



IPOPI
LATIN AMERICAN
PID PATIENTS'
MEETING

OCTOBER 19-20, 2023
MEXICO CITY, MEXICO

an **IPOPI** event

SESIÓN 5

COLLABORATION



SUPPORTED BY





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LATIN AMERICAN
PID PATIENTS'
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an IPOPI event

¿Cómo abordar las futuras pandemias? How to address future endemics?

Moderator: Martine Pergent

Moderadora: Martine Pergent

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COLLABORATION



SUPPORTED BY

GRIFOLS



Vacunación para pacientes con IDPs

Vaccination for PID patients

Dr Tamara Staines Boone, Mexico



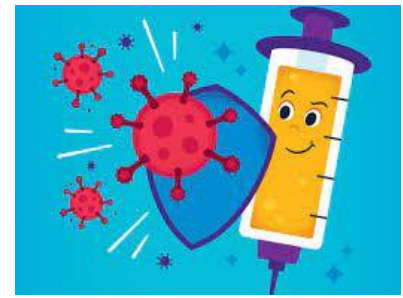
IMMUNIZATION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY



**DRA. AIDÉ TAMARA
STAINES BOONE**



VACUNAS



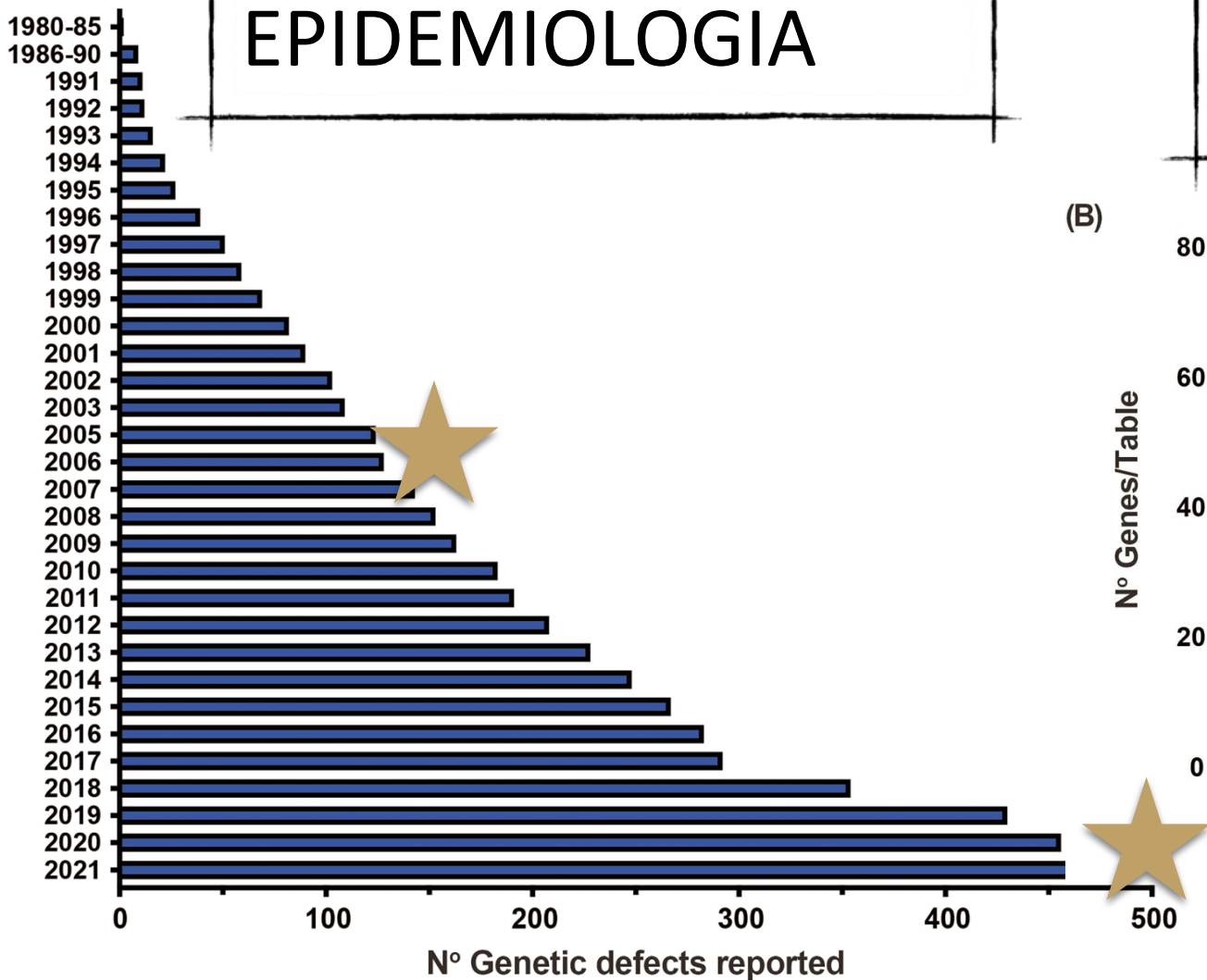
1.-They are the stepping Stone for the prevention of severe infectious diseases

2.-It is considered the technology that has prevented more diseases in the world

3.- Billions of deaths are avoided since the advent of the “modern” era of vaccines

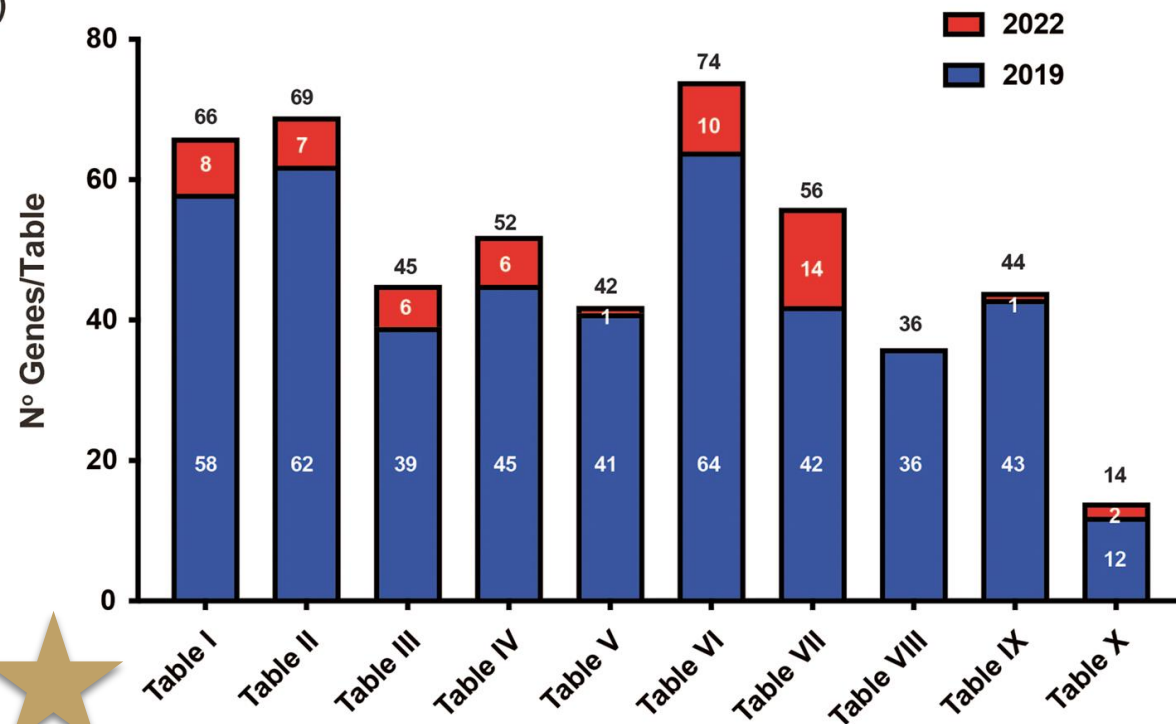
4.- Vaccines against COVID and their immune response in patients with IEI

EPIDEMIOLOGIA



ERRORES INNATOS DE LA INMUNIDAD

(B)





In some severe ICI these infectious agents can proliferate and produce a severe infection

VACCINE INDUCED DISEASE

1. Can we give **live viral or bacterial** vaccines to this specific patient?

2. Will the patient have a **sufficient response** to the vaccine to justify its administration?
para justificar su uso?



Antigens(s)	Vaccine Composition
<i>Inactive or Subunit Vaccines</i>	
Tetanus toxoid	Protein
Acellular pertussis	Protein
Diphtheria toxoid	
Hepatitis A	
Hepatitis B	
<i>Haemophilus influenzae</i> type B (HIB) capsular polysaccharide (poly-ribose phosphate [PRP])	
Human papilloma virus	
Influenza (injection)	
Meningococcal capsular polysaccharide (types A, C, W, Y)	PS conjugate vaccine (4 valent)

Antigens(s)	Vaccine Composition
Rotavirus	Reassortment attenuated virus
Rubella	Attenuated virus
Varicella	Attenuated virus
Bacille Calmette-Guerin	Attenuated mycobacterium



Meningococcal capsular polysaccharide (type B)	PS conjugate vaccine (2 valent)
Pneumococcal capsular	PS conjugate vaccine (PCV), r 13 ent)
	vaccine
	MOVAX 23 ent)



CARTILLA NACIONAL DE VACUNACION

ESQUEMA DE VACUNACIÓN					
Vacuna	Enfermedades que previene	Dosis	Edad de vacunación oportuna	Fecha de aplicación	Lote de la vacuna
BCG		Única	Al nacer	VIVOS ATENUADOS	
Hepatitis B		Única	Al nacer	INACTIVADOS	
Hexavalente DPaT+VPI+Hib+HepB	Difteria, Tosferina, Tétanos, Poliomelitis, Hepatitis B y enfermedades graves por <i>Haemophilus influenzae</i> tipo b, como neumonía y meningitis	Primera	2 meses	INACTIVADOS	
		Segunda	4 meses		
		Tercera	6 meses		
		Cuarta	18 meses		
DPT	Difteria, Tosferina y Tétanos	Refuerzo	4 años	INACTIVADOS	
Rotavirus		Primera	2 meses	VIVOS ATENUADOS	
		Segunda	4 meses		
Neumocócica conjugada	Neumonía, meningitis y otras enfermedades graves causadas por neumococo	Primera	2 meses	INACTIVADOS	
		Segunda	4 meses		
		Refuerzo	12 meses		


ESQUEMA DE VACUNACIÓN

Vacuna	Enfermedades que previene	Dosis	Edad de vacunación oportuna	Fecha de aplicación	Lote de la vacuna
Influenza	Neumonía por virus de la influenza A y B	Primera	A partir de los 6 meses		
		Segunda	Al mes de la primera		
		Una dosis cada temporada invernal	1 año		
			2 años		
			3 años		
SRP (Triple viral)		Primera	12 meses		
		Segunda*	A partir de los 18 meses		

INACTIVADOS

VIVOS ATENUADOS

*Nacidos antes de junio del año 2020 se les aplicará la vacuna SRP a los 6 años.

Otras vacunas	Nombre de la vacuna	Número de la dosis	Fecha de aplicación	Lote de la vacuna
Espacio reservado para vacunas no incluidas en el esquema básico del programa de vacunación universal	VARICELA			
	HEPATITIS A			
	MENINGOCOCO			

VIVOS ATENUADOS

INACTIVADOS

INACTIVADOS

VACUNAS DE
VIRUS VIVOS



VACUNAS DE
BACTERIAS
VIVAS

ROTAVIRUS

VARICELA

POLIO ORAL-SABIN

SRP

HERPES ZOSTER

ADENOVIRUS

BCG

SALMONELLA typhimurium



Published in final edited form as:

J Clin Immunol. 2019 May ; 39(4): 376–390. doi:10.1007/s10875-019-00642-3.

Life-threatening infections due to live attenuated vaccines: early manifestations of inborn errors of immunity

Laura Pöyhönen, MD, PhD^{1,§}, Jacinta Bustamante, MD, PhD^{1,2,3,4,§}, Jean-Laurent Casanova, MD, PhD^{1,2,3,5,6}, Emmanuelle Jouanguy, PhD^{1,2,3}, Qian Zhang, MD^{1,@}

15 LIFE VACCINES



Oral Rotavirus

2009

Measles

1963

Oral poliovirus

1966

BCG

1951

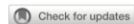
SCID

SCID

AGAMMA

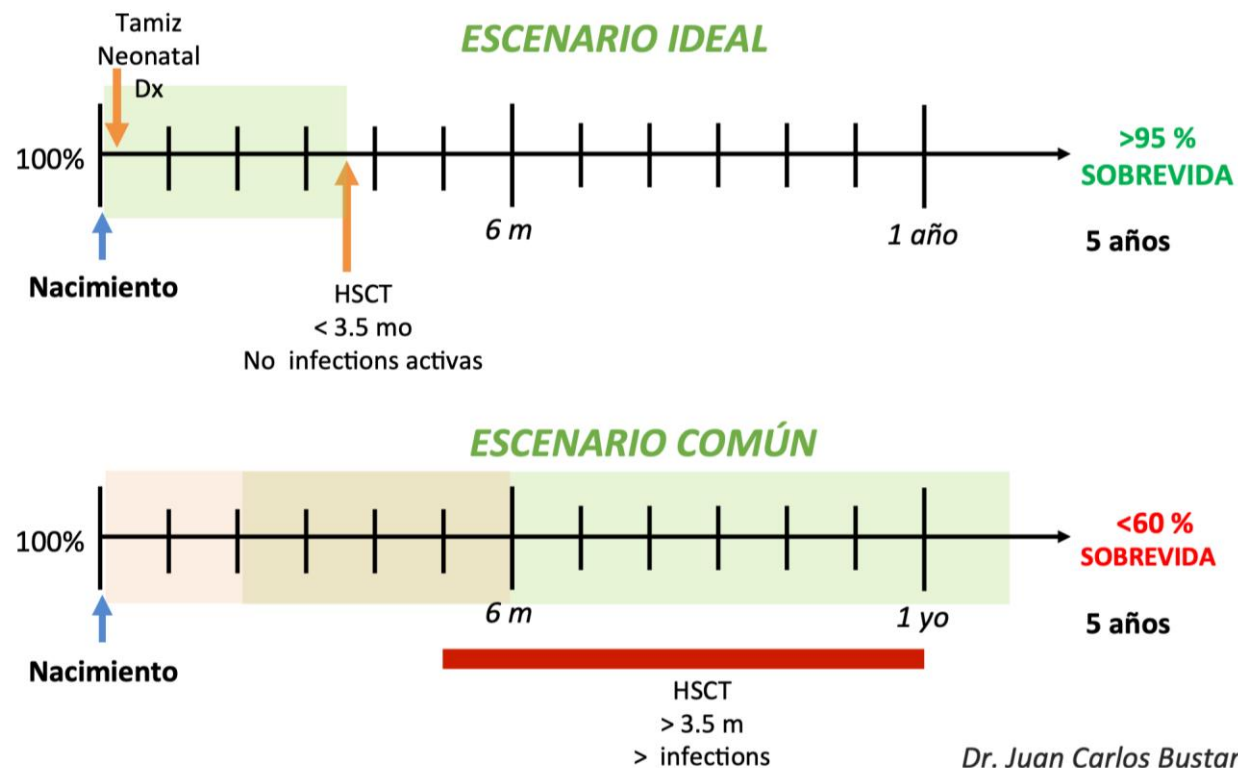
SCID

Latin American consensus on the supportive management of patients with severe combined immunodeficiency



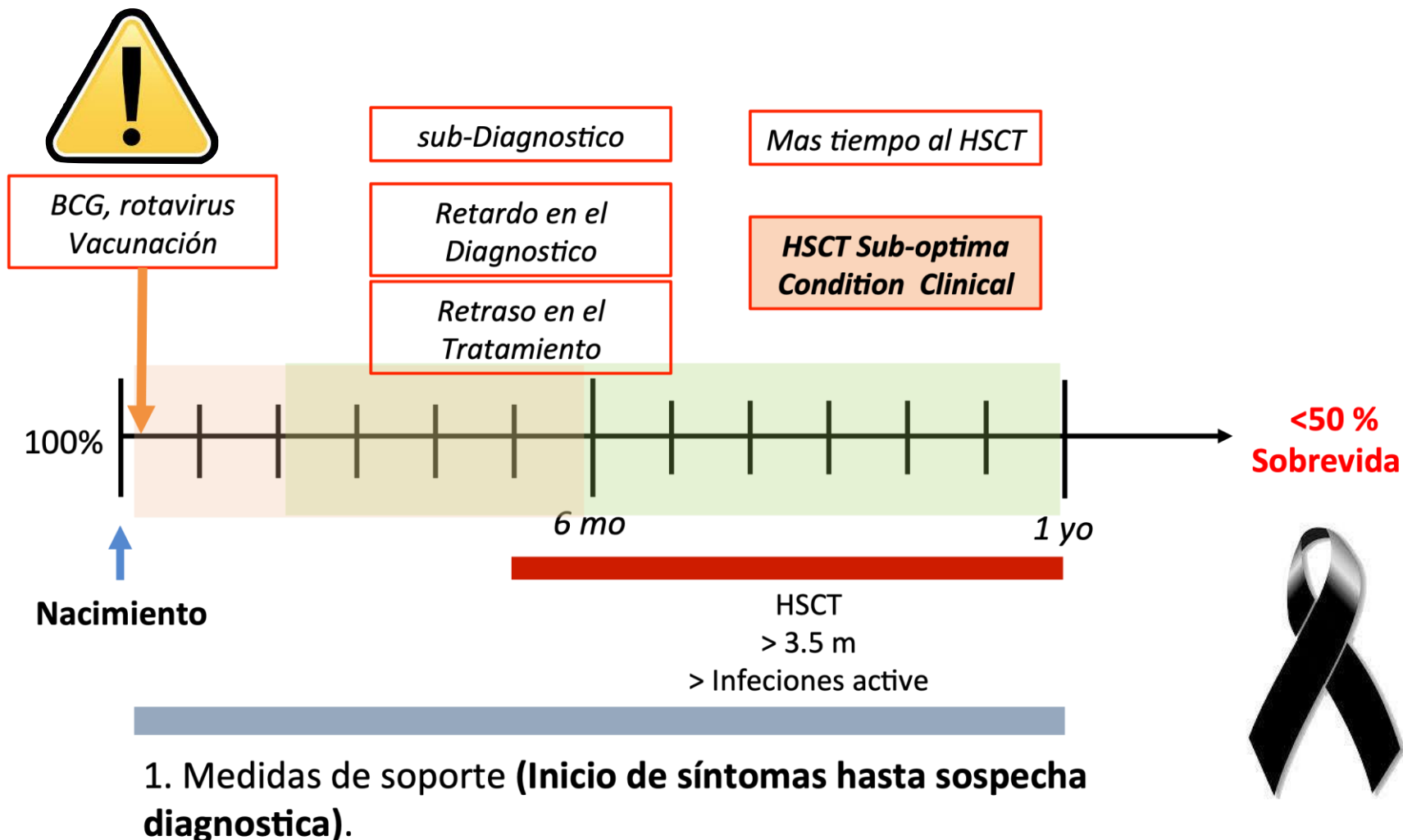
Juan Carlos Bustamante Ogando, MD,^a Armando Partida Gaytán, MD,^a Juan Carlos Aldave Becerra, MD,^b Aristóteles Álvarez Cardona, MD,^c Liliana Bezrodnik, MD,^{d,e} Arturo Borzutzky, MD,^f Lizbeth Blancas Galicia, MD, MSc,^a Diana Cabanillas, MD,^g Antonio Condino-Neto, MD, PhD,^h Agustín De Colsa Ranero, MD,ⁱ Sara Espinosa Padilla, MD, PhD,^a Juliana Folloni Fernandes, MD,^j Jorge Alberto García Campos, MD,^k Héctor Gómez Tello, MD,^l María Edith González Serrano, MD,^a Alonso Gutiérrez Hernández, MD,^m Víctor Manuel Hernández Bautista, MD,^m Gabriele Ivankovich Escoto, MD,^{n,oo} Alejandra King, MD,^o Juliana Lessa Mazzucchelli, MD,^p Beatriz Adriana Llamas Guillén, MD,^q Saul Oswaldo Lugo Reyes, MD, MS,^a Sarbelio Moreno Espinosa, MD,^r Matías Oleastro, MD,^a Francisco Otero Mendoza, MD,ⁱ María Cecilia Poli Harlowe, MD, PhD,^s Oscar Porras, MD, PhD,^a Nideshda Ramírez Uribe, MD,^v Lorean Regairaz, MD,^g Francisco Rivas Larrauri, MD,^m Federico José Saracho Weber, MD,^w Anete S. Grumach, MD,^x Tamara Staines Boone, MD,^y Beatriz Tavares Costa-Carvalho, MD,^z Marco Antonio Yamazaki Nakashimada, MD,^m and Francisco Javier Espinosa Rosales, MD^{aa}

