dilatativa

Incidence, risk factors, and mortality of neonatal and late-onset dilated cardiomyopathy associated with cardiac neonatal lupus. Morel N, IJCA, 2017

- 187 neonates with second- or third-degree CHB
- 18,8 % dilated cardiomyopathy
  - neonatal DCM (n=13, diagnosed at a median age of 0 day [birth - 4 days])
  - late-onset DCM (n=22, diagnosed at a median age of 15.2 months [3.6 months - 22.8 years])
- 11.8% died during a median follow-up of 7 years
- Fluorinated steroids showed no protective effect against late-onset DCM

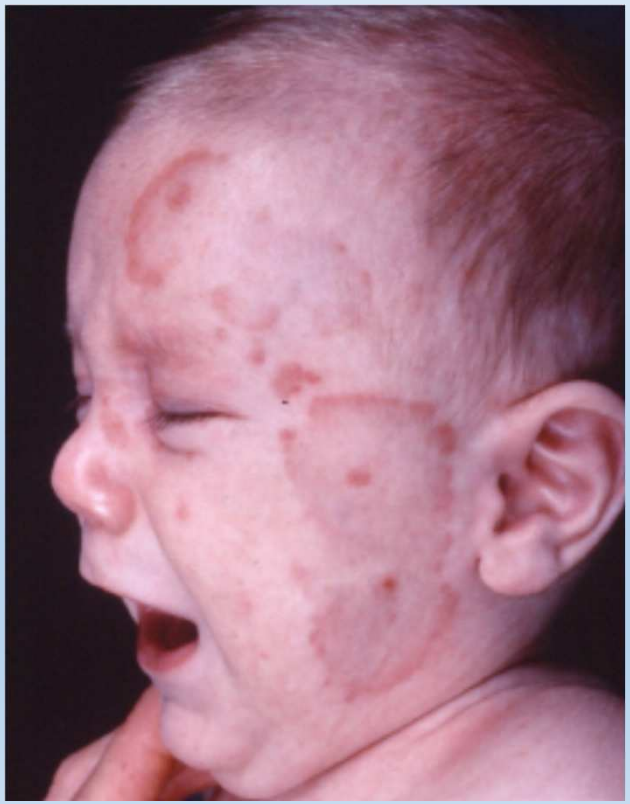
DCM: Probability of survival at 10 years



Lupus neonatale: rash cutaneo

Neiman AR, J Pediatr 2000

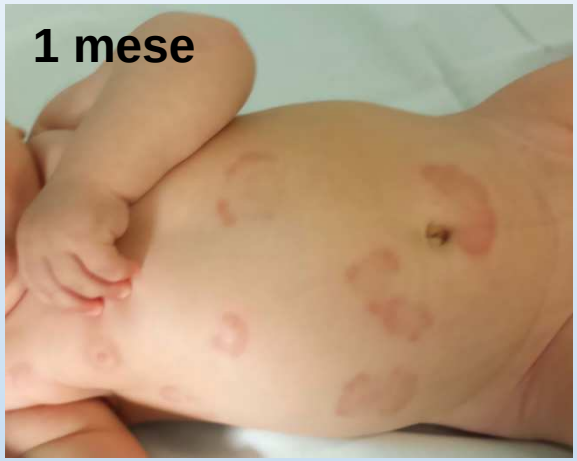
- Neonatal onset, 6 wks from birth
- Rash detected or exacerbated ≤ 2 days after sun exposure 90%
- Duration of typical rash
  - ≤ 4 months 50%
  - ≤ 7 months 80%
  - ≤ 12 months 100%
- Persisting skin rash 20%
- Distribution of rash
  - Head (with or without scalp or neck) 95%
  - Trunk (with or without groin) 25%
  - Extremities 25%
  - Whole body 10%
- Rischio < 1% ?

