Treatment of primary immunodeficiencies

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Faculty Chairman, Children's Hospital
Iceland

Treatment and prevention of primary immunodeficiencies

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What …..

…. can we use to treat or prevent infections

1. Antibiotics
2. Anti-virals
3. Anti-fungals
4. Immunisations
5. Immunoglobulins
6. Haematological interventions
7. Common sense !

Number of bacteria

Number of bacteria

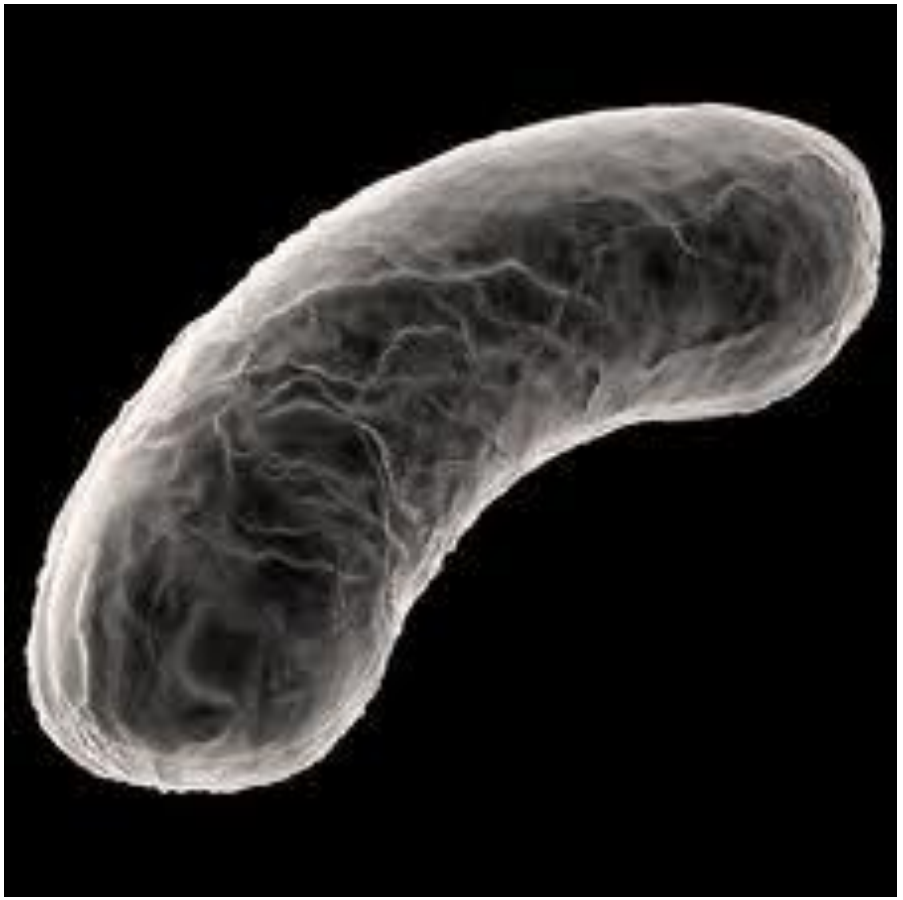
in and on our body: 10^{14}

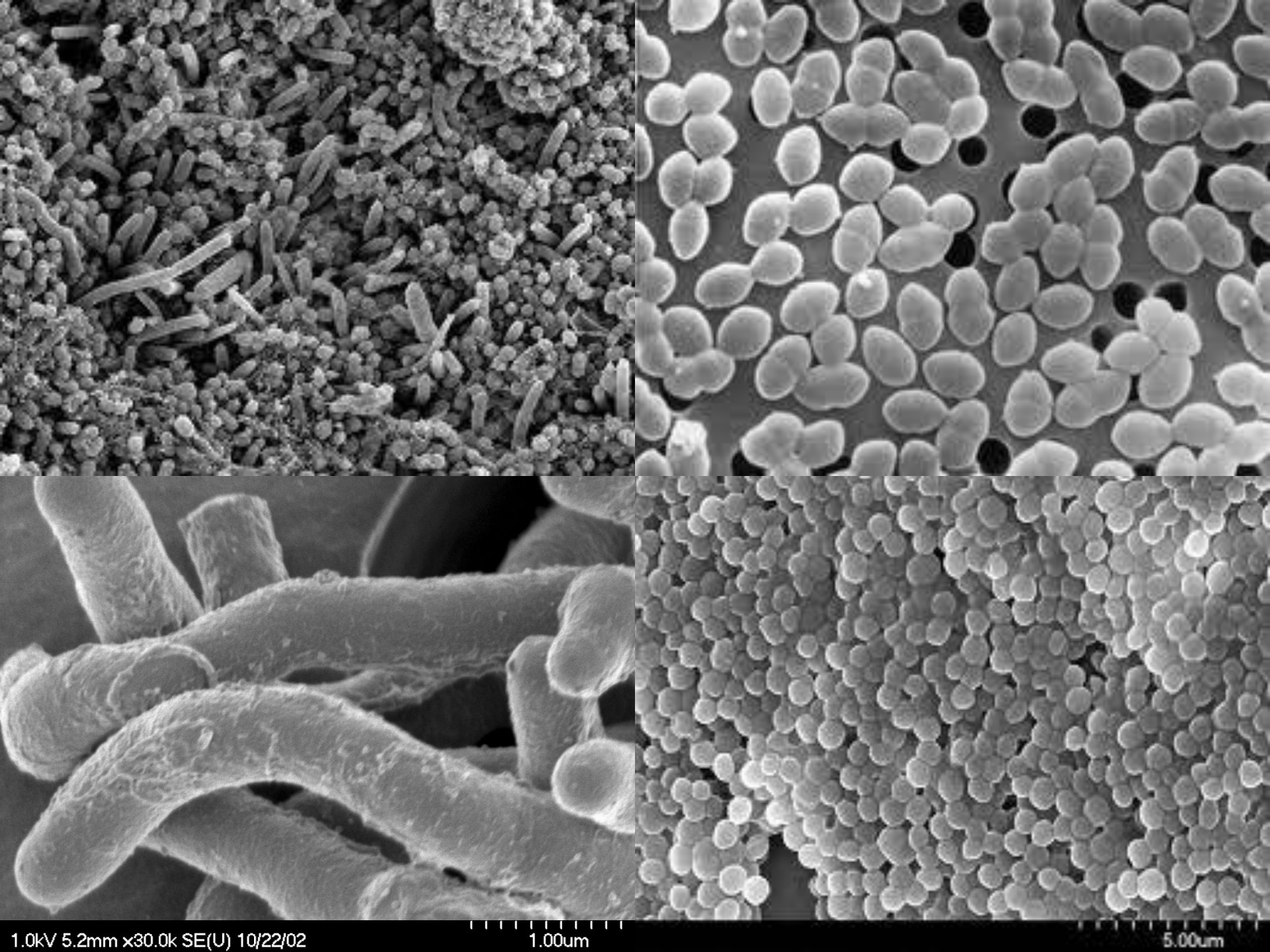
$10^{14} = 100.000.000.000.000$

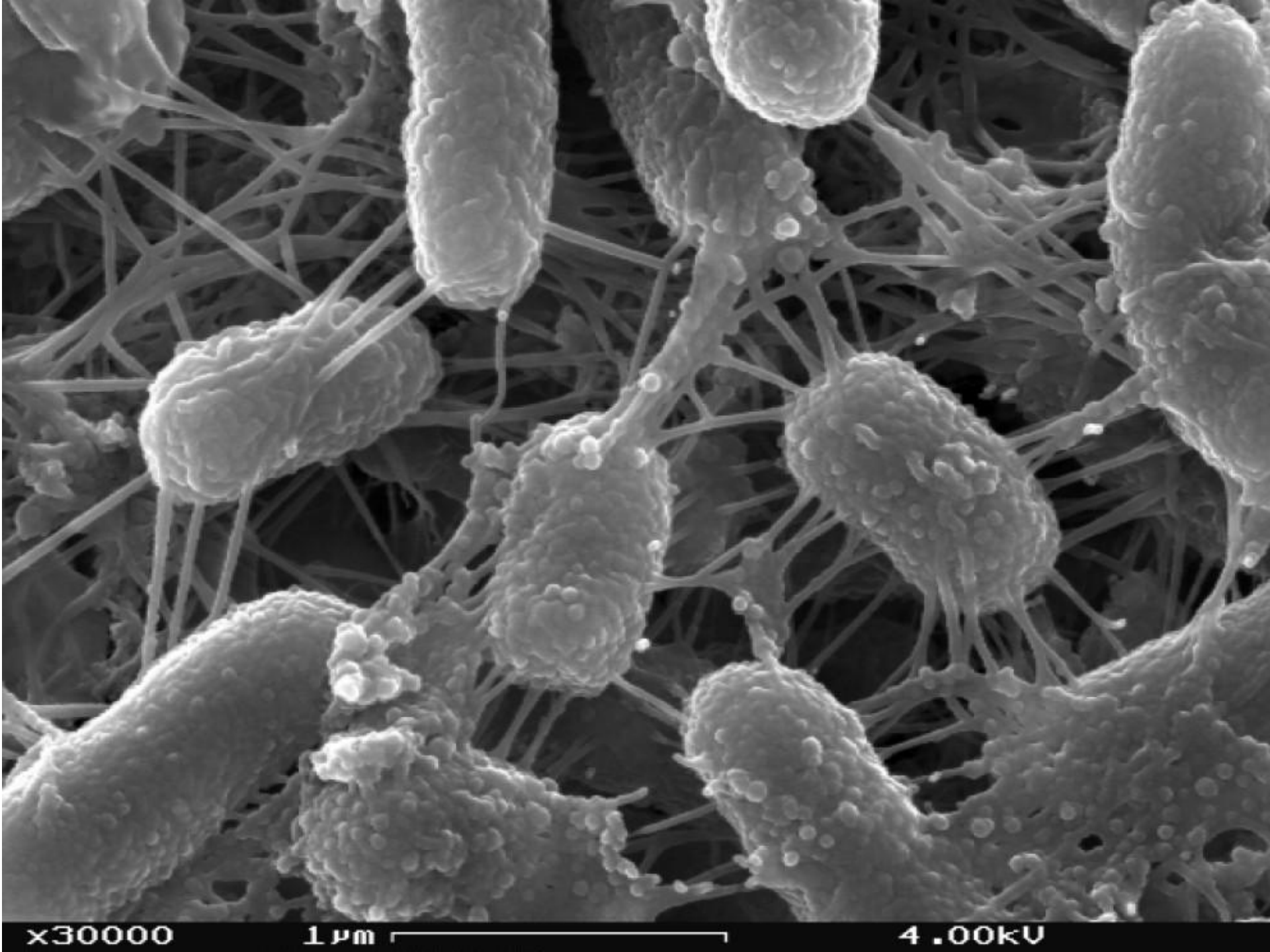
Number of cells: 10^{12}

500 – 1000 different bacteria in and on our body!

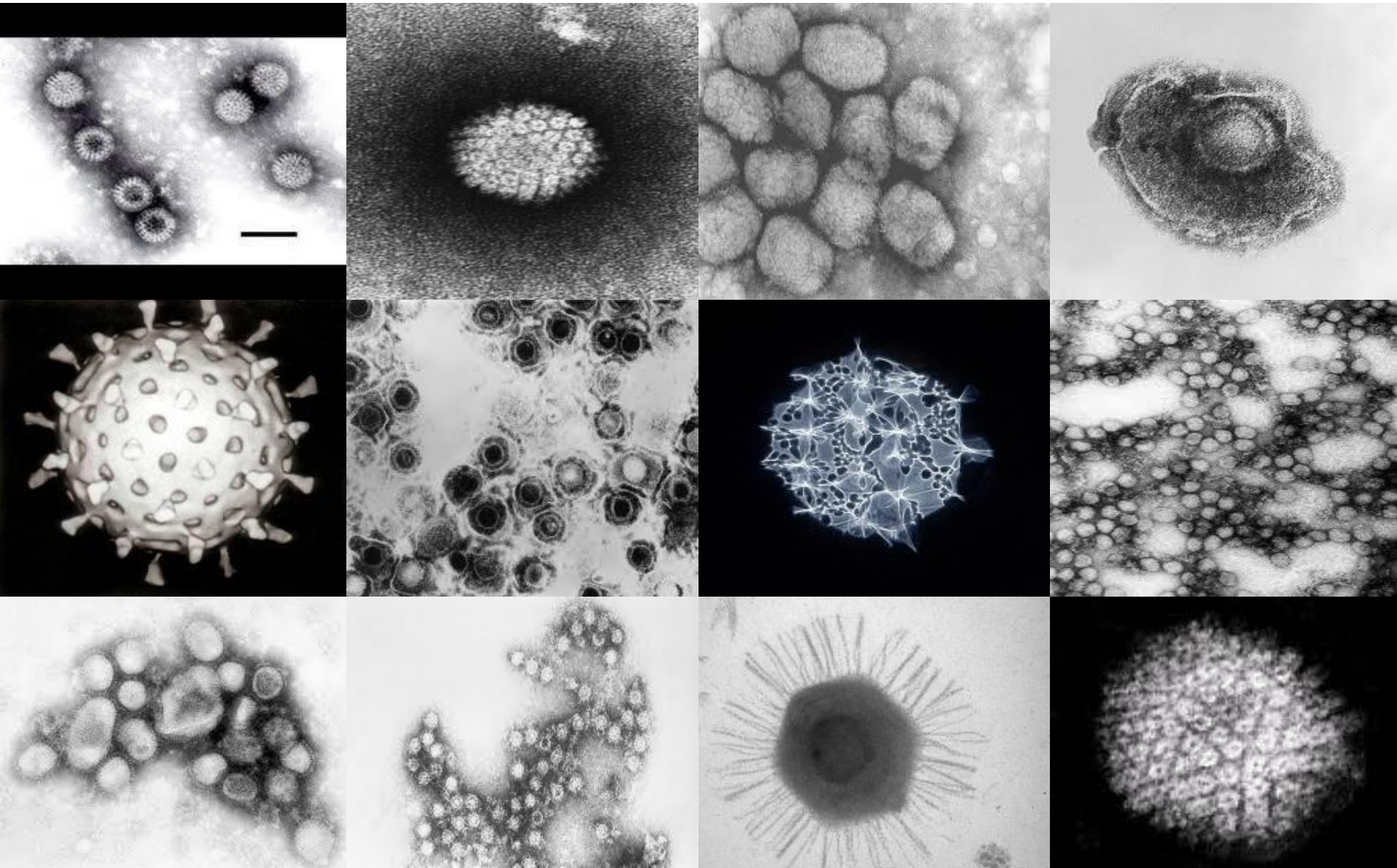
Human race: 8×10^{9}



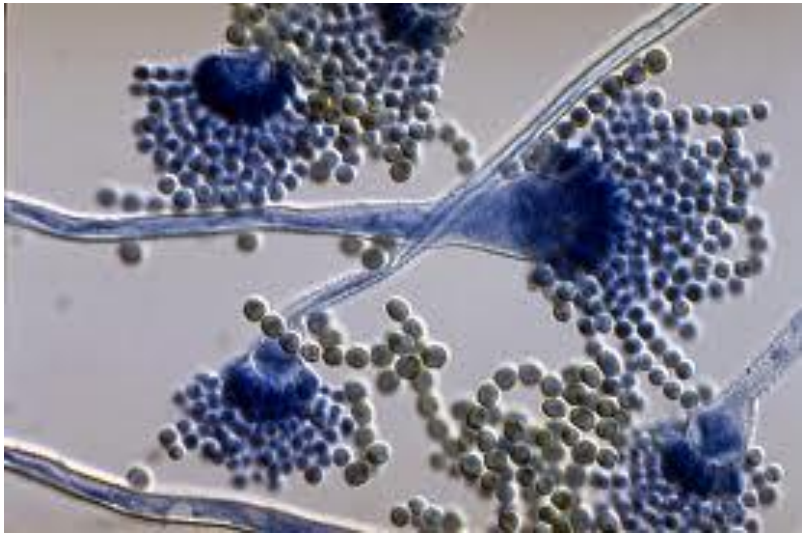

1.0kV 5.2mm x30.0k SE(U) 10/22/02
1.00um
5.00um

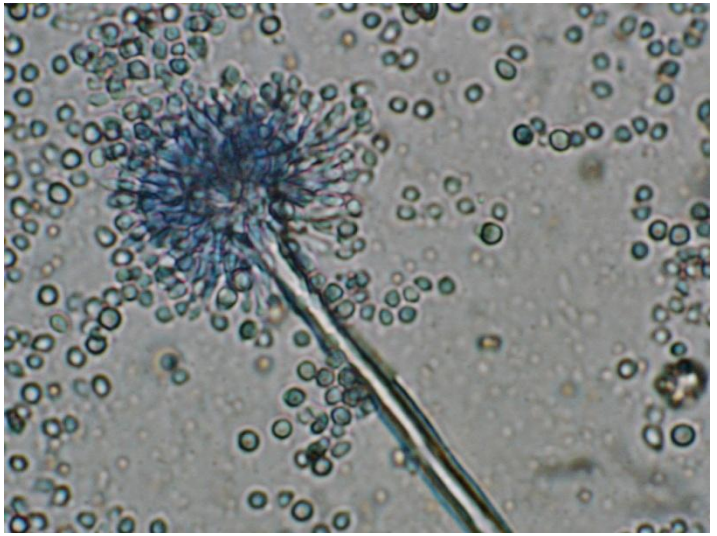

x30000
1μm
4.00kV

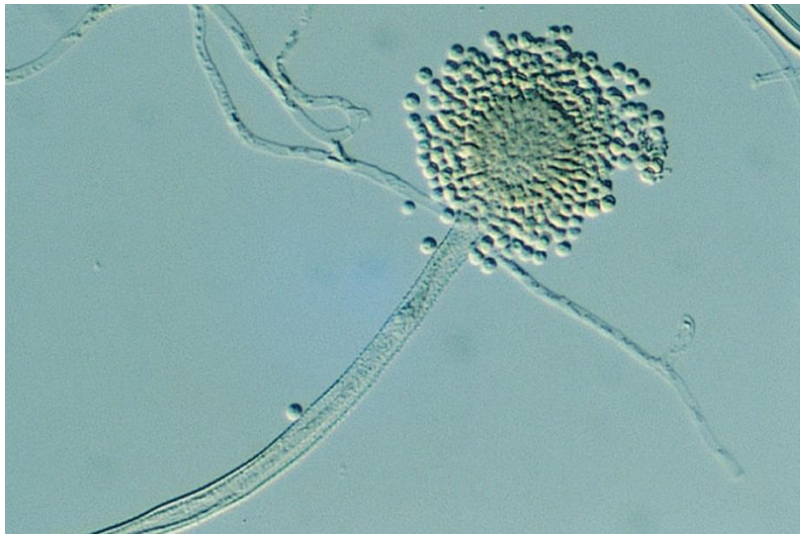
..... And virusses !!!