Mexico City, Aguascalientes, Monterrey, Puebla, Morelos, and Chihuahua,

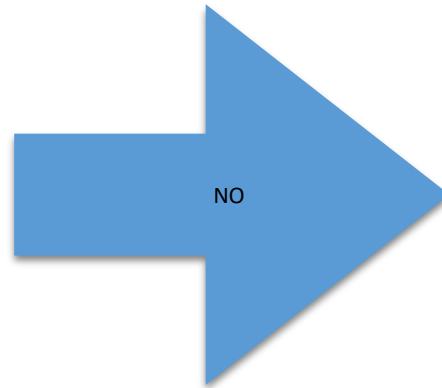


Dr. Juan Carlos Bustamante Ogando

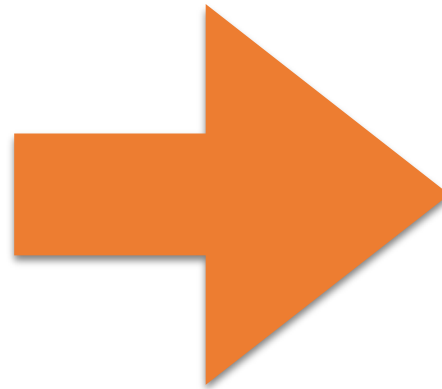
MEXICAN-LATINOAMERICAN SCENE



- SEVERE COMBINED IMMUNODEFICIENCY
- COMPLETE DI GEORGE SYNDROME



BCG
SABIN (POLIO ORAL)
SRP
ROTAVIRUS



INACTIVADAS
NO HACEN DAÑO
NO SON EFECTIVAS

TABLE 13.4 Criteria for administration of live vaccines in partial DiGeorge anomaly.**A. CD4⁺ T cells/mm³:** Age based criterion based on 10th percentile for age for children with partial DiGeorge anomaly¹⁸⁹

Age	0–3 m	3–6 m	6–12 m	1–2 years	2–6 years	6–12 years	12–18 years
Total CD4 ⁺ T cells	>1600	>1800	>1400	>1300	>700	>650	>530

T cell proliferative response to PHA Normal

B. CD4⁺ T cells/mm³: Age based criterion based on HIV guidelines for children with partial DiGeorge anomaly^{182, 190, 193}

Age	<12 m	1–5 years	6–12 years	≥13 years
Total CD4 ⁺ T cells	≥750	≥500	≥200	≥200

T cell proliferative response to tetanus toxoid Normal

C. Criteria for children with partial DiGeorge anomaly of all ages based on CD8⁺ T cell countsCD8⁺ T cell count ≥250**D. Criteria for children with complete DiGeorge anomaly after immune reconstitution after cultured thymus tissue transplantation.**

Off immune suppression

CD4>CD8

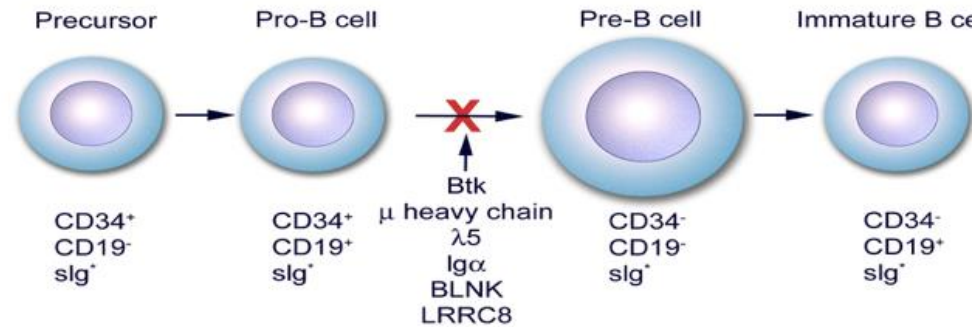
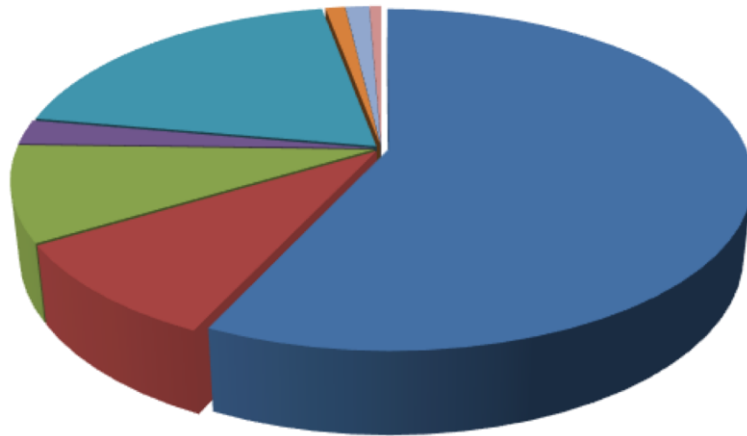
CD8⁺ T cells >100

T cell proliferative response to phytohemagglutinin >100,000 counts per minute

Deficiencias de Anticuerpos

- Affect to the number or the function of LB
- Can be severe or not

Prototipo



- Antibody defects
- Combined Immunodeficiencies
- Phagocyte disorders
- Complement defects
- Syndromes + Immunodeficiencies
- Dysregulation
- Innate immune disorders
- Autoinflammatory disorders
-

X-LINKED AGAMAGLOBULINEMIA

HUMORAL DEFECTS

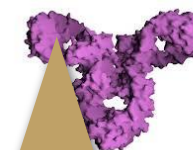
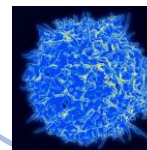
- X-LINKED AGAMAGLOBULINEMIA OR BRUTON
- AGAMAGLOBULINEMIA AR
- COMMON VARIABLE IMMUNODEFICIENCY.

SEVERE

NO

SABIN (POLIO ORAL)
Fiebre amarilla
Tifoidea oral

YES



INFLUENZA
A
COVID
VACCINE

HUMORAL DEFECTS

- SELECTIVE IgA DEFICIENCY
- IGG SUBCLASS DEFICIENCY
- ANTIBODY-SPECIFIC DEFICIENCY

NO

SABIN (POLIO ORAL)
Fiebre amarilla

YES

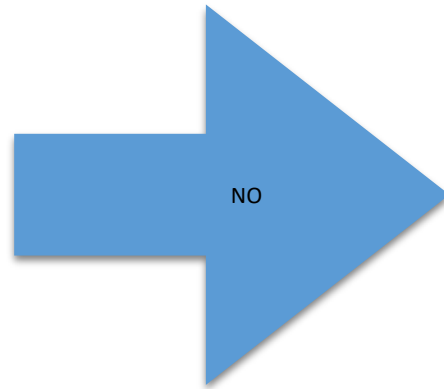
Resto de inmunizaciones
APLICARLAS!!!

NEUMOCOCCAL VACCINE

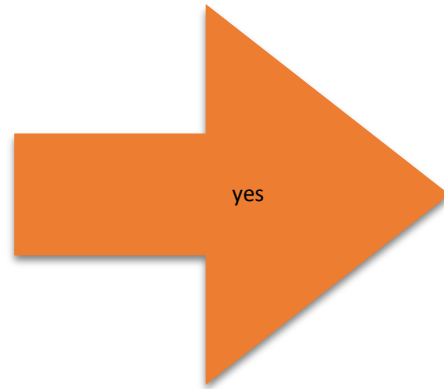
FAGOCYTIC

DEFECTS

- CONGENITAL NEUTROPENIAS
- CHRONIC GRANULOMATOUS DISEASE
- LAD LEUCOCITES ADHESION DEFECTS
- MIELOPEROXIDASE DEFICIENCY



Bacterias vivas (BCG)

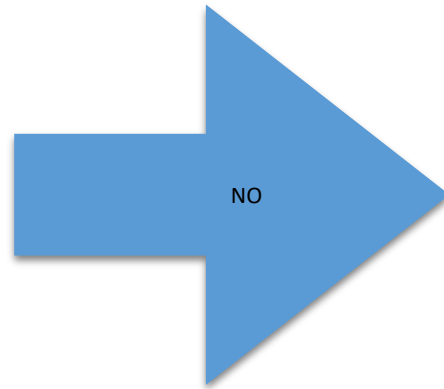


Resto de inmunizaciones
Incluso virales (excepto algunas LAD)

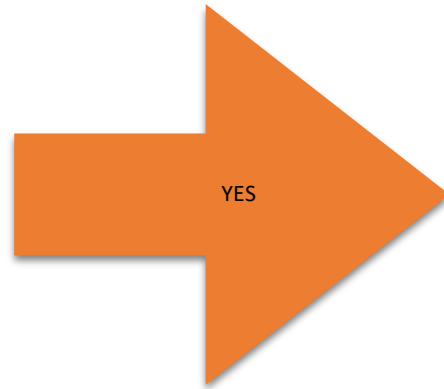
**INFLUENZA
VACCINE**

COMPLEMENT

DEFECTS



NO TIENEN CONTRAINDICACIONES
PARA NINGUNA VACUNA



TODAS SE DEBEN DE APLICAR

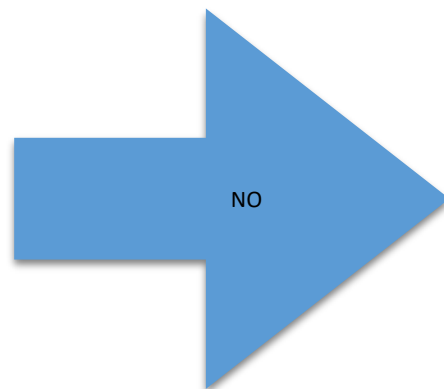
Neisseria meningitidis
Streptococcus pneumoniae
Haemophilus influenza

ASPLENIA

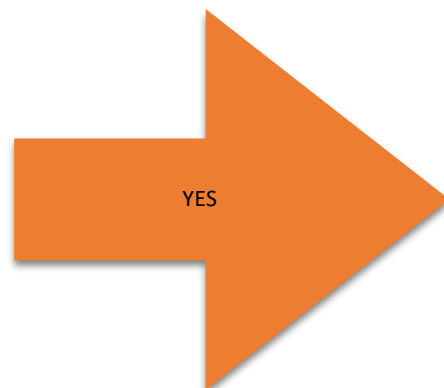
I N N A T E

I M M U N I T Y

- IL12-IFN AXE DEFECTS
- NF-KB DEFECTS
- NEMO DEFICIENCY
- GATA 2 DEFICIENCY



BACTERIAS VIVAS (BCG)
SALMONELLA
VIRALES VIVAS



Resto de inmunizaciones

BCG vaccination in patients with severe combined immunodeficiency: Complications, risks, and vaccination policies

Beatriz E. Marciano, MD,^a Chiung-Yu Huang, PhD,^b Gyan Joshi, PhD,^b Nima Rezaei, MD,^c Beatriz Costa Carvalho, MD,^d Zoe Allwood, MD,^e Aydan Ikinciogullari, MD,^f Shereen M. Reda, MD,^g Andrew Gennery, MD,^h Vojtech Thon, MD,ⁱ Francisco Espinosa-Rosales, MD,^j Waleed Al-Herz, MD,^k Oscar Porras, MD,^l Anna Shcherbina, MD,^m Graham Davies, MD,^e Bénédicte Neven, MD,ⁱⁱ and Sergio D. Rosenzweig, MD, PhDⁱⁱ
Bethesda, Md, Tehran, Iran, São Paulo and Minas Gerais, Brazil, London and Newcastle upon Tyne, United Kingdom, Ankara, Bursa, and Atakum-Samsun, Turkey, Cairo, Egypt, Brno and Prague, Czech Republic, Mexico City and Guadalajara, Mexico, Kuwait City, Kuwait, San Jose, Costa Rica, Moscow, Russia, Krakow, Poland, Medellin, Colombia, Buenos Aires and Córdoba, Argentina, Lisbon, Portugal, Muscat, Oman, Sapporo, Tokyo, Hyogo, and Kyoto, Japan, Hong Kong, China, and Paris, France

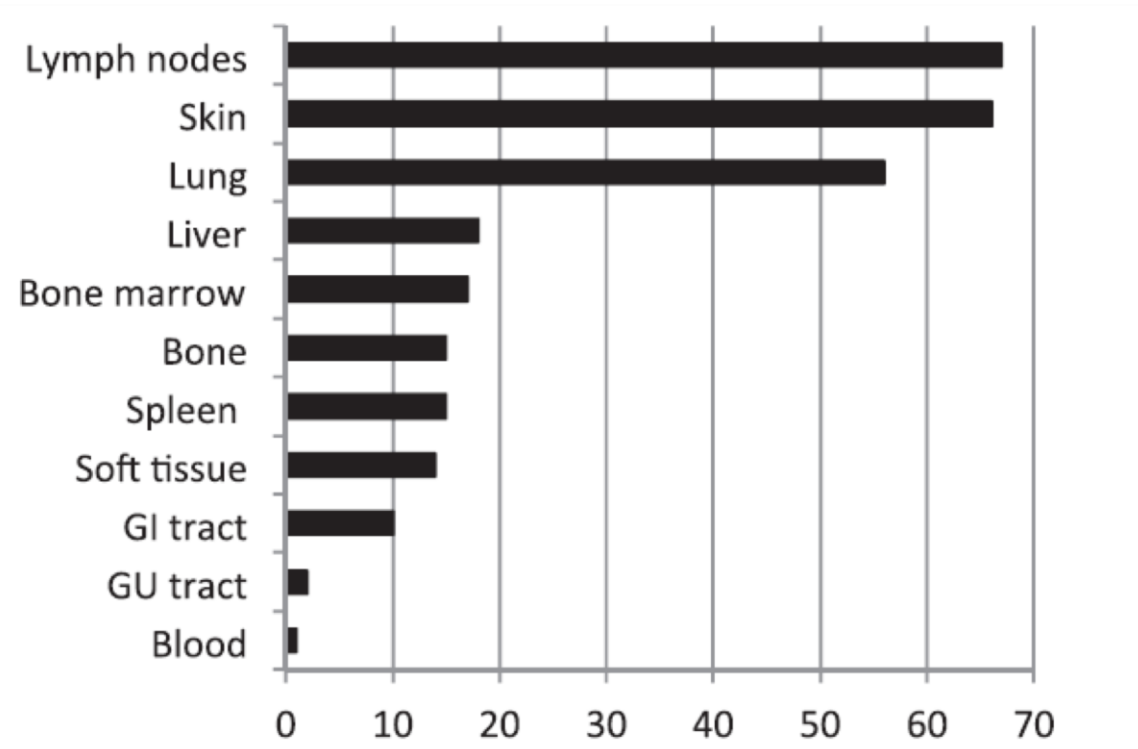
**349 pacientes
(28 centros
17 ciudades)**

**17% localizada
34% diseminada
46 muertes**

**< 250/mL linf T:
Mayor riesgo**

**ABSOLUTAMENTE
CONTRAINDICADA**

51% COMPLICACIONES



Mycobacterial disease in patients with chronic granulomatous disease: A retrospective analysis of 71 cases



Francesca Conti, MD, PhD,^{a,b,c,*} Saul Oswaldo Lugo-Reyes, MD,^{a,b,d,*} Lizbeth Blancas Galicia, MD,^{a,b,d,*} Jianxin He, MD,^e Güzide Aksu, MD,^f Edgar Borges de Oliveira, Jr, PhD,^{a,b,g} Caroline Deswarte, MSc,^{a,b} Marjorie Hubeau, PhD,^{a,b} Neslihan Karaca, MD,^f Maylis de Suremain, AS,^{a,b} Antoine Guérin, MSc,^{a,b} Laila Ait Baba, PhD,^h Carolina Prando, MD, PhD,ⁱ Gloria G. Guerrero, PhD,^{a,b} Melike Emiroglu, MD,^j Fatma Nur Öz, MD,^k Marco Antonio Yamazaki Nakashimada, MD,ⁱ Edith Gonzalez Serrano, MD,ⁱ Sara Espinosa, MD, PhD,ⁱ Isil Barlan, MD,^m Nestor Pérez, MD, PhD,ⁿ Lorena Regairaz, MD,ⁿ

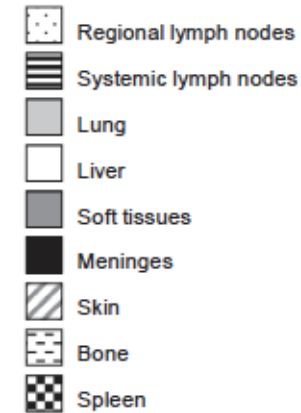
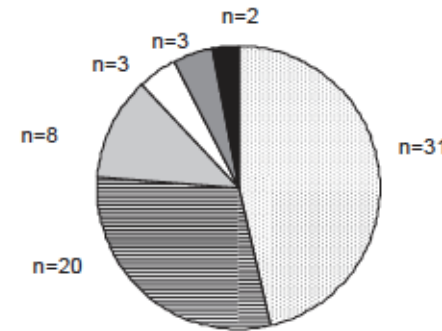
BCG infections

71 PX

98%
BCG

75%
BCGITIS

60%
1st
manifestation



M. tuberculosis infections

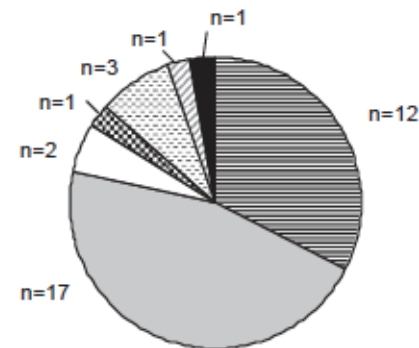
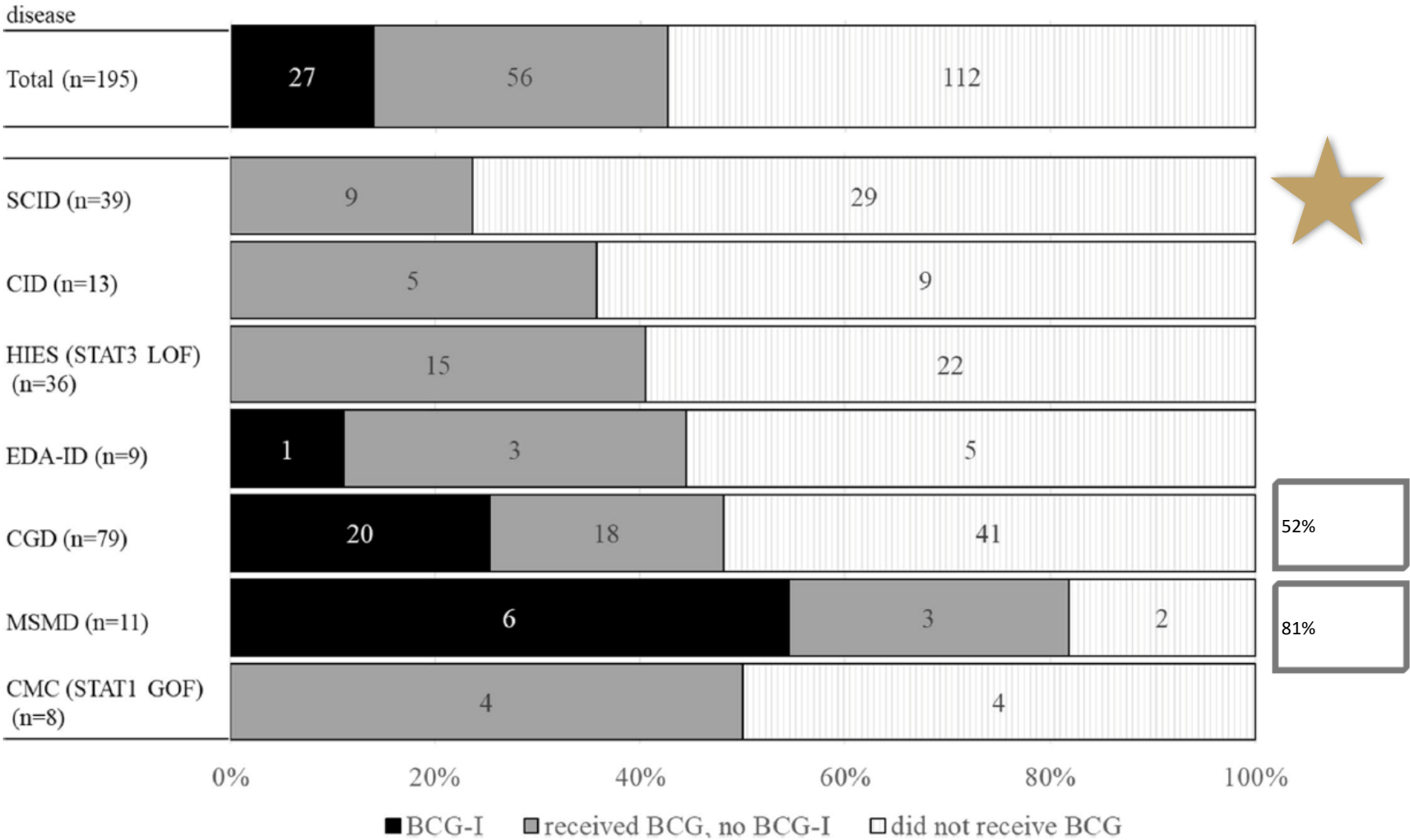


FIG 1. Mycobacterial infection sites in patients with CGD. Numbers of patients with BCG and *M. tuberculosis* infections are shown.

