Difetti immunitari e vaccini: Avversari o alleati?

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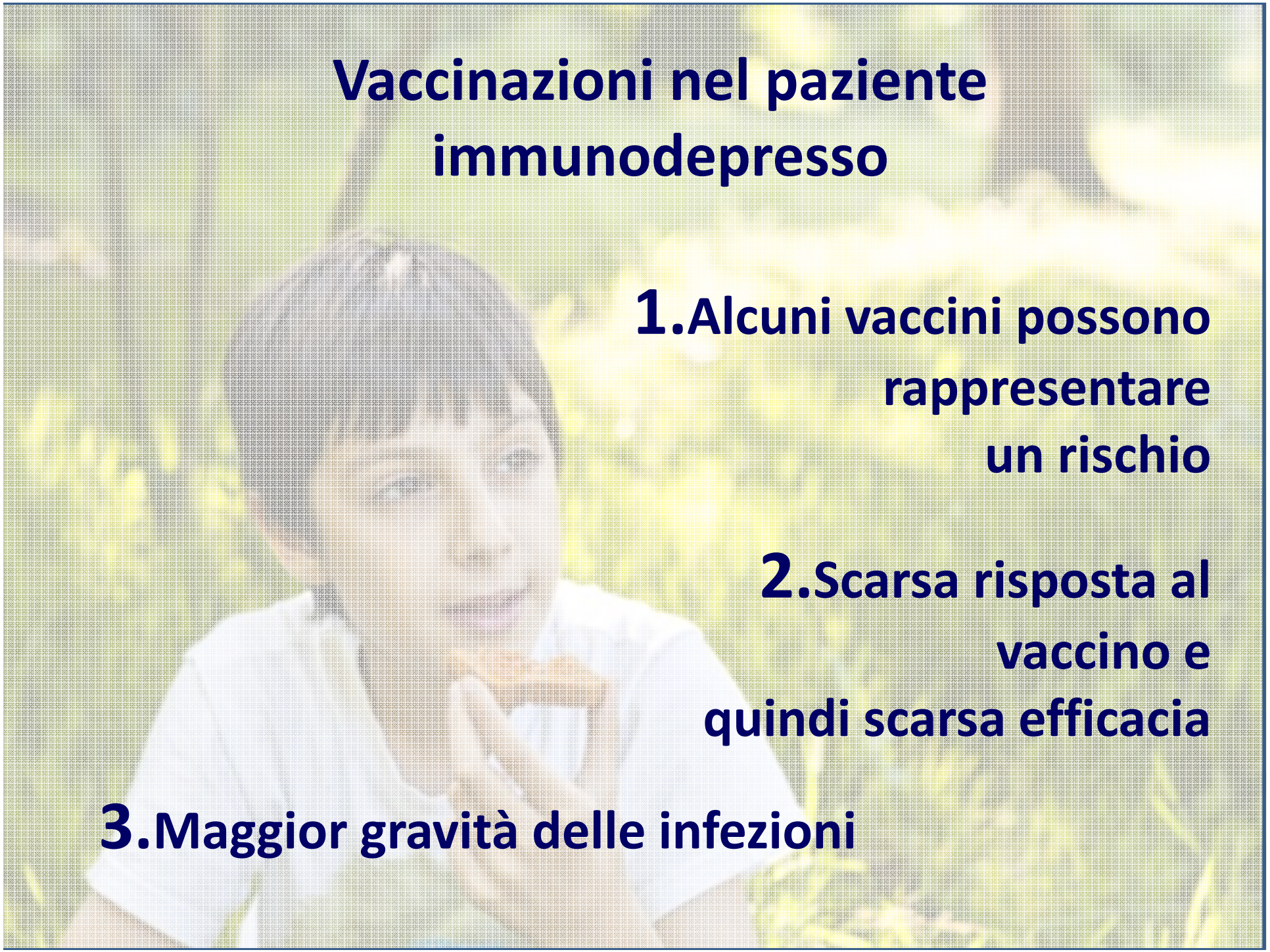
University of Florence
Anna Meyer Children's Hospital
Jeffrey Modell Center for Immunodeficiencies

Vaccinazioni nel paziente immunodepresso



1. Alcuni vaccini possono rappresentare un rischio

2. Scarsa risposta al vaccino e quindi scarsa efficacia

3. Maggior gravità delle infezioni

Categorie a rischio di infezioni **pneumococciche** invasive

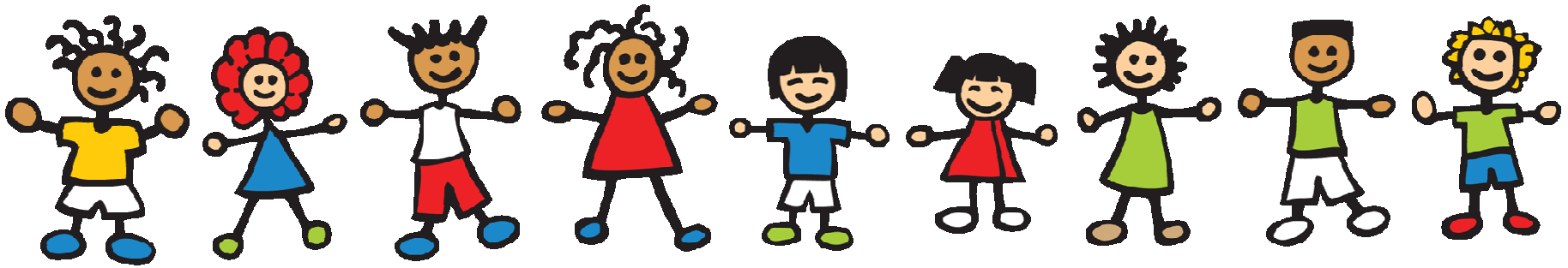
Diabete
Immunodeficienze congenite e acquisite
Emoglobinopatie
Asplenia anatomica e funzionale
Impianto cocleare
Fistole liquorali
Cardiopatie croniche
Malattie polmonari croniche (es.FC, bronchiectasie
Malattie epatiche croniche

Quale delle seguenti condizioni patologiche comporta secondo voi il più alto rischio?

- Diabete
- Immunodeficienze congenite
- Emoglobinopatie
- Asplenia anatomica e funzion
- Impianto cocleare
- Fistole liquorali
- Cardiopatie croniche
- Malattie polmonari croniche (es.FC, bronchiectasie)
- Malattie epatiche croniche

A chi consiglierestе (o avete consigliato) prioritariamente la vaccinazione?