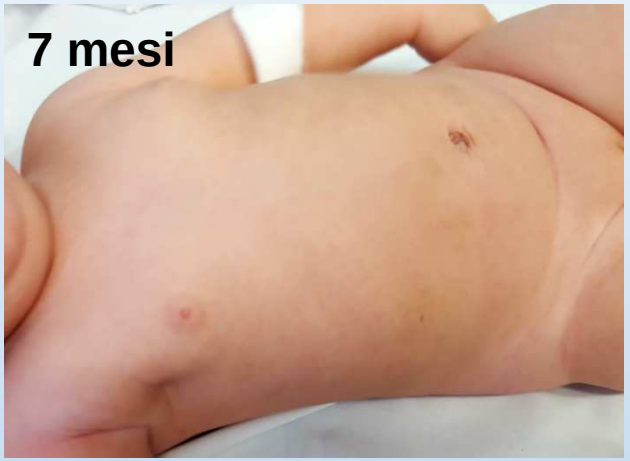


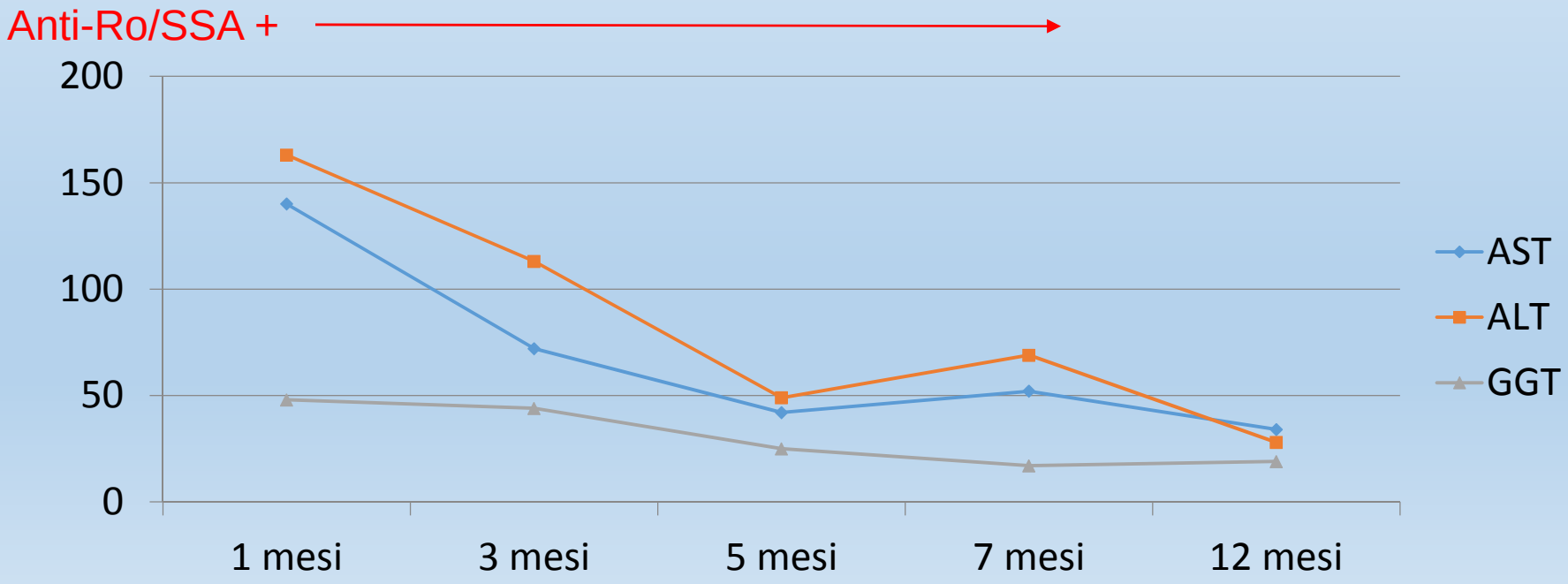
Manifestazioni “minori” in NLE

- **Disturbi di conduzione** (Blocco AV 1° 8% anti-Ro+; *Motta M et al, J Perinatol 2007*)
- **Malattia epatobiliare** (9% of NLE; *Lee LA et al, Pediatrics 2002*)
- **Disturbi ematologici** (4-27% anti-Ro+, immune-related ? *Cimaz R et al, J Pediatr 2003*)
- **Anomalie neuro-radiologiche** (asintomatiche, frequenti)

Lupus Eritematoso Neonatale







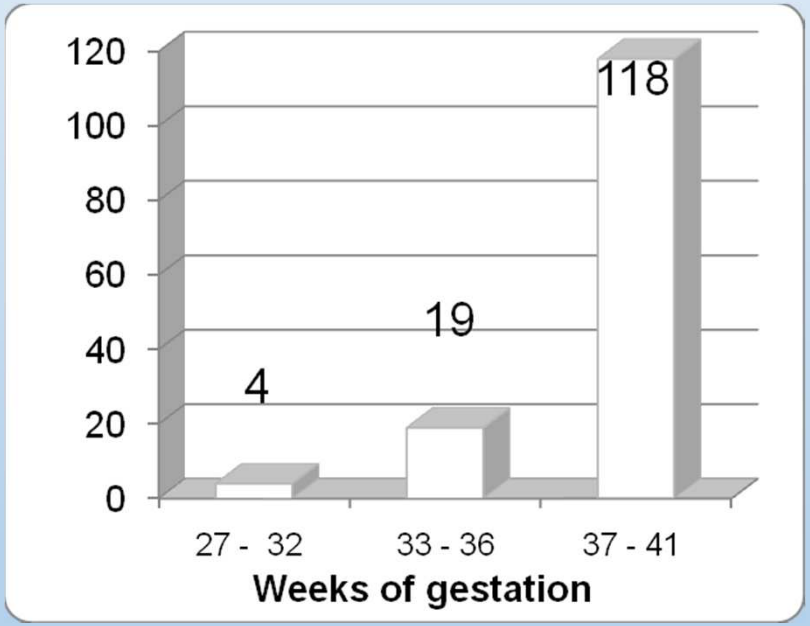
Sindrome da anticorpi anti-fosfolipidi e gravidanza

- Disturbo della coagulazione mediato da anticorpi anti-fosfolipidi (aPL) caratterizzato da trombosi e complicanze della gravidanza
- La presenza di aPL si associa a spontanea e ricorrente perdita della gravidanza
- Il trattamento combinato con eparina e basse dosi di aspirina migliora la prognosi della gravidanza fino al 70%