Vaccination for Patients with Inborn Errors of Immunity: a Nationwide Survey in Japan

Sho Hosaka¹ · Takahiro Kido¹ · Kazuo Imagawa^{1,2} · Hiroko Fukushima^{1,2} · Tomohiro Morio³ · Shigeaki Nishida¹ · Hidetoshi Takada^{1,2}

43% en total recibieron BCG
14 % desarrollo enfermedad



Bacille Calmette–Guerin Complications in Newly Described Primary Immunodeficiency Diseases: 2010–2017

- STAT 1 GOF 27/350
- STAT3 GOF
- Snd de Activacion de Fosfoinositide 3-kinase (APSD)
- Defectos en vías de NF-kB
- GATA 2 (gen codifica para factor de transcripción hematopoyético)

BCG

- 120 millions of dosis per year
- Protection vs Tb militar y meníngea
- LIFE ATTENUATED *Mycobaterium bovis*
- BCGitis 1:2,500 BCGosis 1:100,000

INMUNODEFICIENCIA COMBINADA SEVERA

ENFERMEDAD GRANULOMATOSA CRONICA

SUCEPTIBILIDADES MENDELIANAS A MYCOBACTERIAS

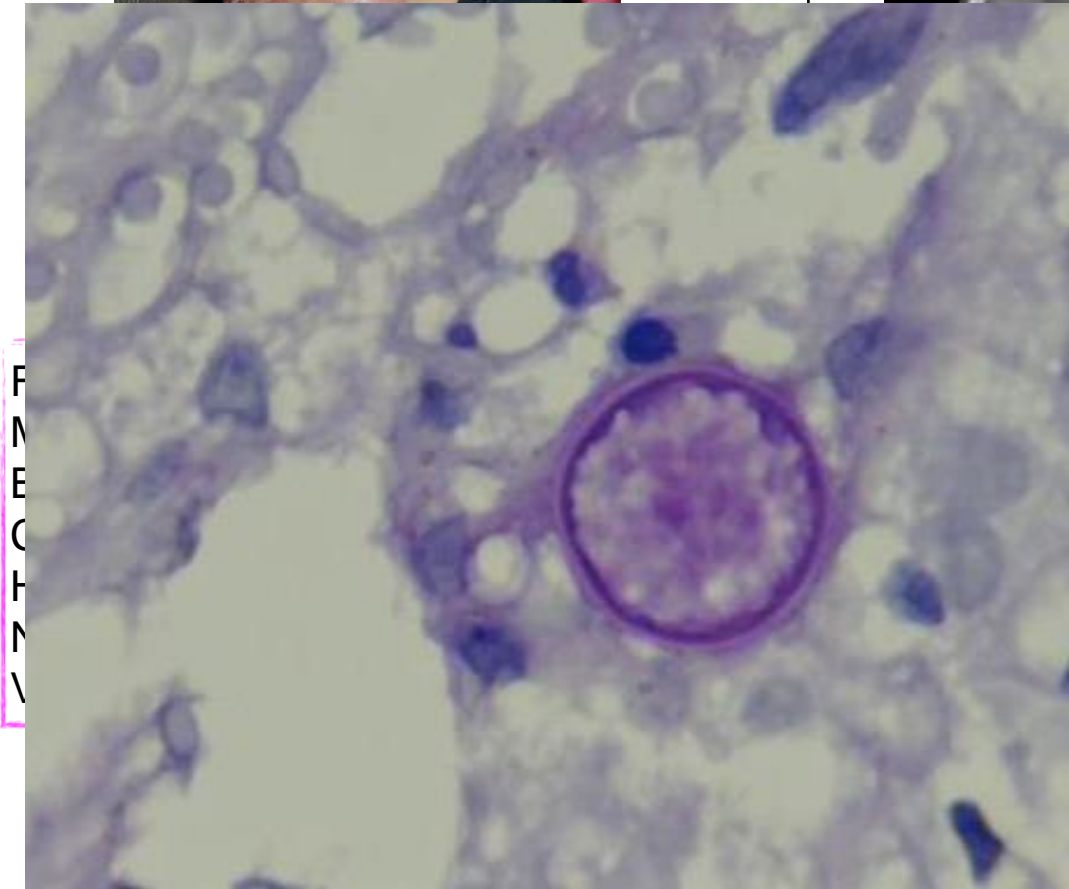
IL12RB1-23-IFN gamma (**77%-81%** DISEMINADA)

JAK1, STAT1,IRF8,SPPL2A,NEMO,TYK2

D
,
T
A
P
P
L
Y



Parame	
Hb	
Leukocy	



Jacinta Bustamante^{16,17,18,23} · Lizbeth Blancas Galicia²

(serology)	
DHR assay	Sir

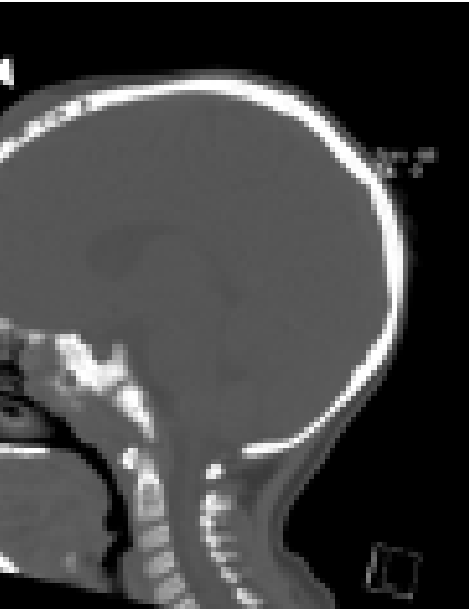


Tabla y DHR cortesía Dra. Liz Blancas



PARÁMETRO	RESULTADO
	6

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNODEFICIENCY

A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency

IRF4 International Consortium*

Interferon regulatory factor 4 (IRF4) is a transcription factor (TF) and key regulator of Immune cell development and function. We report a recurrent heterozygous mutation in IRF4, p.T95R, causing an autosomal dominant combined Immunodeficiency (CID) in seven patients from six unrelated families. The patients exhibited profound susceptibility to opportunistic infections, notably *Pneumocystis jirovecii*, and presented with agammaglobulinemia. Patients' B cells showed impaired maturation, decreased immunoglobulin isotype switching, and defective plasma cell differentiation, whereas their T cells contained reduced T_H17 and T_{FH} populations and exhibited decreased cytokine production. A knock-in mouse model of heterozygous T95R showed a severe defect in antibody production both at the steady state and after immunization with different types of antigens, consistent with the CID observed in these patients. The IRF4^{T95R} variant maps to the TF's DNA binding domain, alters its canonical DNA binding specificities, and results in a simultaneous multimorphic combination of loss, gain, and new functions for IRF4. IRF4^{T95R} behaved as a gain-of-function hypermorph by binding to DNA with higher affinity than IRF4^{WT}. Despite this increased affinity for DNA, the transcriptional activity on IRF4 canonical genes was reduced, showcasing a hypomorphic activity of IRF4^{T95R}. Simultaneously, IRF4^{T95R} functions as a neomorph by binding to noncanonical DNA sites to alter the gene expression profile, including the transcription of genes exclusively induced by IRF4^{T95R} but not by IRF4^{WT}. This previously undescribed multimorphic IRF4 pathophysiology disrupts normal lymphocyte biology, causing human disease.

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UJO
NORMAL

G ITIS



POLIO ORAL SABIN

- Poliomiелitis-poliovuris 1908
- Albert Sabin 1957-1962
- Easy to administer – high efectivity
- 0.1-1% acute flaccid paralysis (PFA)
- Eradication 2017 22 cases in 2 countries

INMUNODEFICIENCIA COMBINADA SEVERA

RAG1-2, ARTEMIS

36 casos reportados PA

AGAMAGLOBULINEMIA

- 7% Excreción prolongada del virus
- 0.6-3% Parálisis flácida -mortalidad 62%

DEFICIENCIA SELECTIVA DE IgA

D
O
N
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T
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Y

TRIPLE VIRAL

- **Measles** 1963 Rubella 1969 Mumps 1967
- Combined since 1971
- High efficacy with diminished incidence 96-99%
- Rare encephalitis due to inclusion

INMUNODEFICIENCIA COMBINADA SEVERA

Infección diseminada por sarampión

VALORAR EN SND DE DI GEORGE

14% presentan reacción LEVE
Incluso segura en LT CD4 600

ERRORES DE INMUNIDAD INNATA IFN TIPO 1

STAT1, IRF 7, IRF9

~~Encefalitis~~ →

STAT2

— ~~Infección~~ Infección diseminada por Sarampión

D
O
'
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ROTAVIRUS

- Rotavirus causes 114 millions of diarrheal cases
- 2.4 millón hospitalisations
- 600,000 deaths per year in the world
- The vaccine ↓ 60-90% of hospitalisations

INMUNODEFICIENCIA COMBINADA SEVERA

20 Px han desarrollado infección crónica o severa

Parecería segura en niños con VIH -SIDA

APLICAR VACUNA ES PEOR???

- Exposición temprana 2 y 4 meses contribuyen a los síntomas graves
- La severidad de la infección es dosis dependiente

D
O
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Y

IMPORTANTE **SI** APLICAR

VACCINE VS NEUMOCOCO

- Specific antibody deficiency
- Congenital Asplenia
- Complement deficiency

VACCINE VS MENINGOCOCO

CONJUGATED VACCINE

- Congenital asplenia
- Antibody deficiency

VACCINE VS PAPILIOMA

RECOMBINANT PROTEIN

- Dock 8
- Epidermolysis verruciformis
- GATA 2
- WHIM O WILD





COVID-19 in the Context of Inborn Errors of Immunity: a Case Series
of 31 Patients from Mexico

31 PACIENTES
6 FALLECIMIENTOS
✱IDCV (3)
✱IDC (1)
✱EGC(1)
✱Auto-inflamatorio (1)

Antibody deficiency 442 Px

MAYOR MORTALIDAD
IFN tipo 1
APECED
IDCV Daño Pulmonar

Combined PID 132 Px

Immune dis-regulation 69 Px

Innate Immunity deficiency 58 Px



[Physiology \(Bethesda\)](#). 2022 Nov 1; 37(6): 290–301. Published online 2022 Aug 9. doi: [10.1152/physiol.00016.2022](#)

PMCID: PMC9550578 | PMID: [35944006](#)

COVID-19 and Inborn Errors of Immunity

[Ottavia M. Delmonte](#),^{✉ 1,*} [Riccardo Castagnoli](#),^{1, 2, 3,*} and [Luigi D. Notarangelo](#)¹

→ IDCV 290

15% Mortality

→ Agama 71

8% Mortality

→ IDCS 22

12% Mortality

→ IDC 110

APECED
CTL4

16% Mortality

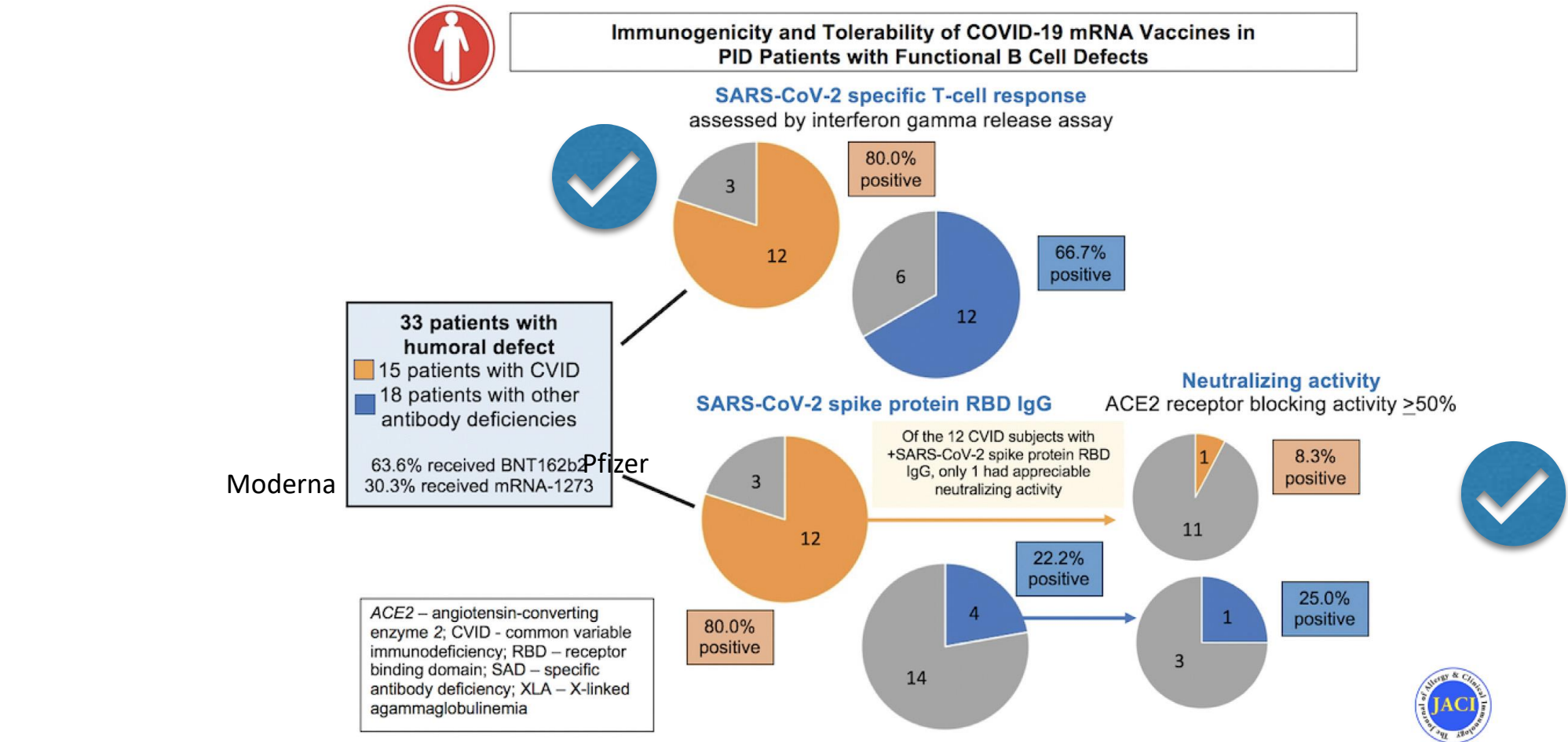
IFN
TLR3

10 % Mortality

Immunogenicity and tolerability of COVID-19 messenger RNA vaccines in primary immunodeficiency patients with functional B-cell defects



Michele N. Pham, MD,^a Kanagavel Murugesan, PhD,^b Niaz Banaei, MD,^{b,c,e} Benjamin A. Pinsky, MD, PhD,^{b,c,f} Monica Tang, MD,^a Elisabeth Hoyte, NP,^d David B. Lewis, MD,^d and Yael Gernez, MD, PhD^d *San Francisco and Stanford,*



50% IgG específicos



Subject no.	Age (years)	Sex	PID diagnosis	Antibody deficiency	Ig therapy	SARS-CoV-2 mRNA vaccine	dose and serology (weeks)	IgG after vaccine	ACE2 blocking activity	SARS-CoV-2 IGRA
1	21	M	Agammaglobulinemia	Yes	Yes	Pfizer-BioNTech	4.43	Negative	—	Positive
2	30	M	XLA	Yes	Yes	Moderna	4.00	Negative	—	Positive
3	30	F	CVID	Yes	Yes	Pfizer-BioNTech	5.86	Positive	50-60%	Positive
4	32	F	CVID	Yes	Yes	Pfizer-BioNTech	8.71	Negative	—	Positive
5	38	F	CVID	Yes	Yes	Pfizer-BioNTech	4.14	Positive	40-50%	Positive
6	40	M	CVID	Yes	Yes	Moderna	5.57	Positive	40-50%	Positive
7	41	F	CVID	Yes	Yes	Pfizer-BioNTech	9.14	Positive	<10%	Positive
8	53	M	CVID	Yes	Yes	Moderna	9.43	Negative	—	Positive
9	56	M	CVID	Yes	Yes	Pfizer-BioNTech	15.00	Positive	<10%	Negative
10	58	F	CVID	Yes	Yes	Pfizer-BioNTech	4.86	Positive	<10%	Positive
11	59	M	CVID	Yes	Yes	Pfizer-BioNTech	7.00	Negative	—	Negative
12	60	F	CVID	Yes	Yes	Pfizer-BioNTech	9.57	Positive	30-40%	Positive
13	63	F	CVID	Yes	Yes	Moderna	9.86	Positive	30-40%	Positive
14	71	F	CVID	Yes	Yes	Moderna	10.71	Positive	20-30%	Positive
15	72	M	CVID	Yes	Yes	Moderna	17.57	Positive	NA	Positive
16	73	F	CVID	Yes	No	Pfizer-BioNTech	24.71	Positive	<10%	Positive
17	79	F	CVID	Yes	Yes	Pfizer-BioNTech	11.29	Positive	<10%	Negative
18	39	F	HGG	Yes	Yes	Moderna	9.57	Positive	60-70%	Positive
19	55	F	HGG	Yes	Yes	Pfizer-BioNTech	6.85	Negative	—	Positive
20	67	F	HGG	Yes	Yes	Pfizer-BioNTech	9.43	Positive	<10%	Positive
21	75	M	HGG	Yes	Yes	Moderna	16.77	Negative	—	Negative
22	53	F	SAD	Yes	Yes	Pfizer-BioNTech	6.57	Positive	40-50%	Positive
23	74	F	SAD	Yes	Yes	Moderna	14.43	Positive	10-20%	Positive
24	43	M	GS with HGG	Yes	Yes	Pfizer-BioNTech	9.86	Negative	—	Negative
25	65	F	GS with HGG	Yes	Yes	Pfizer-BioNTech	5.86	Negative	—	Positive
26	68	F	GS with HGG	Yes	Yes	Moderna	19.00	Negative	—	Negative
27	70	F	GS with HGG	Yes	Yes	Pfizer-BioNTech	19.14	Negative	—	Negative
28	39	M	Hyper IgM syndrome	Yes	Yes	Pfizer-BioNTech	15.71	Negative	—	Positive
29	40	M	Hyper IgM syndrome	Yes	Yes	Pfizer-BioNTech	13.14	Negative	—	Positive
30	19	M	CTLA-4 deficiency	Yes	Yes	Pfizer-BioNTech	6.43	Negative	—	Positive
31	29	M	PIK3R1	Yes	Yes	Pfizer-BioNTech	18.25	Negative	—	—
32	26	F	Ataxia telangiectasia	Yes	Yes	Pfizer-BioNTech	5.71	Negative	—	—
33	20	M	ATP6AP1 gene/immunodeficiency 47	Yes	Yes	Pfizer-BioNTech	4.43	Negative	—	Positive