asplenia
e infezioni
da pneumo



Lorenzo, 6 anni

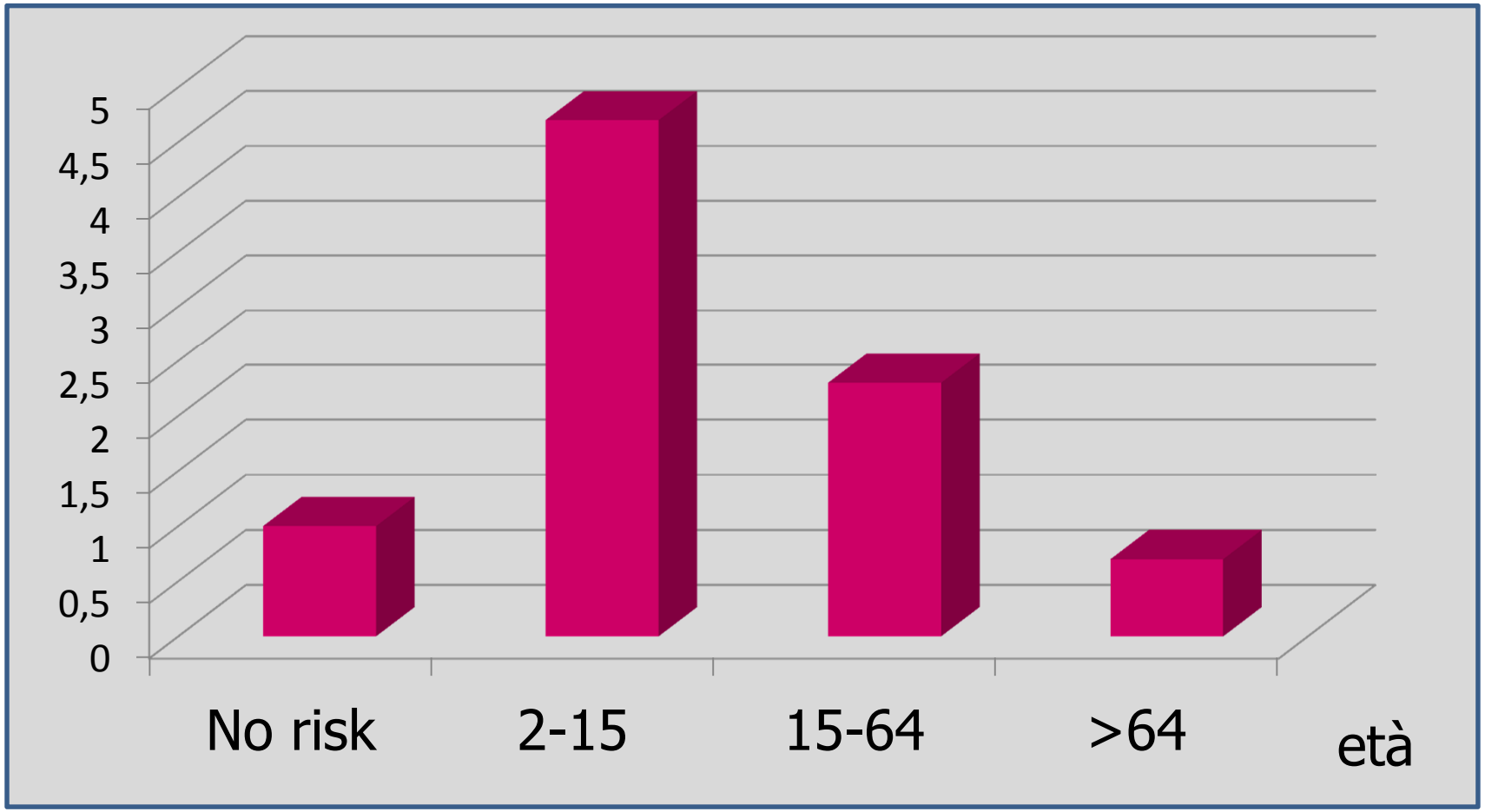
Anamnesi familiare: ndn

Anamnesi fisiologica: tutto nella norma; accrescimento regolare, vaccinazioni come da calendario compreso pneumo e meningo, non varicella

Anamnesi patol. remota: è stato sempre bene

Anamnesi patol. prossima: caduto dal tavolo, urto sullo schienale di una sedia, rottura della milza

Rischio di IPD: Asplenia vs controlli



In età pediatrica il rischio di IPD è 4,5 volte più elevato negli asplenici rispetto alla popolazione generale

The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England

Albert Jan van Hoek [a,*], Nick Andrews [b], Pauline A. Waight [a], Julia Stowe [a], Peter Gates [c], Robert George [d], Elizabeth Miller [a]

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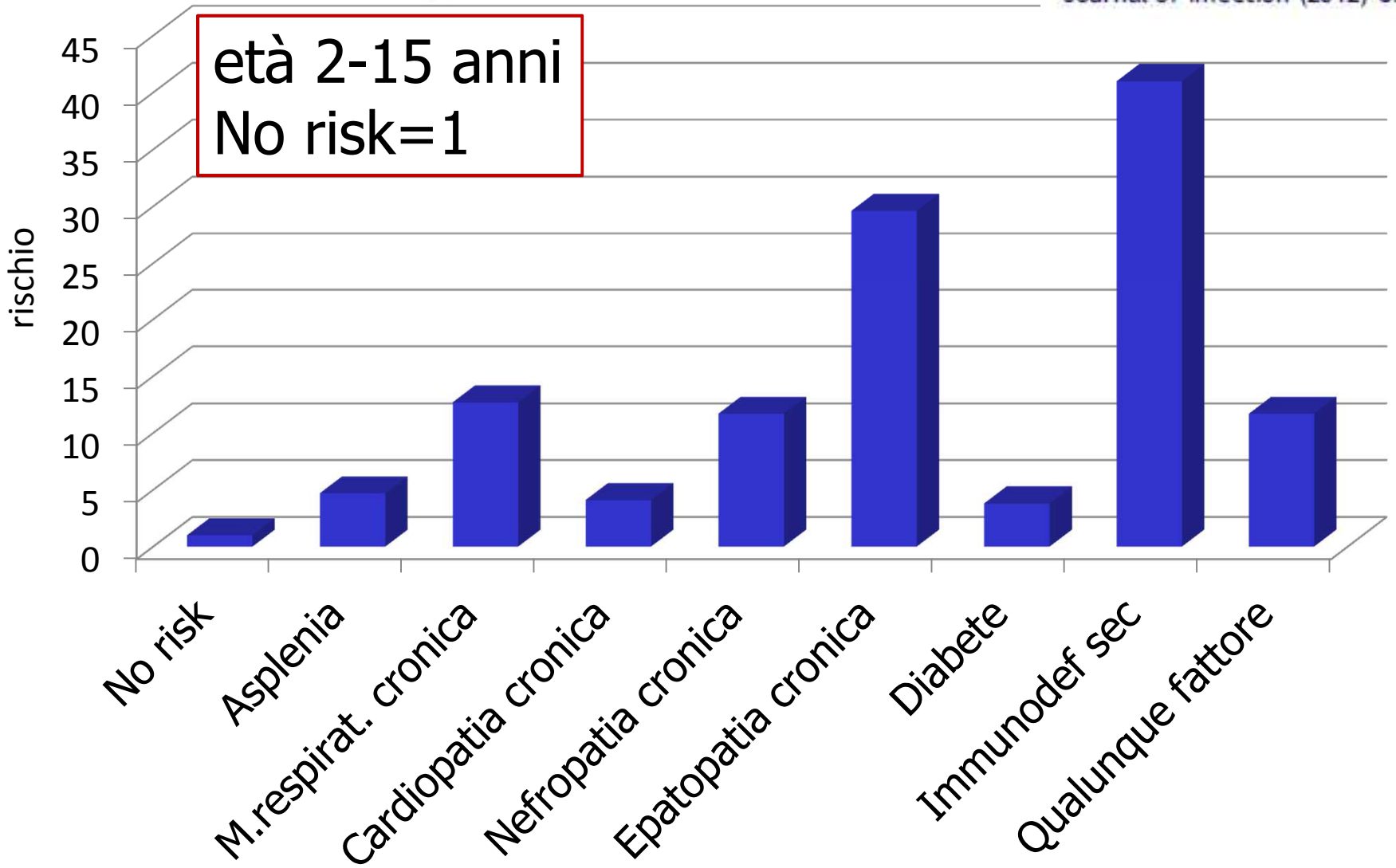
Journal of Infection (2012) 65, 17–24