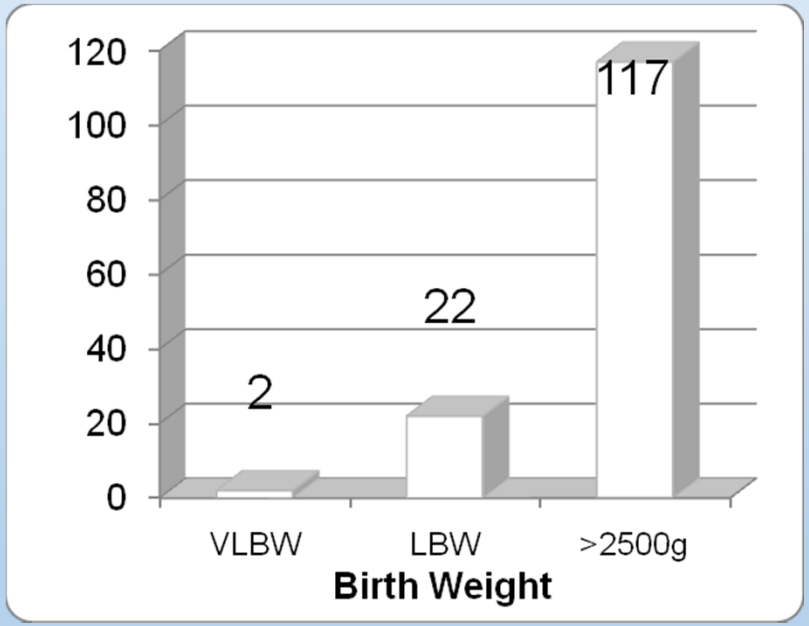
European registry of babies born to mothers with antiphospholipid syndrome. Mekinian A et al, Ann Rheum Dis 2012

Clinical findings in 141 neonates from 138 APS pregnancies

16% Premature Birth



17% Low Birth Weight



11% Small for Gestational Age "dystrophic infants" (N=16)

No clinical evidence of perinatal thrombosis

Neonatal APS registry

Placental transference aPL

aPL	N +neo./+mothers	% +neo./+mothers
LA	**7/45**	**16**
aCL	**24/99**	**24**
aB2GPI	**26/60**	**43**

Neonatal APS registry, Ann Rheum Dis 2012

Anticardiolipin and anti-β2 glycoprotein I antibodies in infants born to mothers with antiphospholipid antibody-positive autoimmune disease: a follow-up study

Motta M et al, Am J Perinatol 2006

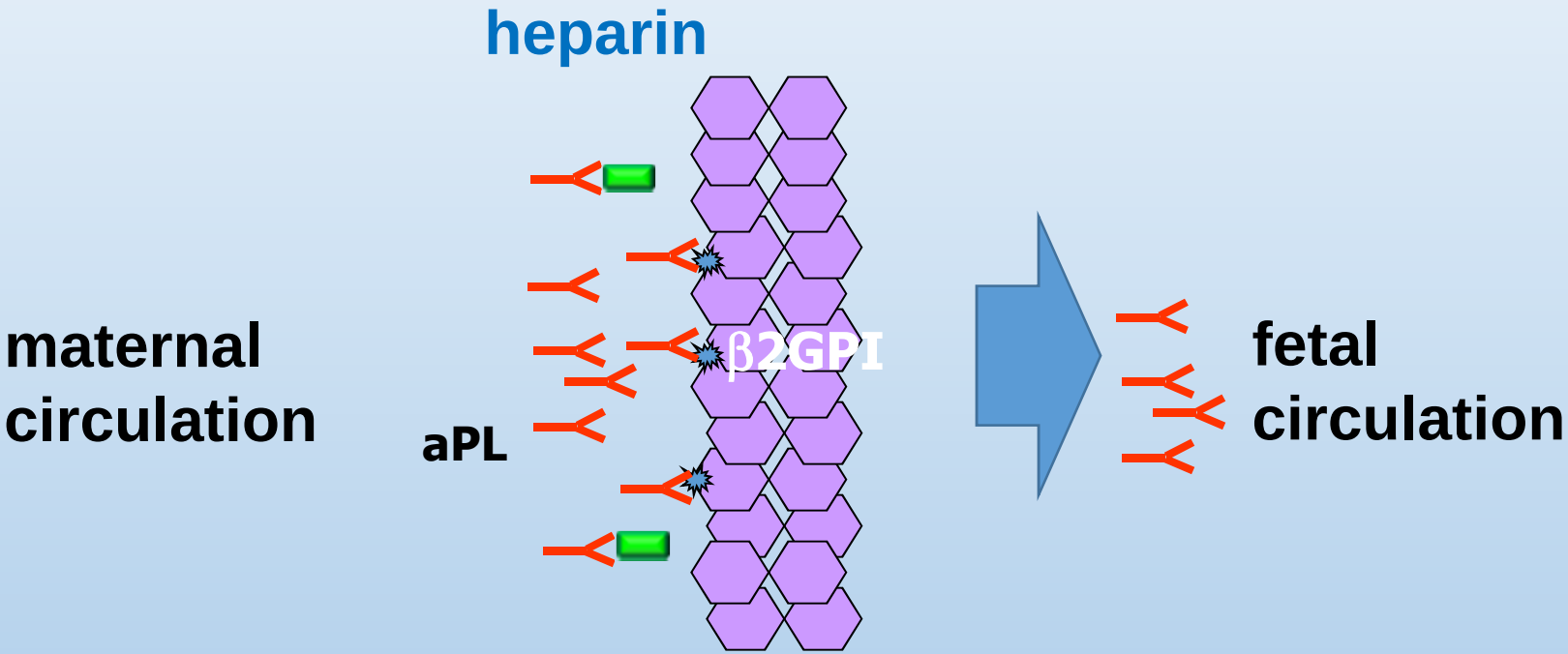
Placental Tranference of Auto-ABs in Infants from Mothers with AD

Autoantibodies (No. of positive mothers during pregnancy)	No. of Positive Infants at Birth (%)
aCL (n = 10)	3 (30)[a]
Anti-β2GPI (n = 13)	4 (30.7)[b]
ANA (n = 22)	18 (81.8)[a,b]