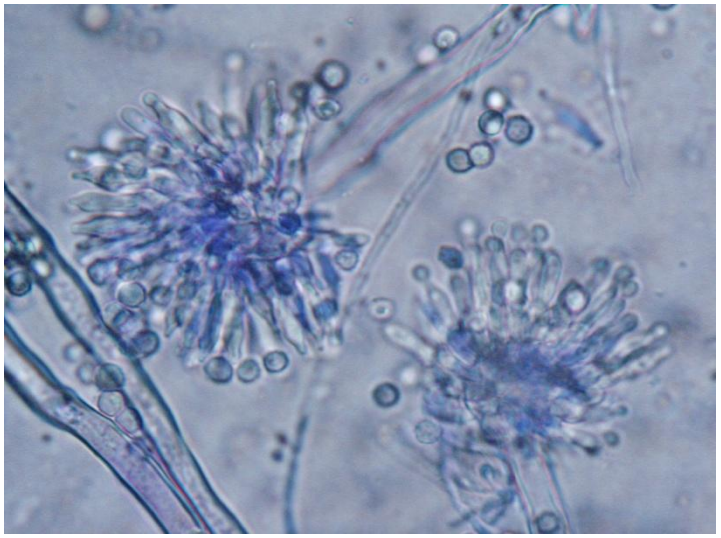


..... and fungi!!



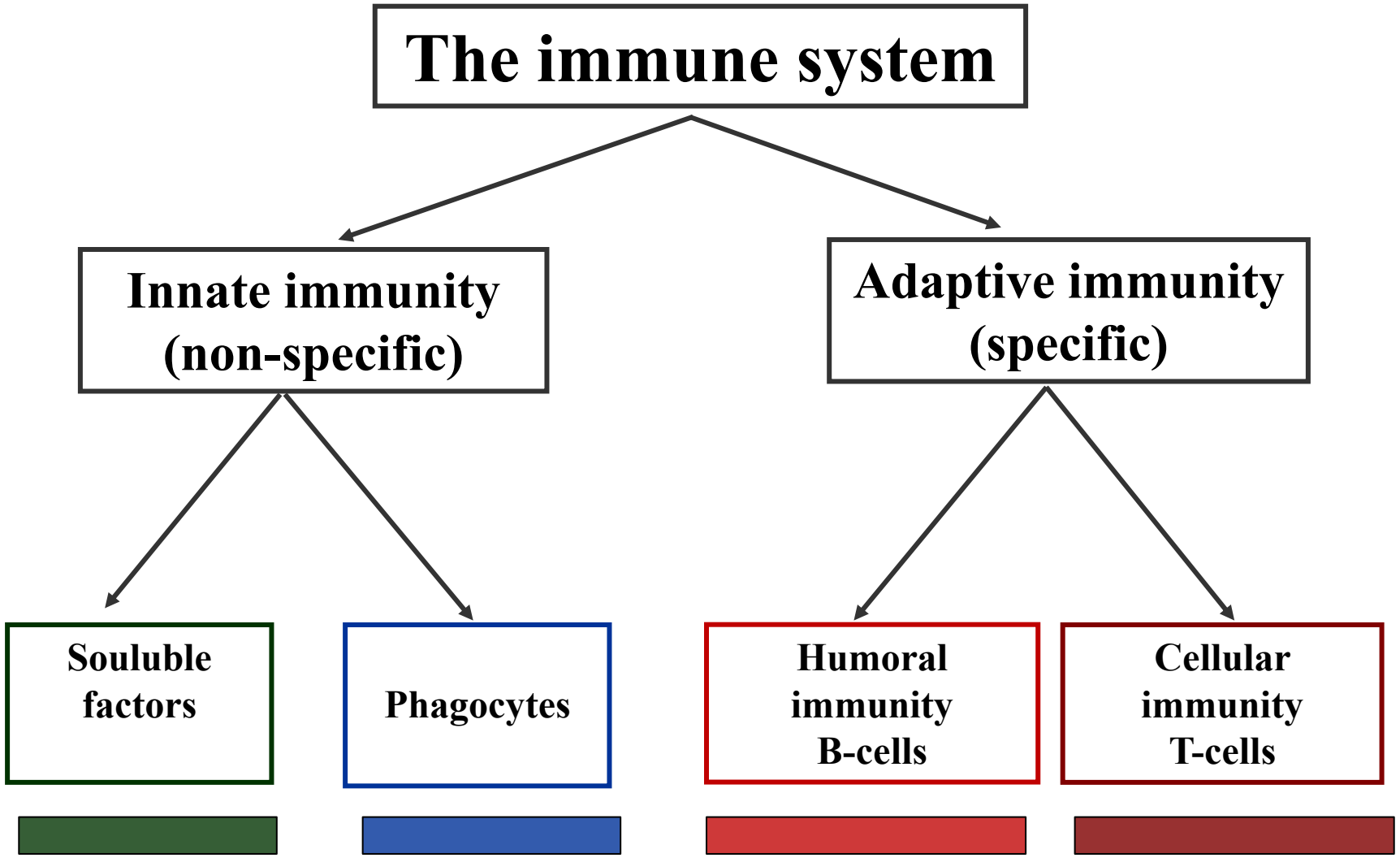







Allspice Berries
Allspice -ground-
Anise Seed
Anise -ground-
Arrowroot Powder
Sweet Basil
Bay Leaf
Bay Leaf -ground-
Caraway Seed
Cardamom Pods
Cardamom Pods -green-
Cardamom Seed
Cardamom -ground-
Cayenne
Celery Flakes
Chili Peppers -crushed-
Chili Powder Blend
Chipotle Chili Peppers
Chamomile
Chervil
Chives
Cilantro
Cinnamon -ground-
Cloves -ground-
Coriander Seed
Coriander -ground-
Cumin Seed
Cumin Seed -ground-
Curry Powder
Dill Weed
Fennel Seed
Fennel Seed -ground-
Fenugreek Seeds
Fenugreek -ground-
Garlic Flakes
Garlic -granulated-
Ginger Root
Ginger Root -ground-
Juniper Berries
Lemon Peel
Lemon Peel -ground-
Lemon Thyme
Mustard Seed
Mustard Seed -brown-
Mustard Seed -ground-
Hot Oriental Mustard
Nutmeg -ground-
Onion Flakes
Onion Granules
Orange Peel
Orange Peel -ground-
Oregano
Sweet Hungarian Paprika
Parsley Flakes
Peppermint
Sweet Green Peppers
Sweet Red Peppers
Poppy Seeds
Poultry Seasoning
Rosemary
Rosemary -ground-
Sage
Sage -rubbed-
Summer Savory
Sesame Seeds
Sesame Seed -black-
Shallots -freeze-dried-
Soup Greens
Spearmint
French Tarragon
Cream of Tartar


THE WALL ◇◇
HAZARDS EXIST THAT ARE NOT MARKED
BE AWARE
SKI WITH CARE


The immune system
Innate immunity (non-specific)
Adaptive immunity (specific)
Souluble factors
Phagocytes
Humoral immunity B-cells
Cellular immunity T-cells

Immune defects

Neutrophil defects

- Number or function
- Skin infections
- Mucous membranes infections
- Granulomas
- Umbilical cord

Humoral defects

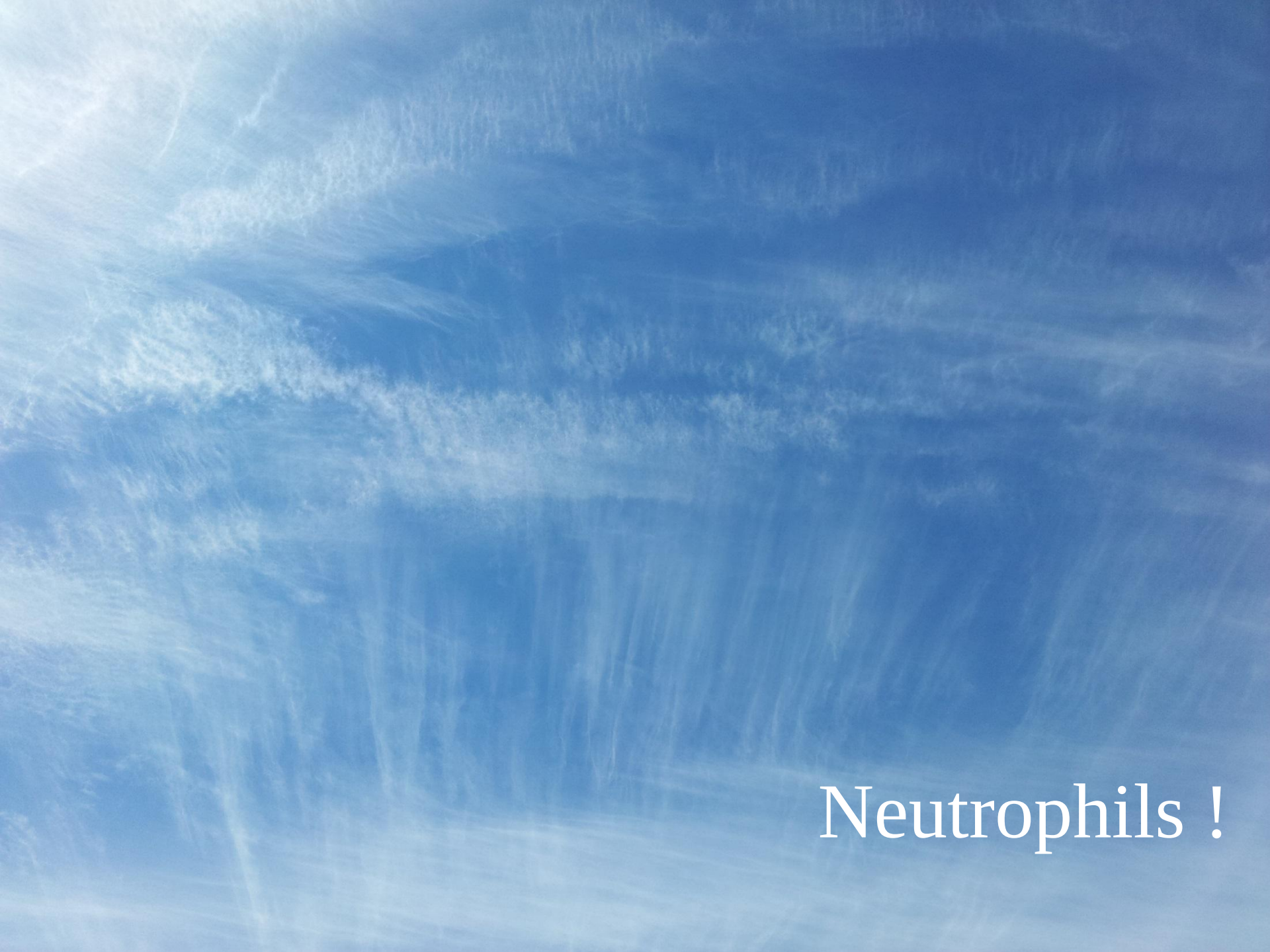
- B-cell defects
- Number and function
- Not in first months of life
- Recurrent infections (RTI)
- Bacterial infections (esp. capsulated)

Complement defects

- Recurrent bacterial infections
- Inf with capsulated bacteria (meningococcus, pneumococcus)
- Autoimmune disorders

Cellular defects

- Early in life
- Recurrent infections, viral, fungal and parasitic
- Malignancies

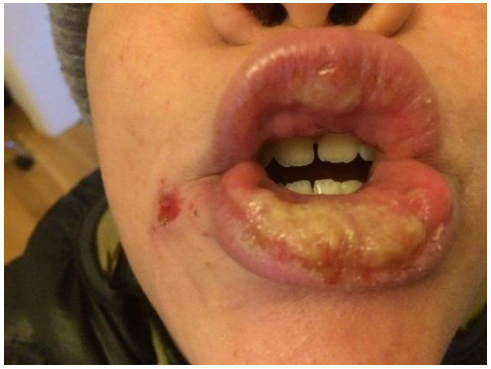

Neutrophils !

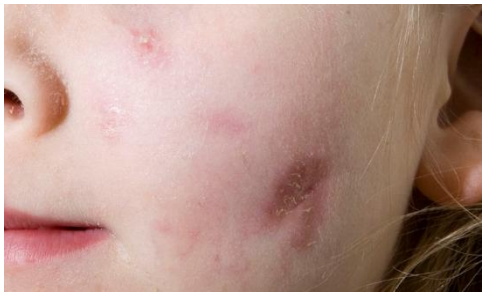
Neutrophil defects

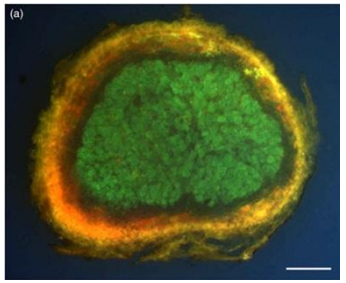
Neutrophil numbers

Neutrophil function

- Recurrent resp inf
- +/- fever
- Skin infections
- Mucous membranes infections
- GE infections / disorders
- Sepsis
- Granulomas and abscesses
- Unusual pathogns
- Umbilical cord !







Neutropenia and neutrophil dysfunction

- ✓ Aplastic anaemia
  Pancytopenia (drugs, toxins, infections, etc.)

- ✓ Postinfectious neutropenia
  Autoimmune / benign

- ✓ Iatrogen
  (drugs, irradiation)

- ✓ Chronic granulomatous disease

10 months of age – recurrent infections

Number of neutrophils in peripheral blood: 0.0 !!