The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England

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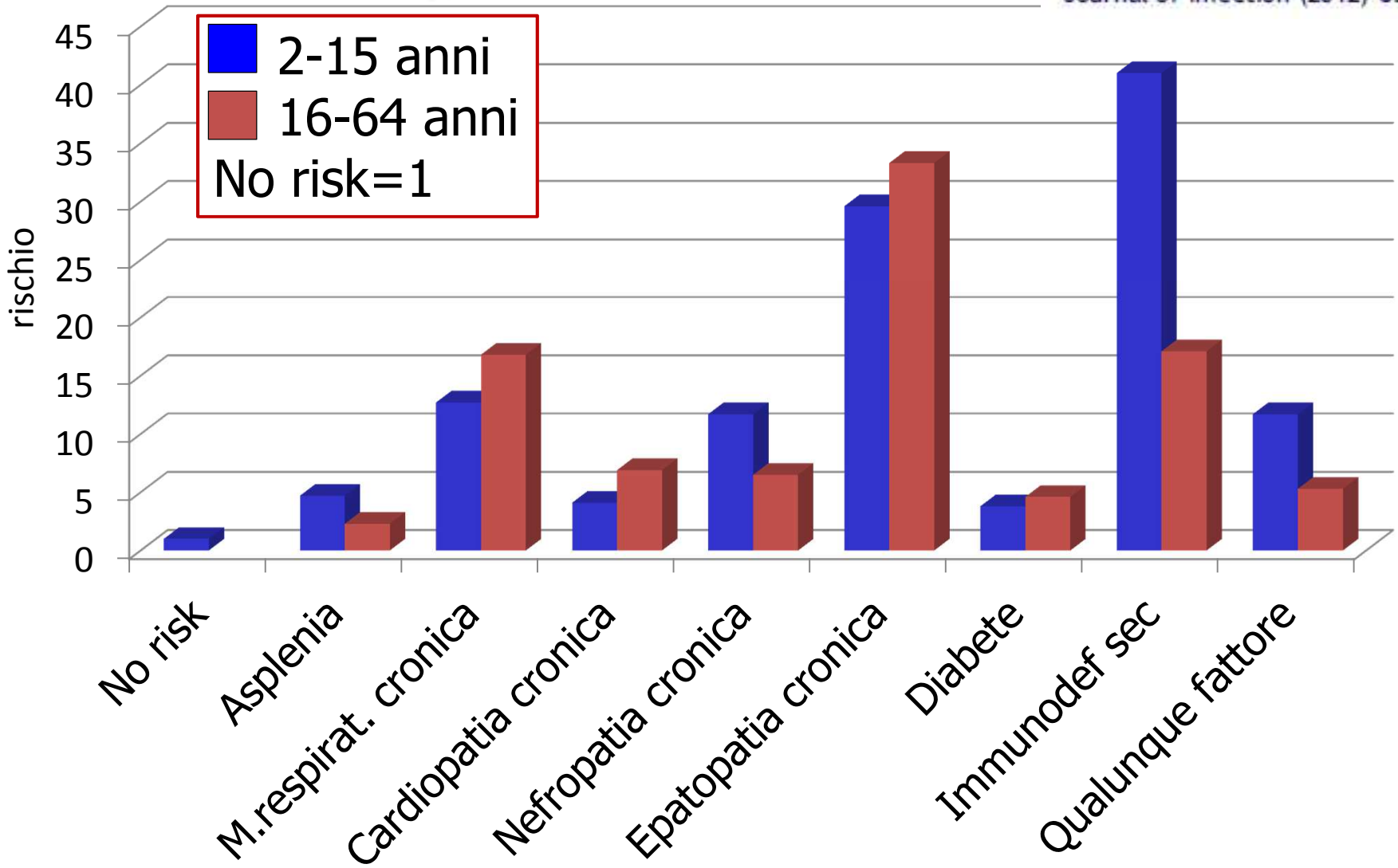
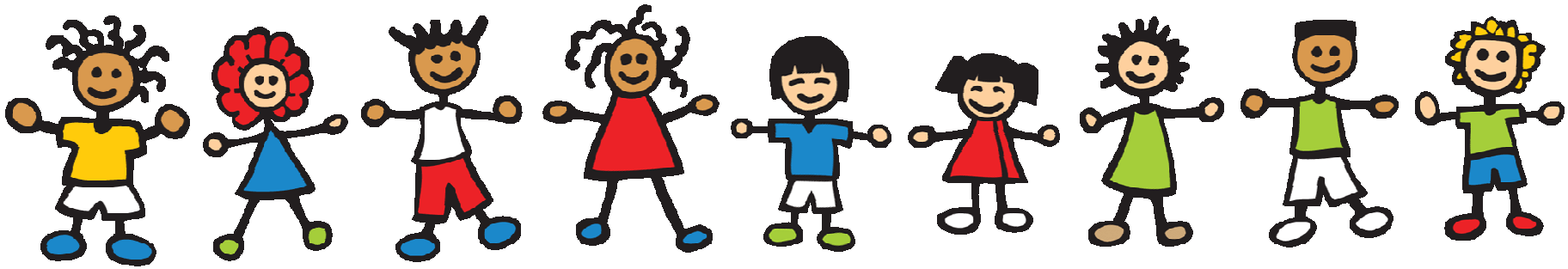


I vaccini vivi e i difetti immunitari



Marta 16 anni

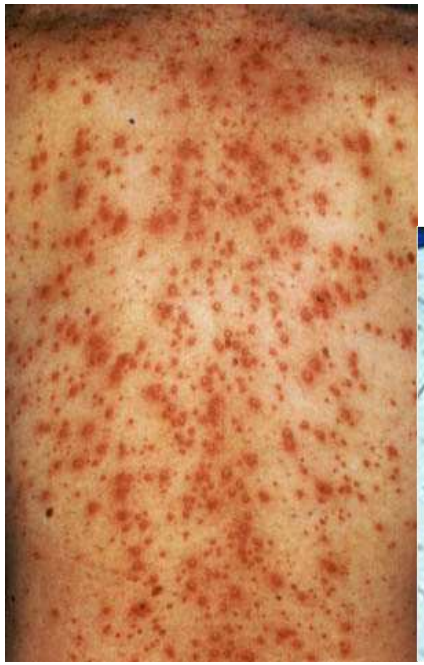
Storia di pregressa neutropenia ciclica (conclusa)