74% respuesta IFN

Antibody responses to COVID-19 vaccine in patients with CVID

Country	Seroconversion Data	Factors Associated with Increased Risk of Failure	Major Adverse Events
USA	6/6 (100%)	NA	None
USA	7/8 (87.5%)	NA	None
USA	12/15 (80%)*	NA	None (see Table 2)
USA	10/10 (100%) after 3 doses†	NA	None
Israel	10/12 (83.3%)	Lower response in older pt	None
Israel	11/15 (73.3%)	B ≤1% or B <6% and smB ≤2% of B	NA
Italy	3/4 (75%)	B <1%	None
Italy	11/33 (33%)‡	Low RBD-specific smB	NA
Italy	8/34 (23.5%)‡	All CVID patients lacked mB and activated mB with high binding capacity	NA
Italy	14/38 (36.8%)‡	smB ≤2% of B; low IgA, IgM	NA
Italy	13/14 (92%)‡	NA	None
Sweden	28/41 (68.3%)‡	NA	None
Wales	43/60 (71.7%)	Low IgA + IgM, low B, ChAdOx1-S recipients	NA
Spain	15/18 (83%),‡ 9/18 (50%) neutralizing Ab	B cell lymphopenia; autoimmune/lymphoproliferation	None

anti-spike antibodies 60%

Cualitative-cuantitative
Sub-optimals

LT response inducedLT

- Age of the patient
- Autoimmunity history
- LB smaller than 2%
- Memory LB les than 2%
- LT lymphopenia
- Reduced activation of LT memory
- Low levels of both IgA and IgM

*Humoral and cellular responses to COVID-19 vaccine in IEI other than CVID**

Country	SARS-CoV-2 Tests Performed	IEI	Evidence of Vaccine Response	Major Adverse Events	Reference
USA	Anti-S Ab; anti-N Ab	XLA ($n = 1$)	No	None	118
		WAS ($n = 1$)	Anti-S Ab +		
		DiGeorge syndrome ($n = 1$)	Anti-S Ab +		
USA	Anti-S Ab; IGRA	Agammaglobulinemia ($n = 2$)	IGRA + (2/2, 100%)	Most frequent adverse event was sore arm. No major adverse events (only one patient reported a flare of enteropathy one week after vaccination).	21
		Hypogammaglobulinemia ($n = 4$)	Anti-S Ab + (2/4, 50%) IGRA + (3/4, 75%)		
		SpAD ($n = 2$)	Anti-S Ab + (2/2, 100%)		

They are effective and safe for patients with IEI

Studies are needed For each IEI

Potential need of additional vaccines or a combinatio

The recommendation is to get vaccinated*

VACUNAS EN PACIENTES QUE RECIBEN ESTEROIDES



APPLY WITH NO PROBLEM

DOSIS



**IN PATIENTS WHO RECEIVE HIGH DOSIS OF STEROIDS FOR PROLONGED TIMES.
VACCINES ARE SUSPENDED AND ARE RESTARTED UP TO 4 WEEKS AFTER DIAGNOSIS IS SUSPENDED IN PAT**

**DOSIS
ALTAS
2mgKgd**



15 days of more

VACUNAS EN PACIENTES QUE RECIBEN TERAPIA BIOLOGICA

INNACTIVATED VACCINES



LIFE VACCINES

14 days before the start of the therapy

Re-evaluation 6 months after suspending the therapy

Vacuna vs COVID
47% OF Ac levels

VACUNAS EN FAMILIARES DE IDP

✦ THE GREAT MAJORITY IS CONSIDERED SAFE!!



VACCINE VS INFLUENZA
GET IT!!!

**VARICELA
VACCINE**

DO NO administer
oral polio

IGIV-VACUNAS

Los pacientes que reciben terapia sustitutiva con **INMUNGLOBULINA** endovenosa o subcutánea (IGIV/SC) tienen suspendida la administración de vacunas



La IGIV/SC tiene niveles protectores de anticuerpos contra la mayoría de las enfermedades que cubren la

**INFLUENZA
VACCINE**

**HEPATITIS
B
VACCINE**

**COVID
VACCINE**

OGLOBULINA interfiere
con la respuesta para vacunas atenuadas

CONCLUSIONES

In a patient with a **PID** we should consider:

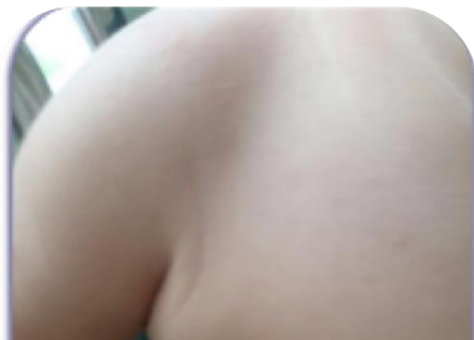
- This vaccine is **SAFE** for that patient in particular?
- Will it be **EFFECTIVE** in this patient?

Vaccines of dead microorganisms, subcomponents are SAFE, they can be administered to **everyone** who has THE CAPACITY TO GENERATE AN INNATE RESPONSE

Live attenuated viral or bacterial vaccines may result in a disseminated disease and are **CONTRAINDICATED** in SOME PIDs

Immunoglobuline can reduce the efficacy of some vaccines, so while IVIG is being applied, vaccines should **NOT** be applied except INFLUENZA,

SOME VACCINES are specifically recommended for patients with PIDs



Q&A

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Enfermedades infecciosas endémicas en la región

Endemic infectious diseases in the region

Prof Gesmar Segundo, Brasil
Prof Gesmar Segundo, Brazil

Endemic infectious diseases in LA

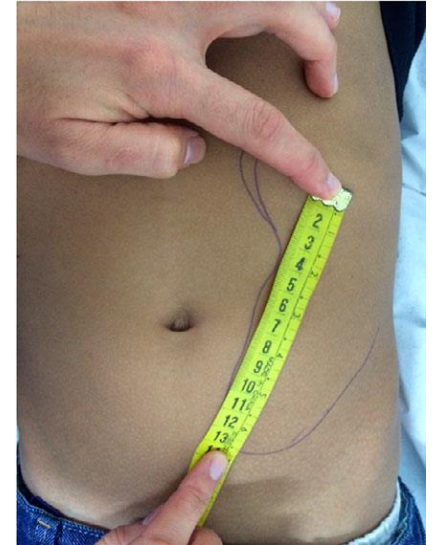
- Pan American Health Organization (PAHO) Elimination initiative – 2019
- Program to promote and accelerate towards to eliminate communicable diseases.
- Some diseases presented direct impact on PID patients

Endemic infectious diseases in LA

- Leishmaniosis
- Paraccoccidioidomycosis
- Histoplasmosis
- Tuberculosis
- Dengue
- Chikungunya
- Zika
- Yellow fever
- Malaria

Kind of Secondary Immunodeficiencies

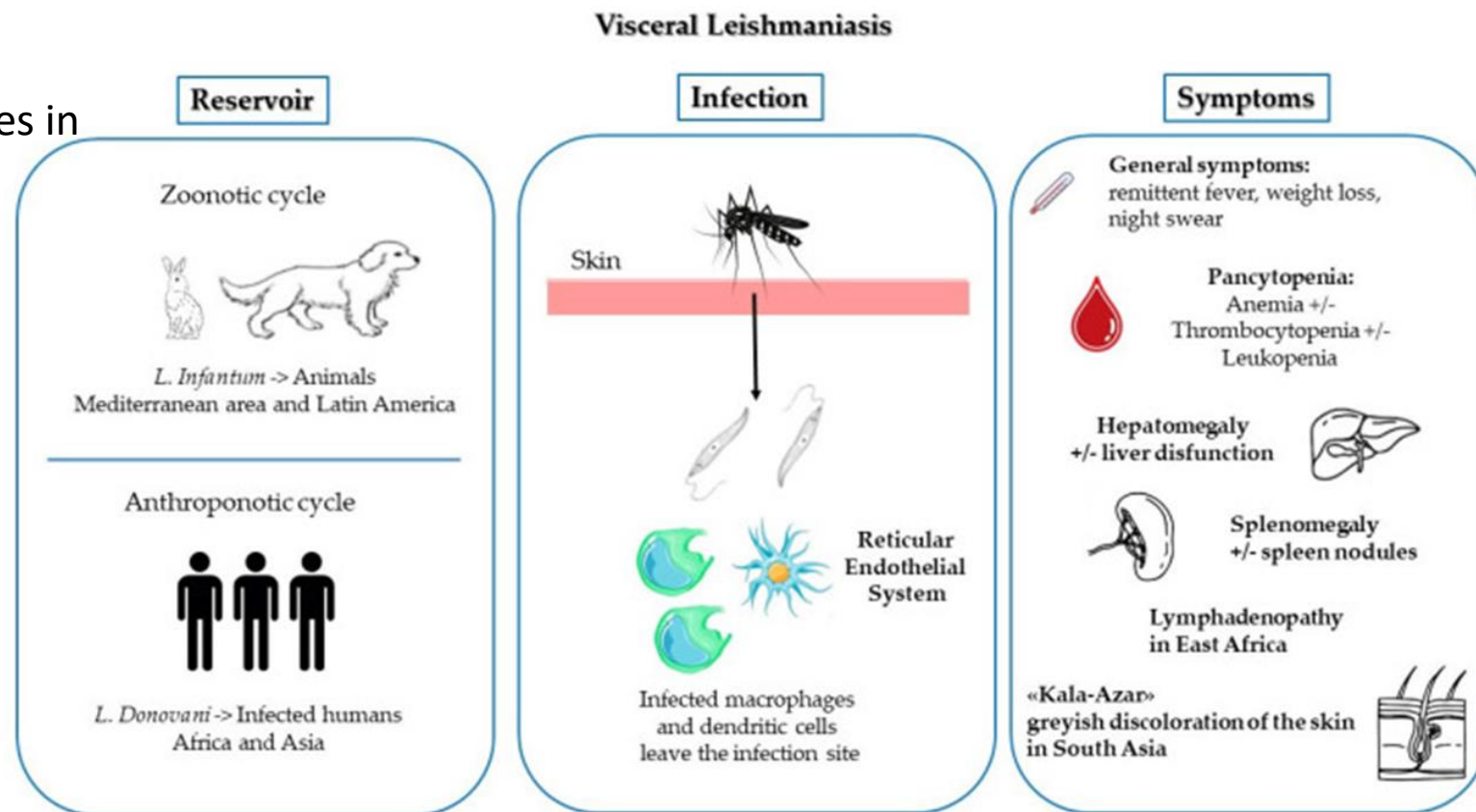
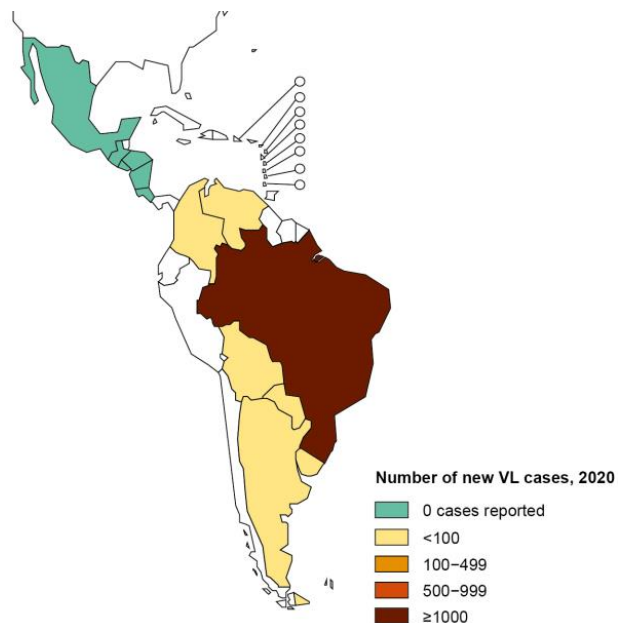
- Chronic disease
- Hepatosplenomegaly
- Cytopenia
- Multiple manifestations



Splenomegaly due to *visceral Leishmania* in a patient with CD40L deficiency

Visceral Leishmaniasis

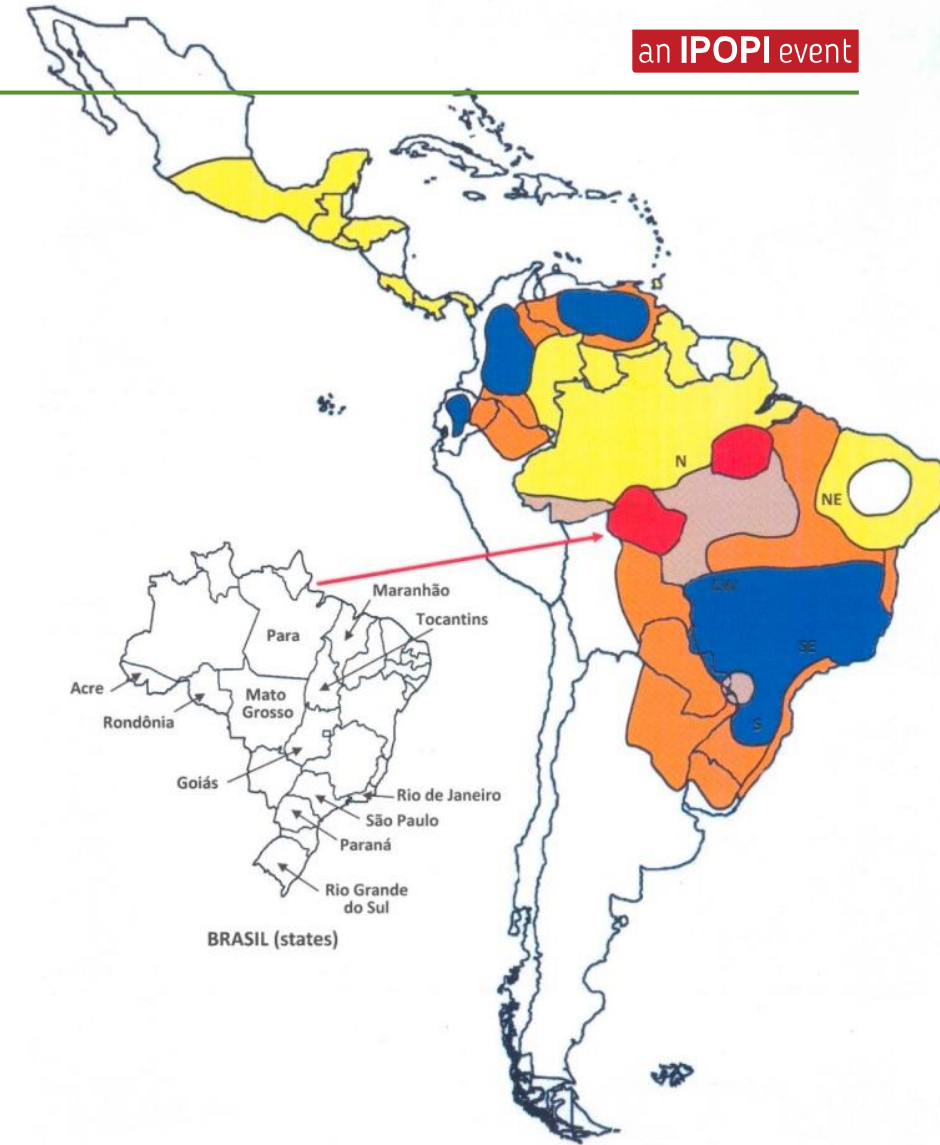
- Visceral leishmaniasis is endemic in 13 countries.
- Average of 3400 cases per year.
- The Brazil reports the great majority of cases in the region (97%) in 2020.



Microorganisms. 2022 Sep 21;10(10):1887.

Paracoccidioidomycosis

- Fungal disease
- Most cases in South America (Brazil)
- from 4 to 9.4 cases/100.000 hab
- Frequent cases descriptions in PID patients
 - MSMD
 - CD40 ligand
 - Combined immunodeficiencies
- People get paracoccidioidomycosis after breathing in the fungus *Paracoccidioides* from the environment
- Paracoccidioidomycosis does not spread from person to person.



Tuberculosis

- More than half of the incident cases (57%) were concentrated in three countries:
- Brazil, Mexico, and Peru.
- The estimated total number of TB deaths in the Region in 2020 was 26,900 deaths (9.6% change in total number of TB deaths between 2015 and 2020).
- Disruptions to diagnosis and treatment caused by the COVID-19 pandemic and supply chain issues have impacted mortality.

