TRAINING CENTER ROMA (Corso malattie emorragiche)
4/8 giugno 2018 – Policlinico A. Gemelli (Roma)

Vaccinazioni ed emofilia si/no

Dott. Matteo Luciani

Centro Emostasi e Trombosi

Dipartimento Ematologia Oncologia e Terapia Genica e Cellulare

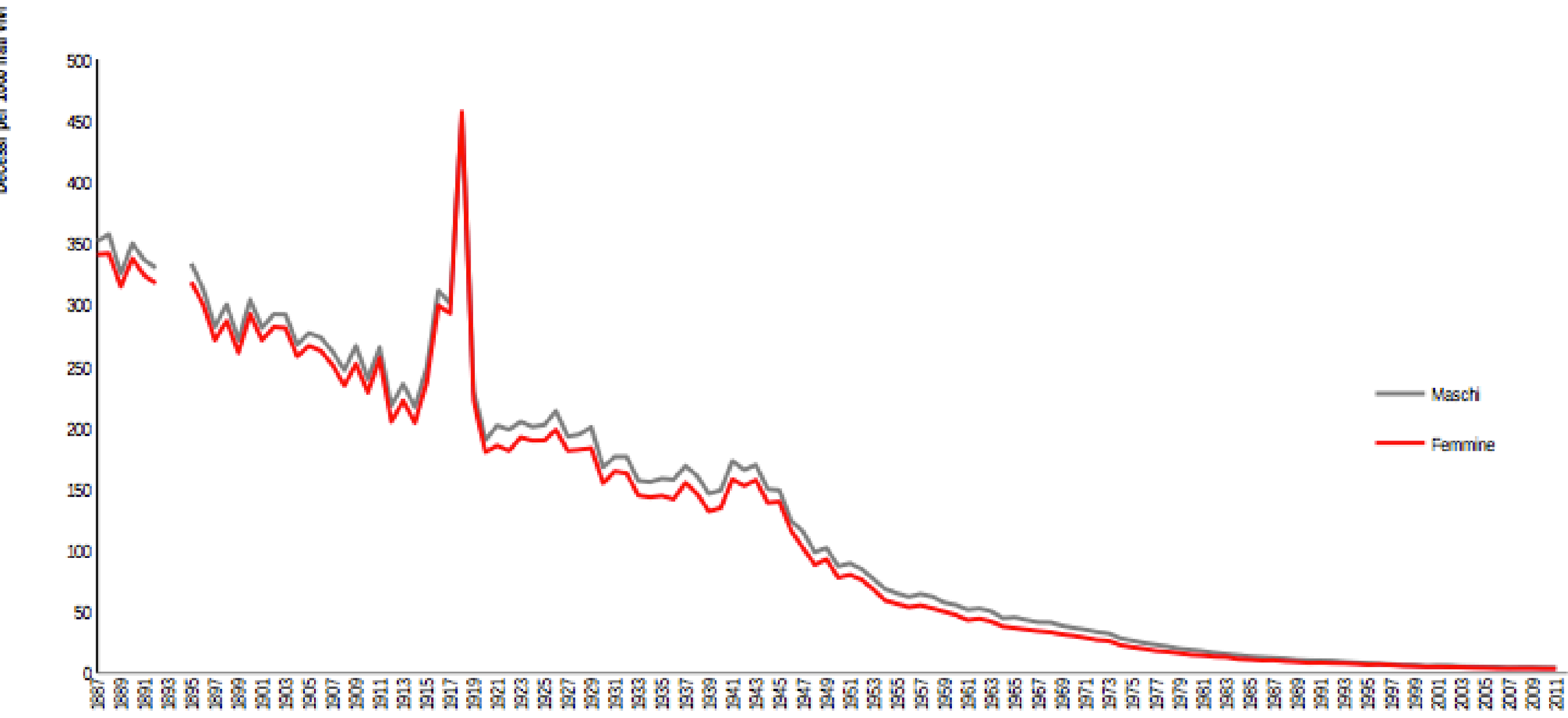
IRCCS Ospedale Pediatrico Bambino Gesù

matteo.luciani@opbg.net

Emofilia e vaccinazioni

- Le vaccinazioni previste per i bambini con MEC sono identiche a quelle della popolazione generale?
- C’è rischio di comparsa di inibitori? Come comportarsi con la profilassi?
- E’ necessario modificare il calendario temporalmente?
- Come vaccinare?

Mortalità infantile<5 anni
(n° decessi per 1000 nati vivi)



EPIDEMIC INFLUENZA
(SPANISH)

This Disease is Highly Communicable.
It May Develop into a Severe Pneumonia.

There is no medicine which will prevent it.

Keep away from public meetings, theatres and other places where crowds are assembled.

Keep the mouth and nose covered while coughing or sneezing.

When a member of the household becomes ill, place him in a room by himself.