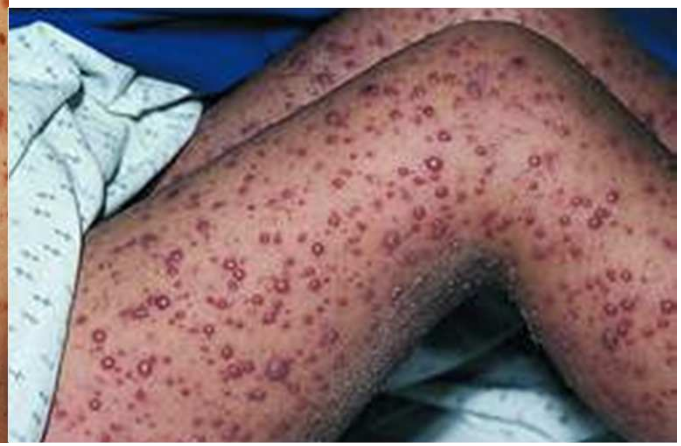
Da 5 giorni eruzione varicellosa

in 4° giornata impronta emorragica

→ricovero presso il DAI di pediatria

Sensorio integro, parametri vitali buoni





Esami Ematici:

GB	**2.950**
Hb	**12.1**
Piastrine	**15.000**
AST	**10.080**
ALT	**4.330**
LDH	**25.750**
DDimeri	**4.780**
AT III	**75%**
fibrinogeno	**150**

Marta 16 anni

Terapia : Acyclovir, Ceftriaxone, plasma, ATIII

In poche ore:

- peggioramento delle condizioni generali
- comparsa di dispnea ingravescente
  Rx Torace→ polmonite interstiziale ➡ Terapia intensiva

Marta 16 anni

- Ulteriore peggioramento
- Progressivo deterioramento dello stato di coscienza
- Necessità di ventilazione assistita.
- Encefalite
- Comparsa di Insufficienza multi-organo

Decesso dopo una degenza di circa 20 giorni

Si apre un' inchiesta sull' operato

- del pediatra di famiglia
- del medico di medicina generale
- del medico specialista ematologo

perché non hanno suggerito la vaccinazione

Guida all'uso dei farmaci 4 anno 2007 Agenzia Italiana del Farmaco AIFA

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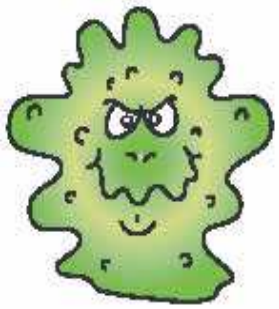
EpiCentro

Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute

CNESPS

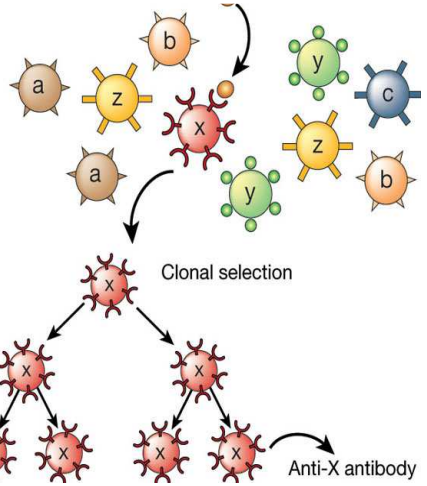
Il vaccino anti-varicella è un vaccino vivo e quindi non deve essere somministrato ai pazienti con immunodeficit….

Come ci difendiamo dalla varicella (e dai virus in generale)?



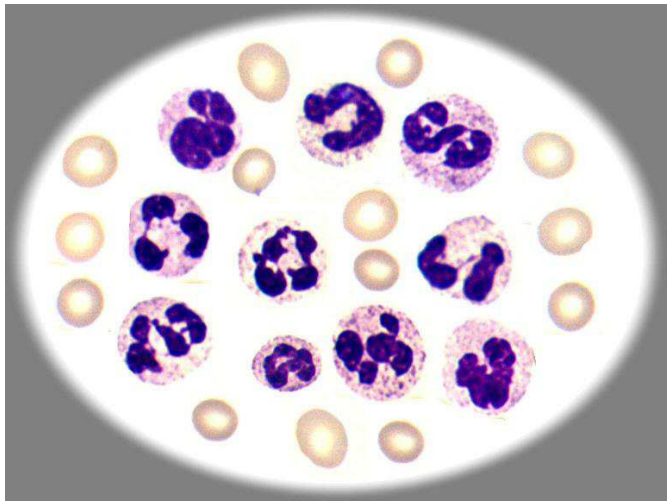
La protezione contro i virus è essenzialmente a carico di

linfociti B (produzione di anticorpi)
linfociti T (citotossici)



Un' immunodeficienza di uno di questi due settori può facilitare eventi avversi da vaccino

soppesare rischio/beneficio (chiediamo consiglio….)



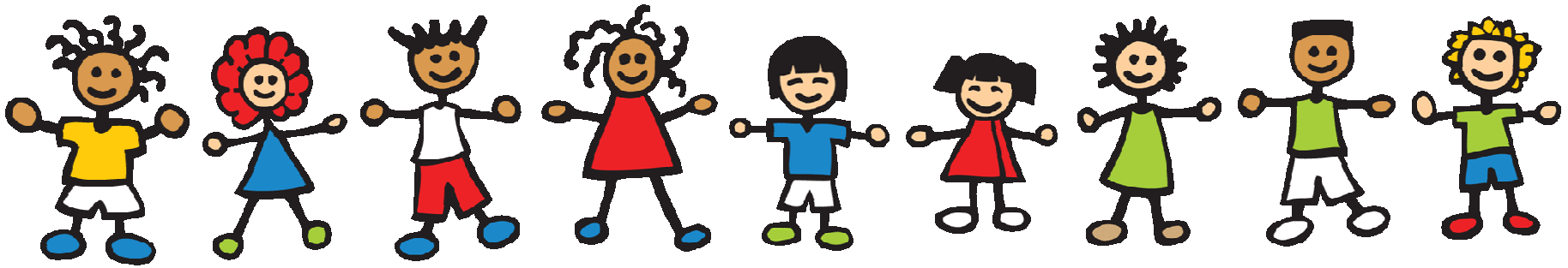
I granulociti neutrofili sono un' arma essenziale nella difesa contro le infezioni batteriche

Un deficit dei granulociti neutrofili non solo non è una controindicazione,

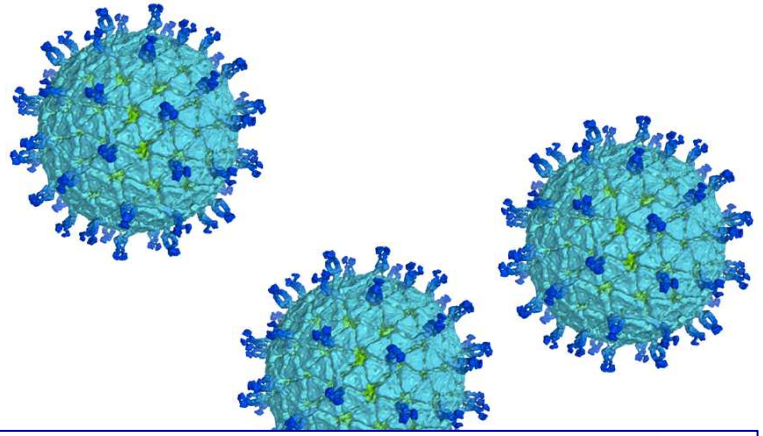
ma può essere considerato una indicazione al vaccino anti-varicella