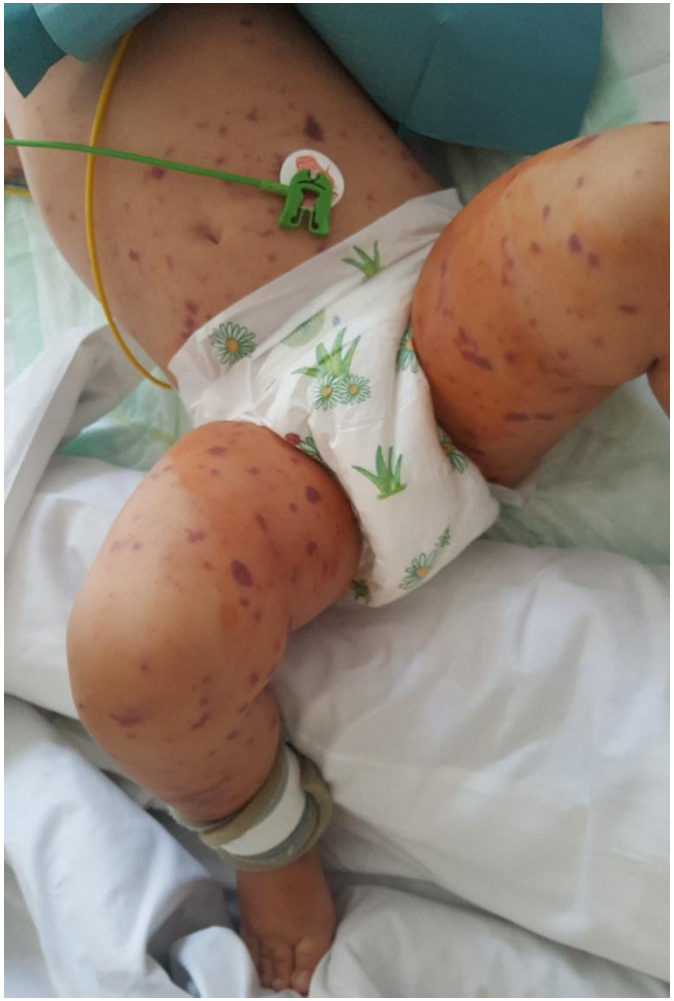
N


Komplement

Complement defects

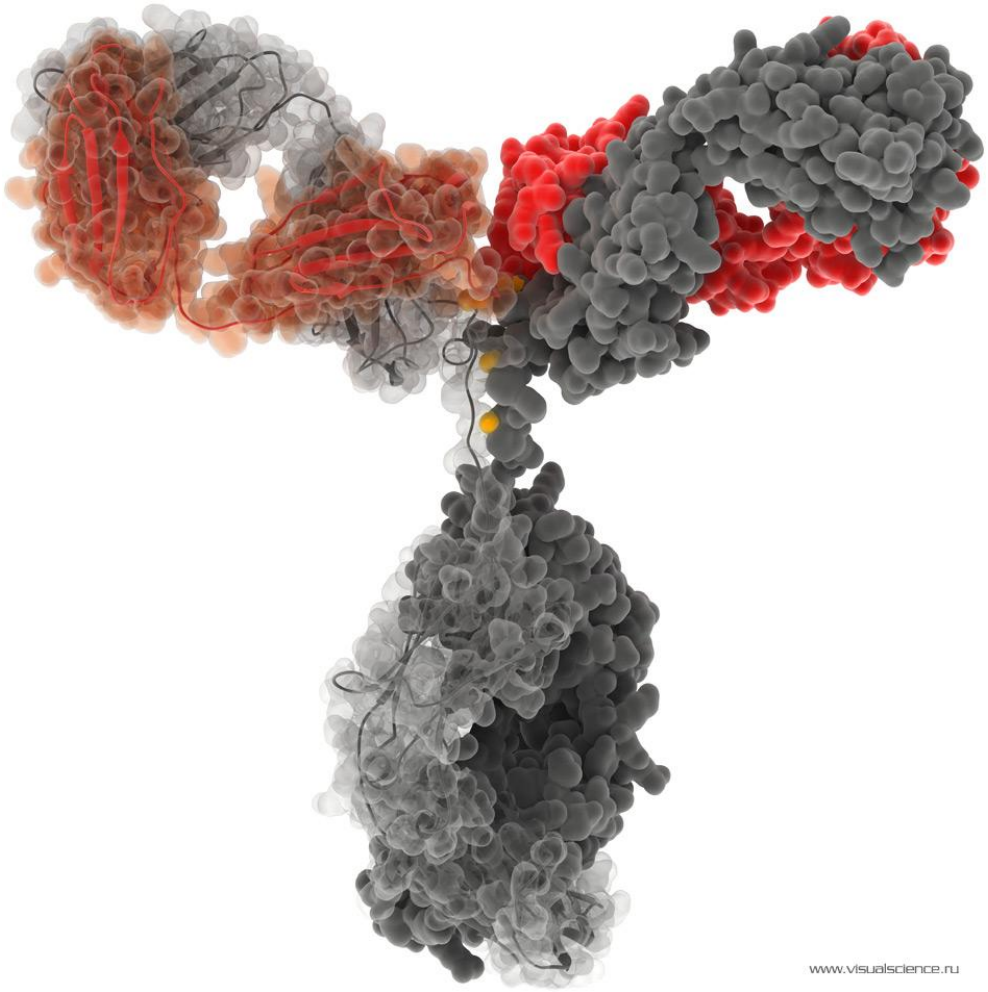
Complement defects

- Recurrent bacterial infections
- Inf with capsulated bacteria (meningococcus, pneumococcus)
- Autoimmune disorders
  - SLE
  - Glomerulonephritis
  - HUS
  - Angio-oedema




B-cells

Immunoglobulins
Unbelievable diversity

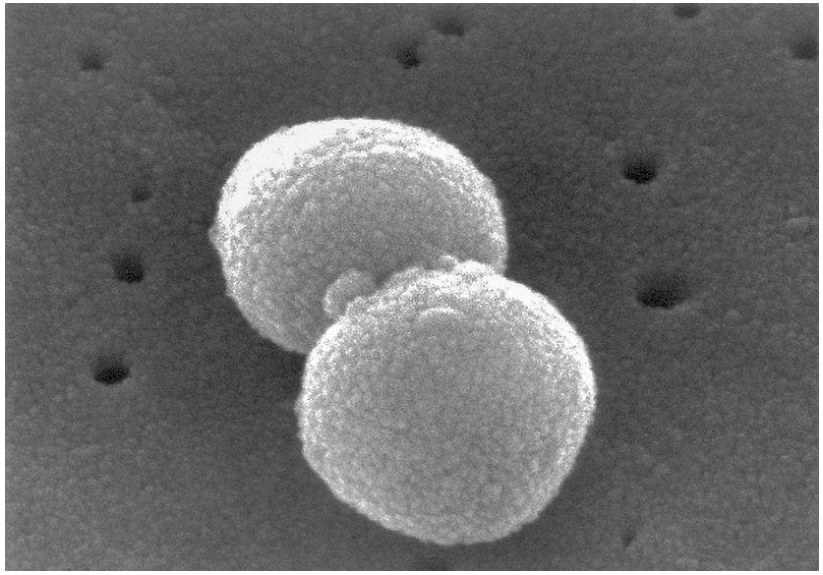


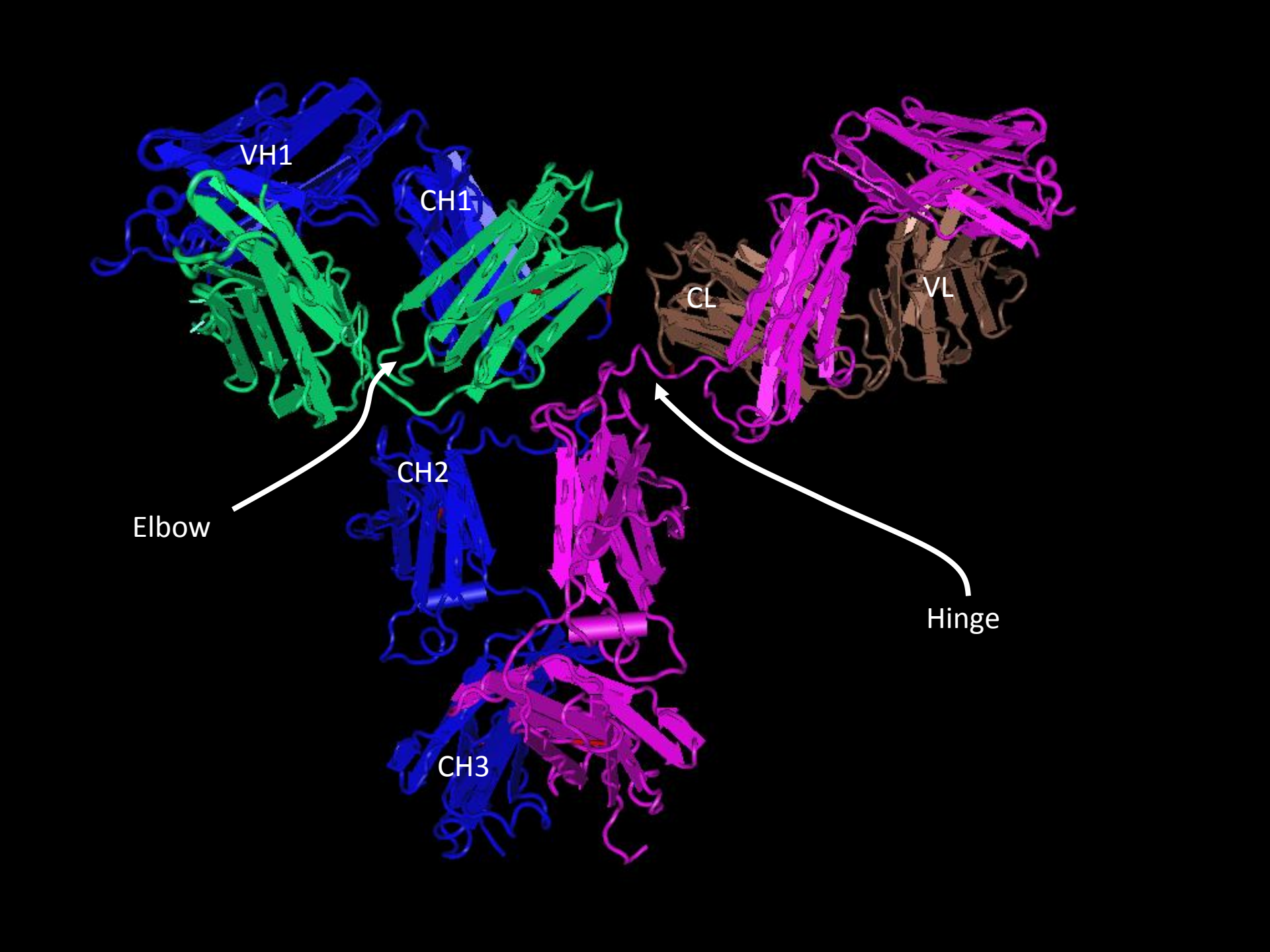
Humoral immune disorders

B-cell defects (T-cell defects?)

Number and function

- ✓ Recurrent infections (RTI)
- ✓ Not in first months of life
- ✓ Bacterial infections (esp. capsulated)
- ✓ Recurrent inf with same microorganisms




VH1
CH1
CL
VL
CH2
Elbow
Hinge
CH3

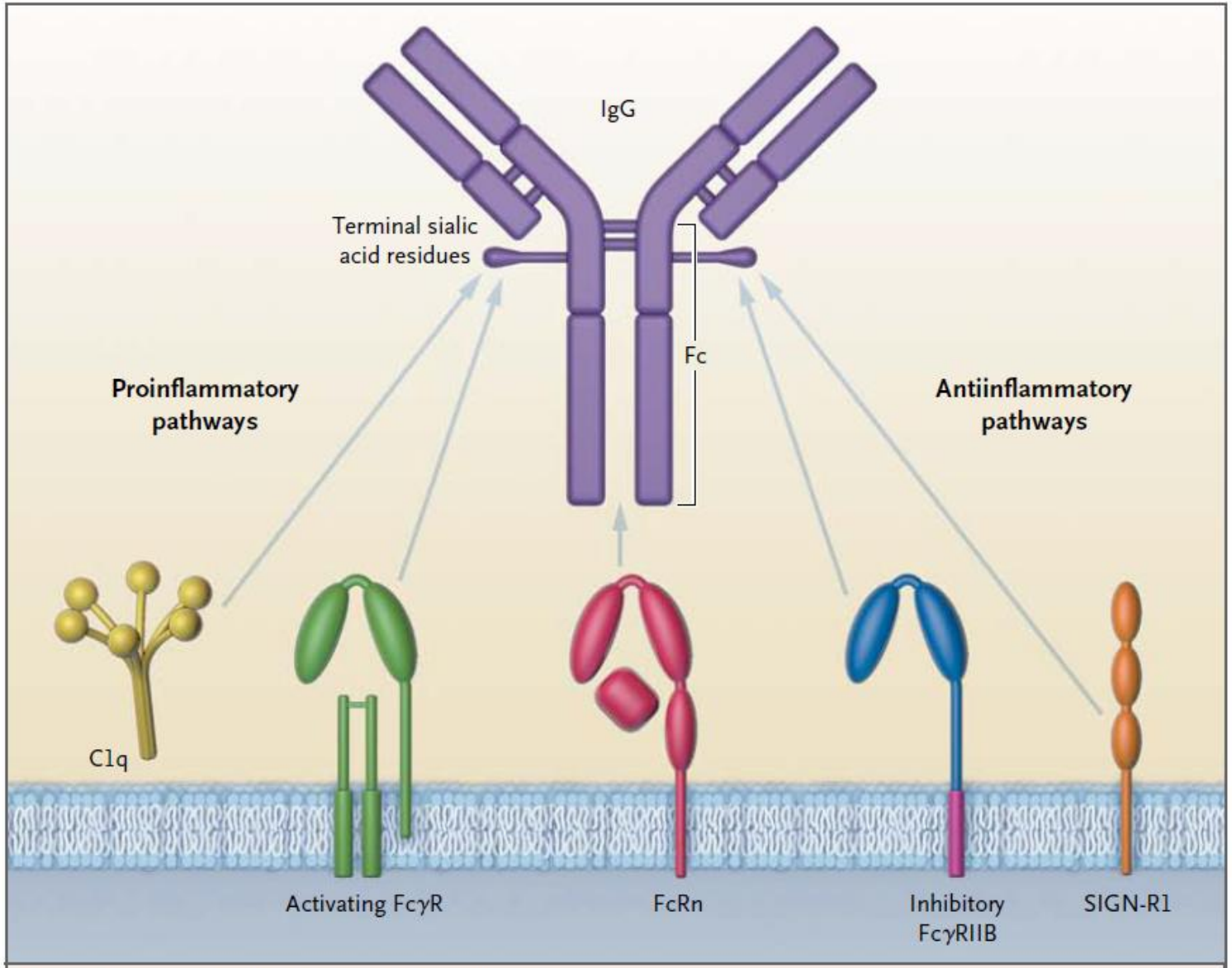
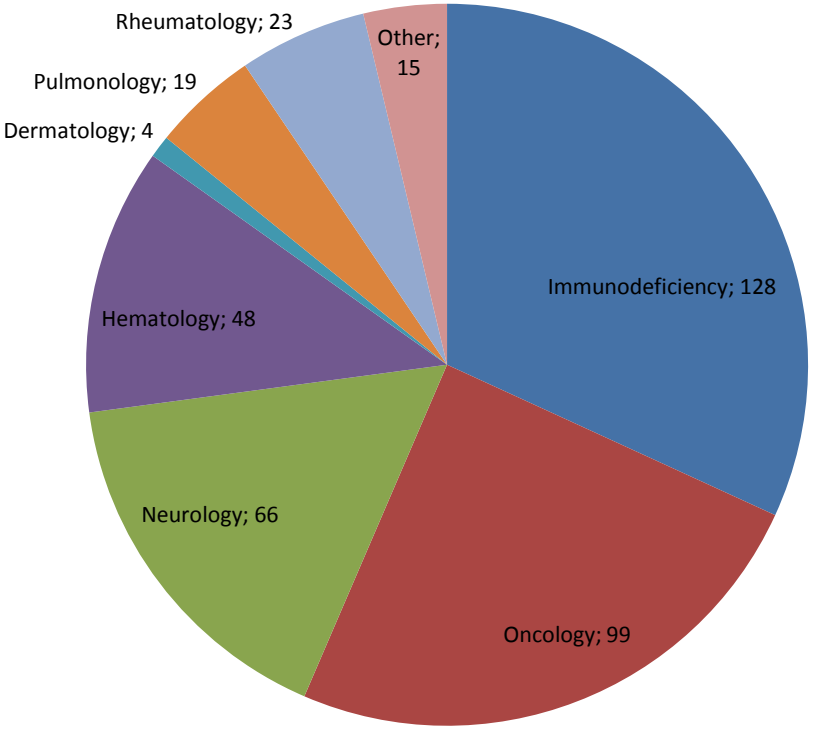


Figure 2. Biologic Activity of IgG–Fc Interacting Partners.