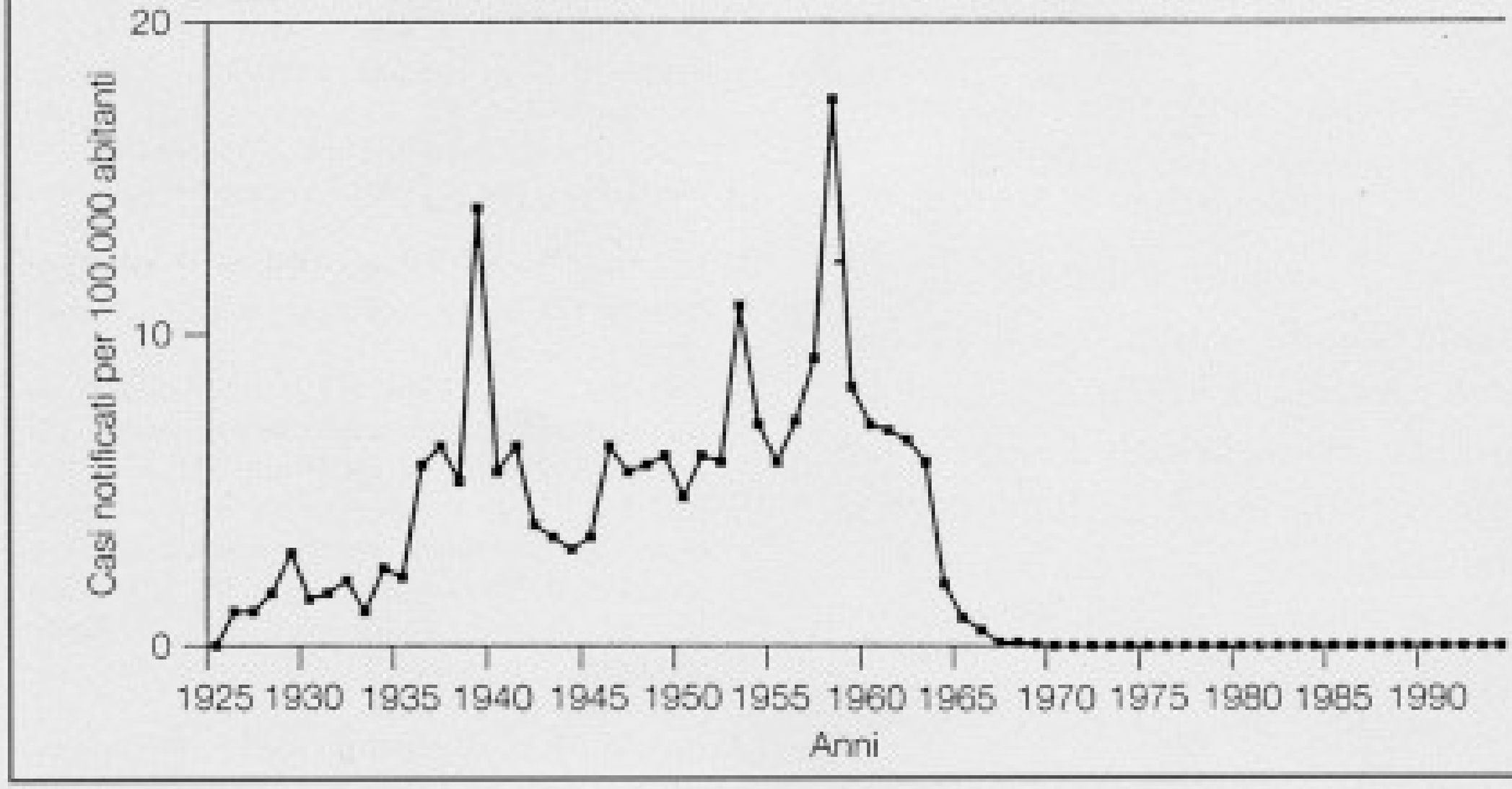
The room should be warm, but well ventilated.

The attendant should put on a mask before entering the room of those ill of the disease.