perché può predisporre a complicanze batteriche

… ancora su vaccini vivi e difetti immunitari



Rotavirus e immunodeficienze



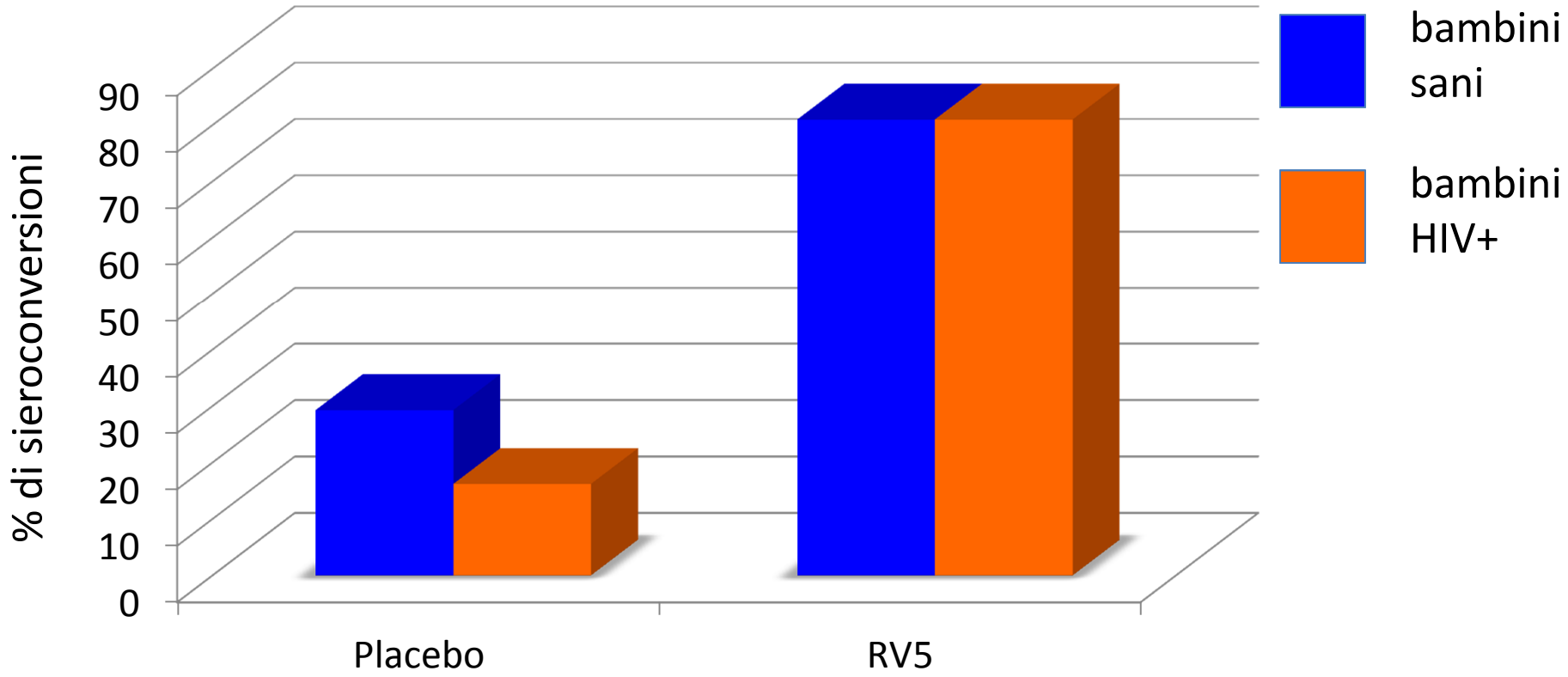
Published in final edited form as:

AIDS. 2017 January 02; 31(1): 49–59. doi:10.1097/QAD.0000000000001258.

Safety and Immunogenicity of a Live Attenuated Pentavalent Rotavirus Vaccine in HIV-Exposed Infants With or Without HIV Infection in Africa

Myron J Levin, MD[a], Jane C Lindsey, ScD[b], Susan S Kaplan, MD[c], Werner Schimana, MD[d], Jody Lawrence, MD[e], Monica M McNeal, MS[f], Mutsa Bwakura-Dangarembizi, MMed[g], Anthony Ogwu, MD[h], Evans M Mpabalwani, MMed[i], Paul Sato, MD[j], George Siberry, MD[k], Margaret Nelson, RN[c], Darcy Hille, MS[c], Geoffrey A Weinberg, MD[l], and Adriana Weinberg, MD[m]

Immunogenicità e sicurezza della vaccinazione anti-Rotavirus in bambini HIV+



Placebo e vaccino: identici anche sotto il profilo di sicurezza

Levin MJ et al., AIDS, 2017

Chronic Infection with Rotavirus Vaccine Strains in UK Children with Severe Combined Immunodeficiency

To the Editors:

Following the recent publication of Klinkenberg et al[1] in Germany of a case of a severe combined immunodeficiency (SCID) patient infected with rotavirus vaccine strain, we would like to report 7 cases in the UK with similar characteristics. These cases have been diagnosed since July 2013, when the rotavirus live vaccine was included in the UK routine childhood vaccination schedule for infants 2 and 3 months of age.[2] SCID is one of the contraindications to receiving this vaccine.[3,4]

We describe 7 infants born in UK with different ethnic backgrounds, all diagnosed with SCID but who received oral rotavirus vaccine before the immunologic diagnosis, and were found subsequently to be infected with rotavirus vaccine strain. This represents 100% of exposed SCID diagnoses presenting to the 2 UK national referral centers since the introduction of rotavirus vaccination. Five presented with chronic diarrhea and 2 with severe failure to thrive. Six required parenteral nutrition at some stage during their admission, and 3 developed significant gastrointestinal complications following corrective therapy, which have prolonged inpatient hospital stay, increased the costs and risk of treatment, and increased the risk of cross-infection to other immunodeficient patients treated on the same wards. Further details of the patients are presented (Table 1).

We believe these are the first patients to be reported in the UK experiencing chronic rotavirus vaccine strain infection. A high penetrance of symptomatic rotavirus infection in SCID patients was predictable, because it was described in the USA following introduction of the vaccine in the routine childhood vaccination schedule in 2006.[5] The requirement to establish a newborn screening program for SCID was therefore reinforced and successfully introduced in many US states from May 2010.[6]

As in many European countries, newborn screening for SCID has not yet been approved in UK; until this happens, it is likely that infants with SCID will continue to be immunized with live vaccines, thus complicating and increasing their hospital stay and treatment costs.

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The authors have no funding or conflicts of interest to disclose.