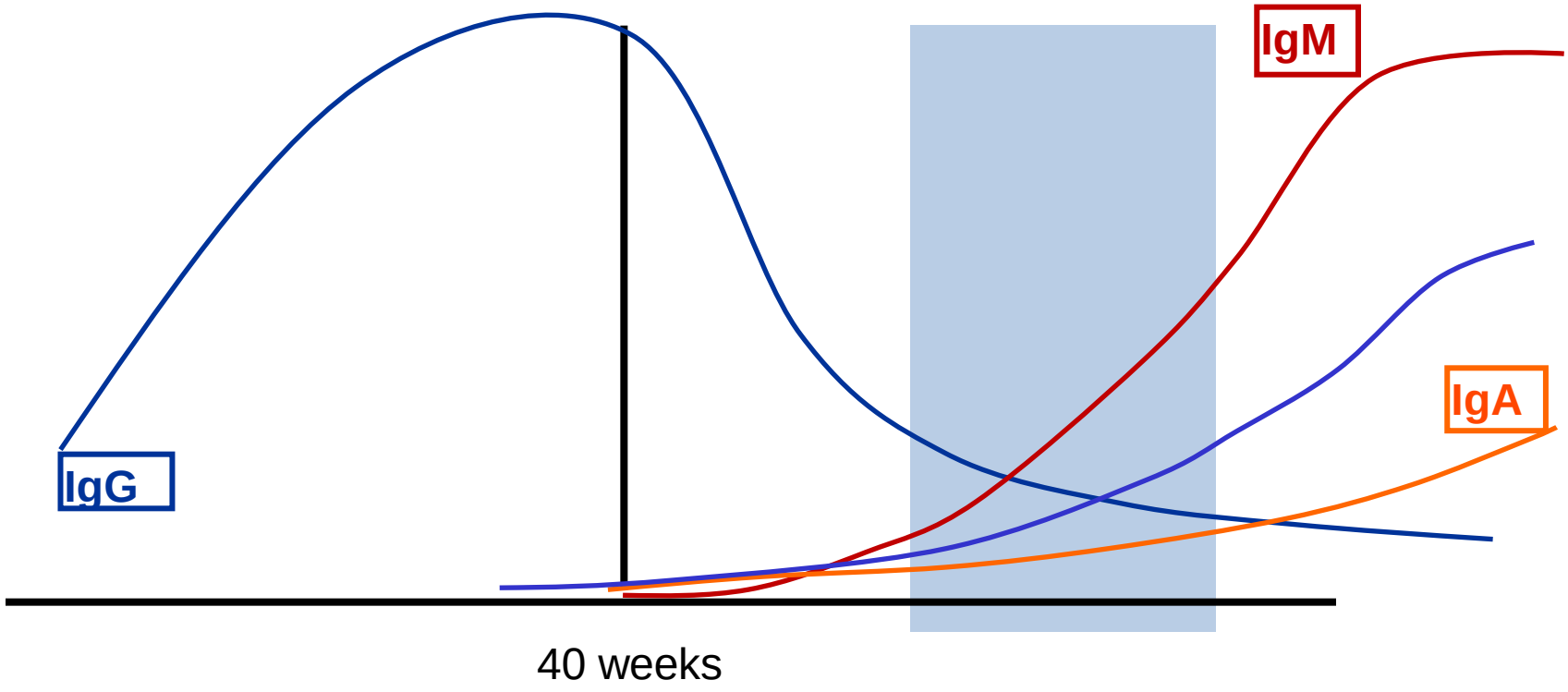
IgG–Fc binds to a variety of proteins that can initiate both proinflammatory pathways (e.g., C1q and activating FcγRs) and antiinflammatory pathways (e.g., inhibitory FcγRIIB and SIGN-R1). These pathways, at least in part, require the presence of terminal sialic acid residues on Fc (α-2,6-sialylated Fc). The neonatal Fc receptor (FcRn) interacts with a distal site on Fc, independent of the sugar side chain. SIGN-R1 denotes surface receptor–specific intercellular adhesion molecule 3–grabbing nonintegrin-related 1.

Use of IVIG



B E Ólafsdóttir
J ALLERGY CLIN IMMUNOL 2013
VOLUME 131, NUMBER 6

Serum immunoglobulins



Humoral immune disorders

Agammaglobulinaemia

Hyogammaglobulinaemia

Transient hypogamma of infancy

IgA deficiency

Subclass deficiency (IgG2 def)

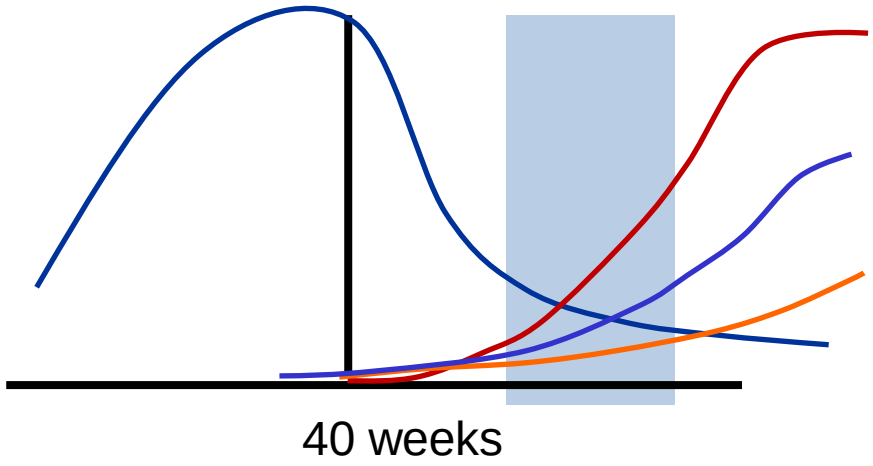
Antibody deficiency

Hyper IgE Sx

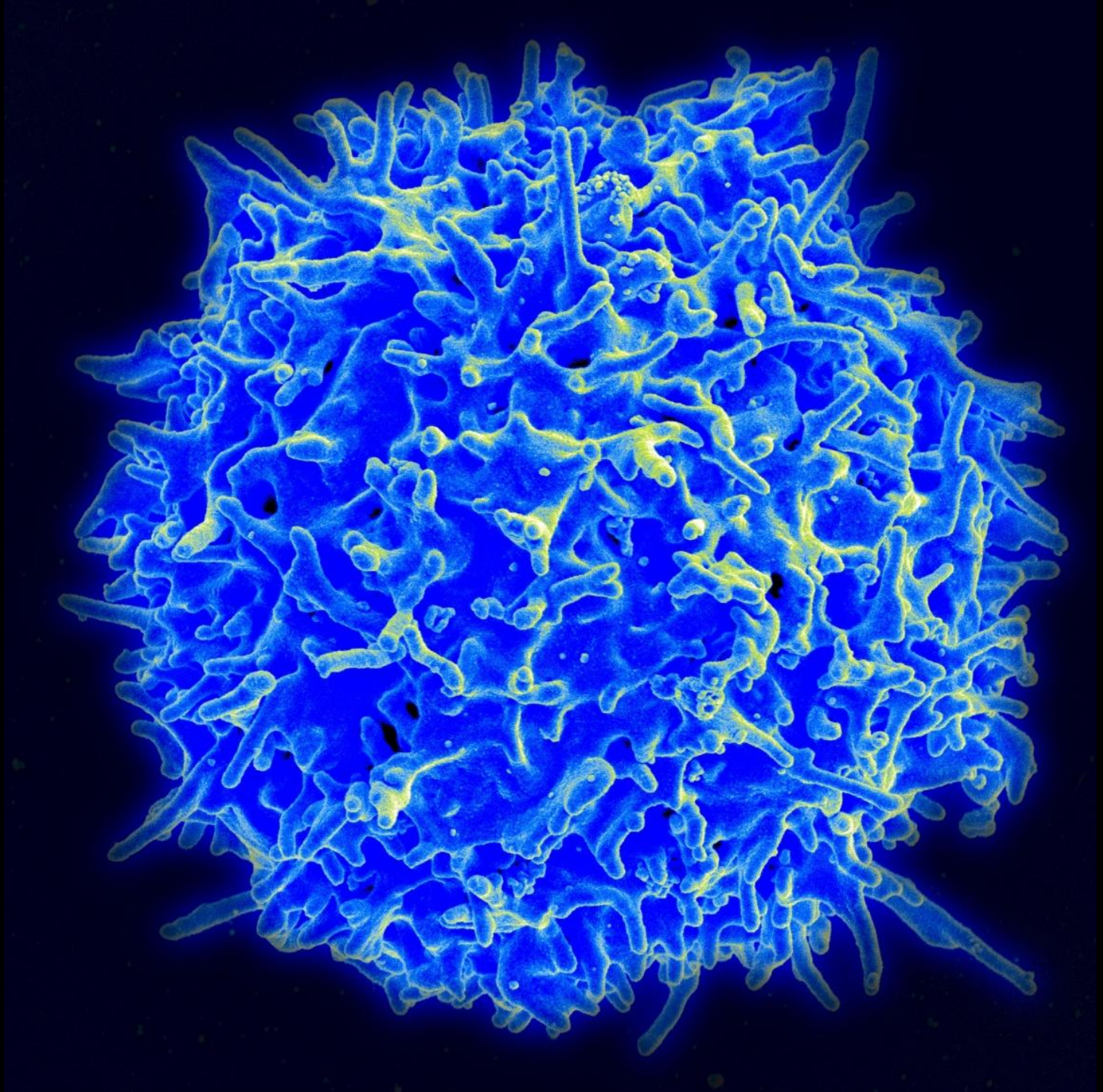
Hyper IgM Sx

Hyper IgD

CVID




T-cells



T cell disorders

Cellular defects
(with B- cell involvement)

- ✓ Early in life
- ✓ Recurrent infections, viral, fungal and parasitic
- ✓ Autoinflammatory reactions
- ✓ Malignancies
- ✓ etc

Immunisations
for immunodeficiet patients

Common childhood vaccines

- ✓ Diphtheria
- ✓ Tetanus
- ✓ Acellular pertussis
- ✓ Poliovirus
- ✓ Haemophilus influenzae type (Hib)
- ✓ Pneumococcal conjugate
- ✓ MenACWY-D

- ✓ Measles,
- ✓ Mumps
- ✓ Rubella
- ✓ Varicella
- ✓ Human papillomavirus
- ✓ Hepatitis A / B
- ✓ Rotavirus
- ✓ Influenza

Immunisations

Immunisation
The Icelandic Saga

Disclosure

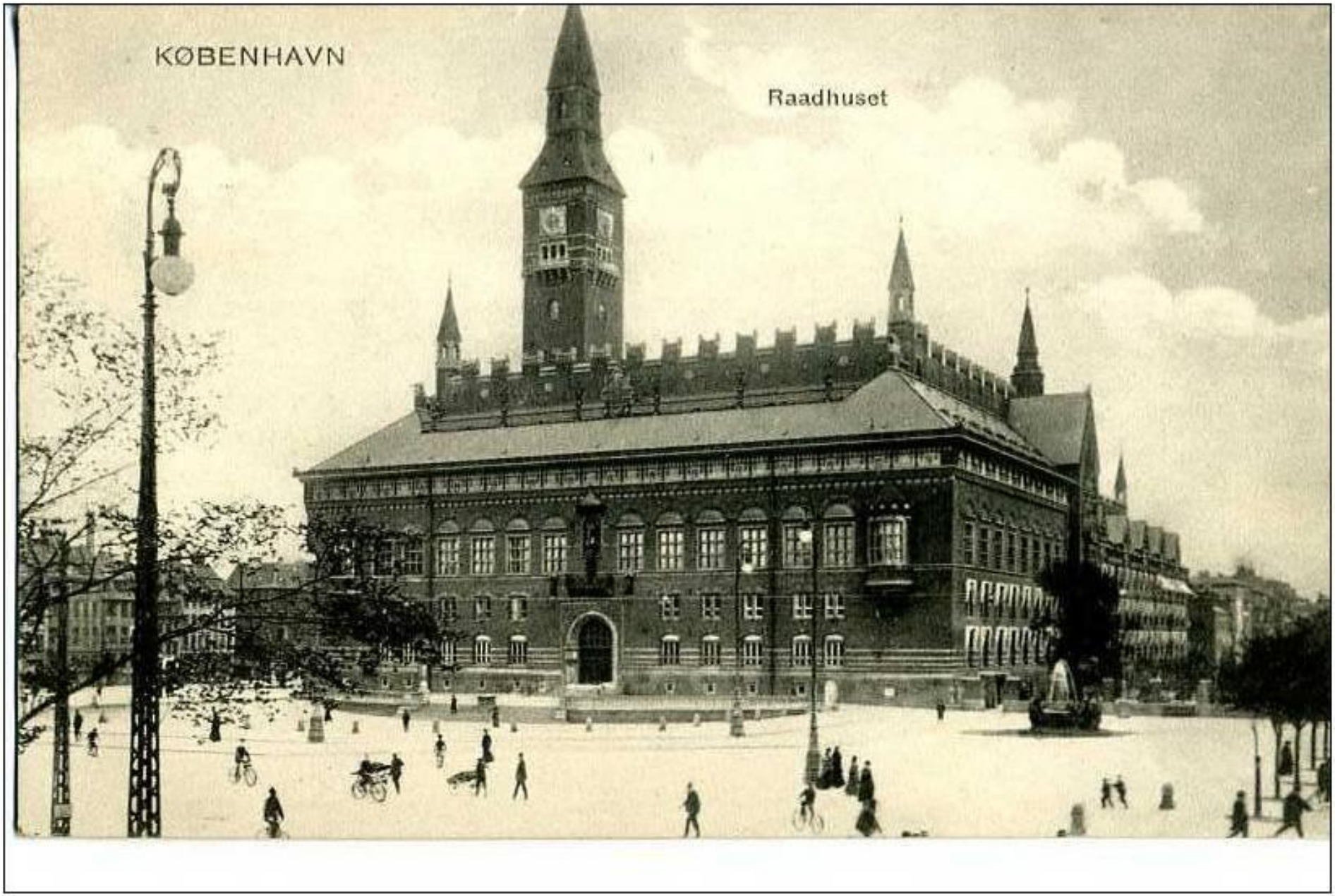
Ásgeir Haraldsson

- ✓ ÁH has done research work partly funded by pharmaceutical industry, consultancy and travel grants also paid by industry
- ✓ Income is paid to research funds, governed by The University/University Hospital, managed and audited by them
- ✓ These research funds are used for academic purposis, partly controlled ÁH
- ✓ ÁH or his family have no shares in any pharmaceytical companies and have no finincial relation to them