AD, autoimmune disease; aCL, anticardiolipin antibody; β2GPI, beta$_2$ glycoprotein I; ANA, antinuclear antibody. [a,b] **p < 0.05**

Mechanisms limiting the placental transference of aPL

Motta M, Early Hum Dev 2009



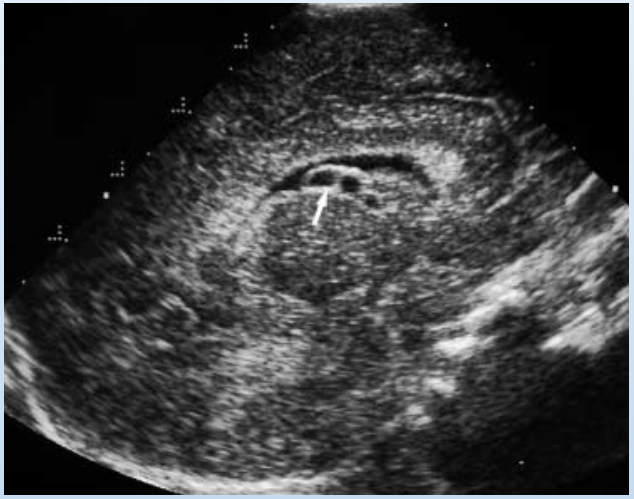
"The trapping of the antibodies in the placenta and their binding with Heparin"

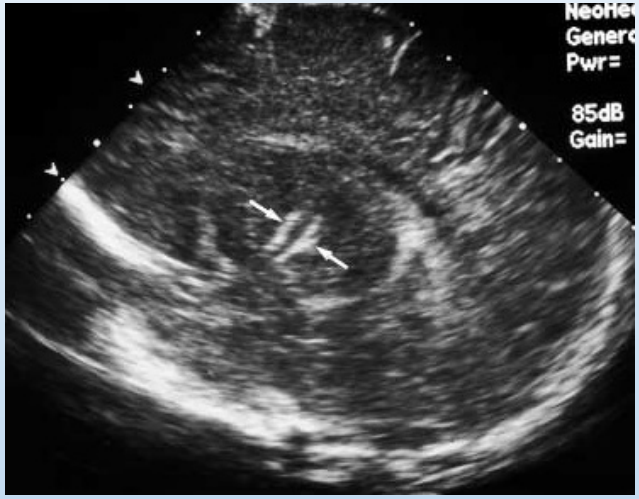
Interessamento Neurologico, Ecografia Cerebrale

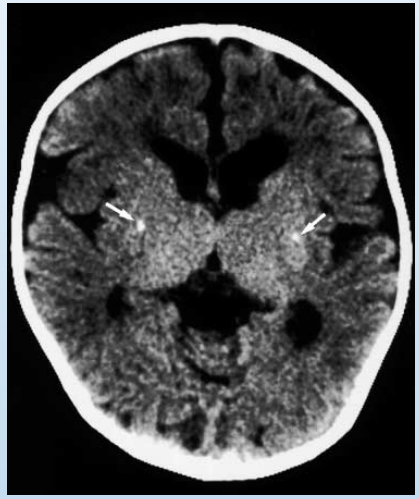
Autore/Anno	Contesto	N	anomalia	Auto-AB
Cabanas 1996	**NLE**	**3/4**	**LSV**	**ANA Anti-Ro/-La**
Prendiville 2003	**NLE**	**7/10**	**LSV SEPC EcoWM**	**ANA Anti-Ro/-La**
Zuppa 2004	**NLE**	**7/11**	**SEPC/SEH**	**Anti-Ro/-La**
Motta 2011	**AD**	**41/114**	**LSV SEPC EcoWM**	**ANA Anti-Ro/La aPL**

LSV: vasculopatia lenticolo-striatale
SEPC: cisti subependimale, SEH: emorragia subependimale
EcoWM: iperecogenecità sostanza bianca

10 of 11 consecutive infants with NLE had cerebral abnormalities on cUS or CT scan







"Subclinical central nervous system disease in NLE is likely to be a transient phenomenon…. The potential for neurologic sequelae is uncertain"

Prendiville JS , Pediatr Dermatol 2003

Cerebral ultrasound abnormalities in infants born to mothers with autoimmune disease