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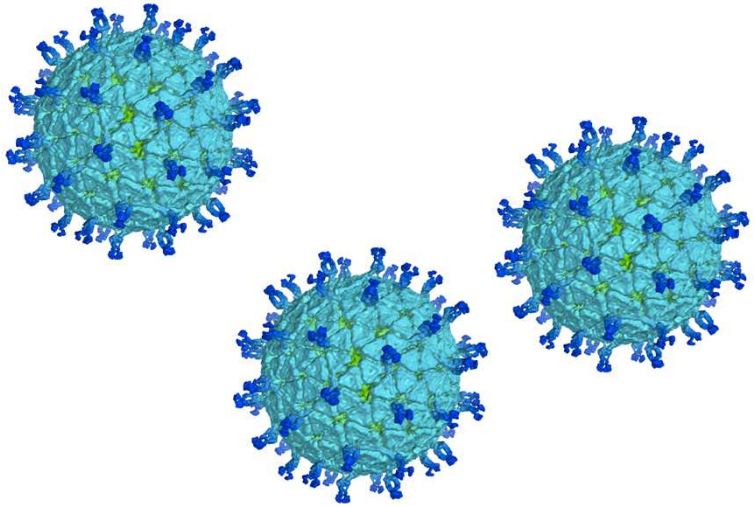
DOI: 10.1097/INF.0000000000000788

	Sex	Age at Presentation (Months)	Symptoms	Molecular Diagnosis	Age Rotavirus Vaccine Administration (Months)	Rotavirus 1st Isolated/Age (Months)	Serotype Vaccine Confirmation	Outcome/ Treatment Status	PN Total Duration Post-Treatment	Rotavirus Cleared (Y/N)
1	F	5	Chronic diarrhea, hepatosplenomegaly, respiratory distress on mechanical ventilation	JAK3	2 and 3	3	G1P8	Unconditioned mMSD bone marrow infusion. GVHD grade IV	42 days	Y
2	M	4	FTT, chronic diarrhoea, materno fetal engraftment, PJP on mechanical ventilation. Norovirus stools	RAG	2 and 3	6	G1P8	MUD BMT. Engrafted	50 days	Y
3	M	4	FTT, chronic diarrhoea, lymphadenopathy, hepatoesplenomegaly, respiratory symptoms. BCGitis	ADA	2 and 3	5	G1P8	Gene therapy. Gradual immune reconstitution, normal blood ADA activity	>120 days (still on PN)	Y
4	M	6	Chronic diarrhoea, respiratory distress on CPAP	CγC	3 and 4	6	Yes. Confirmation awaited	MUD BMT. Engrafted. Lower GI GVHD	>79 (still on PN)	N
5	M	4	Chronic diarrhoea. Omenn's syndrome. PJ isolated	Artemis	2 and 3	4	G1P8	MUD Cord. Engrafted TMA/Lung VOD. Deceased	47 days	Y
6	M	5	Disseminated CMV-blood, lungs, CSF. PJ isolated. Norovirus stools	Undefined	2	4	Awaited	MUD cord. Awaiting engraftment	>22 (still on PN	N
7	F	3	Preterm	Undefined	2	2	Awaited	Unconditioned TCR alfa/ beta depleted haploindentical PBSC infusion.	None	N

BMT indicates bone marrow transplant; CPAP, continuous positive airway pressure; F, female; FTT, failure to thrive; GVHD, graft versus host disease; M, male; mMSD, mismatched sibling donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; PJ, *Pneumocystis jirovecii*; PJP, *Pneumocystis pneumonia*; PN, parenteral nutrition; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

7 bambini con SCID sono stati vaccinati con Rotavirus prima della diagnosi di SCID



5/7 si sono presentati con diarrea cronica
2/7 scarso accrescimento importante

6/7 hanno richiesto nutrizione parenterale
3/7 hanno avuto complicanze gastrointestinali durante la terapia correttiva (BMT) prolungato la degenza
aumento dei costi
aumenyo del rischio dei trattamenti
rischio di cross-infezione ad altre SCID in reparto

Morillo-Gutierrez B, PIDJ 2015; 34(9):1040

As in many European countries, newborn screening for SCID has not yet been approved in UK; until this happens, it is likely that infants with SCID will continue to be immunized with live vaccines, thus complicating and increasing their hospital stay and treatment costs.

The requirement to establish a newborn screening program for SCID was therefore reinforced and successfully introduced in many US states from May 2010.[6]

Morillo-Gutierrez B, PIDJ 2015; 34(9):1040

Morbidity and Mortality Weekly Report (*MMWR*)

Addition of Severe Combined Immunodeficiency as a Contraindication for Administration of Rotavirus Vaccine

Weekly
June 11, 2010 / 59(22);687-688

Il vaccino Rotavirus (sia RV5 che RV1) è controindicato in bambini che sono stati diagnosticati SCID

SCID includes a group of rare, life-threatening disorders caused by at least 15 different single gene defects that result in profound deficiencies in T- and B-lymphocyte function (*3*). The estimated annual incidence of SCID is one case per 40,000--100,000 live births, or a total of approximately 40--100 new cases among infants in the United States each year (*3*). SCID usually is diagnosed after an infant has acquired a severe, potentially life-threatening infection caused by one or more pathogens. Infants with SCID commonly experience chronic diarrhea, failure to thrive, and early onset of infections. Chronic, wild-type rotavirus infection has been reported in infants with SCID, with resulting prolonged diarrhea or shedding of rotavirus (*4*). Diagnosis and hematopoietic stem cell transplantation before onset of severe infections offer the best chance for long-term survival of SCID patients (*3,5*).

The median age at diagnosis of SCID is 4--7 months, which overlaps with the ages for rotavirus vaccination recommended by ACIP (ages 2, 4, and 6 months for RV5; ages 2 and 4 months for RV1). Prenatal diagnosis is possible for the minority of infants with a known family history of SCID. Newborn screening for SCID through evaluation of dried blood spots is available in two states, Massachusetts and Wisconsin. On January 21, 2010, the Federal Advisory Committee on

E’ importante fare una consulenza immunologica in tutti i bambini che abbiano la certezza o il sospetto di deficit immunitario PRIMA di fare la vaccinazione con Rotavirus