Copenhagen harbour 1885

Stockholm early 1900

Copenhagen 1882



Copoenhagen – Raadhuset 1900

1900

Total population (growing): < 80.000
Under five mortality rate: 150/1000

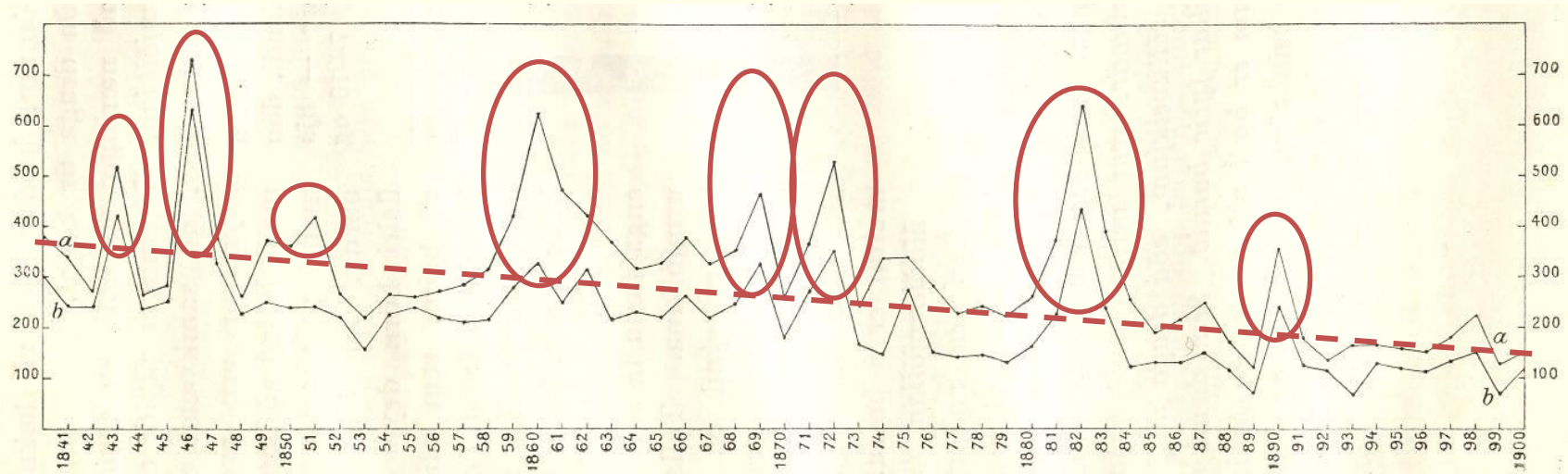
1840

Total population (growing): < 57.000
Under five mortality rate: > 350/1000

Iceland around 2016

Iceland around 2016

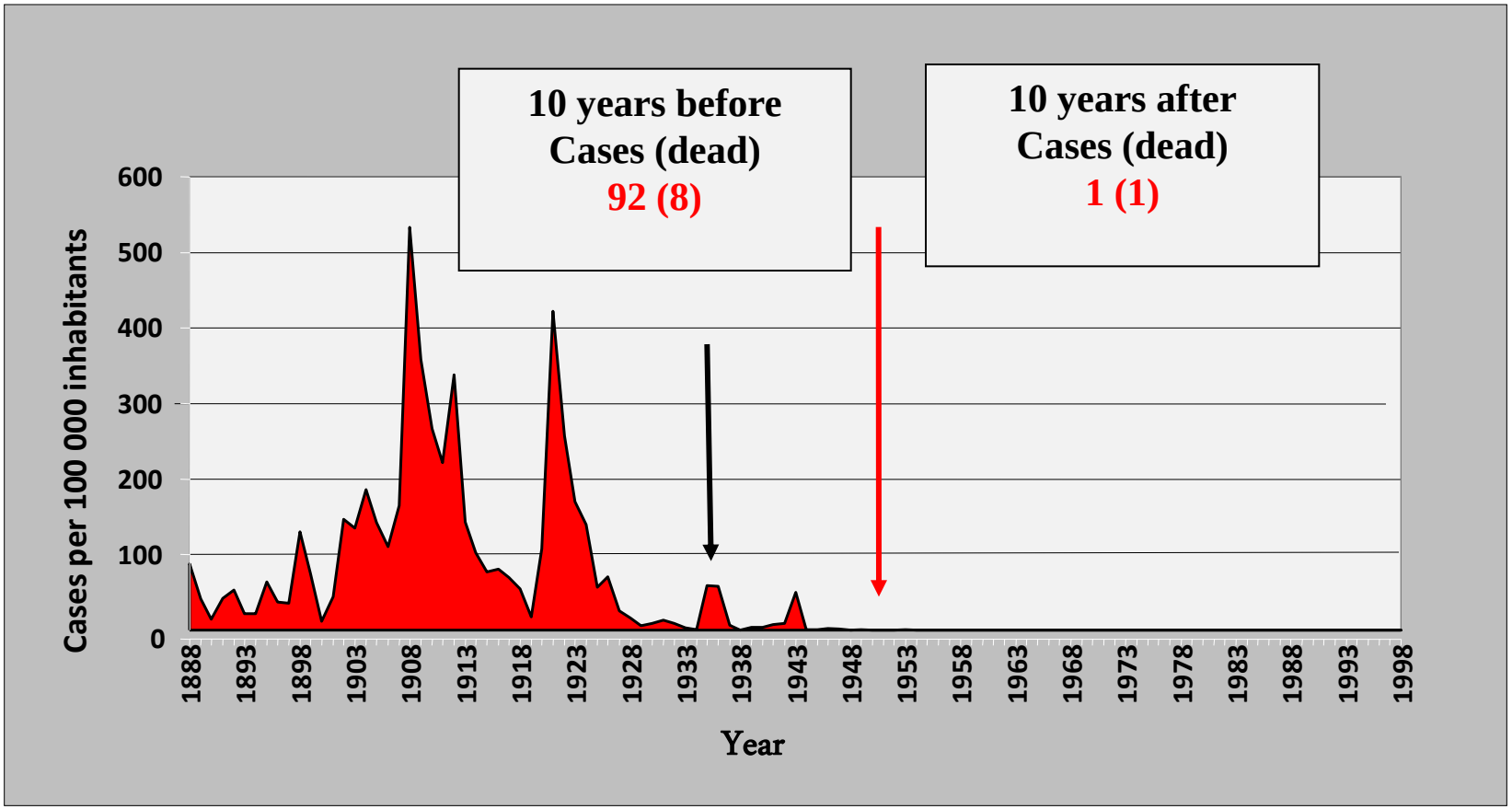
Total population: 332.000
Under five mortality rate:
Approximately < 2.0 /1000



111. mynd.

Efri línan (a) sýnir ‰ dáinna innan 5 ára, neðri línan (b) innan 1 árs. Andvanafæðingar eru alstaðar frádregnar.
Barnadauði á Íslandi frá 1841—1900.

Diphtheria in Iceland



First tried in 1935, probably stopped an epidemic
1950: All infants offered immunisation against diphtheria

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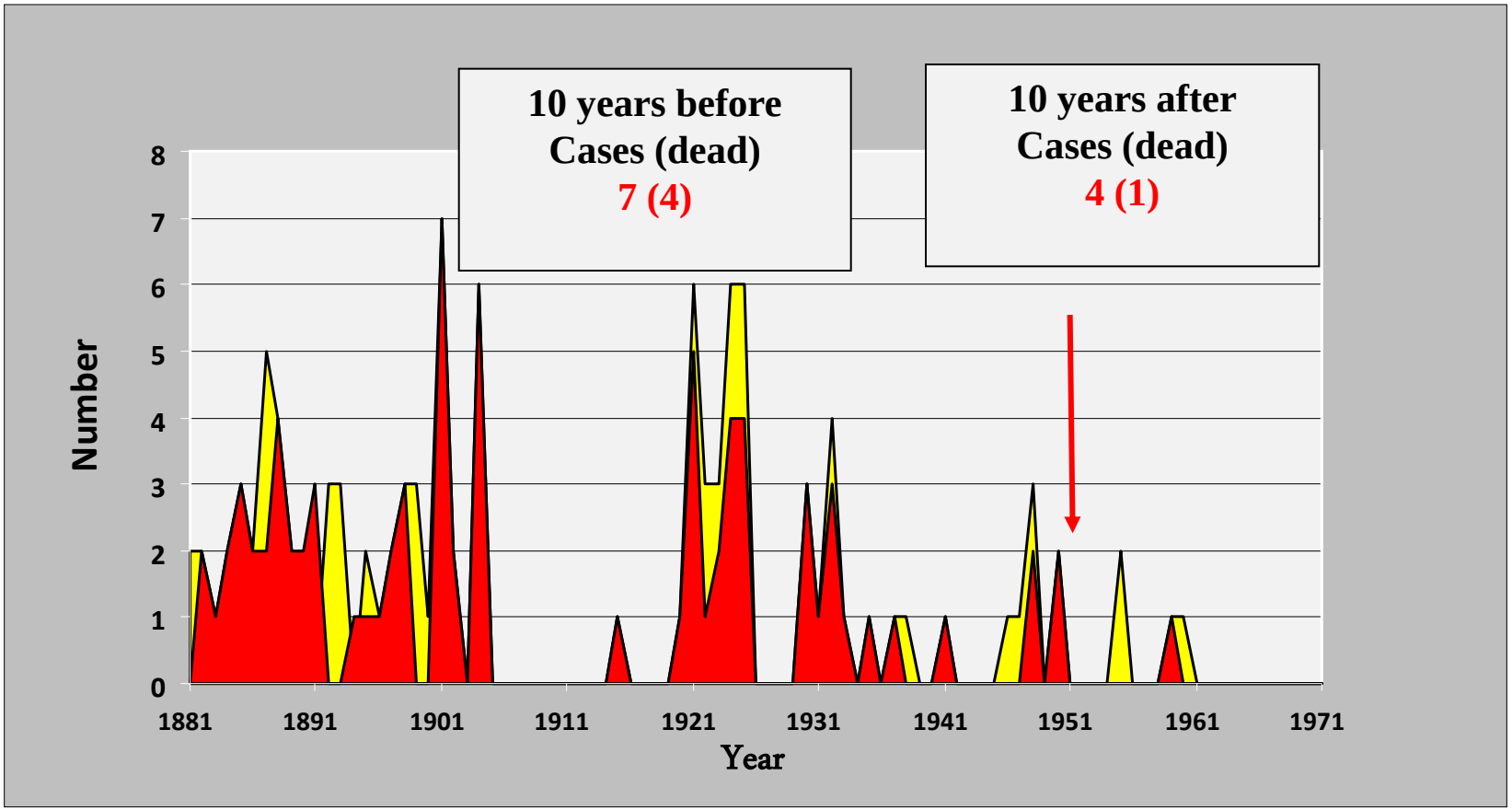
Directorate of Health

Tetanus in Iceland



1953 Immunisation started
Last case: 2008

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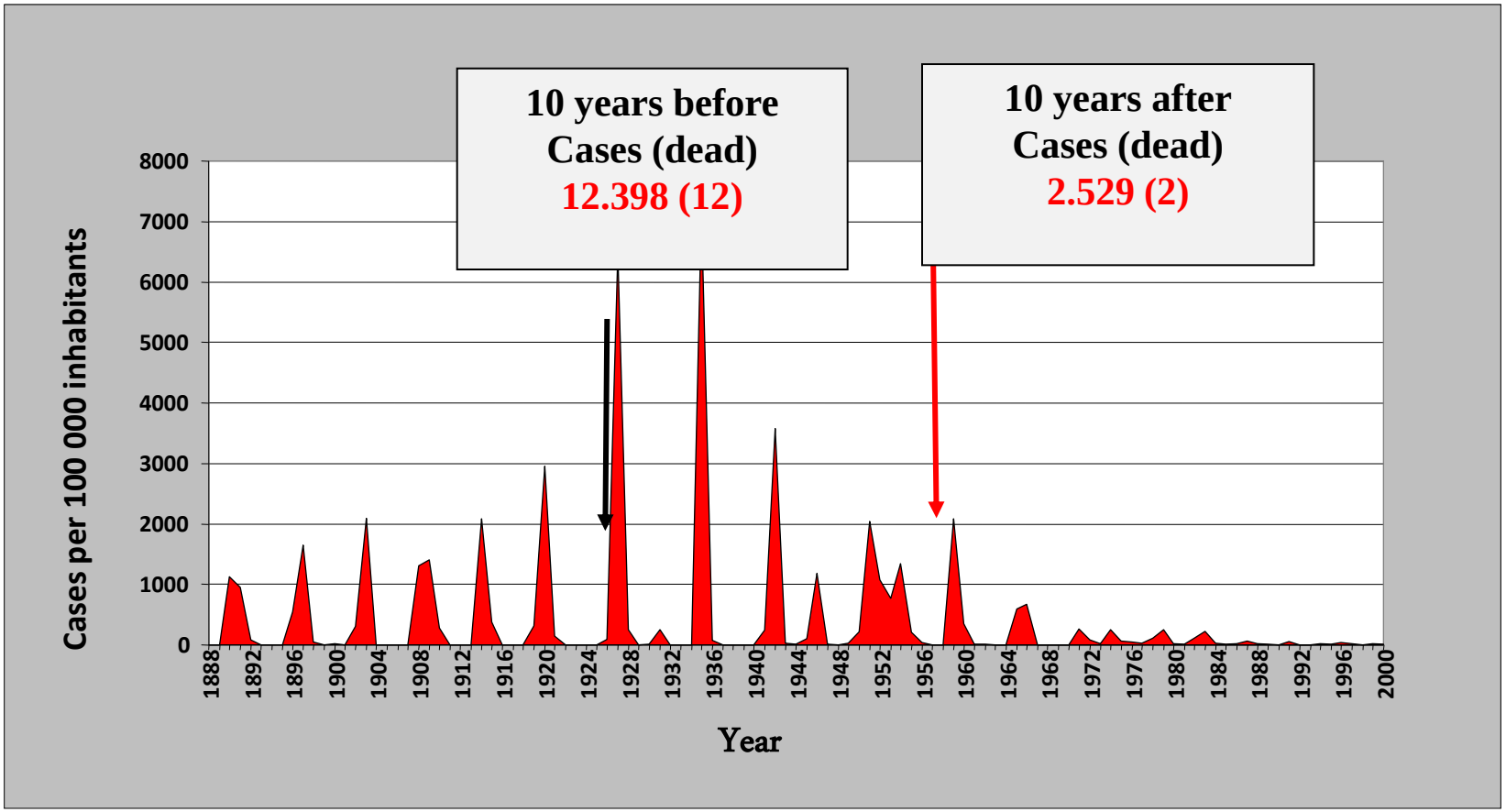
Pertussis in Iceland



1927 Immunisation tried. Infant immunisation from 1959
2000:Acellulair pertussis, 2007 added to immunisation at 14 y

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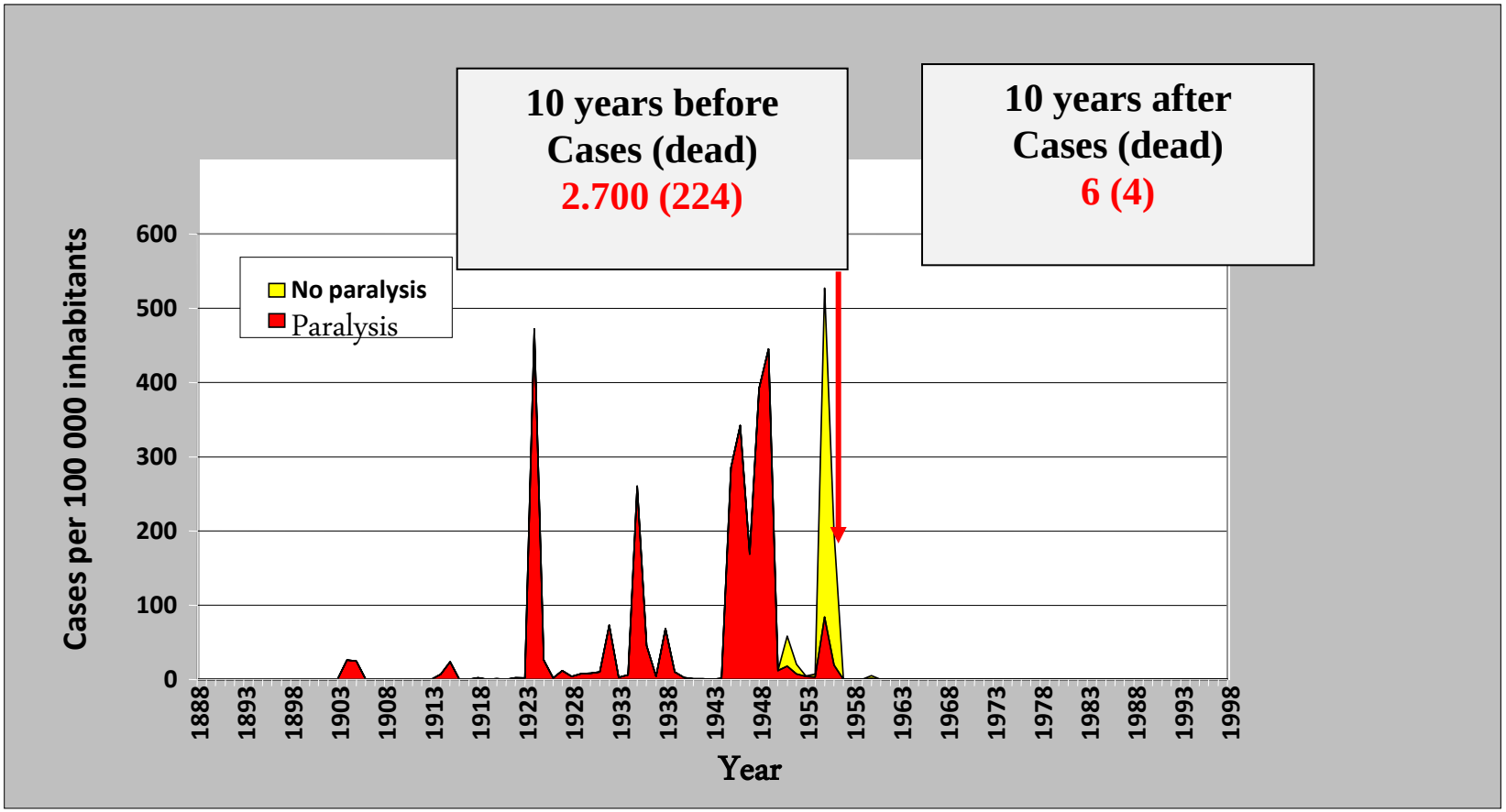
Poliomyelitis in Iceland