Motta M et al, *Arch Dis Child Fetal Neonatal Ed 2011*

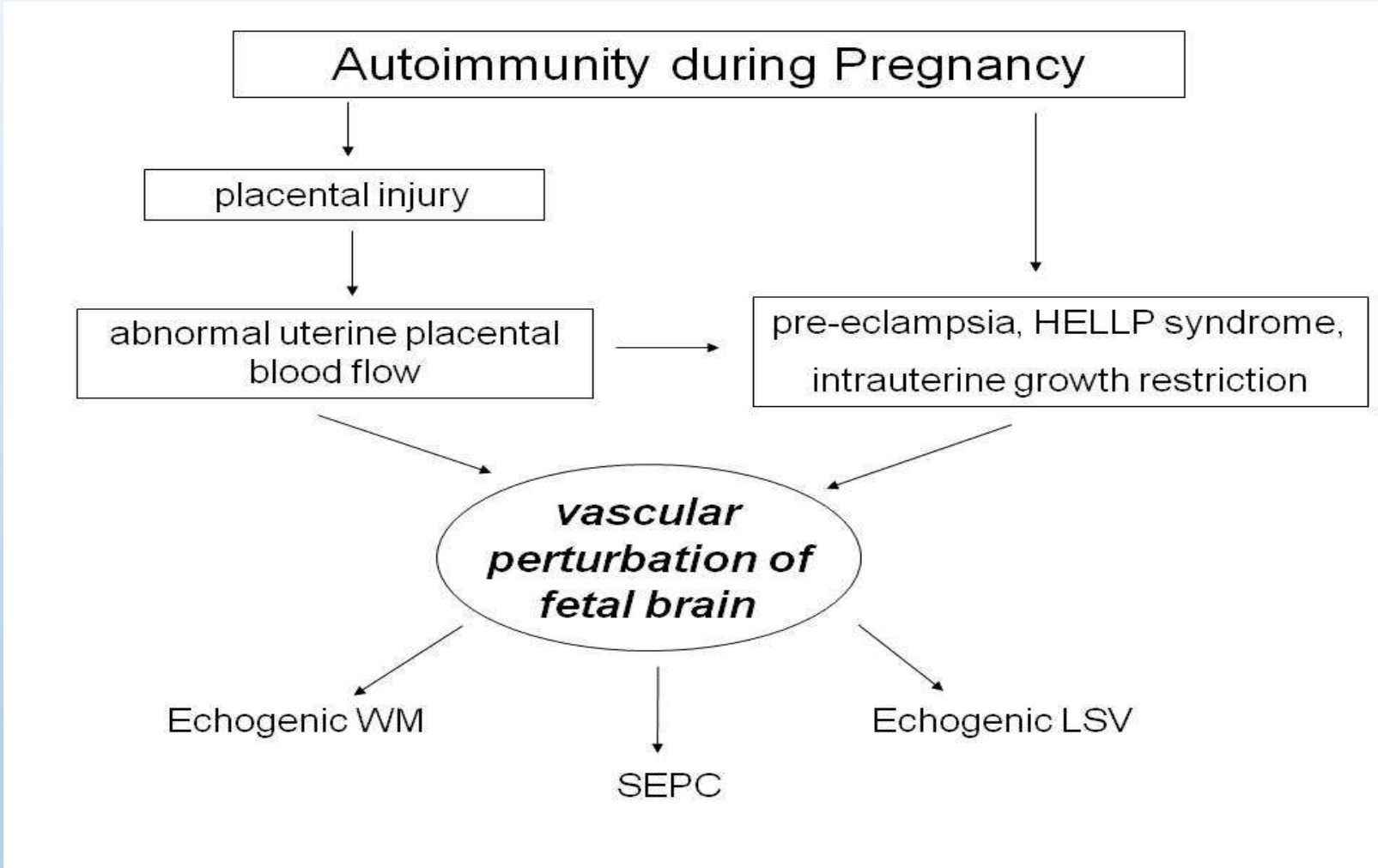
Relationship between cerebral abnormalities on cUS and exposure to perinatal risk factors related to maternal AD

	Non-parametric test	
Perinatal risk factors	**Cerebral abnormalities on cUS in exposed vs unexposed infants**	**p Value**
aPL	6/15 vs 17/55	0.506
Anti-Ro/SSA	2/16 vs 20/63	0.211
Glucocorticoid	24/68 vs 17/46	0.856
Low-dose aspirin	37/104 vs 4/10	0.745
Hydroxychloroquine	16/43 vs 25/71	0.829
Azathioprine and/or ciclosporin A	9/17 vs 32/97	0.114
Preterm birth	9/20 vs 32/94	0.354
LBW	9/18 vs 32/96	0.176
IUGR	5/10 vs 36/104	0.333

"…fetal brain injury may be due to a combination of several factors in this clinical setting."

Proposed pathogenic mechanism

Motta M et al, *Arch Dis Child Fetal Neonatal Ed 2011*



?? clinical relevance and prognostic value of cerebral abnormalities detected by cUS