Immunodeficienza

Terapia IS

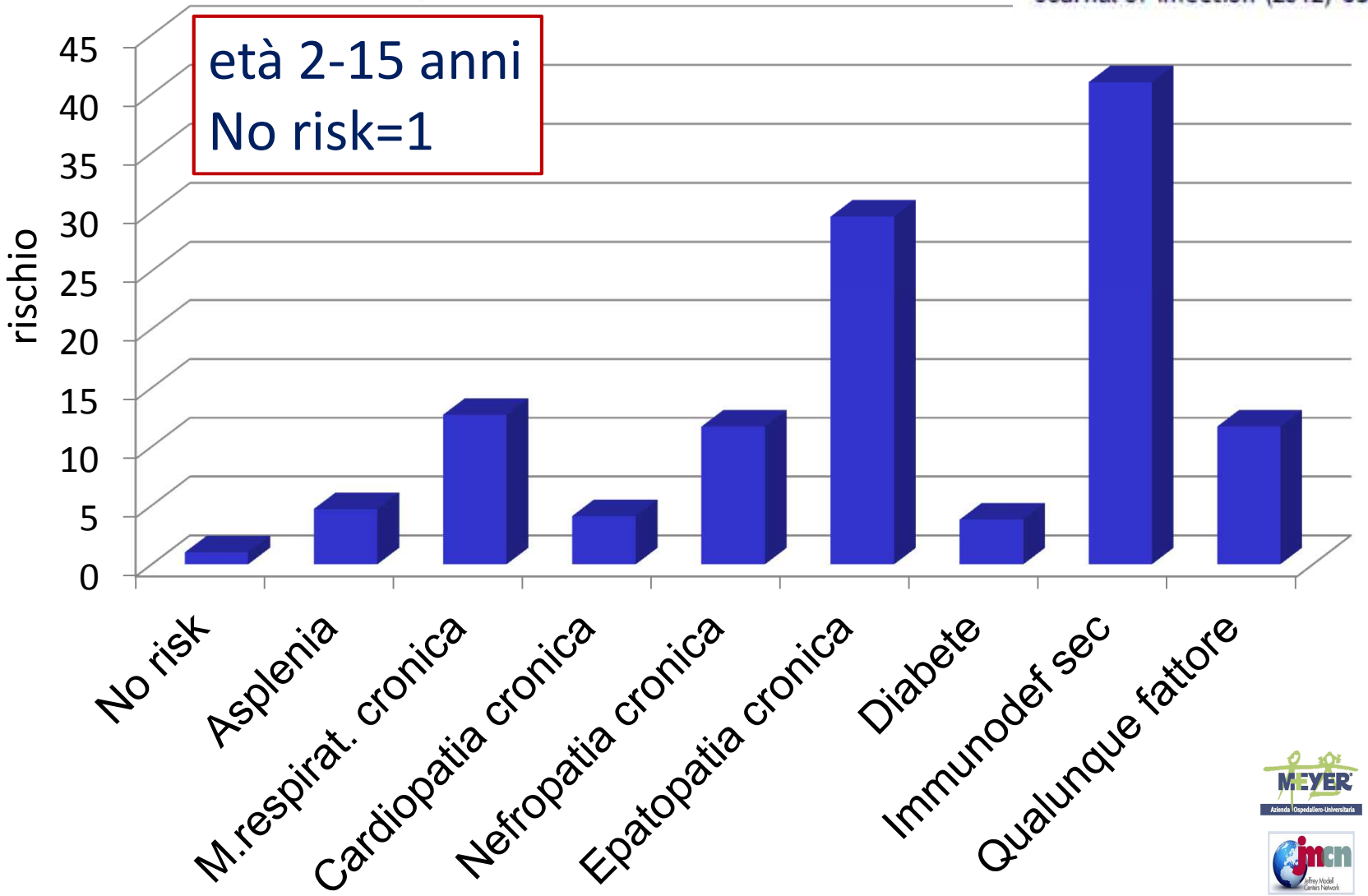
Autoimmunità

The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England

Albert Jan van Hoek [a,*], Nick Andrews [b], Pauline A. Waight [a], Julia Stowe [a], Peter Gates [c], Robert George [d], Elizabeth Miller [a]

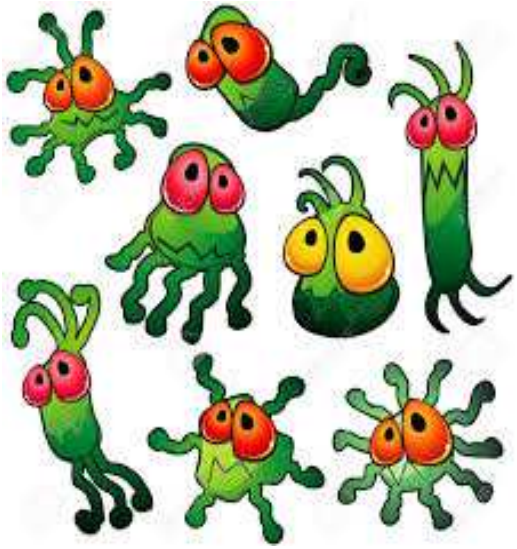
ELSEVIER

Journal of Infection (2012) 65, 17–24



Vaccinazioni e malattie reumatiche autoimmuni (AIRD)

1. sono in generale più predisposti e più vulnerabili alle infezioni (malattia di base+tipo di terapia)



20-58% dei decessi in pazienti con AIRD infezioni pneumococciche, da virus (influenza, HSV, CMV), fungine e parassitarie.

Listing J. Rheumatology (2013)

Malattie reumatiche autoimmuni (AIRD) e infezioni

Rischio relativo:

- **2.47 per RA**
- **4.2 per sclerodermia**
- **3.2 per sindrome di Sjögren**
- **5.0 per LES**

Infezioni da HPV
24.6% nei pz con LES vs
10.4%popolazione generale
++ HPV-16 (sierotipo ad alto rischio)
Ridotta capacità di clearance

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Patients with Inflammatory Bowel Disease Are at Risk for Vaccine-Preventable Illnesses

Gil Y. Melmed, M.D.,[1] Andrew F. Ippoliti, M.D.,[1] Konstantinos A. Papadakis, M.D.,[1] Tram T. Tran, M.D.,[2]

Vaccinazioni e malattie reumatiche autoimmuni (AIRD)

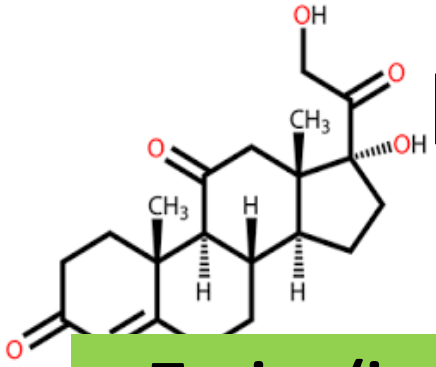
2. I vaccini sono efficaci nelle AIRD?

Dipende dal tipo di vaccino, malattia di base e terapia…

Vaccino anti-pneumococcico

CORTICOSTEROIDI
TNF INIBITORI
ANTI-IL6

METOTREXATE+TNF INIBITORI
METOTREXATE
ABATACEPT
ANTI-CD20



Immunodepressione iatrogena: STEROIDI

- Topico (inalante, cutaneo, intrarticolare)
- Dose fisiologica/sostitutiva (iposurrenalismo)
- Dose non alta (<2mg/kg o < 20mg/die se >10kg)

TUTTI I VACCINI

- Dose alta >/= 2mg/kg o >20mg/die se >10kg x max 7gg

TUTTI I VACCINI quando sospende la TP

- Dose alta >/= 2mg/kg o >20mg/die se >10kg x più di 7gg

I vaccini UCCISI POSSONO NON ESSERE EFFICACI (dosare titolo anticorpale) Meglio farli 2 settimane prima dell'inizio della terapia.
I vaccini VIVI si possono fare solo dopo 4 settimane dalla sospensione della TP o 4 settimane prima della terapia steroidea.