In 2021 the following was reported:



215,116 new cases, with 70% treatment coverage, an increase of 2% compared to 2020 (68%)

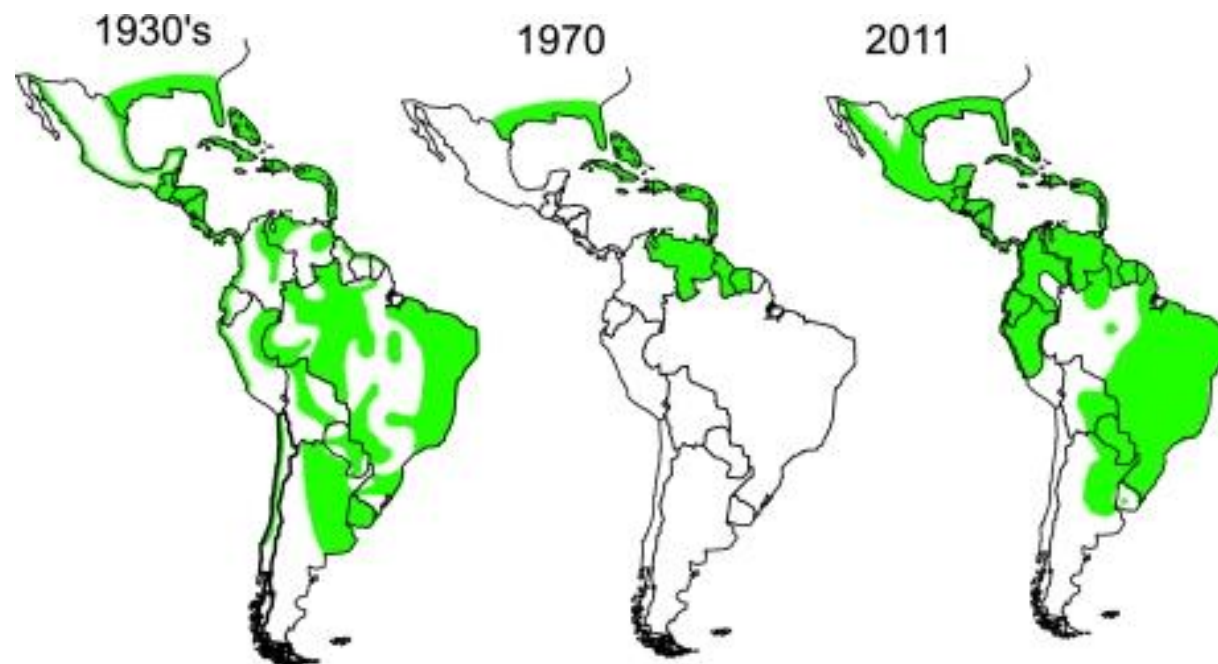
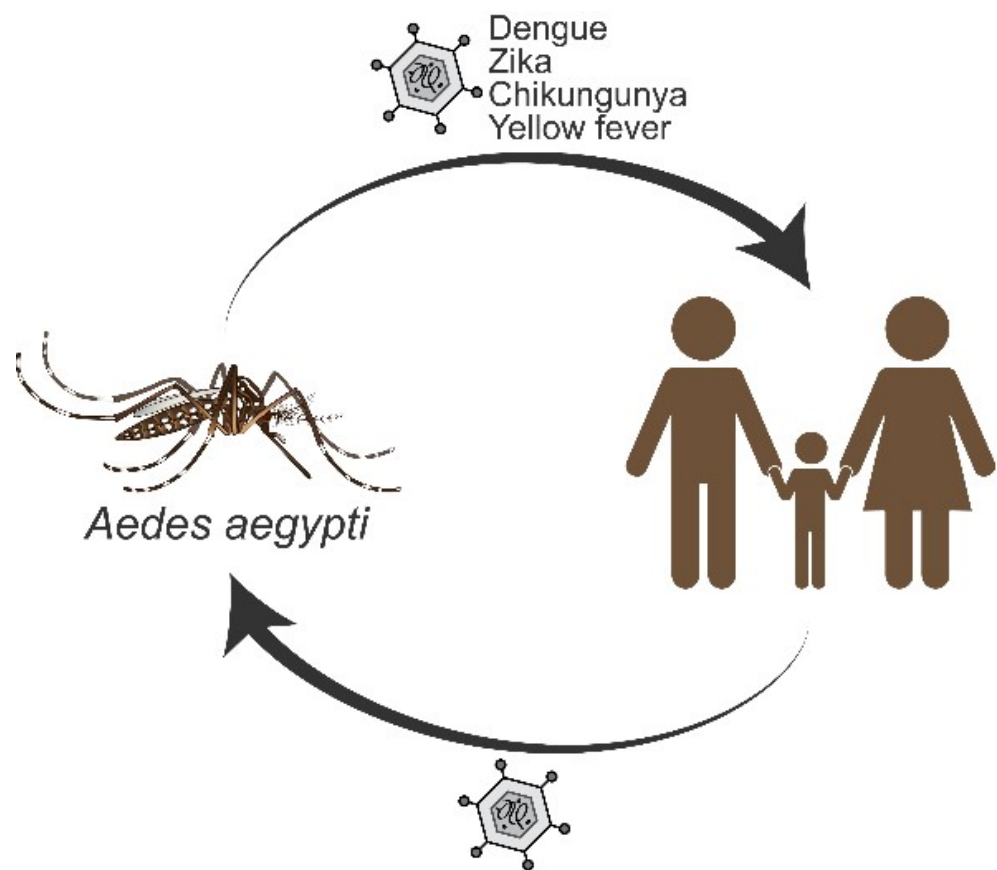


170,734 TB patients knew their HIV status (79%), with a concerning decreasing trend over the **last three years**



4,573 people started treatment for drug-resistant TB, 10% more than in 2020

Dengue, Zyka and Chikungunya



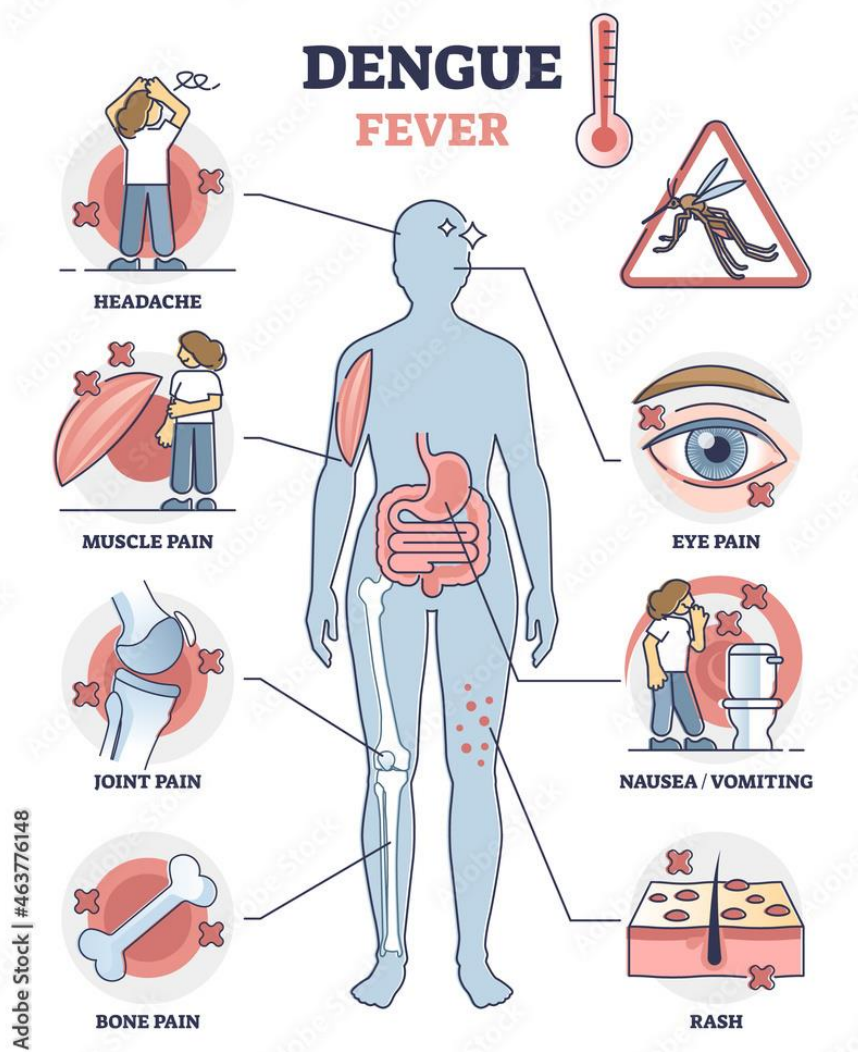
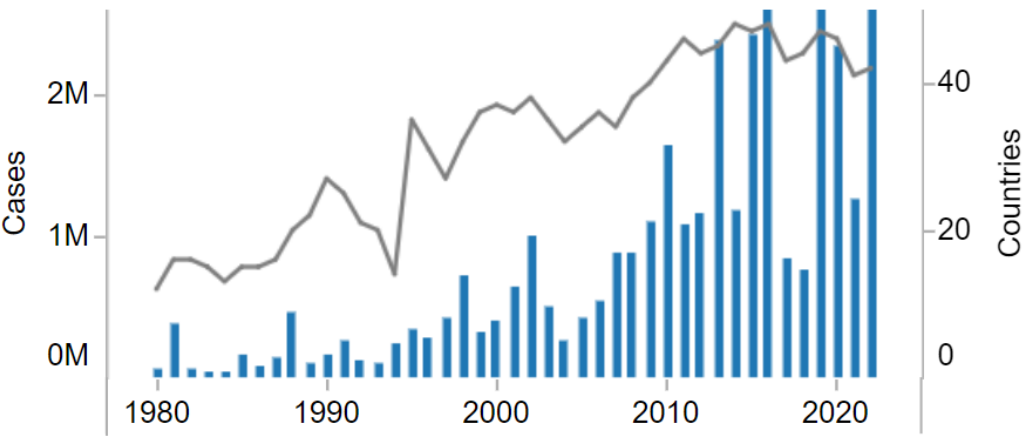
Dengue



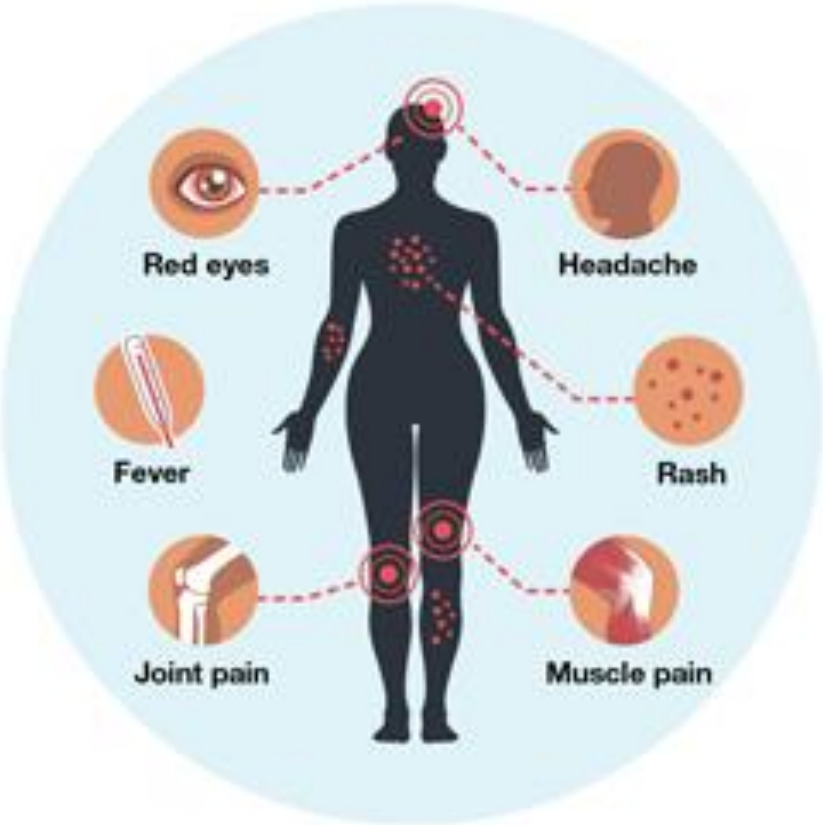
Approximately **500 million** people in the Americas are today at risk of dengue

Dengue Reported Cases 2022

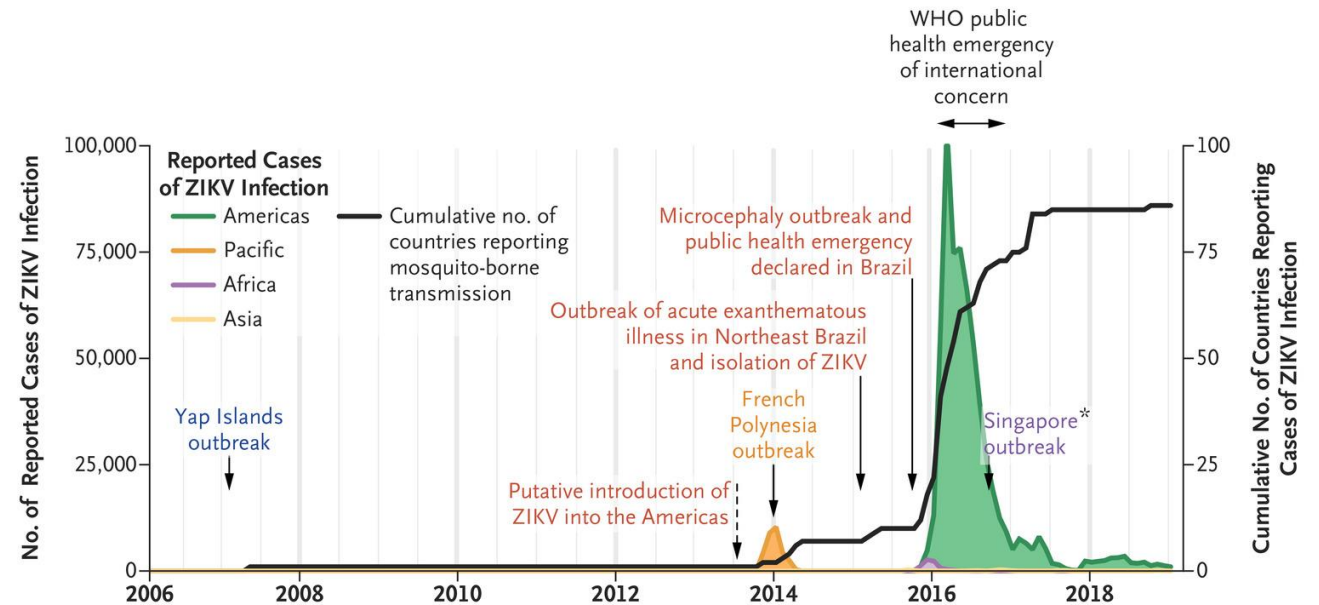
Region	Total	Confirmed	Severe	Deaths
The Americas	2,811,452	1,370,138	4,607	1,290



Zika

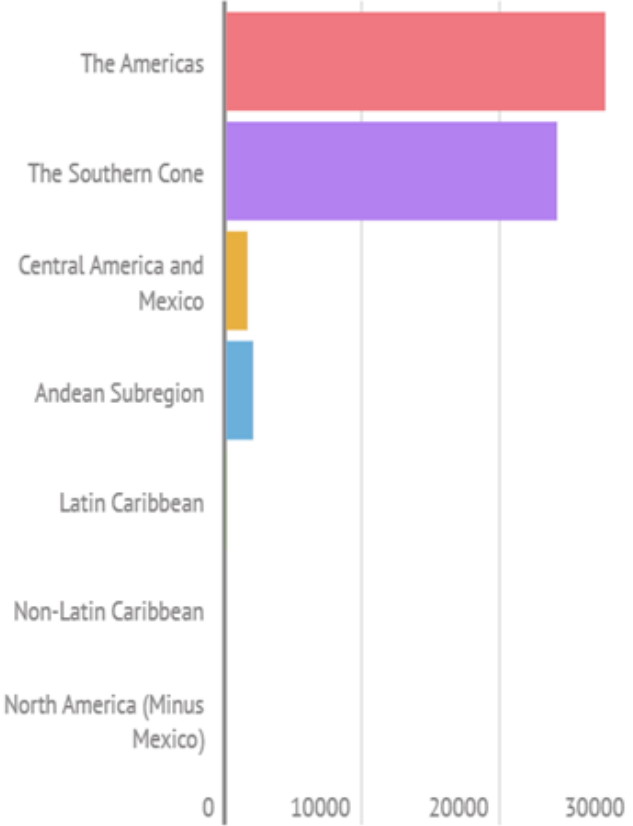


A Cases of ZIKV Infection



Zika

2019



Modes of Infection

- Mosquito
- Sexual
- Blood transfusion
- Pregnancy

Patient with Infection

- Asymptomatic (50–80%)
- Mild disease (20–50%)
- Complications (<1%)

Severe Complications

- Neurologic: Guillain-Barré syndrome, acute myelitis, acute transient polyneuritis, meningoencephalitis
- Ocular: hypertensive iridocyclitis, unilateral acute maculopathy, bilateral posterior uveitis, chorioretinal scars
- Thrombocytopenic purpura
- Transient myocarditis
- Overall case fatality <0.01% (mostly among immuno-suppressed patients and those with coexisting conditions)

Pregnant Patient with ZIKV Infection (symptomatic or asymptomatic)



20–30%
Fetuses and Neonates
with Infection

70–80%
Fetuses and Neonates
without Infection

Fetuses and Newborns of Women Infected during Pregnancy



Fetal Loss 4–7%



Congenital Zika Syndrome 5–14% (microcephaly 4–6%)

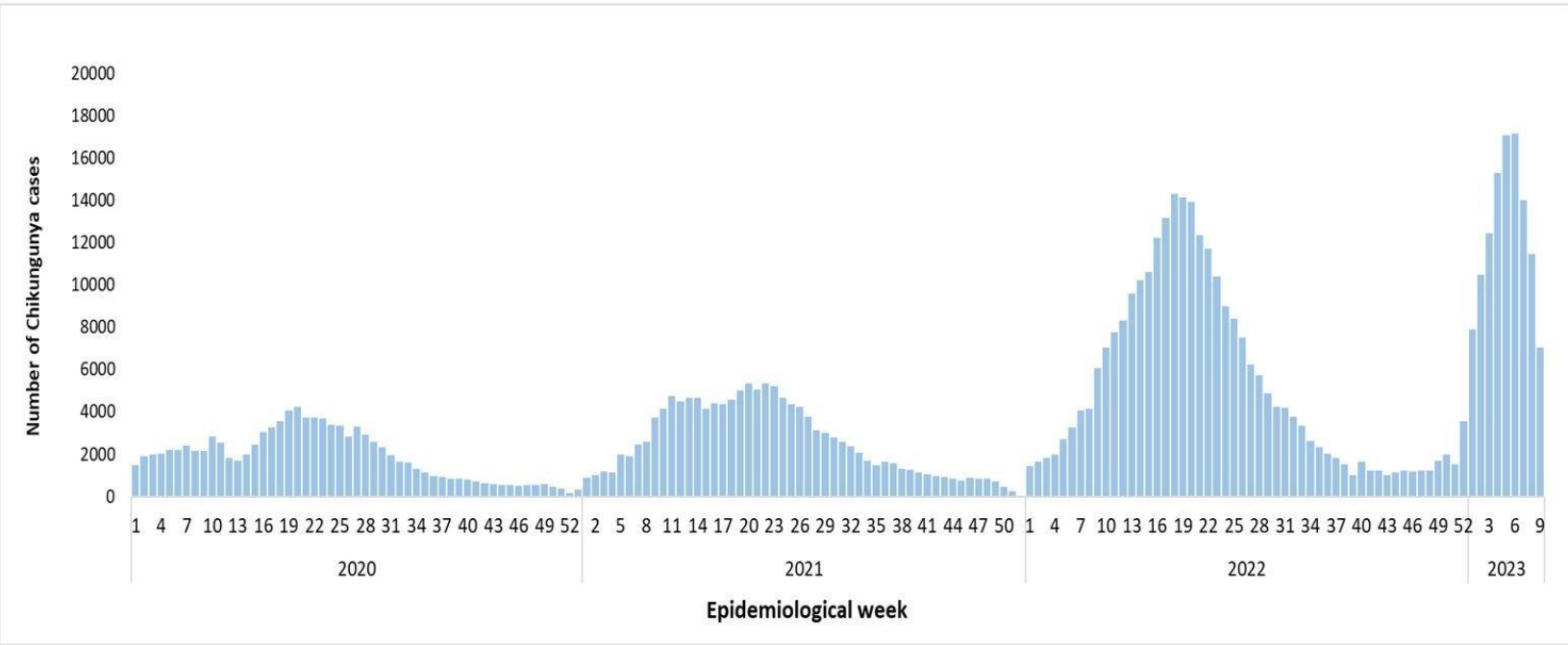
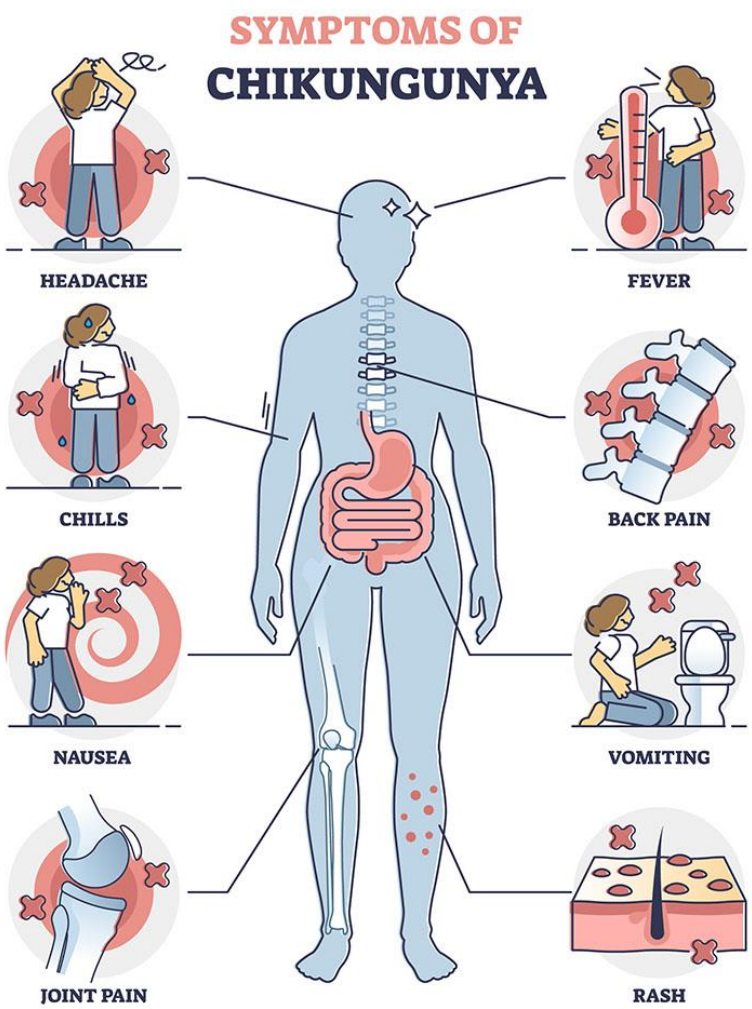


Asymptomatic Medium- and long-term sequelae



Uninfected

Chikunguia



Source: PAHO/WHO Health Information Platform for the Americas (PLISA per its acronym in Spanish) as provided by Ministries and Institutes of Health of the countries and territories of the Region of the Americas. Washington DC: PAHO.