1956 Immunisation started
1960: Last cases with paralysis, 1963: Last case (foreign origin)

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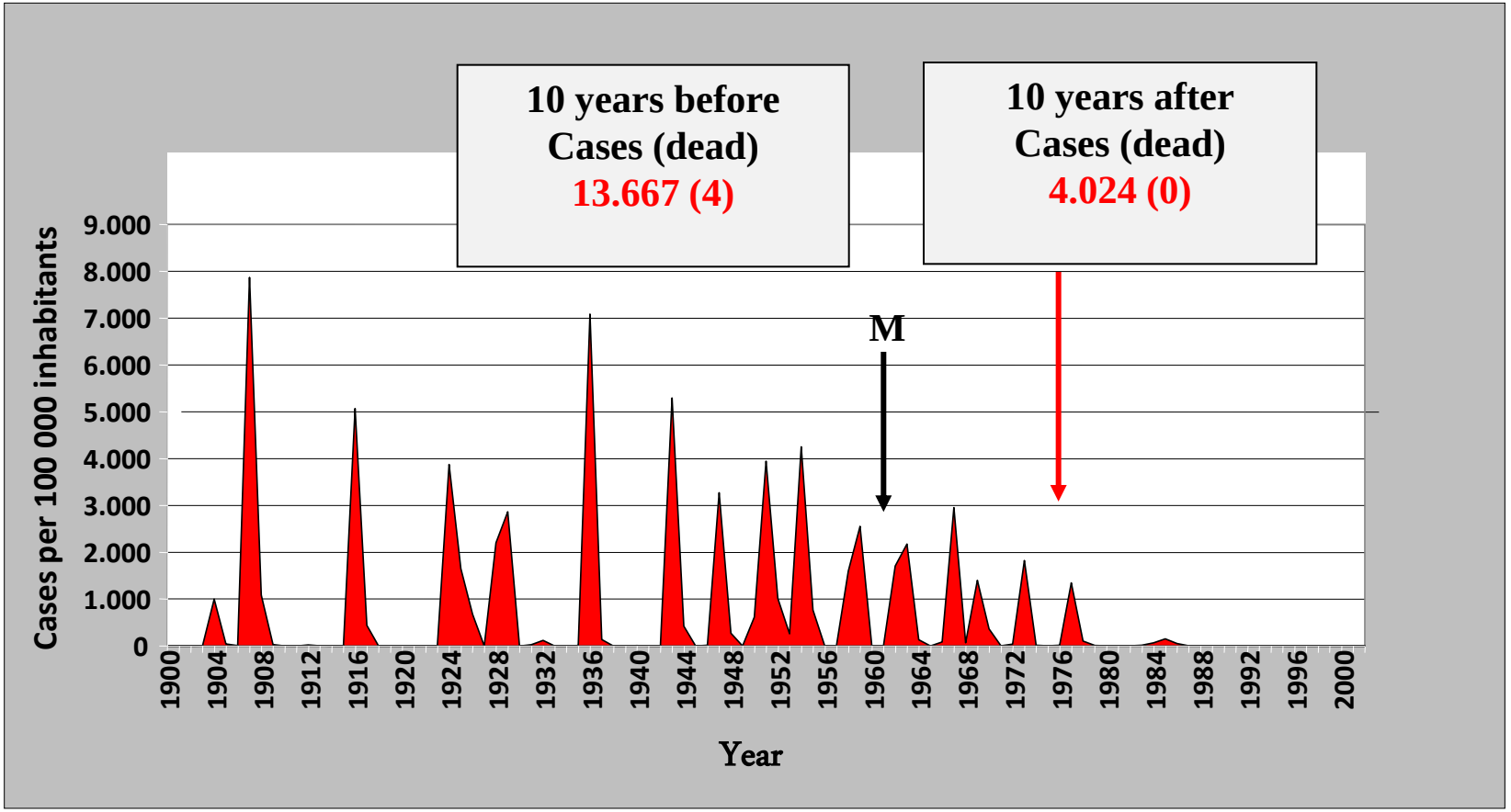
Measles in Iceland



1960: Immunisation started, 1976: Started at 2 years of age
1989: Immunisation with MMR at 18 months of age started

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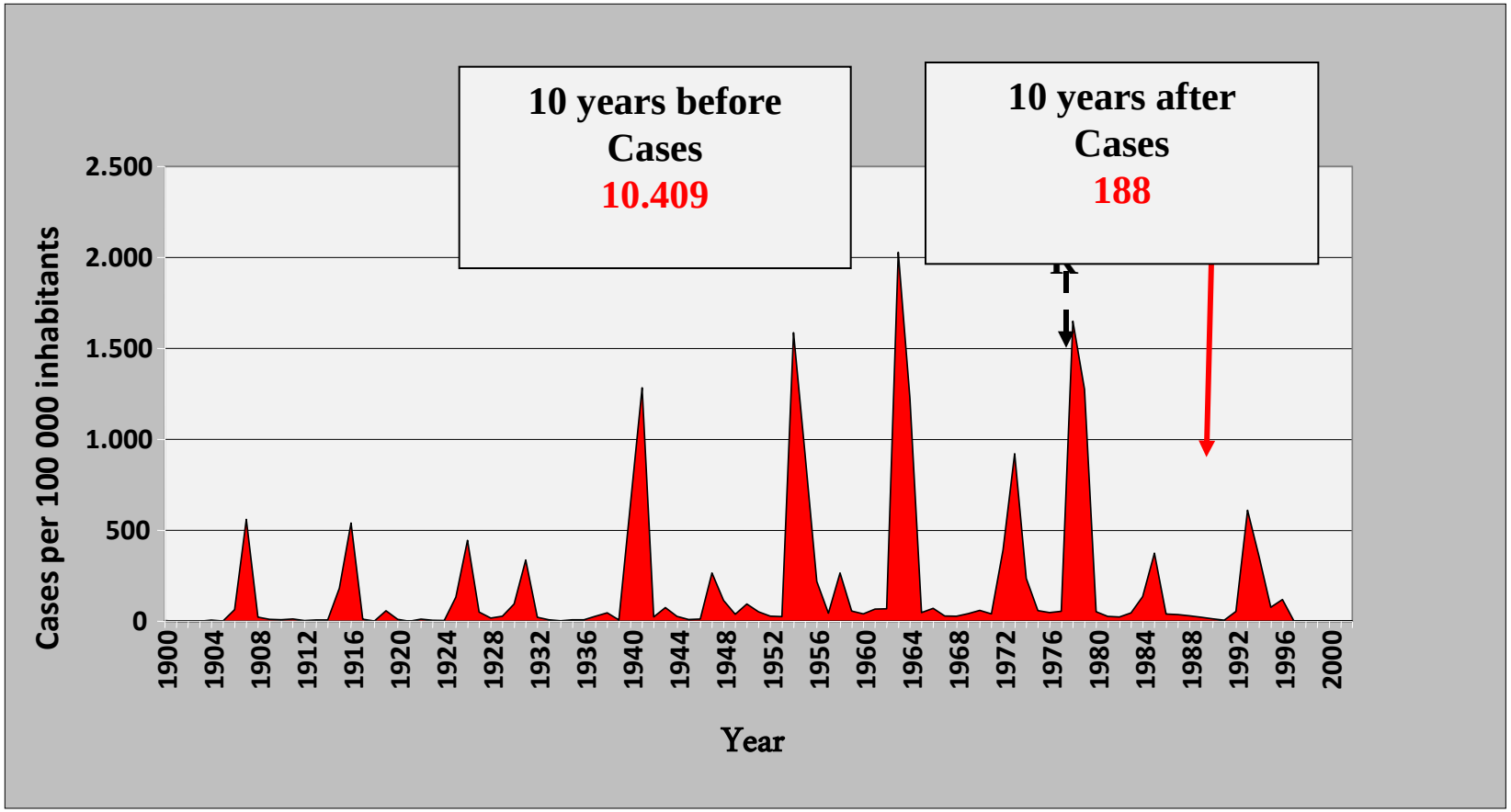
Directorate of Health

Rubella in Iceland



1977: Immunisation started, girls at 12 years of age
1989: Immunisation with MMR at 18 months of age started

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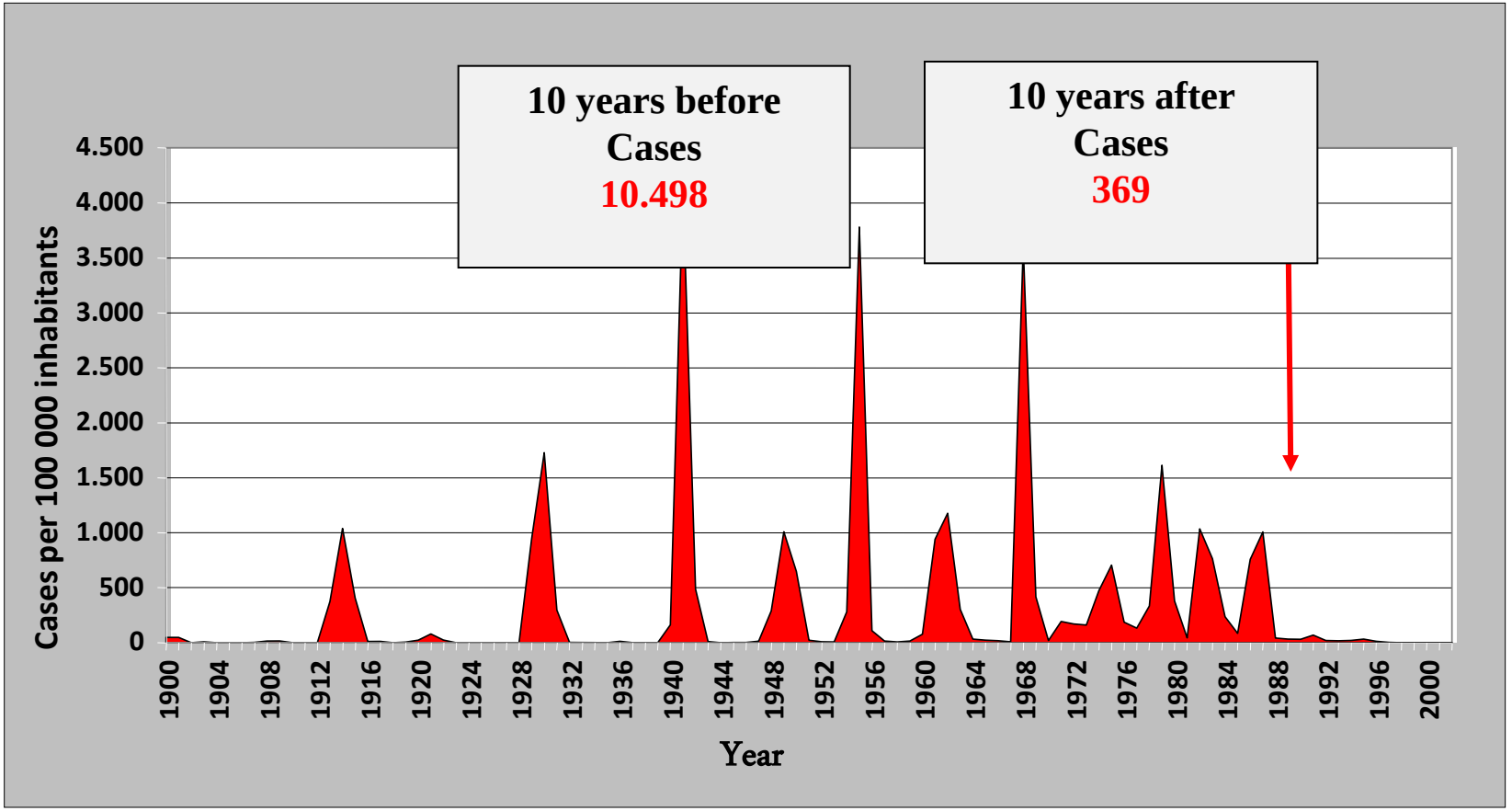
Directorate of Health

Mumps in Iceland



1989: Immunisation with MMR at 18 months of age started
Booster at 12 years of age

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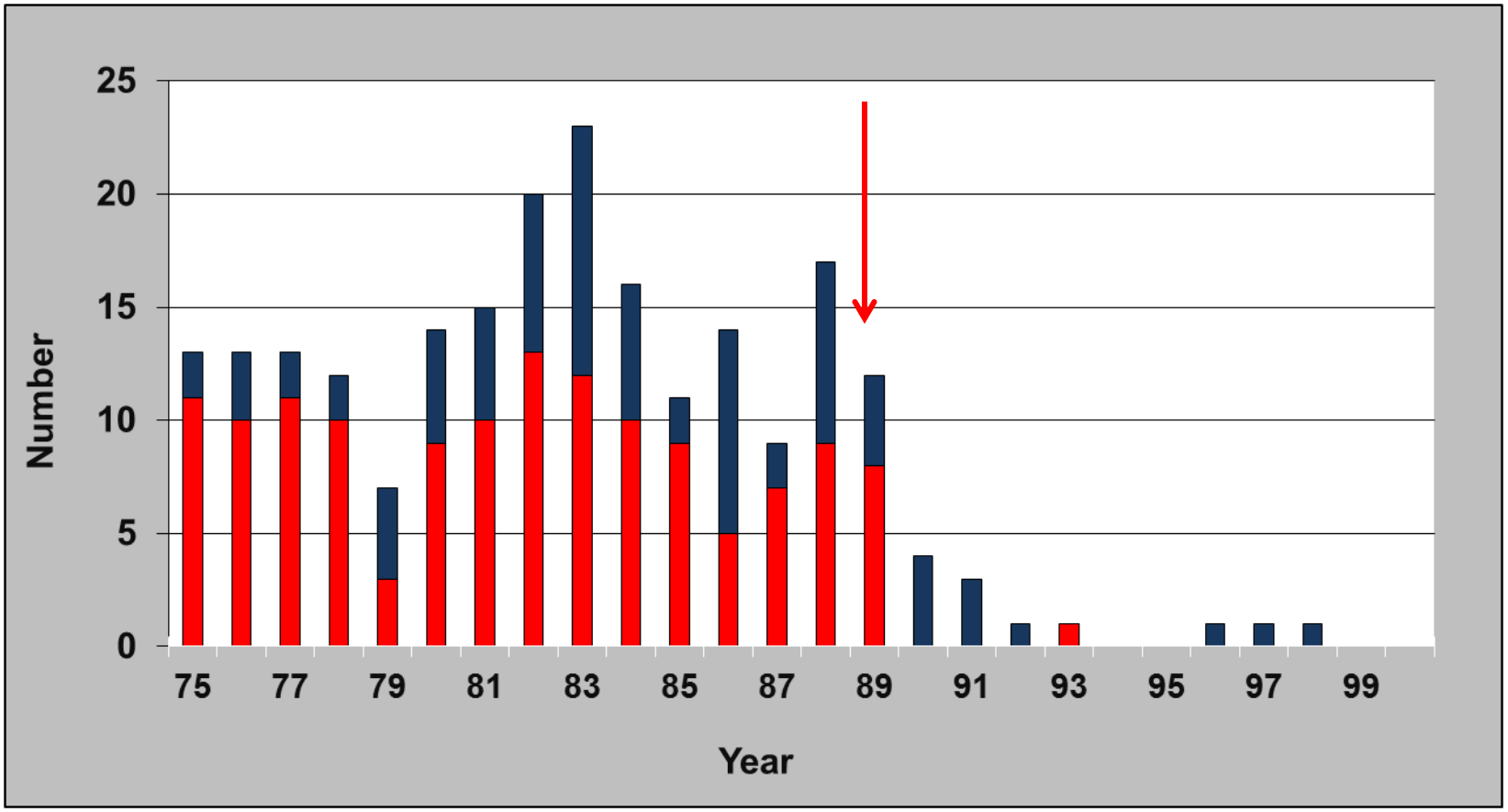
Directorate of Health