Immunodepressione iatrogena

1. Dosi immunosoppressive, maggiori di:

ccs > 20mg/die o >/= 2mg/kg/die

methotrexate 15 mg/m^2/settimana

ciclosporina 2.5 mg/kg/die

sulfasalazina 40 mg/kg/die e sino a 2 g/giorno

azatioprina 1-3 mg/kg

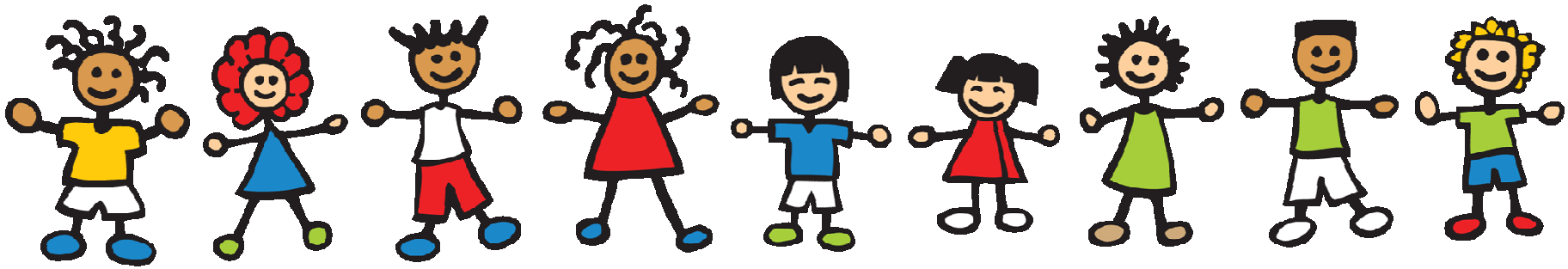
ciclofosfamide 0.5-2 mg/kg/die per via orale

leflunomide 0.25-0.5 mg/kg/die

6-mercaptopurina 1.5 mg/kg/die

2. uso di anticorpi monoclonali

farmaci biologici ed infezioni da pneumo



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Vaccination Issues in Patients with Inflammatory Bowel Disease Receiving Immunosuppression

Seper Dezfoli, MD,

Gastroenterology & Hepatology Volume 8, Issue 8 August 2012

Tutti i pazienti in terapia con anti-TNF devono ricevere la vaccinazione antipneumococcica prima dell'inizio della terapia

Effettuare vaccinazione anti-pneumococcica prima dell'inizio con terapia con anti-TNF

Pneumococcal vaccination should be a routine procedure in the management of patients treated with TNF-α antagonists and it should be the responsibility of the physician prescribing the TNF-α antagonist to ensure each patient receive the vaccine

Wright SA et al., Rheumatology 2004, 43:523

Vaccinazioni e autoimmunità: sicurezza

Anti-pneumococco: nessun incremento dell'attività di malattia in pz con LES, artrite psoriasica, Sjögren syndrome

Anti-HBV: no aumento dello score di malattia in pz con AR, in 28 pz con LES, in 13 pz con Behçet

Anti-influenzale: No aumento di riacutizzazioni di LES (vaccinati 11.5% vs non vaccinati 10.5%), sclerosi sistemica o nella sindrome di Sjogren dopo vaccinazione

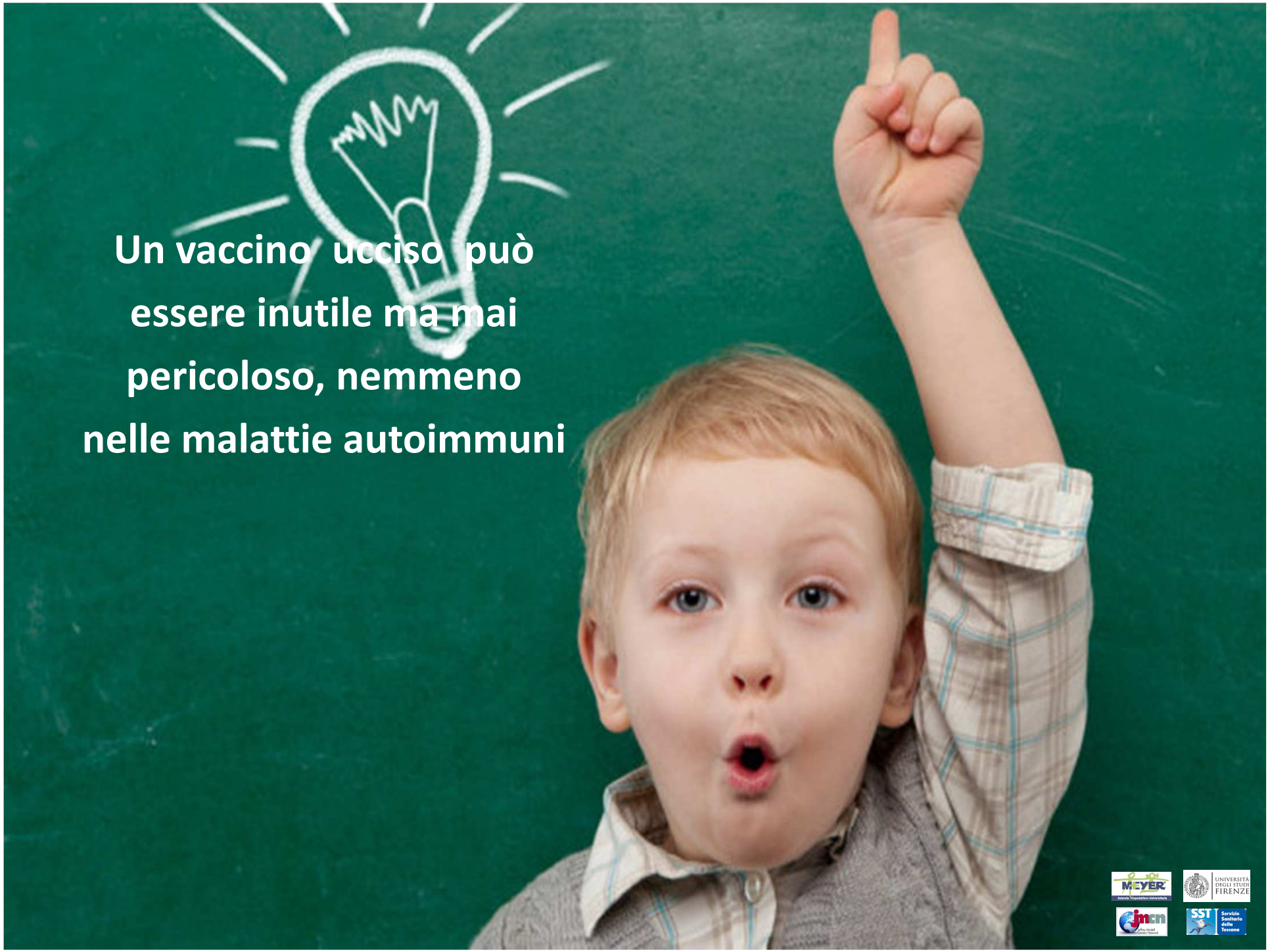
Kuruma, Lupus 2007
Lu C. Vaccine 2011
Shakra J Rheumatol 2002,

Immunodepressione iatrogena: i farmaci biologici

Per i vaccini uccisi meglio vaccinare prima perché possono essere meno efficaci in corso di terapia

Per i vaccini vivi SI PUÒ SOLO :

1. **vaccinare prima, almeno 4 settimane prima dell'inizio della terapia;**
2. **dopo 1-6 mesi dalla fine della terapia, se in dubbio eseguire test immunologici quantitativi e qualitativi**


Un vaccino ucciso può
essere inutile ma mai
pericoloso, nemmeno
nelle malattie autoimmuni

Se abbiamo qualche dubbio sulla somministrazione,
piuttosto che rinunciare completamente possiamo confrontarci con altri colleghi che effettuano le
"vaccinazioni difficili"

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