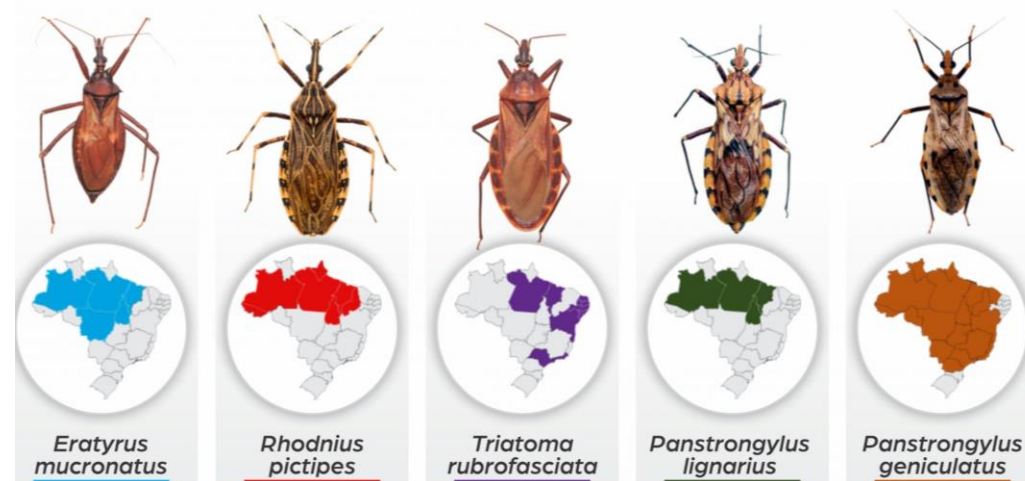
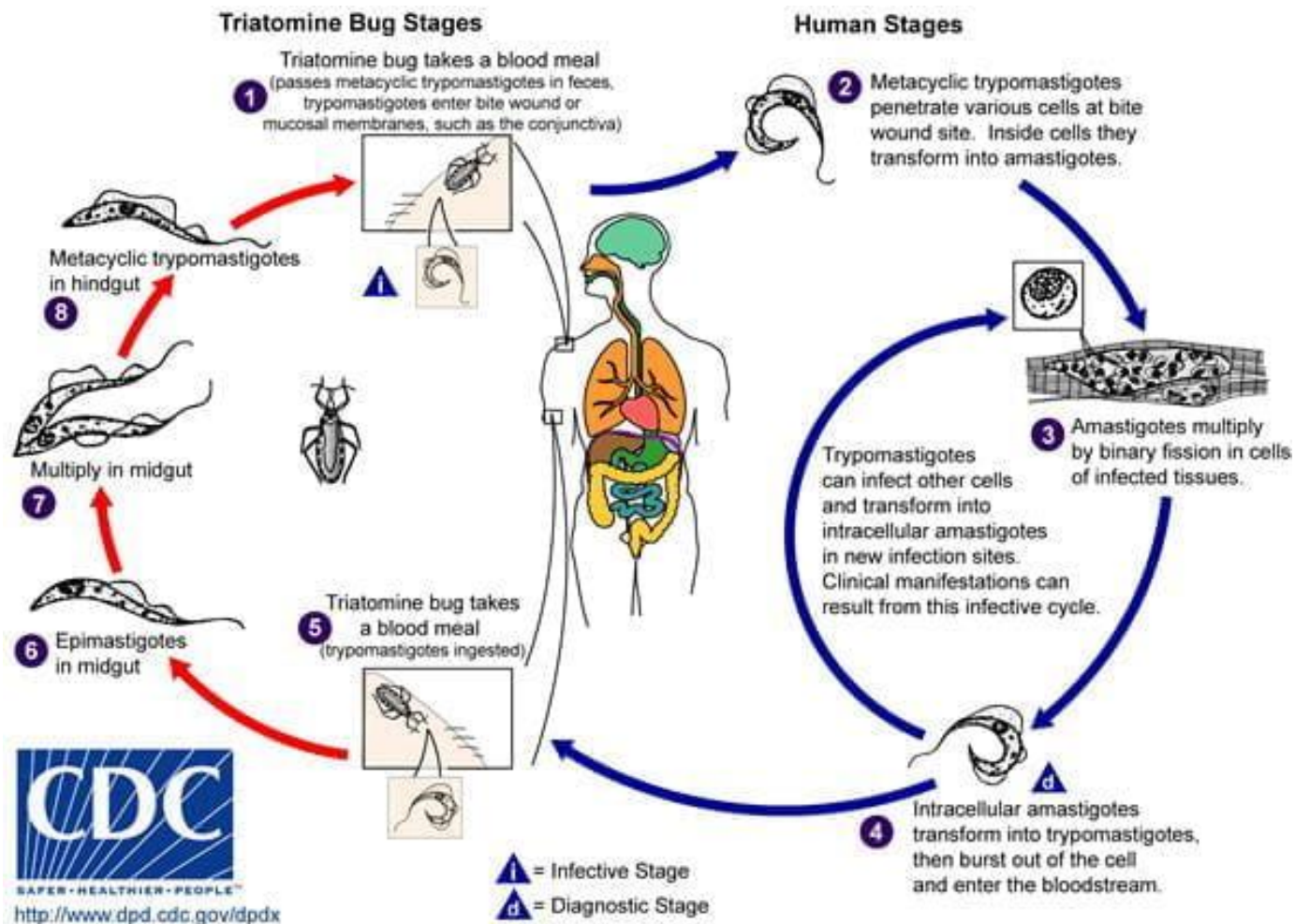
Yellow fever

- In 2018, Bolivia, Brazil, Colombia, French Guiana, and Peru reported confirmed cases
- In Brazil, the historical area of yellow fever enzootic transmission expanded since mid-2016 to coastal areas previously considered risk-free.
- Four seasonal waves of human cases followed.
- Overall, in 2019-2021, 457 human cases were reported in five of the above countries,
 - of which 414 (90.1%) in Brazil, 31 (6.8%) in Peru, 8 (1.8%) in Venezuela, and two (0.4%) in Bolivia and French Guiana respectively.
- Limited availability of vaccine doses and COVID-19 disruptions have adversely impacted yellow fever immunization in the region.



Chagas Disease

- Endemic in 21 countries in the Americas
- About 70.2 million individuals in living in areas at risk.
- Each year an estimated 30,000 new cases resulting from vector transmission occur
- Interruption of vector borne transmission have been achieved in 17 countries of the region
- Multicountry program initiatives in the Southern Cone, Andean countries, and Central America have furthered best practices exchange and commitment from the countries and partners.
- Implementation of universal screening of blood donors across the countries have advanced interruption by blood transfusion.
- Latest estimates of number of people with Chagas disease ranges from 6 to 7 million.



Malaria



482,000 cases in **2015**, and **520,000** cases in **2021**, of which **74%** were caused by *P. vivax*, while **26%** were caused by *P. falciparum*

- Venezuela (398,000)
- Brazil (152,294)
- Colombia (78,109)
- Peru (24,322)
- Nicaragua (13,200)



169 deaths in **2015**, and **126** in **2021**

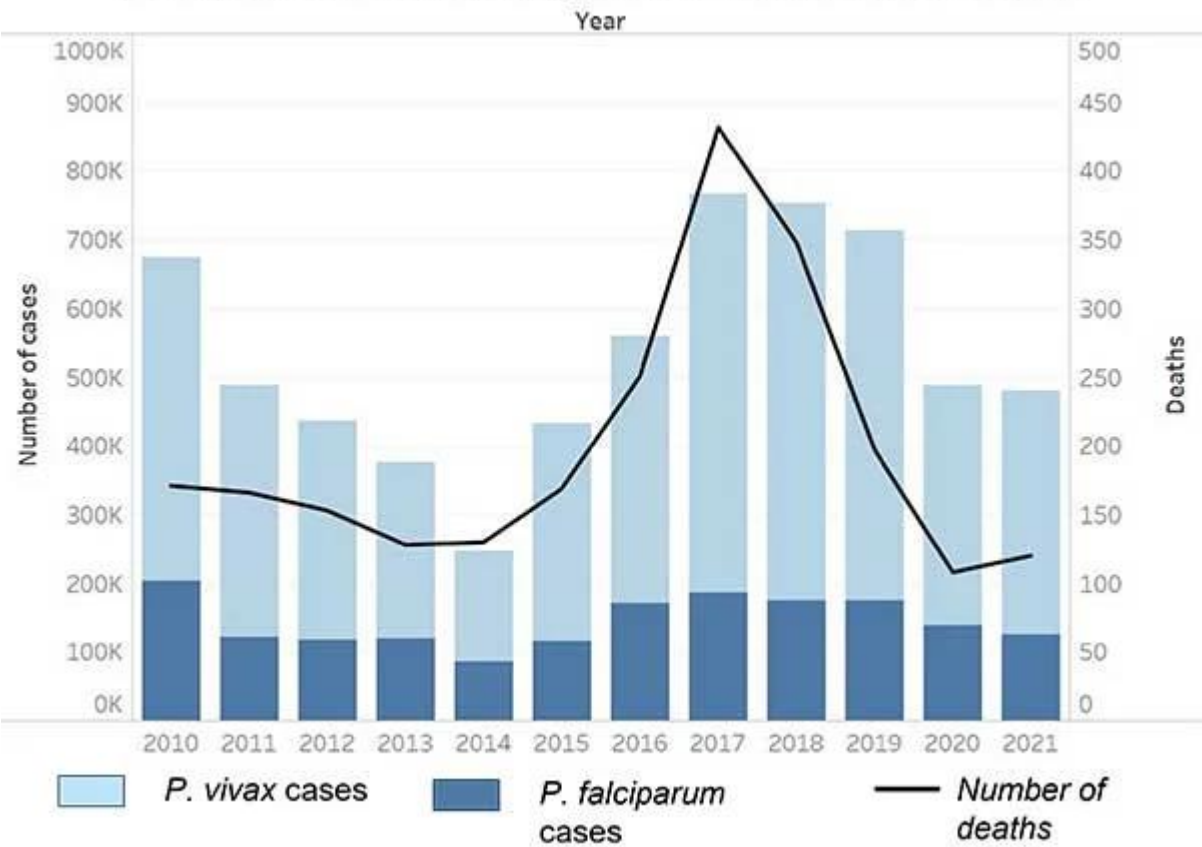


There has been an **8%** increase in the number of cases



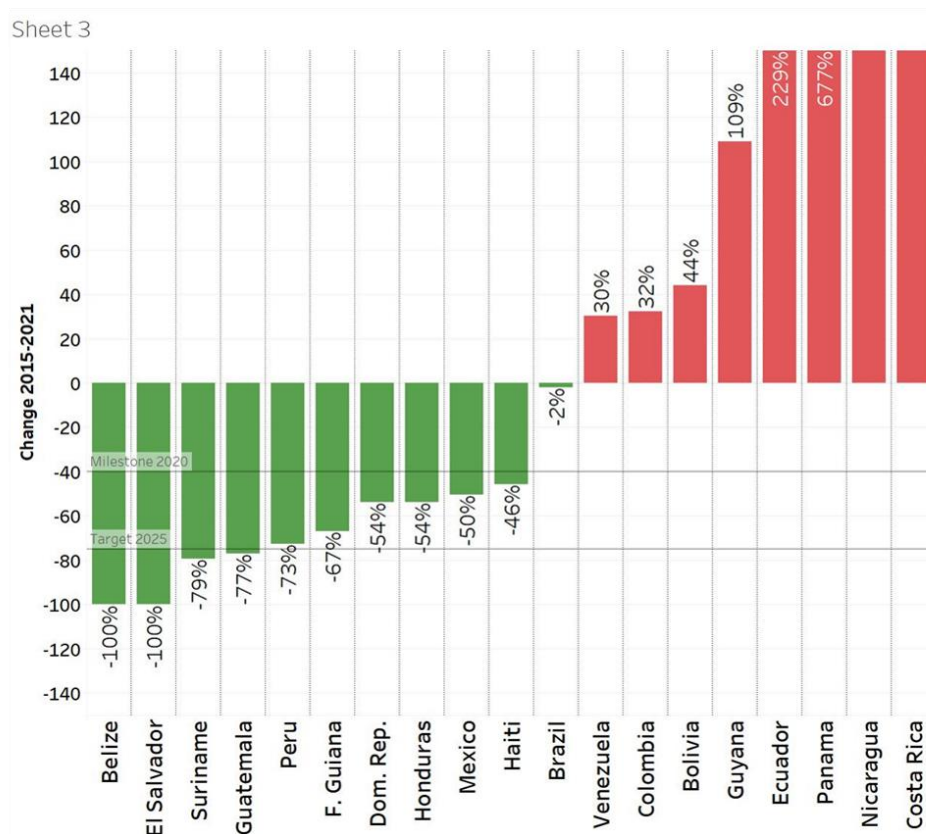
There has been a reduction of deaths of **26%**