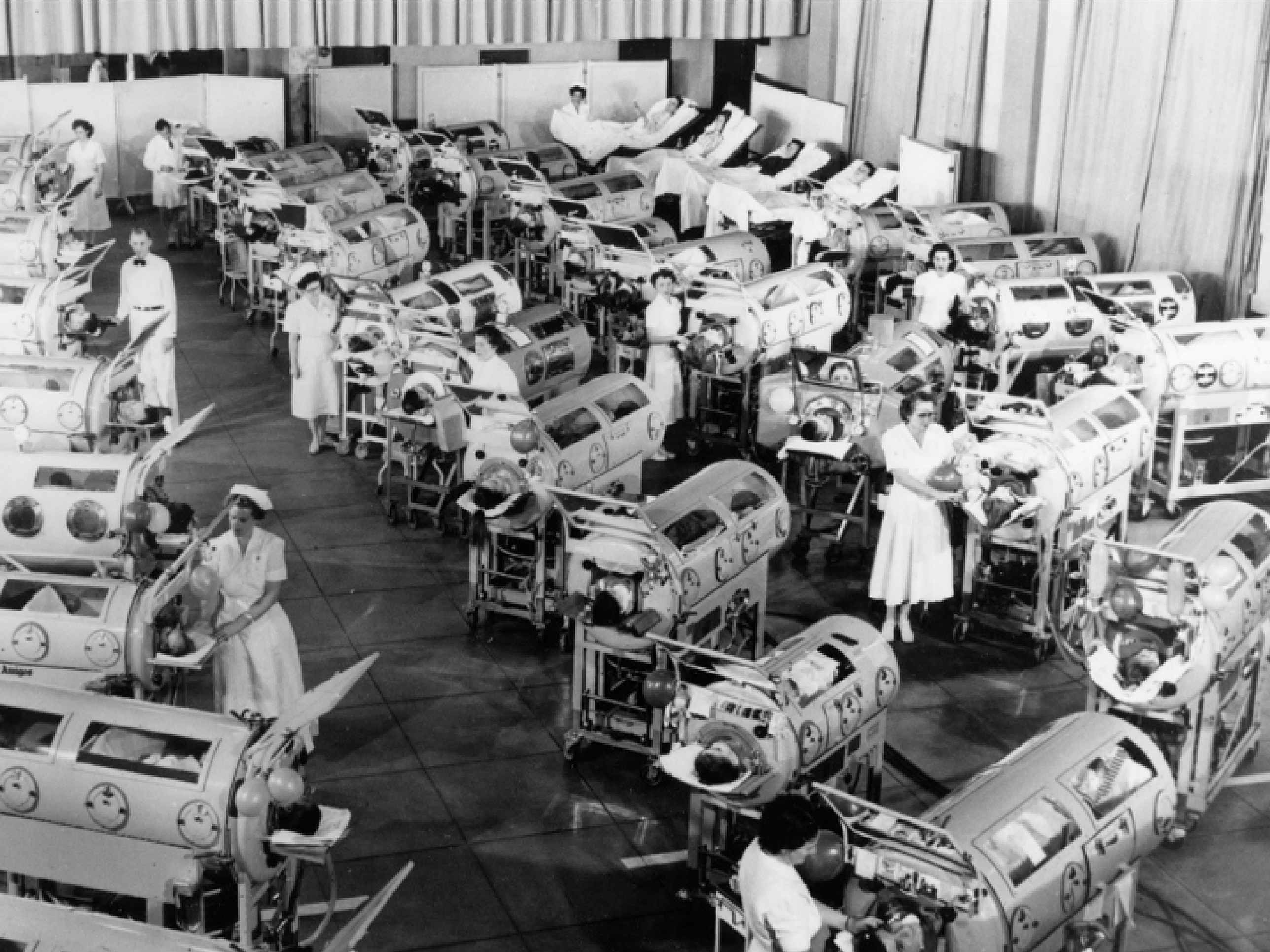
TO MAKE A MASK

ISSUED BY THE PROVINCIAL BOARD OF HEALTH

Poliomielite: morbosità in Italia



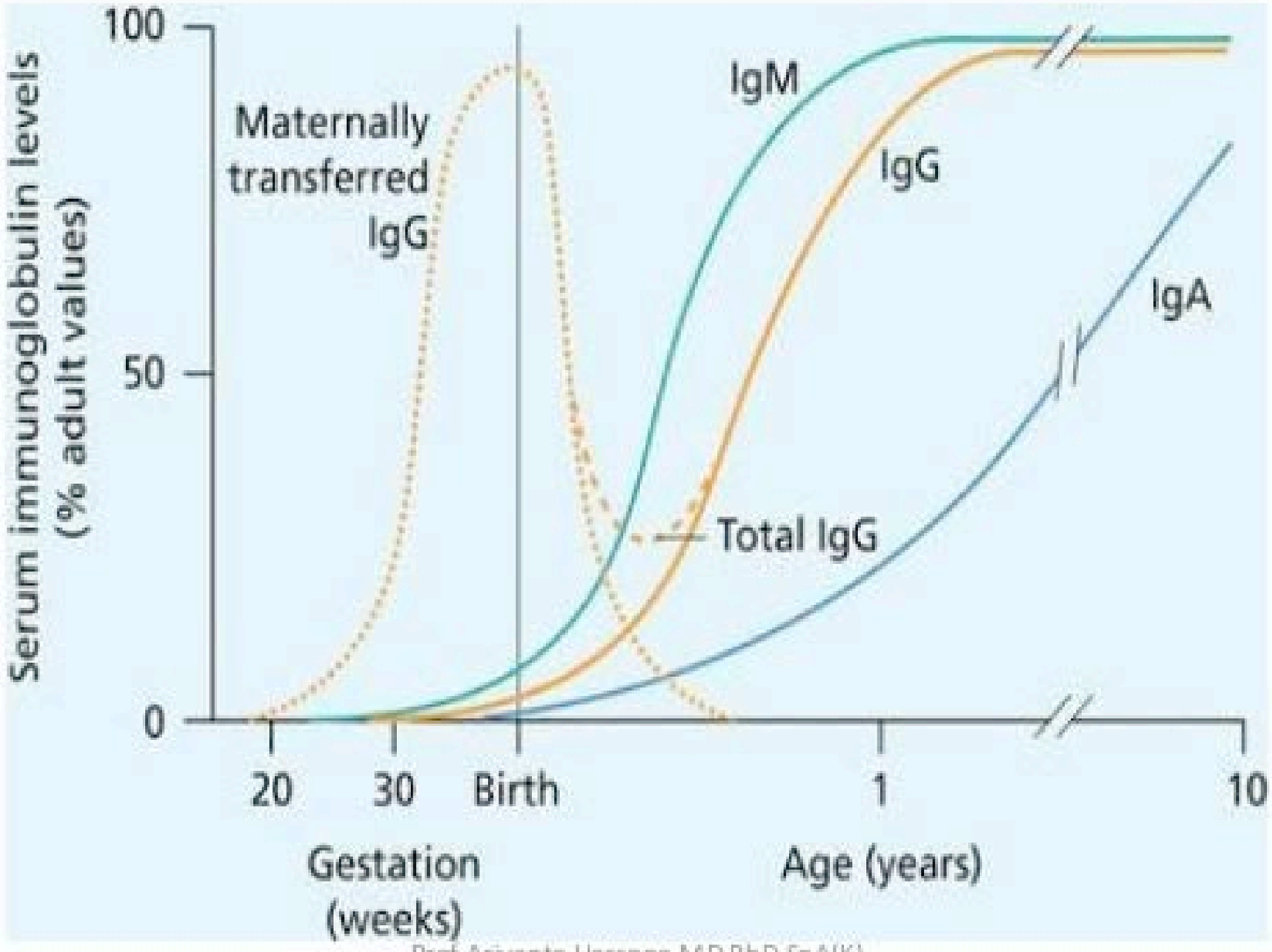
Fonte: Ministero della Sanità - Dipartimento di Prevenzione



Il calendario vaccinale

Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	⇨	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni	Soggetti ad aumentato rischio
DTPa**		DTPa		DTPa			DTPa				DTPa***	dTpaIPV	1 dose dTpa**** ogni 10 anni			(1)
IPV		IPV		IPV			IPV				IPV					
Epatite B	EpB- EpB*	Ep B		Ep B			Ep B									(2)
Hib		Hib		Hib			Hib									(3)
Pneumococco		PCV		PCV			PCV								PCV+PPSV	(4)
MPRV								MPRV			MPRV					(6)
MPR								*oppure* MPR + V			*oppure* MPR + V					(5)
Varicella																(6)
Meningococco C								Men C[§]				Men ACWY coniugato				(7)
Meningococco B*^		Men B	Men B		Men B			Men B								
HPV												HPV°: 2-3 dosi (in funzione di età e vaccino)				(8)
Influenza															1 dose all'anno	(9)
Herpes Zoster															1 dose#	(10)
Rotavirus		Rotavirus## (due o tre dosi a seconda del tipo di vaccino)														
Epatite A																(11)