World Health Organization
Regional Office for Europe

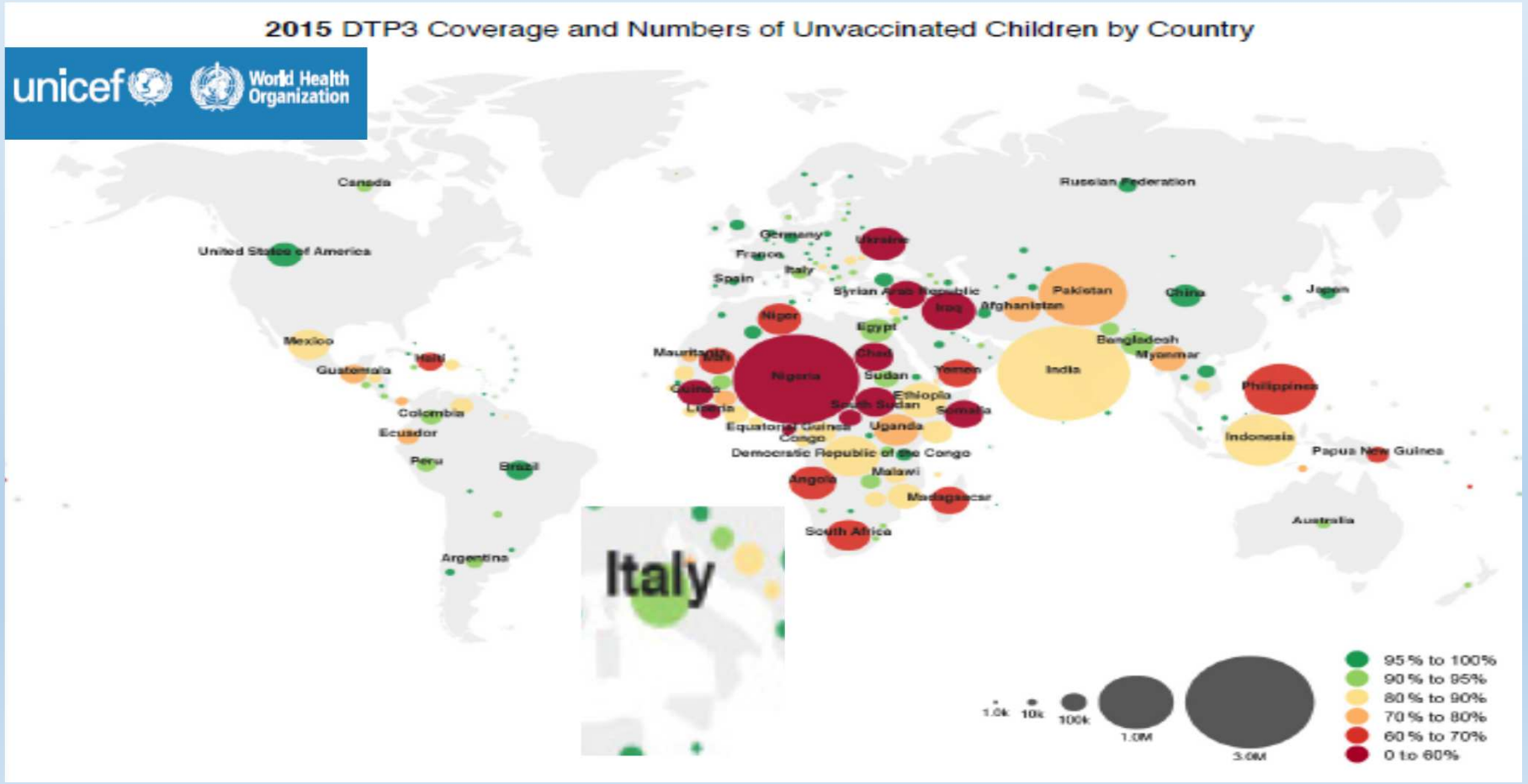
24-30 aprile 2017

I vaccini? Funzionano!