*Hi*b in Iceland



1989: Immunisation against *Haemophilus influenza* type b starts

Meningitis **Sepsis/blood stream infections**

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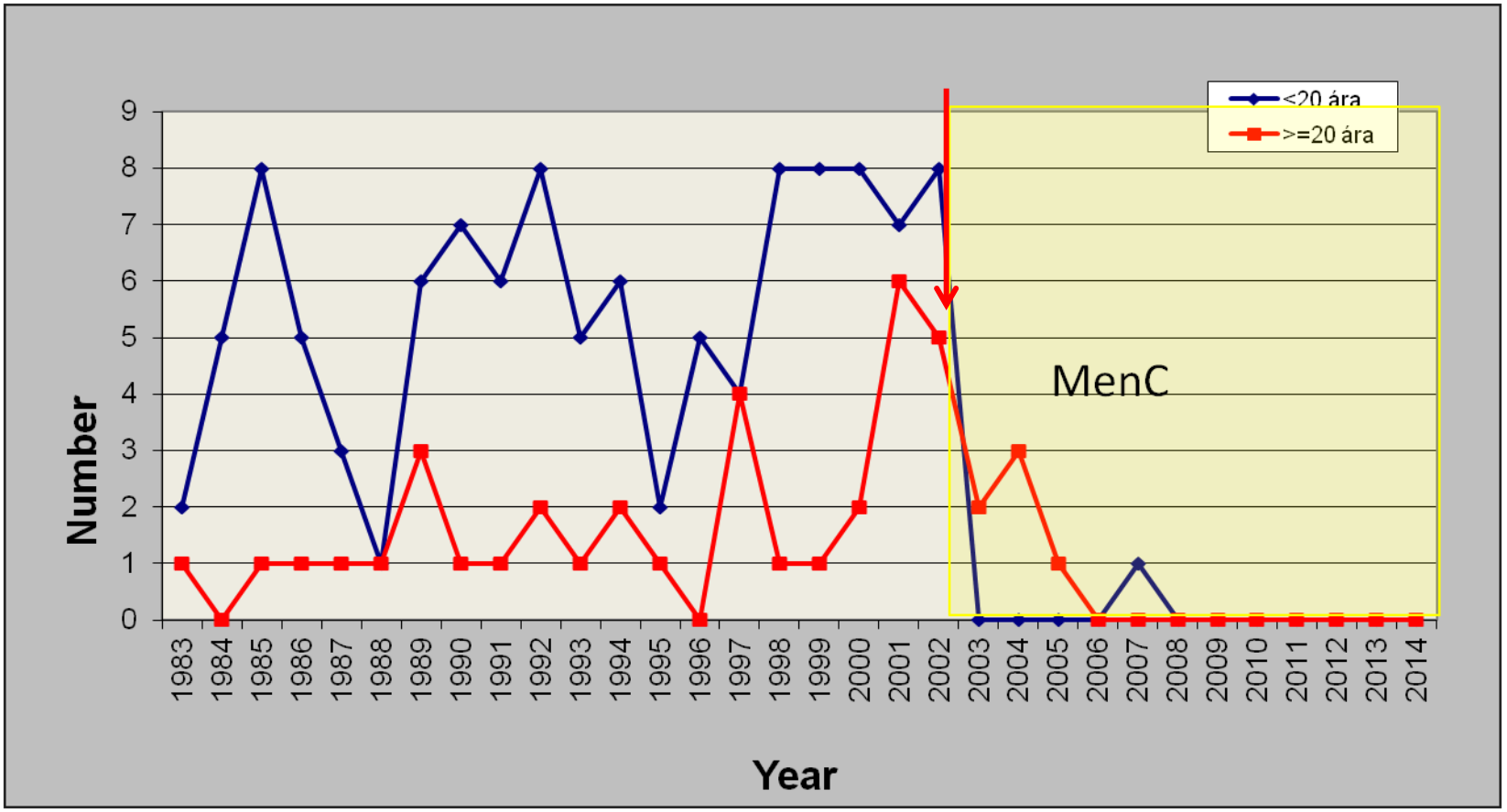
Directorate of Health

Men C in Iceland



1989: Immunisation against *Str Meningititis* serotype *C* starts

< 20 years of age **> 20 years of age**

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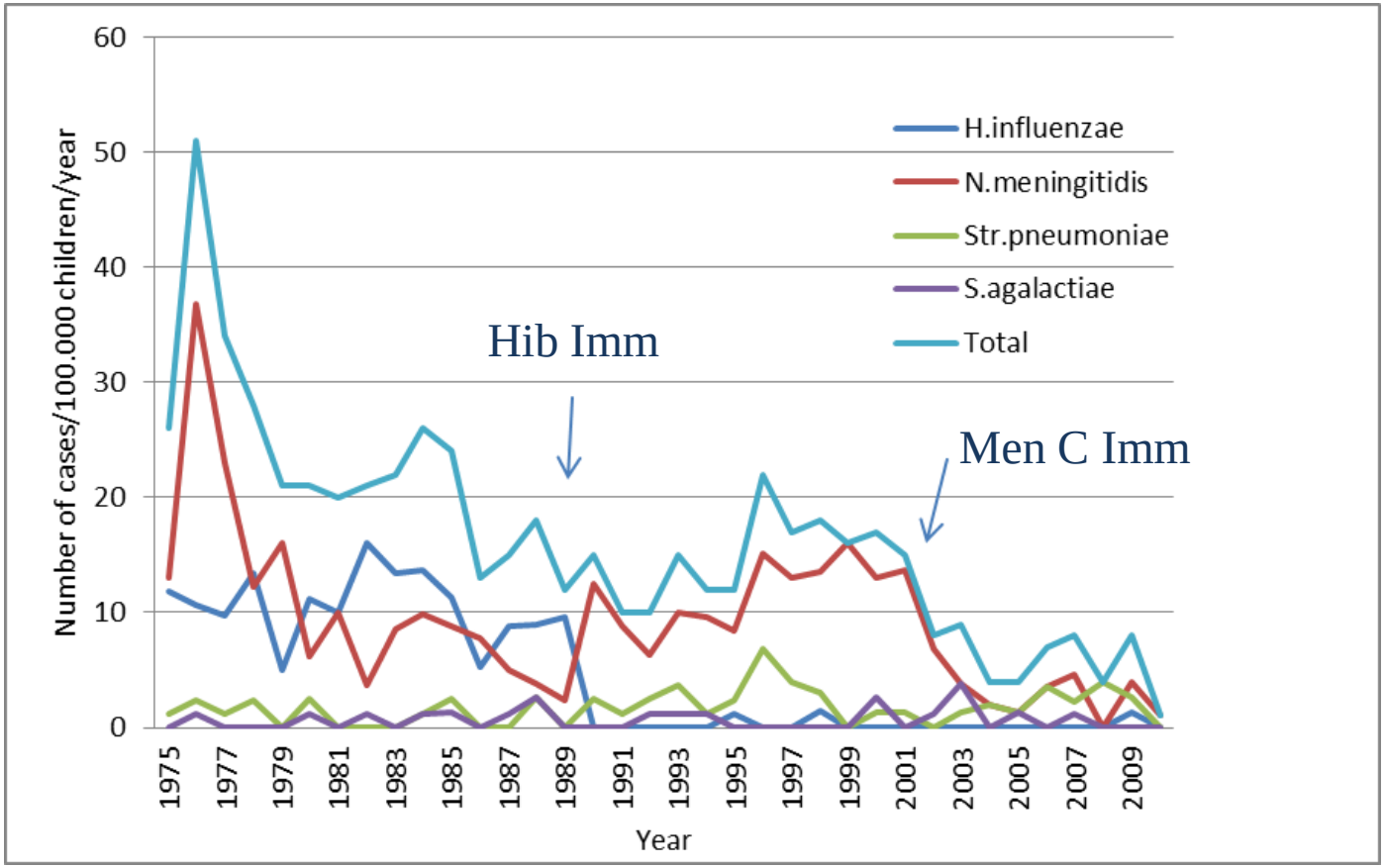
Meningitis in Icelandt



Bacterial meningitis in children in Iceland, 1975–2010: A nationwide epidemiological study

KOLFINNA SNAEBJARNARDÓTTIR[1], HELGA ERLENDSDÓTTIR[1,2], INGI KARL REYNISSON[1], KARL KRISTINSSON[1], SANDRA HALLDÓRSDÓTTIR[1], HJÖRDÍS HARDARDÓTTIR[2], THÓRÓLFUR GUDNASON[1,3,4], MAGNÚS GOTTFREDSSON[1,5] & ÁSGEIR HARALDSSON[1,3]

Scandinavian Journal of Infectious Diseases, 2013

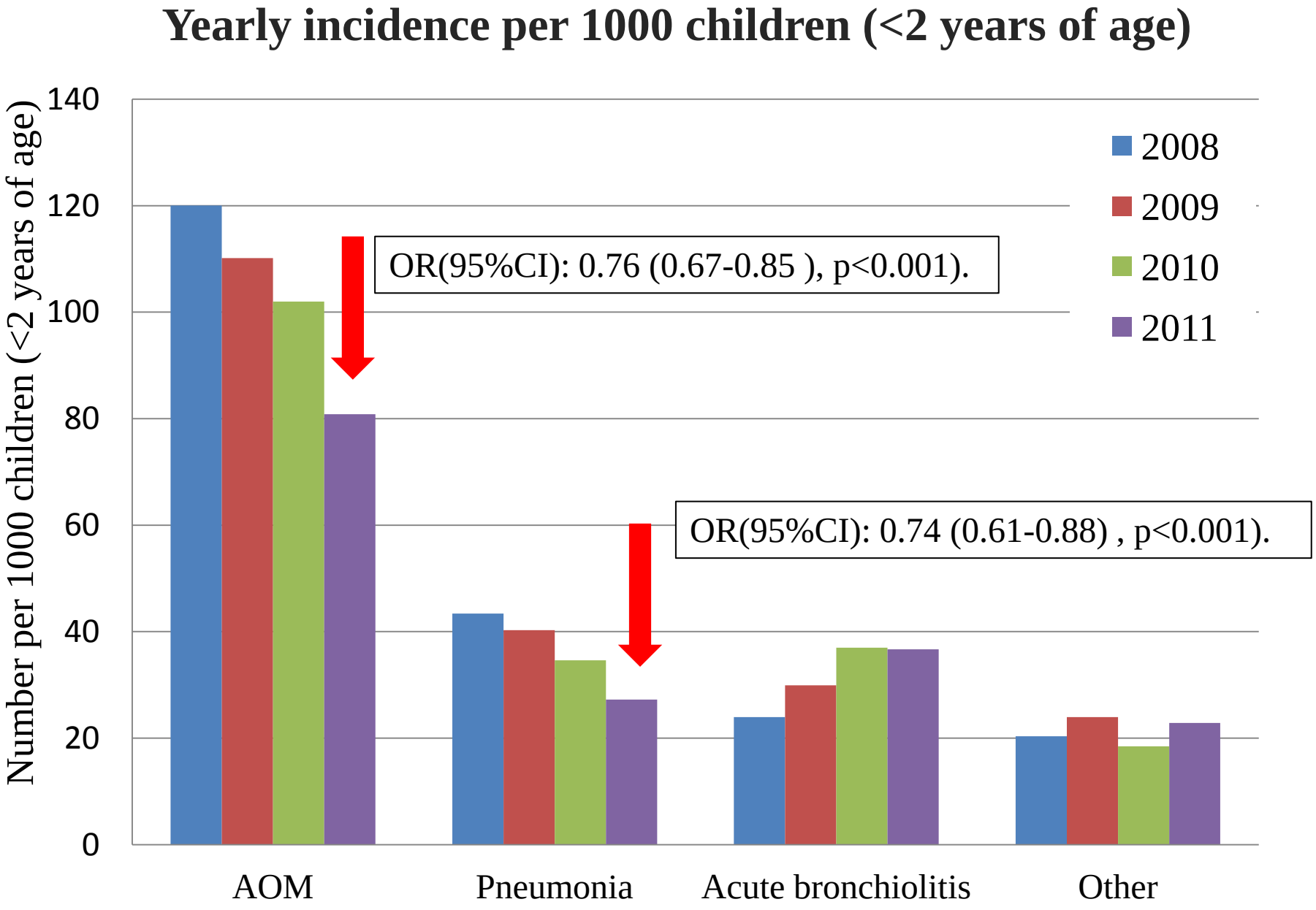
The VIce study

Vaccinations in Iceland

Principal investigators

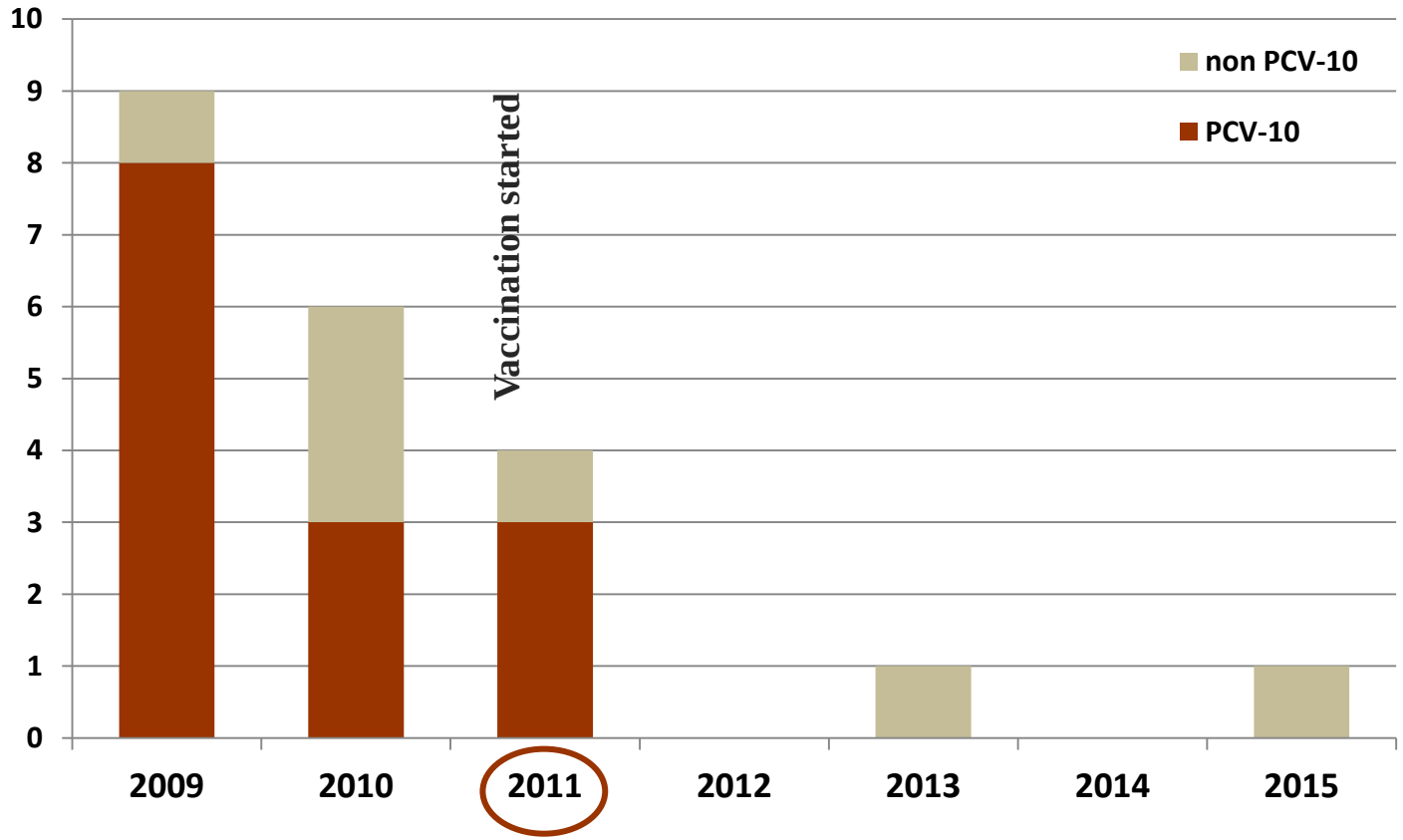
Ásgeir Haraldsson, Karl G Kristinsson, Helga Erlendsdóttir

Nasopharyngeal carriage	Antibiotic usage	Serotype replacement
Clinical samples	Antibiotic resistance	Molecular distribution
Invasive disease	RTI infections in prim care	Public health changes
Respiratory tract infections	Tympanic tube placements	Society cost
Acute otitis media	Infections in adults	Etc !