Figure 2
Serum immunoglobulin levels and age



Sintomi – Stati morbosi - Situazioni	Vaccino	Vaccinare?
Disturbo/disordine della coagulazione (es. emofilia, malattia di Von Willebrand)	tutti	si vedi nota

Nota: nei pazienti con disturbi della coagulazione o in terapia anticoagulante è necessario valutare attentamente il rischio di sanguinamento prima di somministrare qualsiasi vaccino per via intramuscolare.[4]
La via sottocutanea può essere utilizzata solo se l'efficacia è riconosciuta equivalente, negli altri casi deve essere utilizzata la via intramuscolare con le seguenti precauzioni:
-quando possibile, dovrebbe essere ottimizzato il controllo del disturbo della coagulazione prima di seguire la vaccinazione[4]
-nei pazienti in terapia specifica per l'emofilia o terapia simile, la vaccinazione può essere effettuata per via intramuscolare programmando la somministrazione del vaccino dopo breve tempo dalla somministrazione della terapia
-in ogni caso deve essere utilizzato un ago sottile di 23 gauge o meno e deve essere applicata una pressione ferma sul sito di iniezione per almeno 2 minuti [3,8,11] fino a 5 minuti.[4,123]
Il paziente o i familiari devono essere informati sul rischio di ematoma da iniezione. Vedi anche "Anticoagulante" - sezione D.

GUIDA ALLE CONTROINDICAZIONI ALLE VACCINAZIONI

Quinta edizione - Luglio 2017

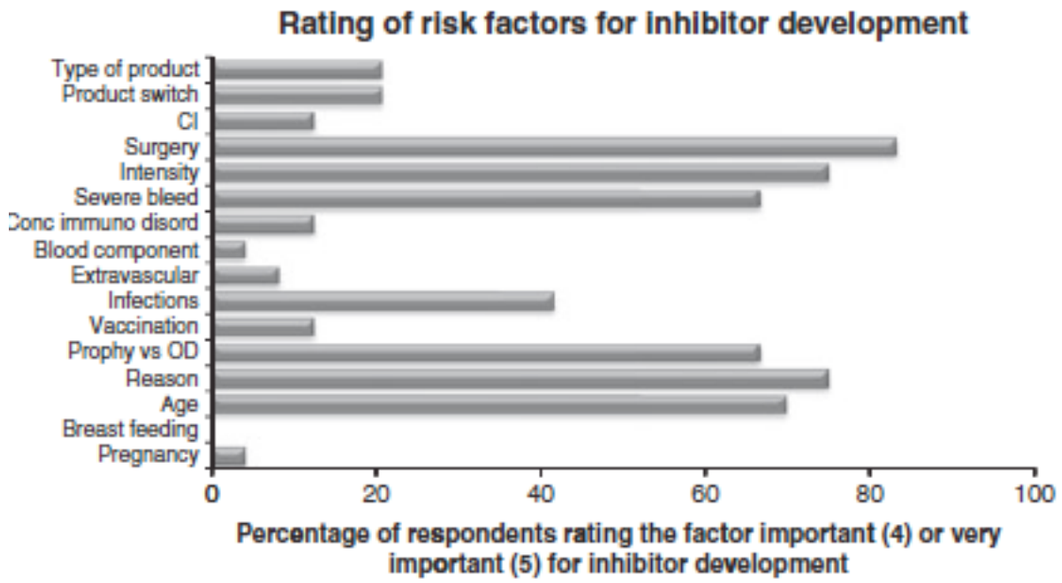
A cura di Giovanni Gallo, Rosanna Mel, Elisa Ros e Antonietta Filia

Emofilia, vaccinazioni e inibitori: quali i dati della letteratura

Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report

J. ASTERMARK,* C. ALTISENT,† A. BATOROVA,‡ M. J. DINIZ,§ A. GRINGERI,¶ P. A. HOLME,** A. KARAFOULIDOU,†† M. F. LOPEZ-FERNÁNDEZ,‡‡ B. M. REIPERT,†§§ A. ROCINO,¶¶ M. SCHIAVONI,*** M. VON DEPKA,††† J. WINDYGA‡‡‡ and K. FIJNVANDRAAT§§§ ON BEHALF OF THE EUROPEAN HAEMOPHILIA THERAPY STANDARDISATION BOARD (EHTSB)