Proteggono la salute in ogni fase della vita

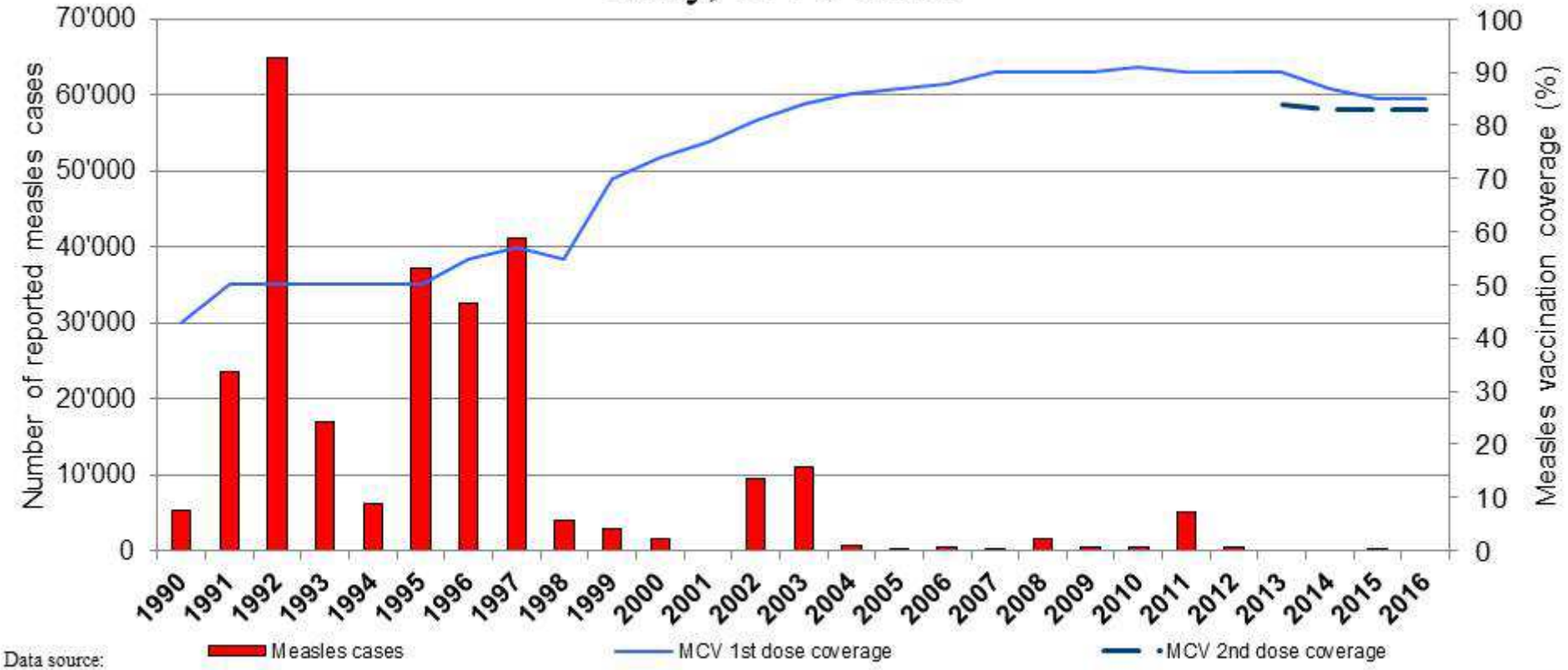
Istituto Superiore di Sanità

Settimana europea delle vaccinazioni



Date of chart: 11/09/2017

Reported measles cases and MCV vaccination coverage, Italy, 1990-2016

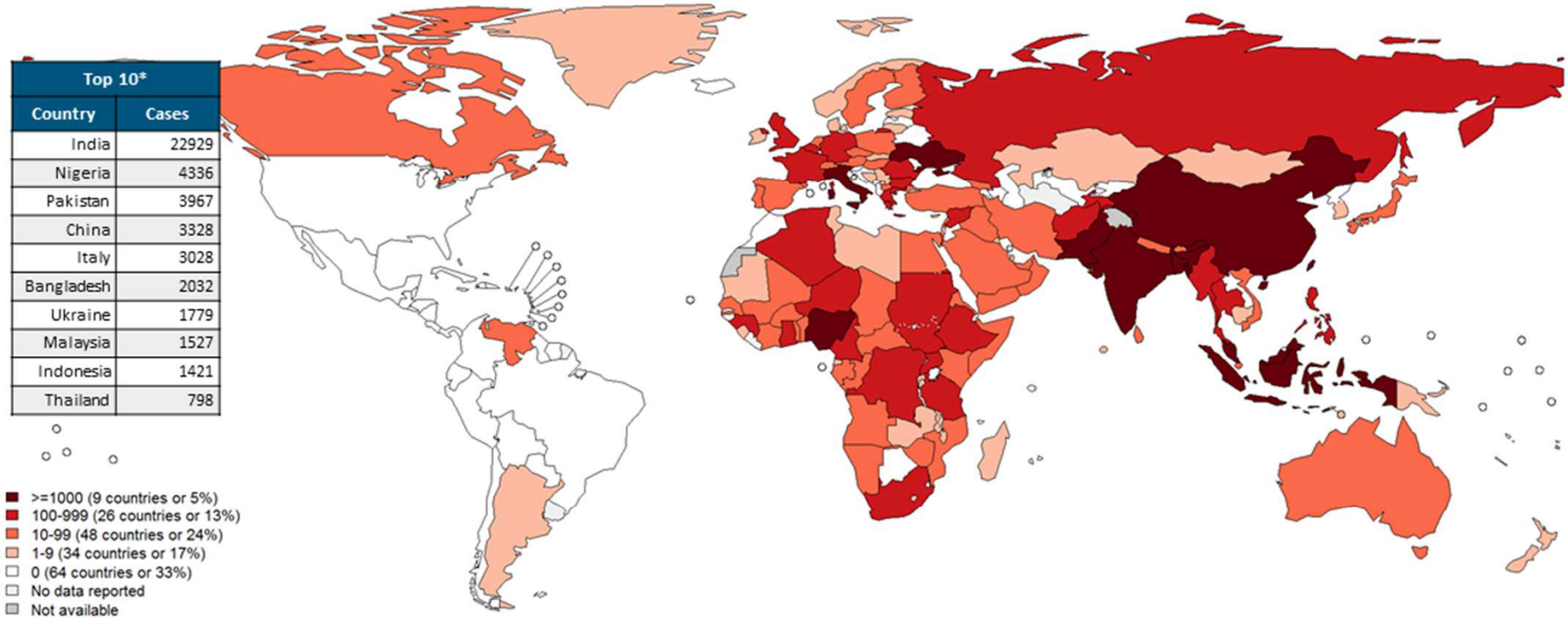


Data source:
Measles cases - Reported by National Authorities to WHO annually: Measles Containing Vaccines (MCV) vaccination coverage (Data as of 05 Sep. 2017);
WHO/UNICEF immunization coverage estimates 1990-2016 (Data as of 15 July 2017) ;
Supplementary Immunization Activities (SIA): WHO/EPI database (Data as of 05 Sep. 2017).
http://www.who.int/entity/immunization/monitoring_surveillance/data/Summary_Measles_SIAs_2000_2016.xls

WHO

Number of Reported Measles Cases (6M period)

Top 10*	
Country	Cases
India	22929
Nigeria	4336
Pakistan	3967
China	3328
Italy	3028
Bangladesh	2032
Ukraine	1779
Malaysia	1527
Indonesia	1421
Thailand	798



World Health Organization

Data source: IVB Database

Disclaimer:
The boundaries and names shown and the designations used on this map do notimply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Based on data received 2017-11 - Surveillance data from 2017-04 to 2017-09 - * Countries with highest number of cases for the period

Immune system development in infants born to mothers with AD and exposed in utero to immunosuppressive agents

Studies	n° of Infants*	Mothers treatment	Main results on immunity assessment
Cimaz 2004, Tox Lett	9	GC, CsA, AZA	**normal serum Ig, IgG subclasses and Ly. subpopulations; normal response to HBV vaccination**
Airò 2006, Lupus	8	High doses GC	**normal thymic function (TRECs); normal T-cell competence**
Cimaz 2007, Lupus	22	GC, CsA, HCQ	**response to tetanus vaccination: no relationship with specific drug exposure**
Biggioggero 2007, Lupus	14	GC, CsA, AZA	**normal serum Ig, IgG subclasses and Ly. subsetspopulations; normal production IL-2 and INF-γ (in vitro)**
Motta 2007, Am J Perinatol	19	GC, CsA, AZA, HCQ	**normal Ly. subpopulations (B1-cells and CD25); normal Ig production (in vitro)**