Confirmed new cases and deaths. 2010 - 2021. American Region



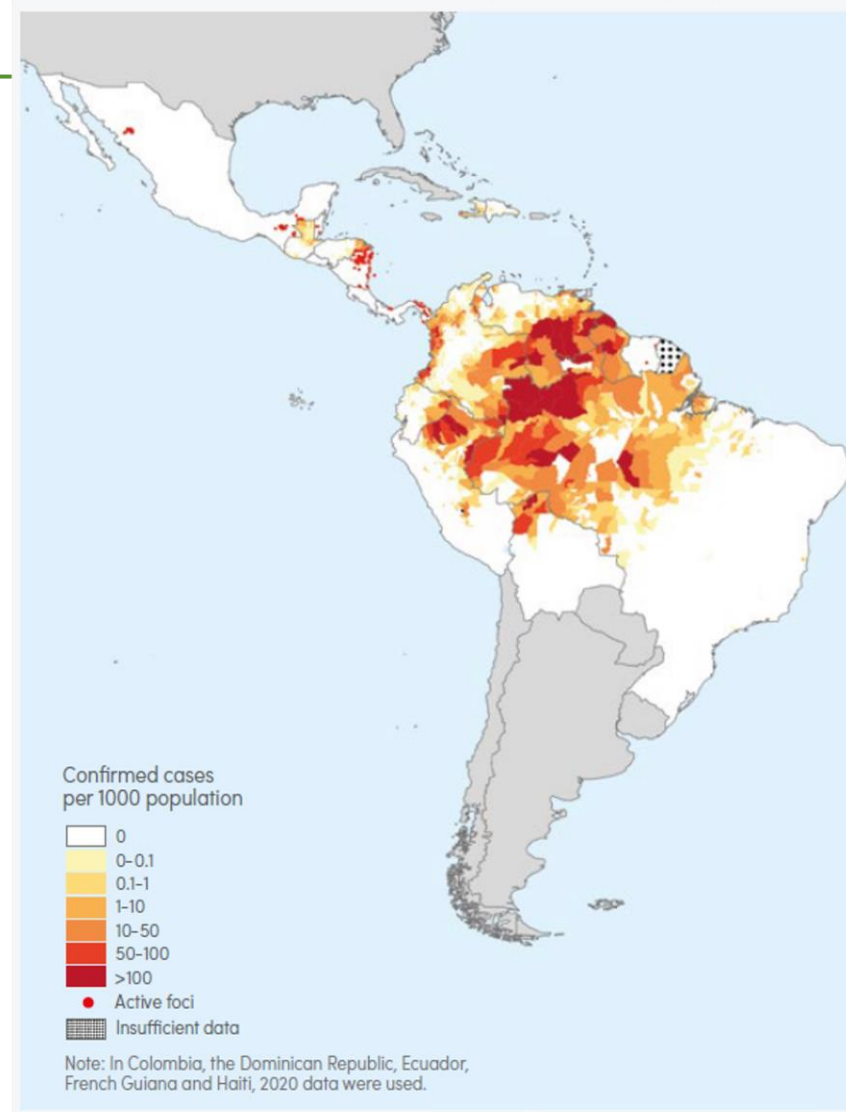
Malaria

Percentage of reduction in morbidity 2015 - 2021



Confirmed malaria cases per 1000 population, 2021

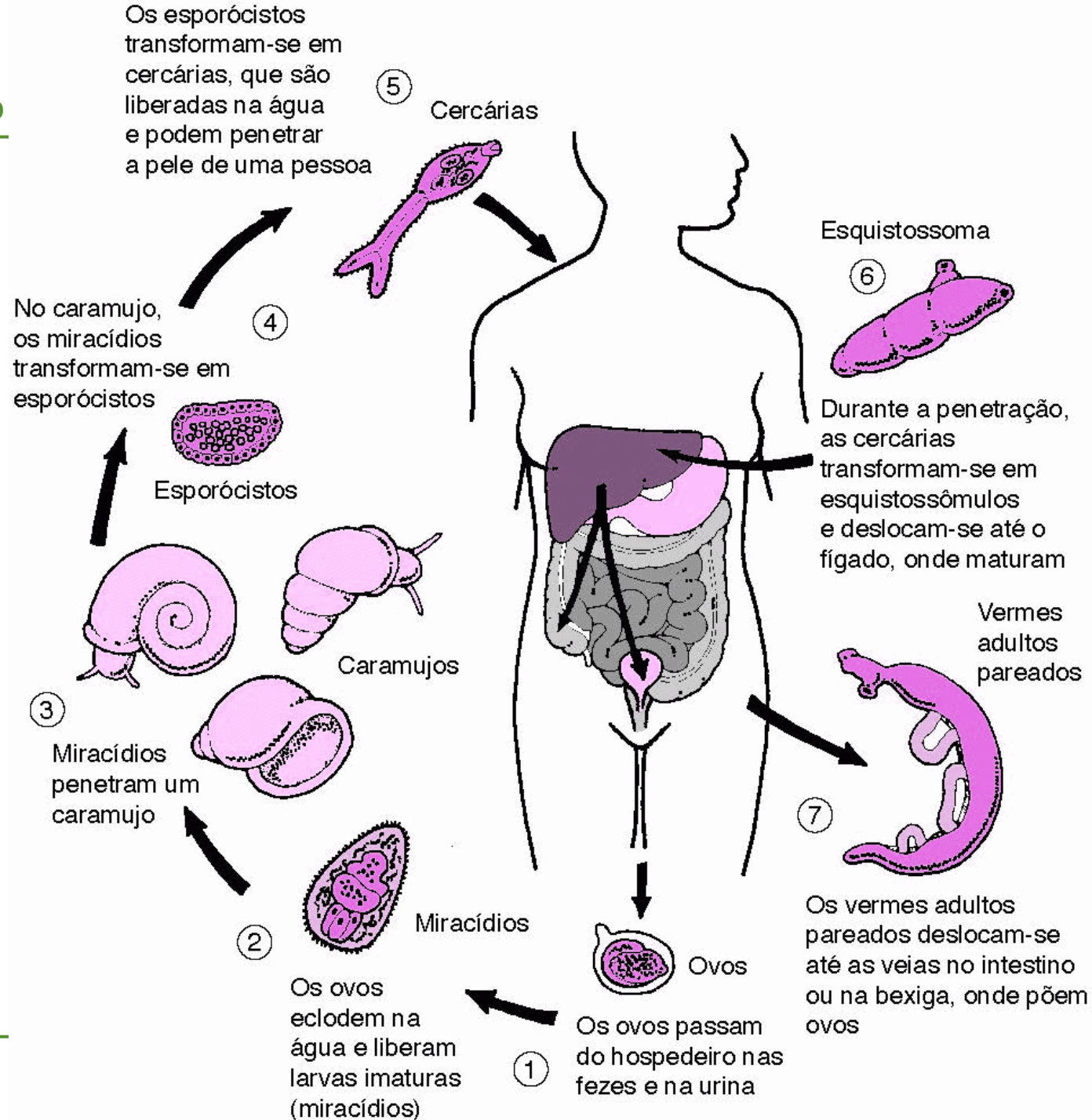
an IPOPI event



World malaria report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

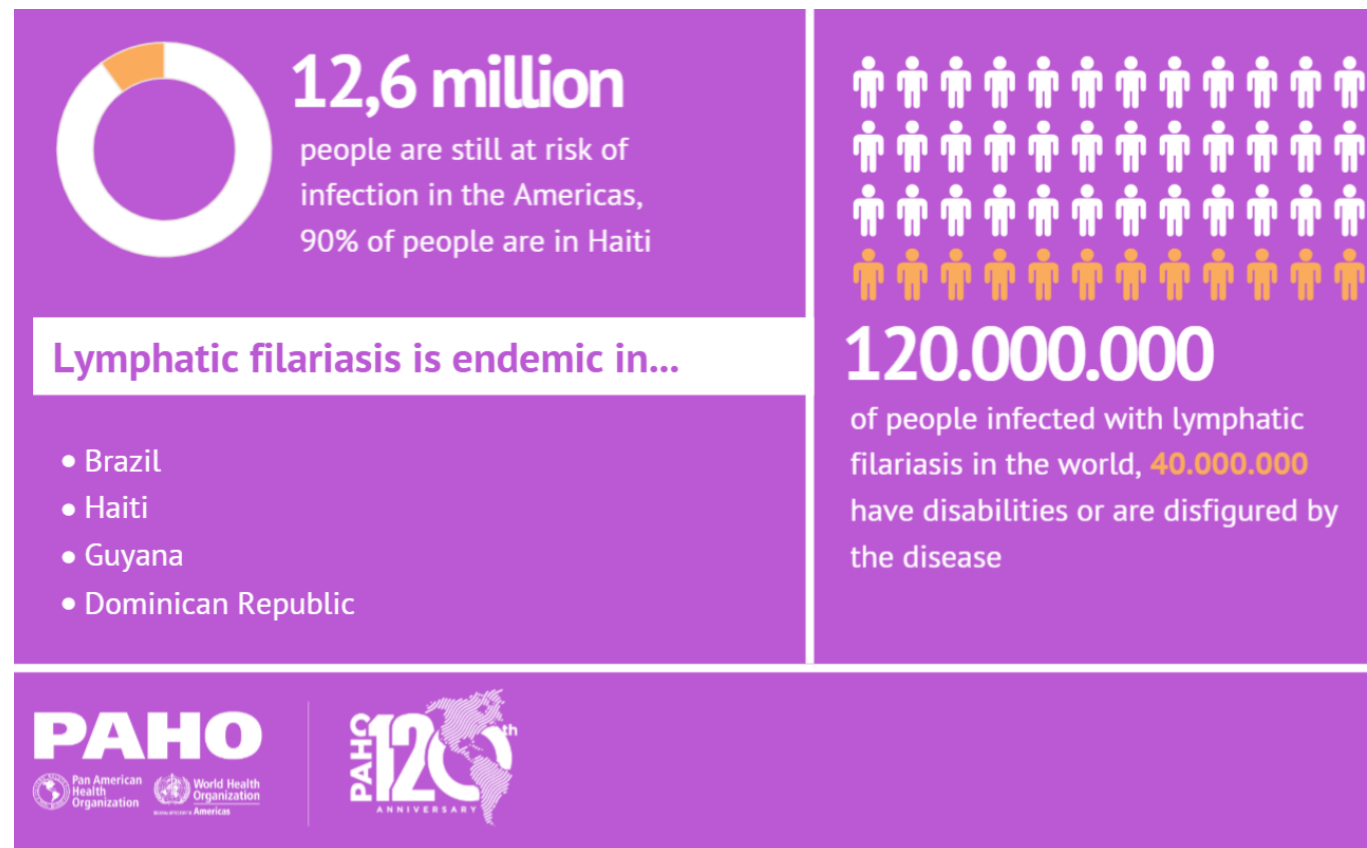
Schistosomiasis

- Estimates suggest 25 million people are at risk of infection, most of them in Brazil.
- Disease is still endemic in several foci in Brazil and Venezuela.
- Elimination has been likely achieved in Antigua and Barbuda, Dominican Republic, Guadeloupe, Martinique, Montserrat, Puerto Rico, Saint Lucia, and Suriname.
- Further studies and compilation of evidence are required to verify interruption of transmission in these countries.



Lymphatic Filariasis

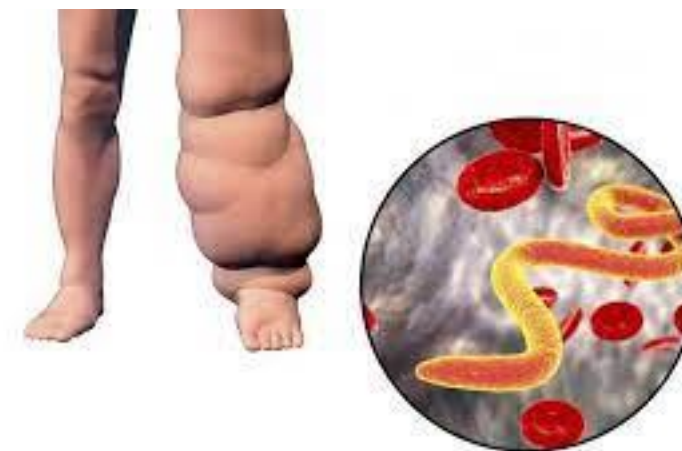
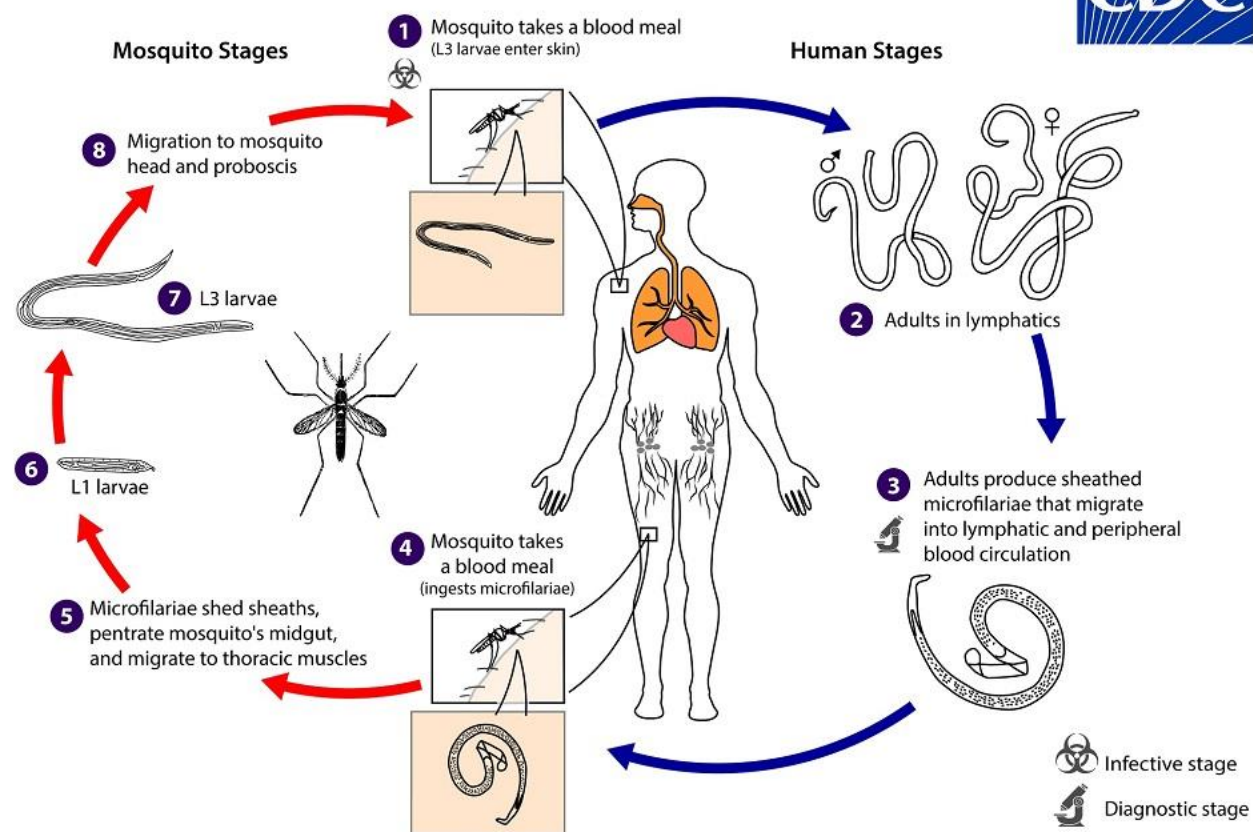
- Over 4.1 million people living in two countries of the Americas required mass drug administration for lymphatic filariasis in 2021.
- Only four countries in the region remain with lymphatic filariasis.
- Brazil and Dominican Republic stopped mass drug administration and are close to achieving elimination, Guyana likely by 2026, and Haiti by 2030 at latest.



Lymphatic Filariasis

1DPDx

Wuchereria bancrofti



Summary

- Many challenges to solve endemic infectious diseases
- Basic sanitation
- Treatment of patients
- Vector control difficulties
- Mores studies about PID and this endemic diseases

Q&A

COLLABORATION



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Resistencia antimicrobiana

Antimicrobial resistance

Perspectiva médica:Cuál es el problema?

Physician perspective: What is the problem?

Prof Silvia Sánchez-Ramón, España
Prof Silvia Sánchez-Ramón, Spain

Antimicrobial Resistance in PID

Dra. Silvia Sánchez-Ramón, MD PhD
Head immunology Dept & Associate Professor
Hospital Clínico San Carlos, Madrid
Universidad Complutense de Madrid



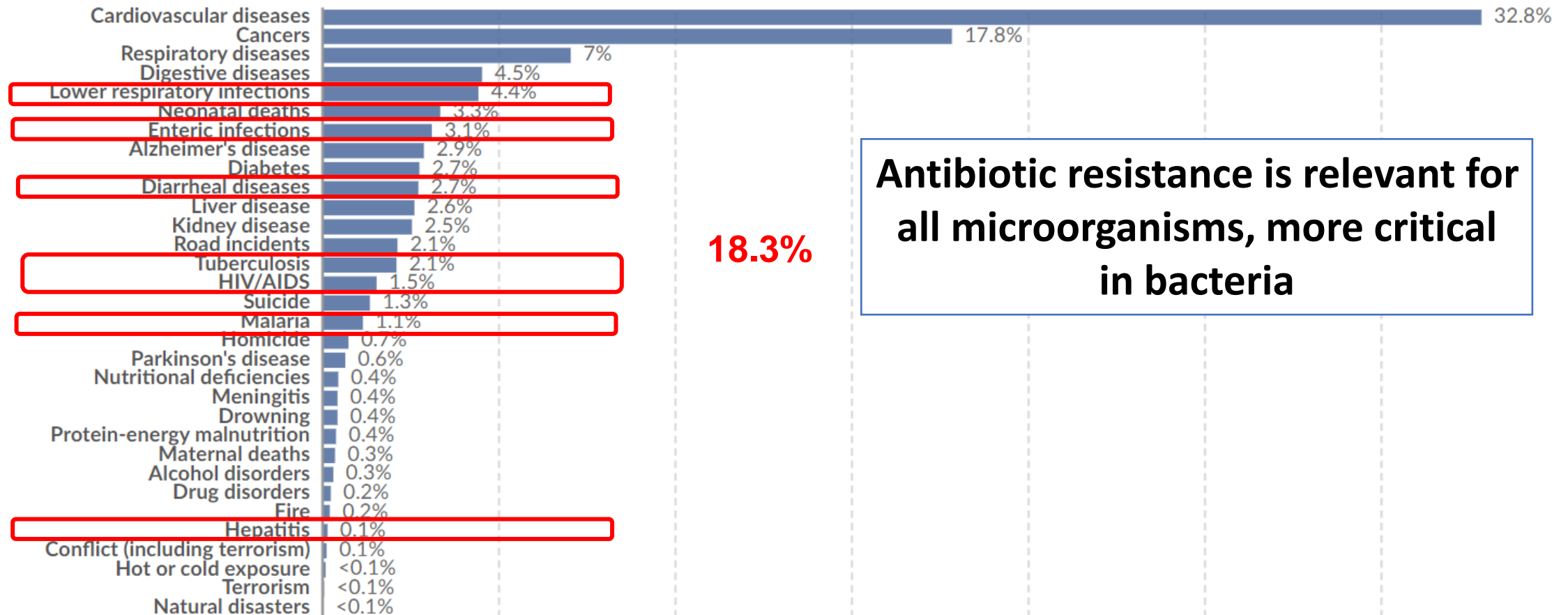
natureOUTLOOK

Global Risks



Into the Postantibiotic Era

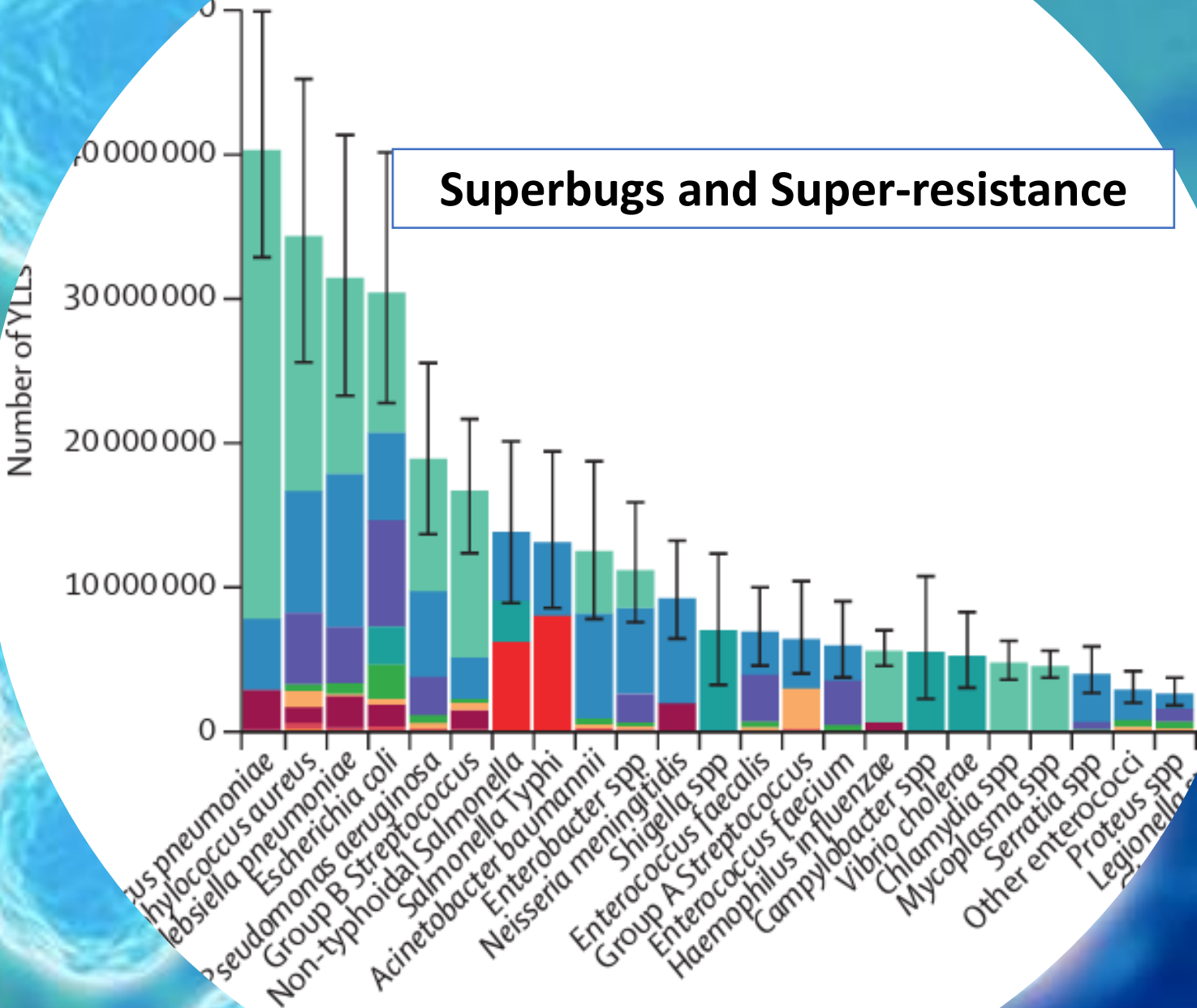
Need for new anti-infective alternatives



Years of Life Lost due to 33 bacterial pathogens in 2019: systematic analysis for the Global Burden of Disease Study 2019

Neumococo
Estafilococo aureo
E Coli
Klebsiella pneumoniae
Pseudomona aeruginosa

Lancet 2022; 400: 2221–48



Pathogen

High risk scenario for antimicrobial resistance

- ICU: risk of nosocomial infections in patients with underlying comorbidities
- Surgery: AB prophylaxis has reduced post-Op infection to <2%.
- Cancer: 1,300 cancer drugs in 2020 vs 27 new Abs
- Transplants
- Immunosuppressed PID patients: 75% of physicians administer prophylactic ABs in routine treatment of PID patients. Treatment of acute infections in IDP generally requires aggressive broad-spectrum ABs.

Resistencia antimicrobiana en PID

Susceptibilidad antimicrobiana en los cultivos bacterianos de pacientes con PID frente a pacientes inmunocompetentes: 257 cultivos de 86 pacientes PID:

CoNS, Pseudomonas spp. y E.coli fueron los patógenos más frecuentemente aislados de pacientes PID.

No existen protocolos basados en evidencia para la administración de AB en PID. Las guías disponibles están basadas en opinión experta y en resultados de estudios observacionales.

Cotrimoxazol para la profilaxis antibacteriana en pacientes con EGC ha tenido resultados prometedores.

Kuruvilla et al., **cotrimoxazole** fue el AB más recomendado para profilaxis AB en PID.