Haemophilia (2010), **16**, 747–766



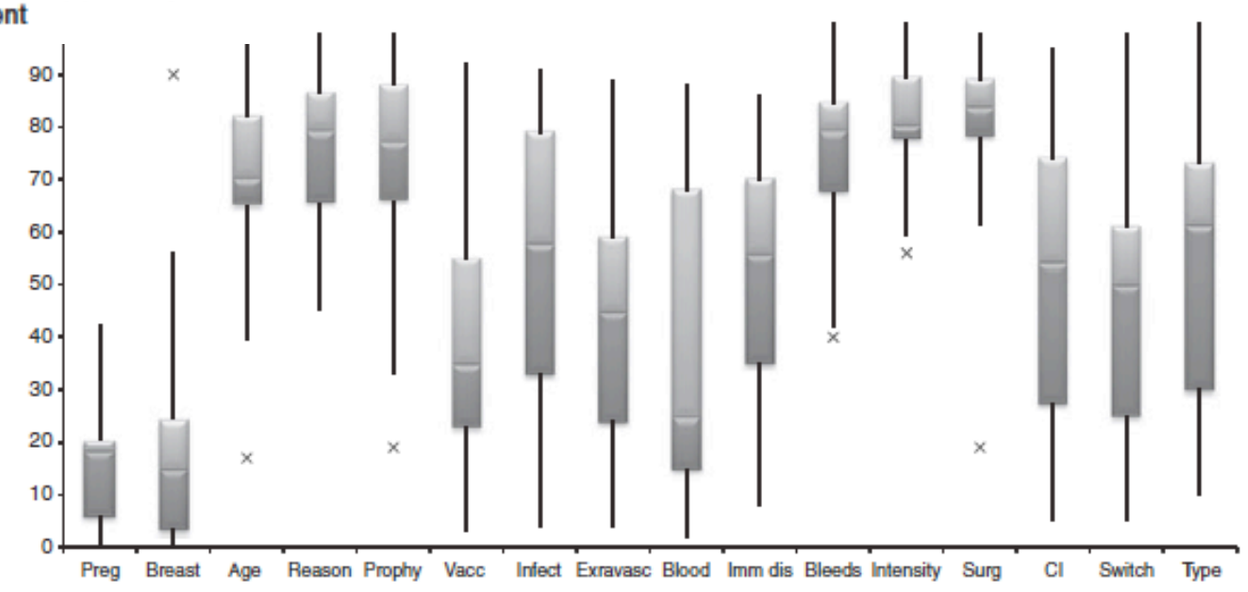


Fig. 2. Results of the survey of the European Haemophilia Therapy Standardisation Board group. Participants (n = 24) were asked to rate how each factor influenced their clinical practice on a scale of 0–100.

Published in final edited form as:
Expert Rev Clin Immunol. 2012 May ; 8(4): 311–317. doi:10.1586/eci.12.21.

The evolution of the danger theory

Polly Matzinger
Ghost Laboratory, Laboratory of Cellular & Molecular Immunology, National Institute of Allergy & Infectious Diseases/NIH, Building 4 Room 211, Bethesda, MD 20894, USA pcm@helix.nih.gov

Against the self–non-self theory, the danger theory claims that self constituents can trigger an immune response, if they are dangerous (e.g., cellular stress, some autografts, etc.); and non-self constituents can be tolerated, if they are not dangerous (e.g. the fetus or commensal bacteria)

Danger theory

“if you could give the clotting factor at a time when other alarm signals are not present, an immune response should not be raised, even though the protein is foreign.”

“avoided times at which the child was bleeding or bruised, receiving a vaccine, undergoing surgery, or experiencing a cold or other illness. “

Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study

Samantha C. Gouw,[1,2] Johanna G. van der Bom,[3] and H. Marijke van den Berg,[1] for the CANAL Study group

[1]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, the Netherlands; [2]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

The CANAL Study (Concerted Action on Neutralizing Antibodies in severe hemophilia A) was designed to describe the relationship between treatment characteristics and inhibitor development in previously untreated patients with severe hemophilia A. This multicenter retrospective cohort study investigated 366 consecutive patients born between 1990 and 2000. The outcome was clinically relevant inhibitor development, defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery. Eighty-seven (24%) patients developed inhibitors (69 high titer [19%]). The incidence of inhibitors appeared to be associated with age at first treatment, decreasing from 41% for those treated within the first month of age to 18% in those treated after 18 months; after adjustment for treatment intensity, this association largely disappeared. Surgical procedures and peak treatment moments at start of treatment increased inhibitor risk (relative risk [RR], 3.7; 95% confidence interval [CI], 2.0-7.1; and RR, 3.3; CI, 2.1-5.3, respectively). Regular prophylaxis was associated with a 60% lower risk than on-demand treatment (RR, 0.4; CI, 0.2-0.8). Our findings suggest that the previously reported associated between an early age at first exposure and the risk of inhibitor development is largely explained by early, intensive treatment. The latter appears to be an independent risk factor for inhibitor development. In addition, early, regular prophylaxis may protect patients with hemophilia against the development of inhibitors. (Blood. 2007;109:4648-4654)

Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study

Samantha C. Gouw,[1] H. Marijke van den Berg,[2] Kathelijn Fischer,[2,3] Günter Auerswald,[4] Manuel Carcao,[5] Elizabeth Chalmers,[6] Hervé Chambost,[7] Karin Kurnik,[8] Ri Liesner,[9] Pia Petrini,[10] Helen Platokouki,[11] Carmen Altisent,[12] Johannes Oldenburg,[13] Beatrice Nolan,[14] Rosario Pérez Garrido,[15] M. Elisa Mancuso,[16] Anne Rafowicz,[17] Mike Williams,[18] Niels Clausen,[19] Rutger A. Middelburg,[20] Rolf Ljung,[21] and Johanna G. van der Bom[20,22] for the PedNet and Research of Determinants of INhibitor development (RODIN) Study Group

BLOOD, 16 MAY 2013 • VOLUME 121, NUMBER 20

Recombinant and plasma-derived factor VIII products conferred similar risks of inhibitor development, and the content of von Willebrand factor in the products and switching among products were not associated with the risk of inhibitor development. Second-generation full-length recombinant products were associated with an increased risk, as compared with third-generation products.

THROMBOSIS AND HEMOSTASIS

Concurrent influenza vaccination reduces anti-FVIII antibody responses in murine hemophilia A

Jesse D. Lai,[1] Paul C. Moorehead,[2,3] Kate Sponagle,[1] Katharina N. Steinitz,[4] Birgit M. Reipert,[4] Christine Hough,[1] and David Lillicrap[1]

[1]Department of Pathology & Molecular Medicine, Queen's University, Kingston, ON, Canada; [2]Discipline of Pediatrics, Faculty of Medicine, Memorial University, St. John's, NL, Canada; [3]Section of Pediatric Hematology/Oncology, Janeway Children's Health and Rehabilitation Centre, St. John's, NL, Canada; and [4]Baxalta Innovation GmbH, Vienna, Austria

Key Points

- Vaccination against influenza, with and without the adjuvant MF59, decreases the risk of inhibitor development in HA mice.
- Decreased FVIII immunogenicity may be attributed to antigenic competition via T-cell chemotaxis toward the site of vaccination.