*No severe or recurrent infections occurred in a total of 72 children involved in these studies

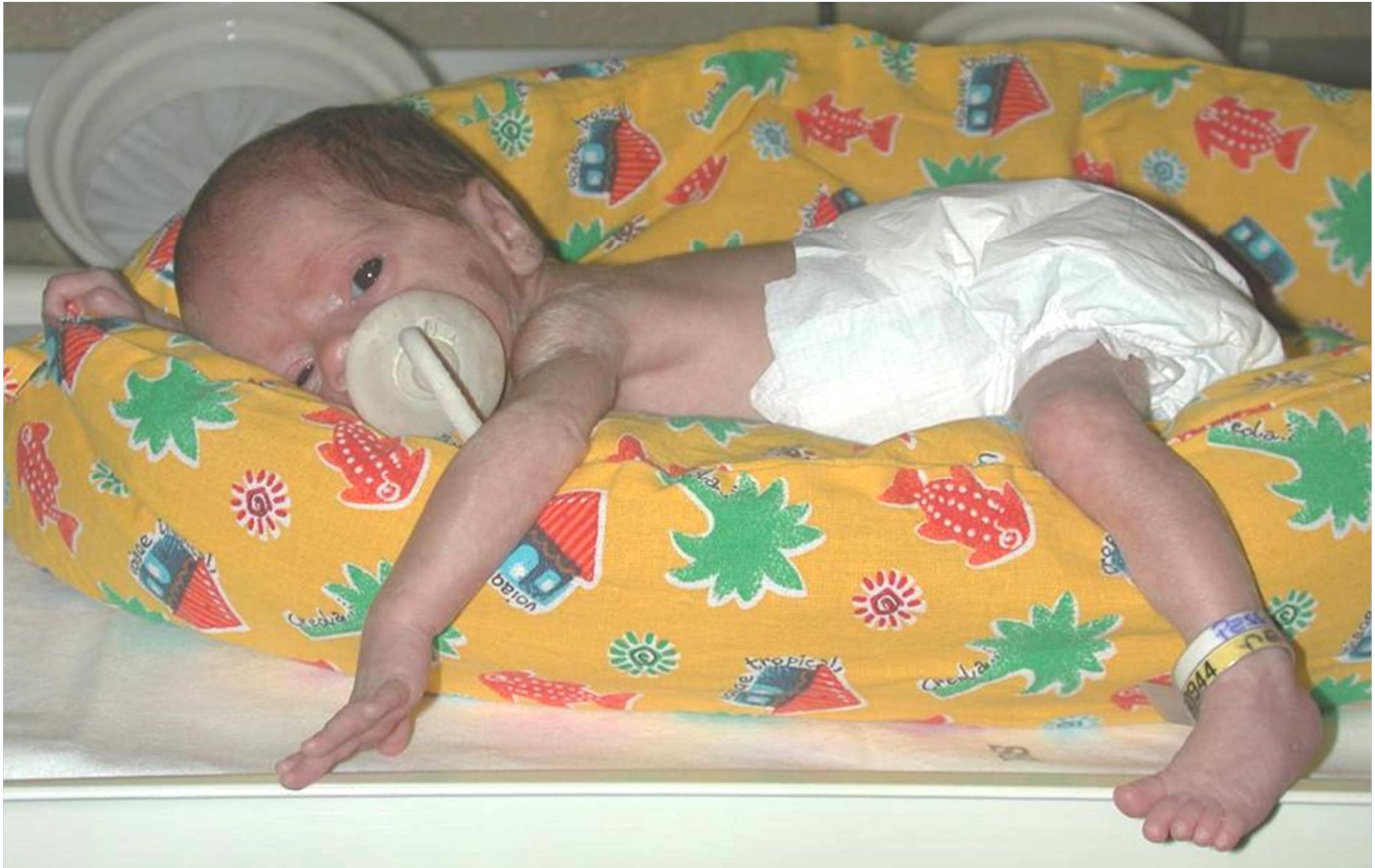
European League Against Rheumatism (EULAR), ARD 2015

Farmaco	Compatibilità con allattamento
Corticosteroids	SI
Hydroxychloroquine	SI
Methotrexate	NO
Sulfasalazine	SI (1)
Leflunomide	Dati non disponibili
Azathioprine (<2mg/Kg/day)	SI
Ciclosporin	SI (2)
Tacrolimus	SI (2)
Cyclophosphamide	NO
Mycophenolate Mofetil	NO
Anti-TNF	SI (2)
Other biologics	Dati non disponibili

(1) Neonato a termine, (2) Dati limitati

Conclusioni

- Il Lupus Neonatale è una patologia autoimmune acquisita (anti-Ro/anti-La); il CCHB (1-2%) è irreversibile, le altre manifestazioni sono transitorie
- In questi bambini sono descritte una serie di anomalie cerebrali (cUS) ma l'eventuale associazione con auto-Ab materni non è chiara
- Nella Sindrome da aPL le complicanze della gravidanza sono frequenti; il passaggio transplacentare di aPL è limitato (30%), il rischio di eventi trombotici neonatali è basso
- Evidenze cliniche e di laboratorio suggeriscono una normale funzione immune nei bambini esposti in utero a immunosoppressori
- In molti casi l'allattamento materno è possibile



Ospedale dei Bambini di Brescia