Yearly incidence per 1000 children (<2 years of age)
Number per 1000 children (<2 years of age)
140
120
100
80
60
40
20
0
2008
2009
2010
2011
OR(95%CI): 0.76 (0.67-0.85), p<0.001).
OR(95%CI): 0.74 (0.61-0.88) , p<0.001).
AOM
Pneumonia
Acute bronchiolitis
Other

Children < 18 years

Iceland 2009-2014



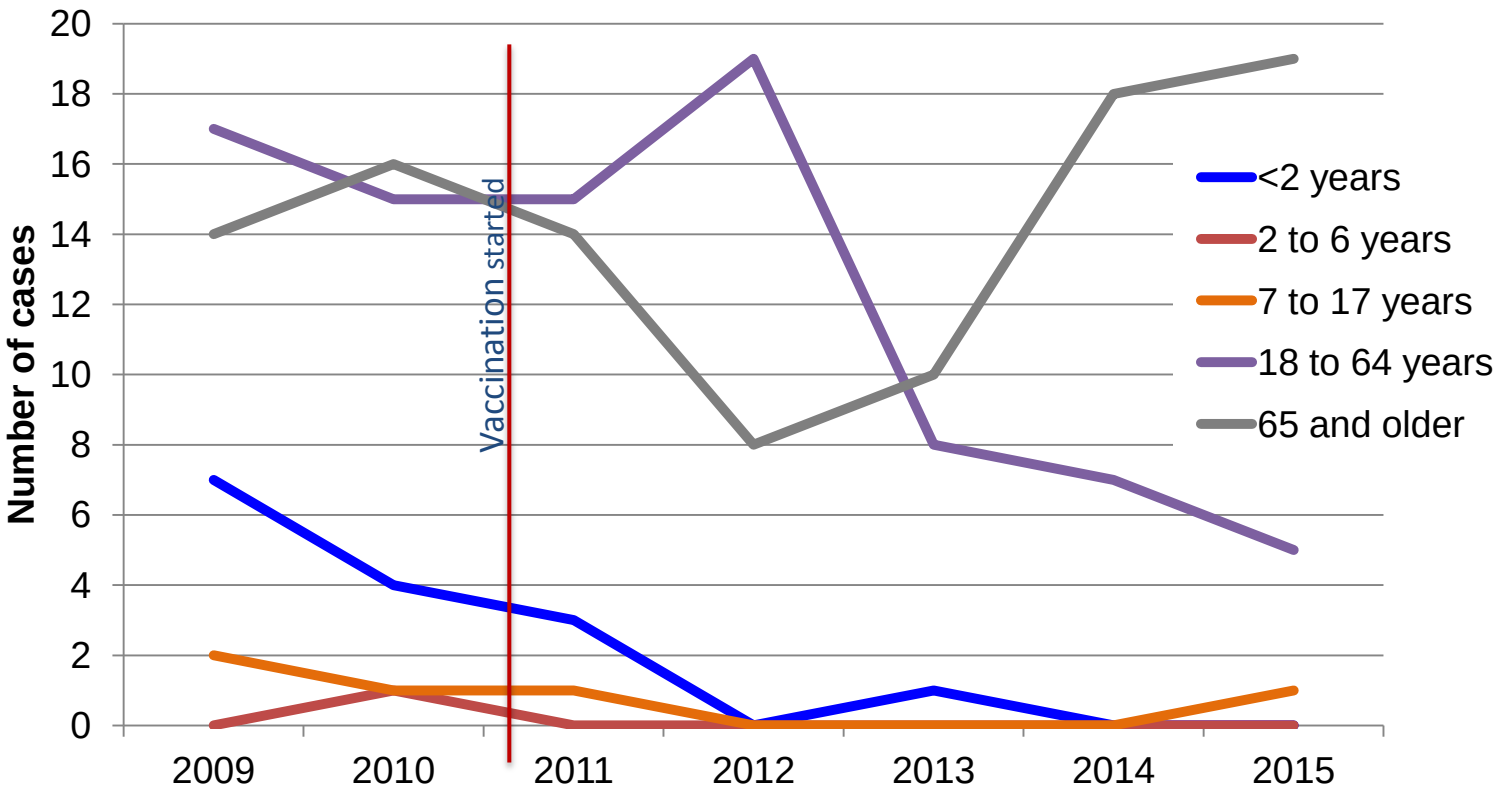
The only non-vaccine serotype that increased in incidence was serotype 22F ?

IPD; pre- and post immunisation

	2009	2010	2011	2012	2013	2014	2015	Total no.
<2 years	7	4	3	0	1	0	0	15
2 to 6 years	0	1	0	0	0	0	0	1
7 to 17 years	2	1	1	0	0	0	1	5
18 to 64 years	17	15	15	19	8	7	5	86
65 and older	14	16	14	8	10	18	19	99
Total all age groups	**40**	**37**	**33**	**27**	**19**	**25**	**25**	**206**
Incidence/100.000	12,5	11,6	10,4	8,4	5,9	7,7	7,6	
Vaccine types	25	22	13	13	6	7	3	89
Non-vaccine types	14	13	20	14	11	18	17	107

	2009-2011	2012-2015	
Total	11.4	7.4	
<2 years	48.3	2.8	p=0.01
18-64 yeas	8.0	5.1	p=0.04

IPD according to age



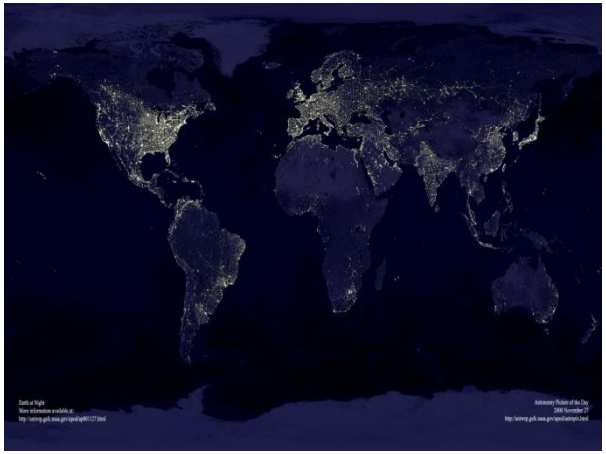
Number of children < 7 years of age with IPD:
2009-2011: 15 vs 2012-2015: 1

ECCMID 2016: The VIce study. Kristinsson et al.

ESPID 2015: The VIce study. Erlendsdóttir et al.

We have come along way…..

Where do we stand today ?



Where do we stand today ?

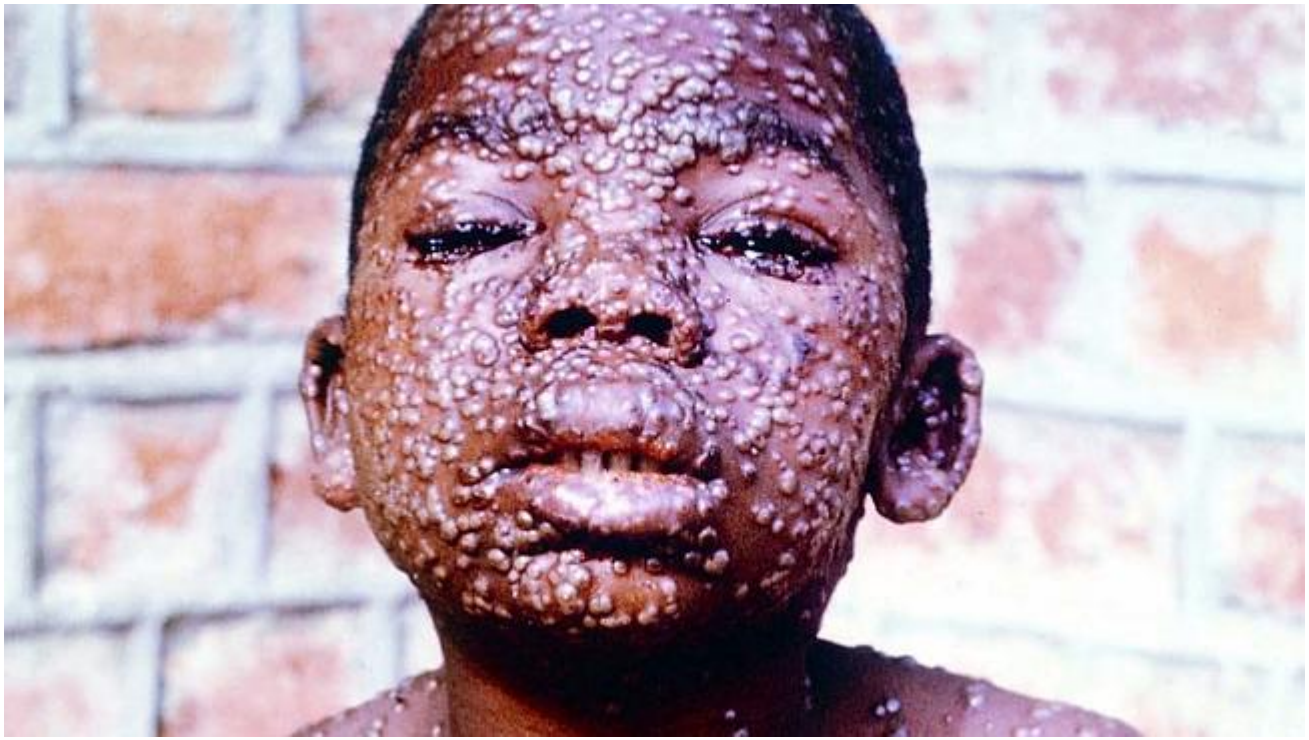
Under five mortality: > 6 million children

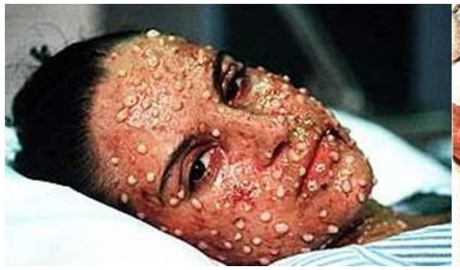
6.3 million children under the age of five died in 2013

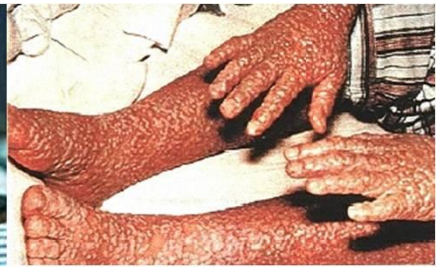
More than half is preventable !

More than half of these early child deaths are due to conditions that could be prevented or treated with access to simple, affordable interventions

Small Pox

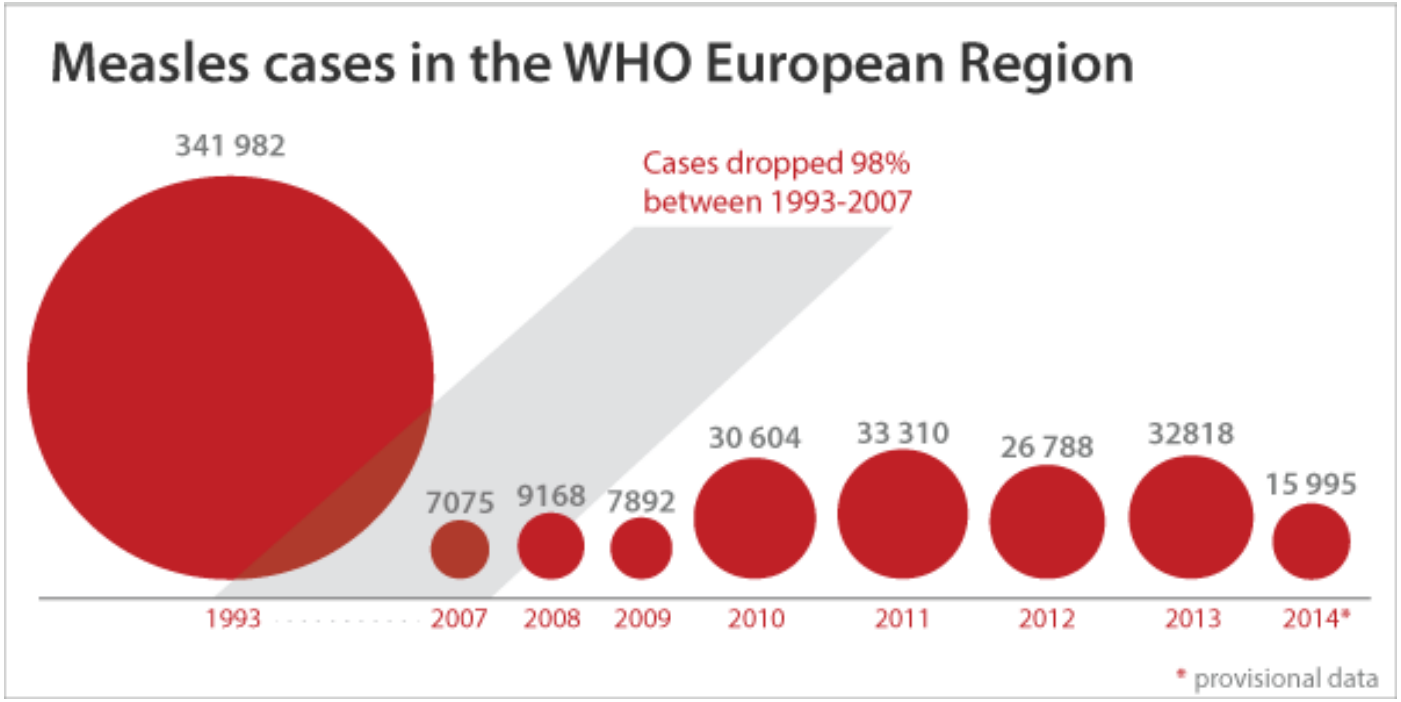


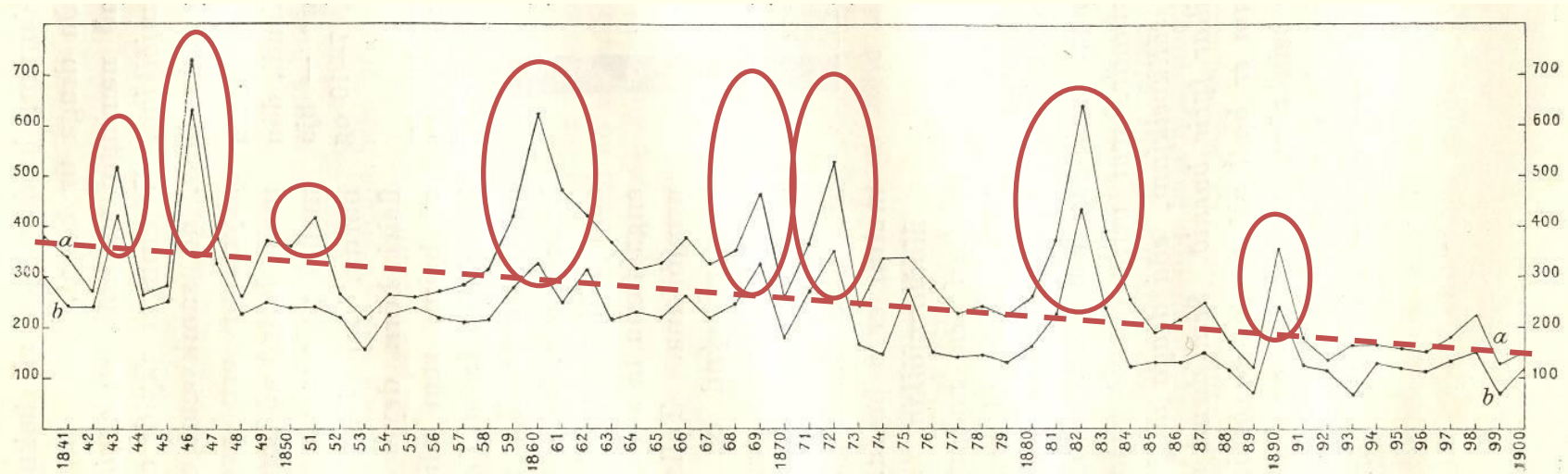




Poliomyelitis

Measles in Europe





111. mynd.

Efri línan (a) sýnir ‰ dáinna innan 5 ára, neðri línan (b) innan 1 árs. Andvanafæðingar eru alstaðar frádregnar.
Barnadauði á Íslandi frá 1841—1900.

A practical approach to serious infections in children

An ESPID supported three day training course in Iceland 4-6 February 2016

(Reduced price for ESPID members)

The aim of the course is to train front-line doctors who look after children, using a practical approach to recognise and manage a wide range of serious infections, identifying the seriously unwell child and considering differential diagnoses.
The emphasis will be on interactive small-group workshops (max 10 people per workshop). The number of participants is therefore limited.



Further information: www.cpreykjavik.is/static/files/ESPID/course_info.pdf

Register your interest: *seriousinfections.espidcourse@gmail.com*
By registering your interest, you will receive priority access to the early bird registration when this opens.

LOK !!!