Inflammatory signals such as pathogen- and danger-associated molecular patterns have been hypothesized as risk factors for the initiation of the anti–factor VIII (FVIII) immune response seen in 25% to 30% of patients with severe hemophilia A (HA). In these young patients, vaccines may be coincidentally administered in close proximity with initial exposure to FVIII, thereby providing a source of such stimuli. Here, we investigated the effects of 3 vaccines commonly used in pediatric patients on FVIII immunogenicity in a humanized HA murine model with variable tolerance to recombinant human FVIII (rhFVIII). Mice vaccinated intramuscularly against the influenza vaccine prior to multiple infusions of rhFVIII exhibited a decreased incidence of rhFVIII-specific neutralizing and non-neutralizing antibodies. Similar findings were observed with the addition of an adjuvant. Upon exposure to media from influenza- or FVIII-stimulated lymph node or splenic lymphocytes, naïve $CD4^+$ lymphocytes preferentially migrated toward media from influenza-stimulated cells, indicating that antigen competition, by means of lymphocyte recruitment to the immunization site, is a potential mechanism for the observed decrease in FVIII immunogenicity. We also observed no differences in incidence or titer of rhFVIII-specific antibodies and inhibitors in mice exposed to the live-attenuated measles-mumps-rubella vaccine regardless of route of administration. Together, our results suggest that concomitant FVIII exposure and vaccination against influenza does not increase the risk of inhibitor formation and may in fact decrease anti-FVIII immune responses. (*Blood.* 2016;127(26):3439-3449)

"might in fact have had a tolerogenic effect."

Accepted: 19 November 2017
DOI: 10.1111/hae.13387

ORIGINAL ARTICLE

WILEY Haemophilia

Vaccinations are not associated with inhibitor development in boys with severe haemophilia A

H. Platokouki[1] | K. Fischer[2] | S. C. Gouw[3] | A. Rafowicz[4] | M. Carcao[5] |
G. Kenet[6] | R. Liesner[7] | K. Kurnik[8] | G. E. Rivard[9] | H. M. van den Berg[10]

- Sono stati inclusi 375 PUP con emofilia A grave (registro PedNet) vaccinati tra 1 e 75 giornate di esposizione o che abbiano sviluppato inibitori

- I bambini sono stati divisi per finestra temporale di esposizione al Fattore VIII in rapporto alla vaccinazione (24, 72 o 120 ore) e per non esposizione

- 77/375 (20,5%) hanno sviluppato inibitori (47 ad alto titolo)

- non è stata rilevata alcuna differenza statisticamente significativa relativamente allo sviluppo di inibitori tra i soggetti vaccinati esposti e non esposti al Fattore VIII

Come vaccinare?

- Quale via?
- Somministrare i vaccini per via alternativa è “off label”
- E’ necessario infondere il fattore carente quando si effettua una vaccinazione per via intramuscolare?

Modalità di somministrazione intramuscolo o sottocute?

1. **Persons with bleeding disorders should be vaccinated, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless covered by infusion of clotting factor concentrates. (Level 4) [17]**
2. If intramuscular injection is to be given:
   - It is best done soon after a dose of factor replacement therapy.
   - An ice pack can be applied to the injection area for five minutes before injection.
   - The smallest gauge needle available (usually 25-27 gauge) should be used.
   - Pressure should be applied to the injection site for at least five minutes [18].

WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL
WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

Accepted: 26 June 2017
DOI: 10.1111/hae.13316

ORIGINAL ARTICLE

WILEY Haemophilia

Subcutaneous diphtheria and tetanus vaccines in children with haemophilia: A pilot study and review of the literature

B. A. Schaefer | R. A. Gruppo | E. S. Mullins | C. Tarango

NATIONAL HEMOPHILIA FOUNDATION
www.hemophilia.org

MASAC Document #221

MASAC RECOMMENDATIONS ON ADMINISTRATION OF VACCINES TO INDIVIDUALS WITH BLEEDING DISORDERS

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on October 5, 2013, and adopted by the NHF Board of Directors on October 6, 2013.

1. Centers for Disease Control and Prevention (CDC) Guidelines

It is highly recommended (See MASAC Recommendation #218, page 5, Section G.1 and G.2) [1] that patients with bleeding disorders continue to follow the American Academy of Pediatrics' and CDC's vaccine recommendation route and schedule for their age. These recommendations can be found on the CDC website as follows:

2. Protocol for Administration of Vaccines

MASAC recommends that when giving immunizations, the following procedures be followed:

1. A fine-gauge needle (23 gauge or smaller caliber) should be used. [2]
2. Firm pressure should be applied to the site for at least 2 minutes without rubbing.[2]
3. The patient and/or caregiver should be informed that there is risk of hematoma development at the injection site.[2]
4. Anticipatory guidance should be given regarding when to call the physician or HTC regarding any adverse reactions such as hematoma, fever, warmth, redness.[2]
5. For pain/fever relief [2], avoid aspirin and NSAIDS (such as ibuprofen, naproxen sodium) because of the potential risk of bleeding. Acetaminophen is a safe alternative, but should be used with caution, especially in individuals at risk for liver disease.
6. If the patient is receiving prophylaxis treatment for hemophilia, vaccination could be given within one day afterwards to decrease the risk of developing a hematoma.[2]

A. Pneumococcal polysaccharide (PPSV) [3]
B. Polio, inactivated (IPV) [3]
C. Hepatitis A [4]
D. Hepatitis B [5-7]

Materials and Methods

Total patients (number)	27
Current age (years)	15.2 ± 3.4
Moderate/Severe Hemophilia A (number)	9/18
Known diagnosis at birth (number)	9
Median age at diagnosis (months)	5

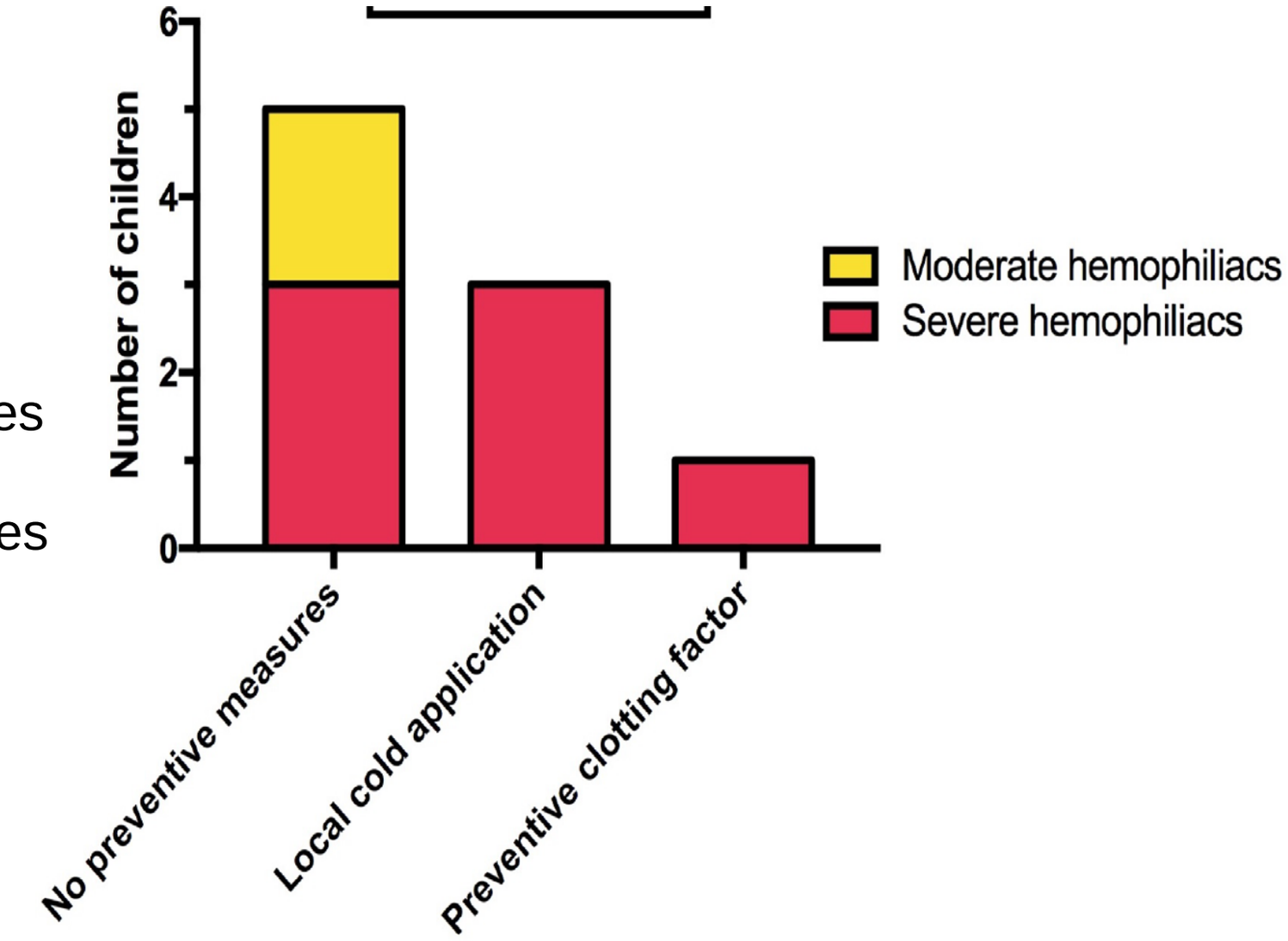
We explored the type of vaccinations, the method of injection, the development of hematomas and whether a medical evaluation was required. Data were confirmed by phone interviews and recorded on a standardized questionnaire.

Patients diagnosed at birth

9 children
2 moderate
7 severe

- 4 adopted preventive measures

- 5 use any preventive measures



NONE developed hematomas after IM vaccines

Events occured in hemophiliac children not yet diagnosed at first vaccine dose

18 patients

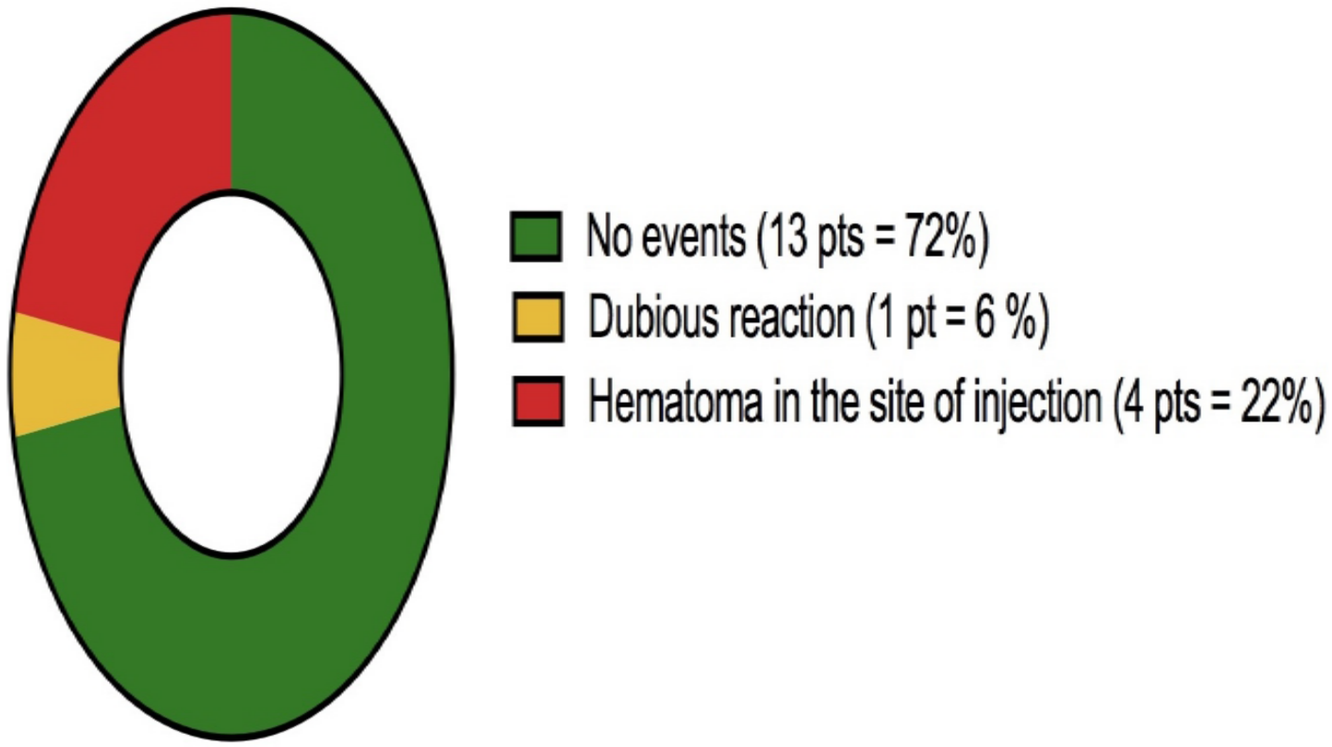
7 moderate

11 severe

- 13 patients did not present any event,

- 1 child displayed a dubious reaction,

- 4 children developed hematomas in the site of injection after the first dose, requiring medical evaluation

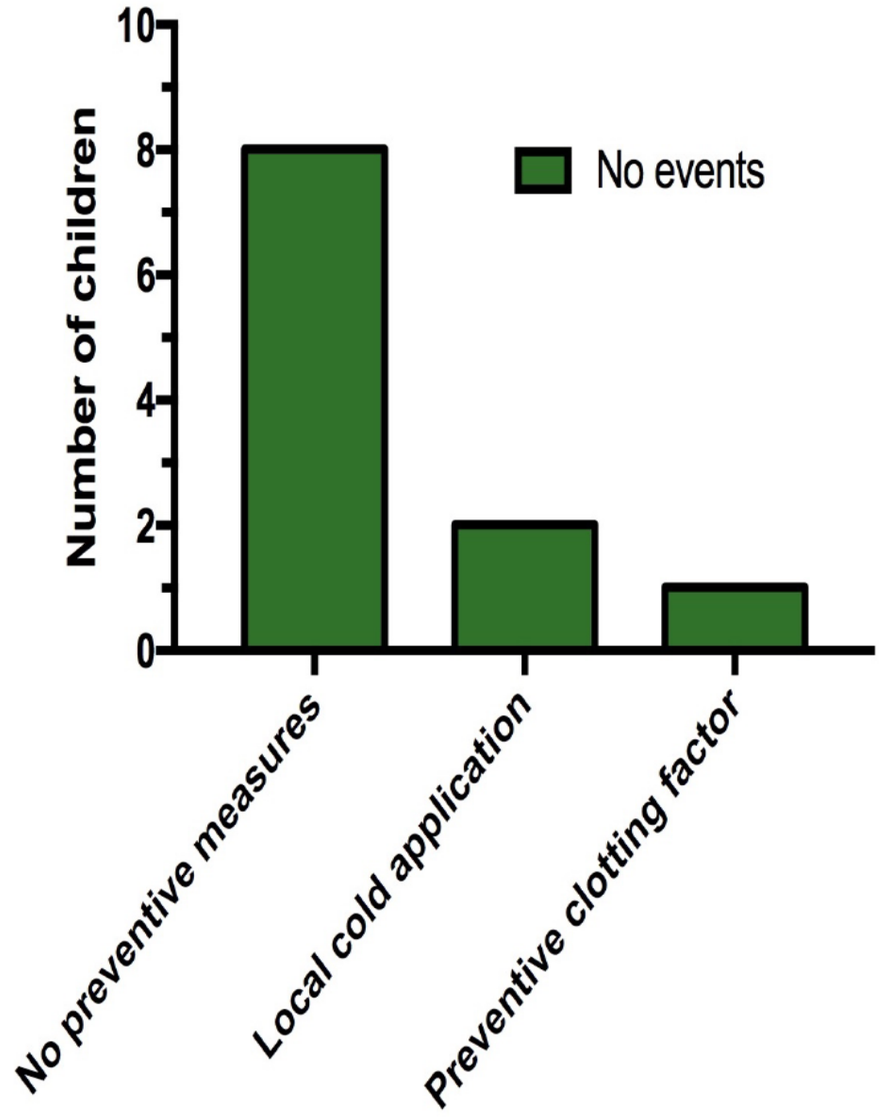


Thereafter among the 11 patients patients affected by **severe** Hemophilia A :

- 8 use any preventive measures

- 3 adopted preventive measures

Patients with **moderate** hemophiliacs (7 patients) did not adopt any preventive measures at next administrations



NONE developed hematomas after IM vaccines

Conclusioni

- I bambini affetti da MEC devono essere vaccinati secondo calendario, senza ritardi ingiustificati
- Non ci sono evidenze della letteratura relativamente alla comparsa di inibitori in pazienti trattati col fattore carente e sottoposti a vaccinazioni
- E’ preferibile la somministrazione sottocute; quando non possibile, adottare misure di prevenzione (ghiaccio, ago sottile)
- Se il bimbo è in profilassi, effettuare la vaccinazione il più precocemente possibile rispetto all’infusione del fattore carente
- Se il bimbo non è in profilassi da valutare infusione fattore e/o antifibrinolitici dal giorno prima per os