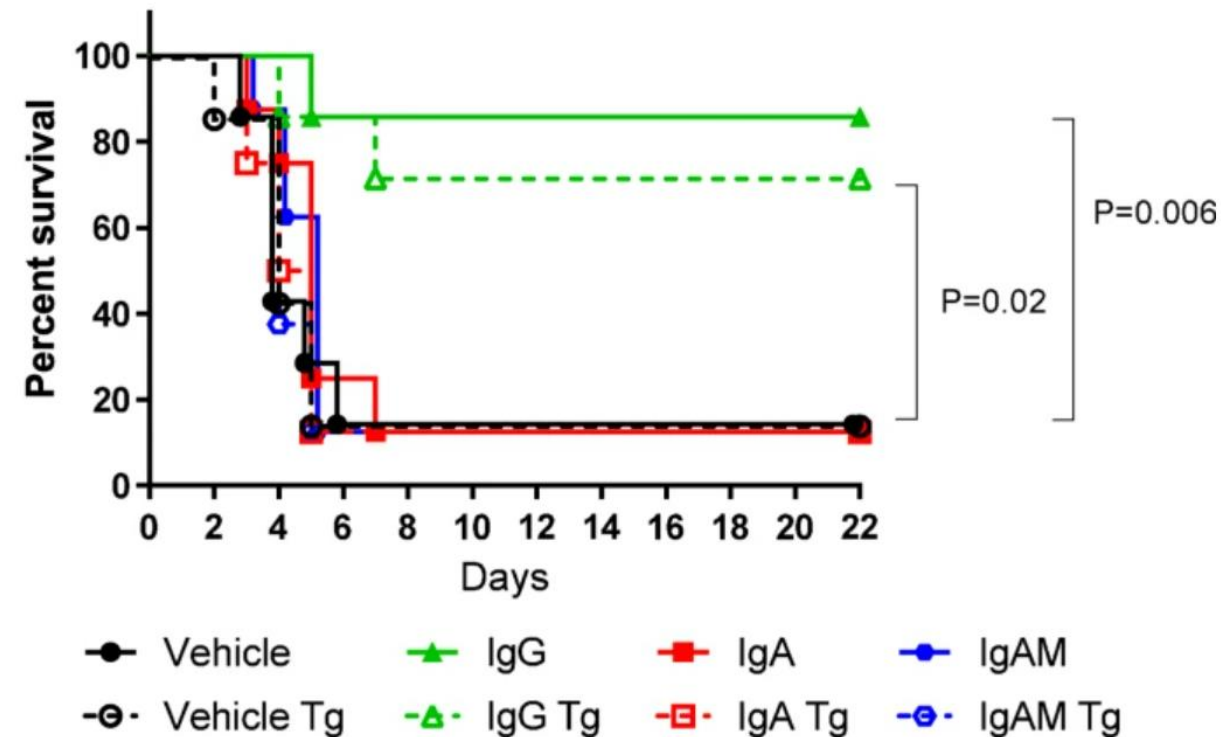
Medidas epidemiológicas e higiénicas para contener la infección: lavado de manos, aislamiento, desinfección; tratamiento domiciliario siempre que sea posible.

plasma-derived Ig directly administered into the lungs via nebulisation

Highly concentrated nebulised Ig in the lung without loss of function

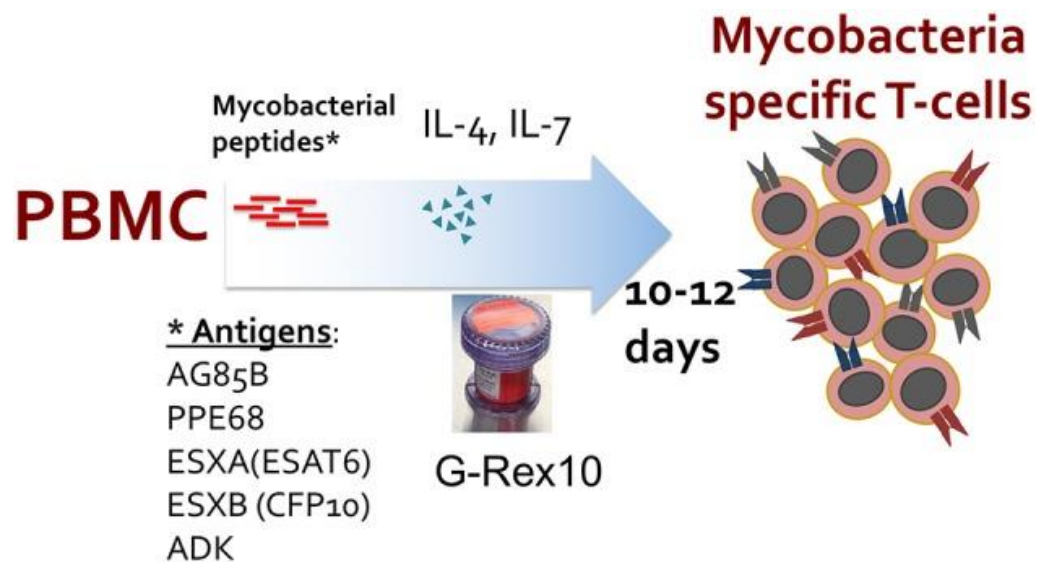
Robust and reproducible aerosol generation from 10% polyclonal IgG 2 ml in 3.5 min

Prophylactically administered plasma-derived human IgG shows a high degree of protection against acute *S. pneumoniae* infection in mice. Opsonophagocytosis-mediated opsonophagocytosis is the major correlate of protection against pneumococcal infection.



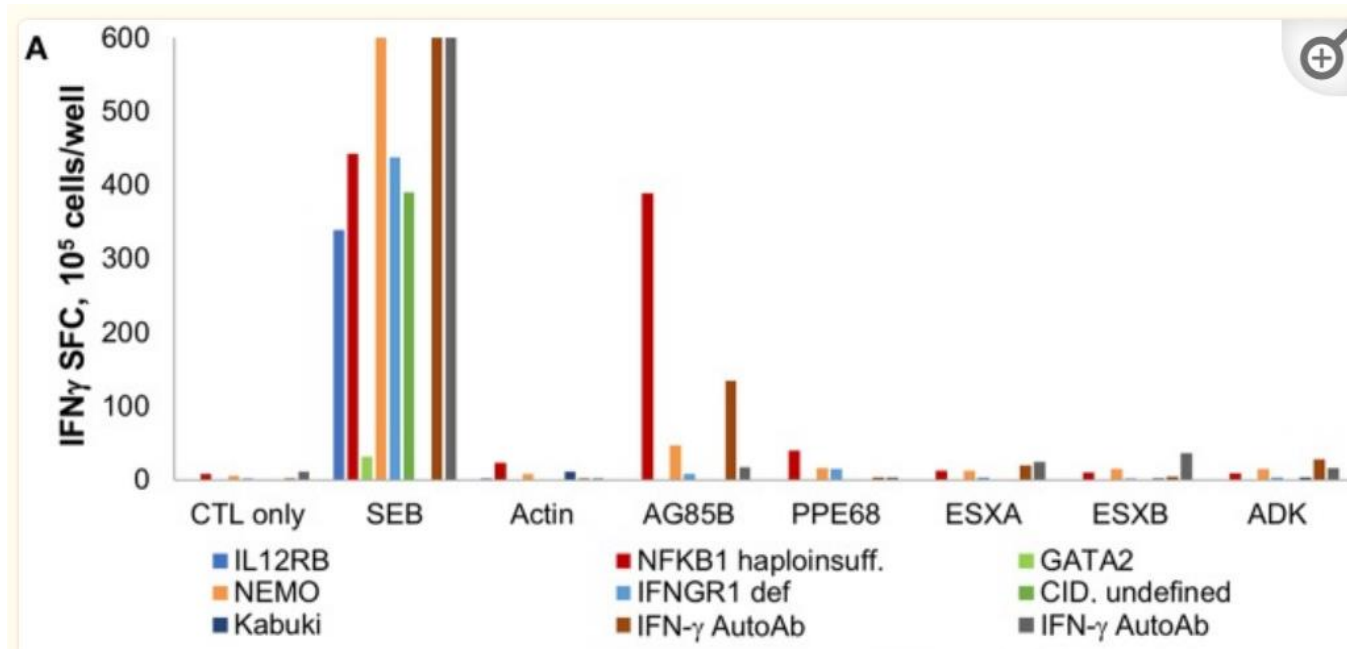
Antimicrobial resistance in PIDs

In cellular PID or phagocyte deficiency there is an increased risk of mycobacterial infections and AMR. Increased risk of mortality during HSCT: Mycobacteria-specific T lymphocytes.



2 de 7 pacientes PID respondieron

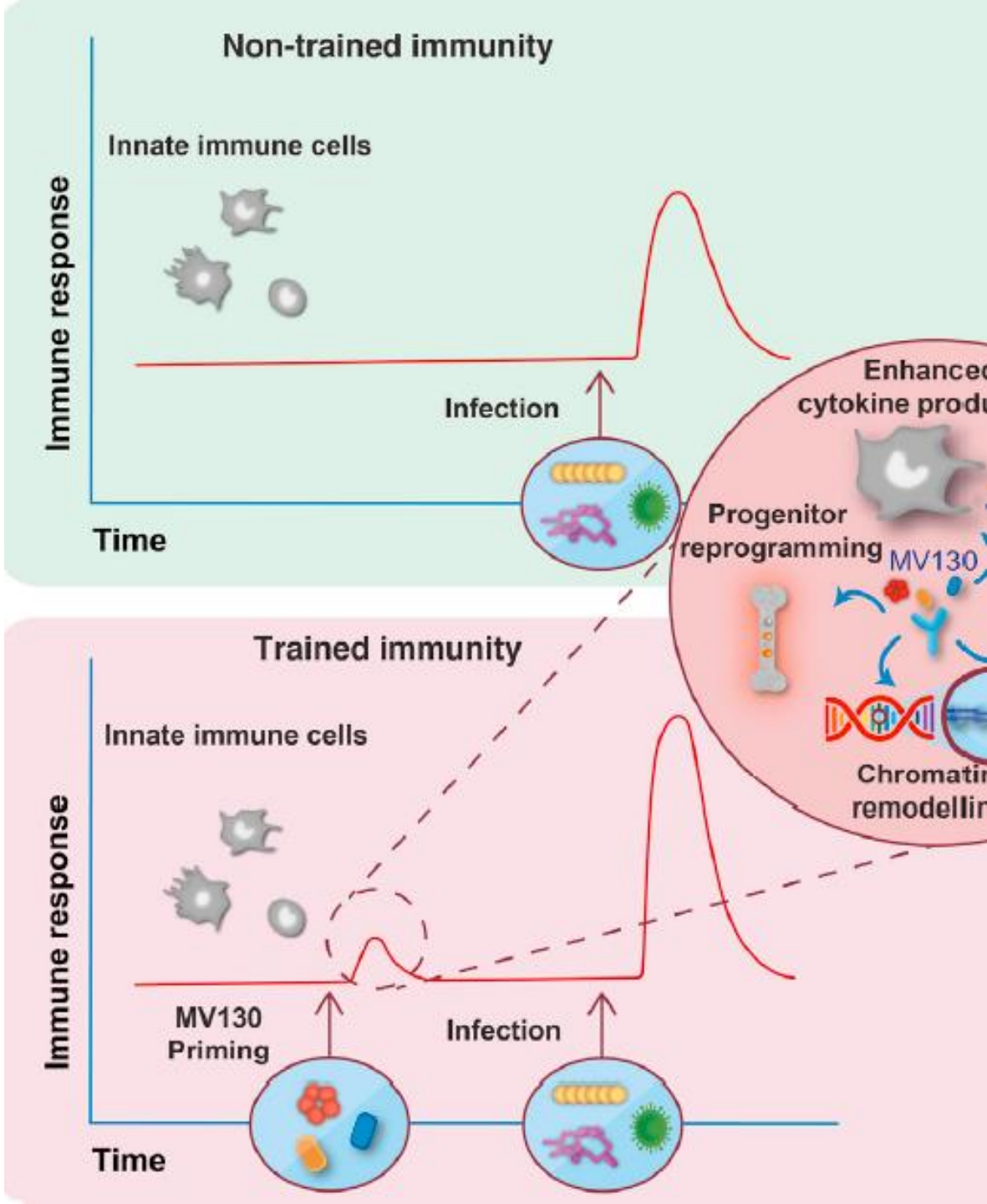
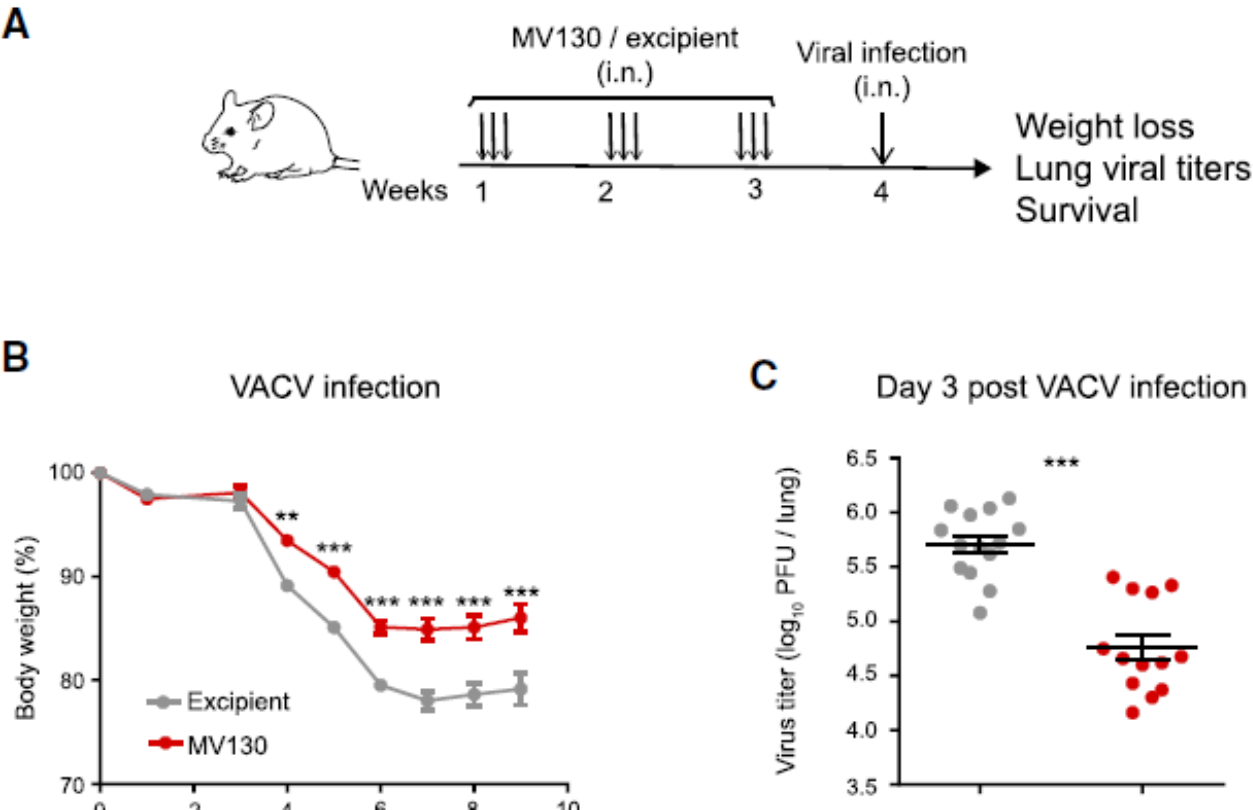
Patel S. Front Immunol 2019



SEB, staphylococcal enterotoxin B

Trained immunity
induction by the
inactivated
mucosal vaccine MV130
protects against
experimental viral
respiratory infections

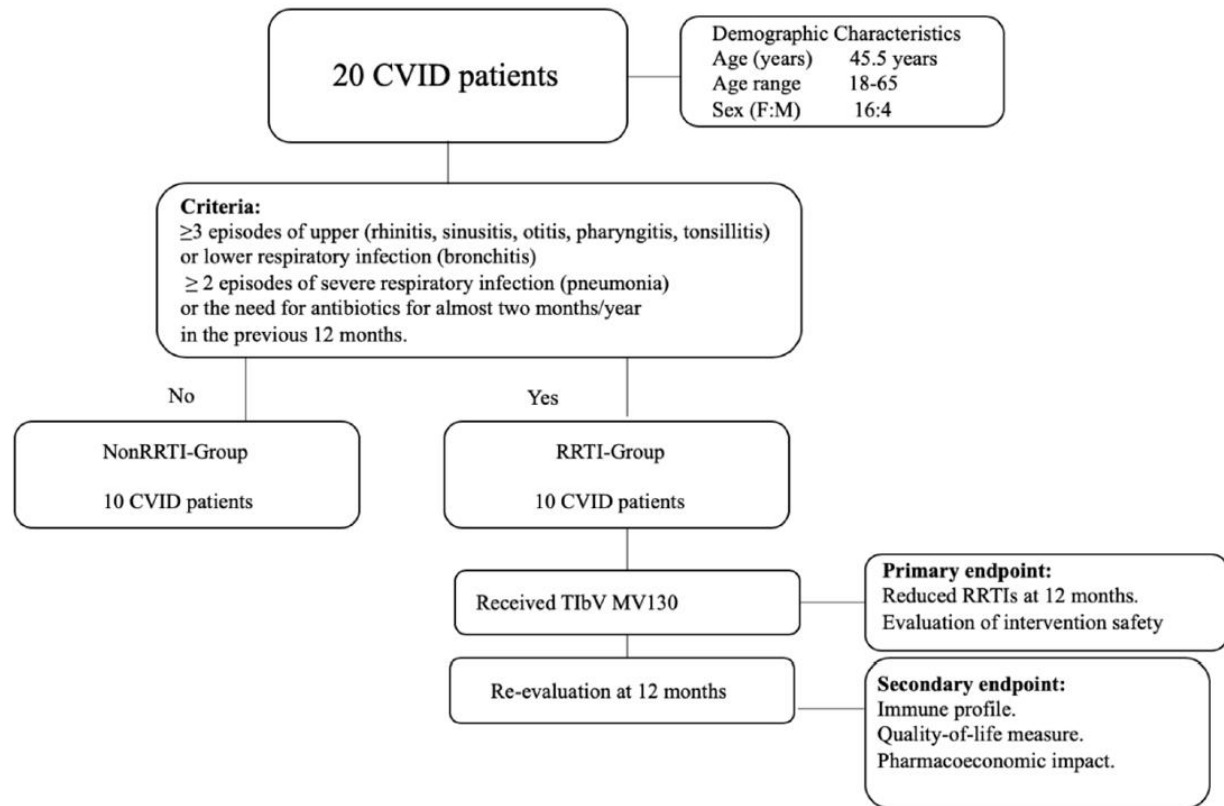
Brandi Cell Rep 2022





Article

Trained Immunity Based-Vaccines as a Prophylactic Strategy in Common Variable Immunodeficiency. A Proof of Concept Study



- Daily immunisation for 3 months:
 - Staphylococcus spp,
 - S. pneumoniae,
 - K. pneumoniae,
 - B. catarrhalis,
 - H. influenzae)

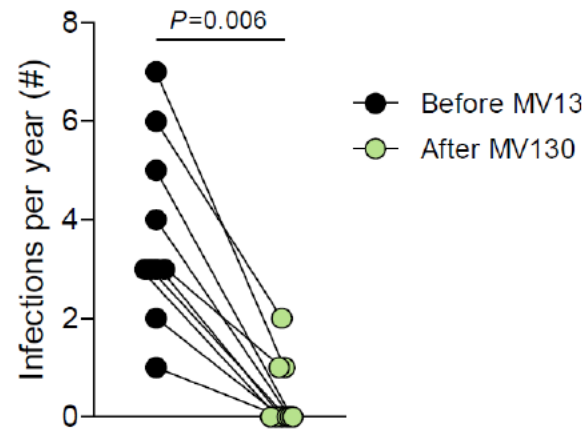
MV130 decreased the infection rate in IDVCs

Respiratory tract infections

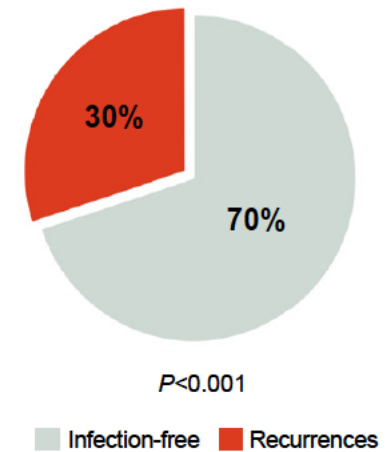
A

Subjects	Episodes before MV130	Episodes after MV130
#1	3	0
#2	3	0
#3	1	0
#4	7	1
#5	4	0
#6	3	0
#7	2	0
#8	5	0
#9	6	2
#10	3	1

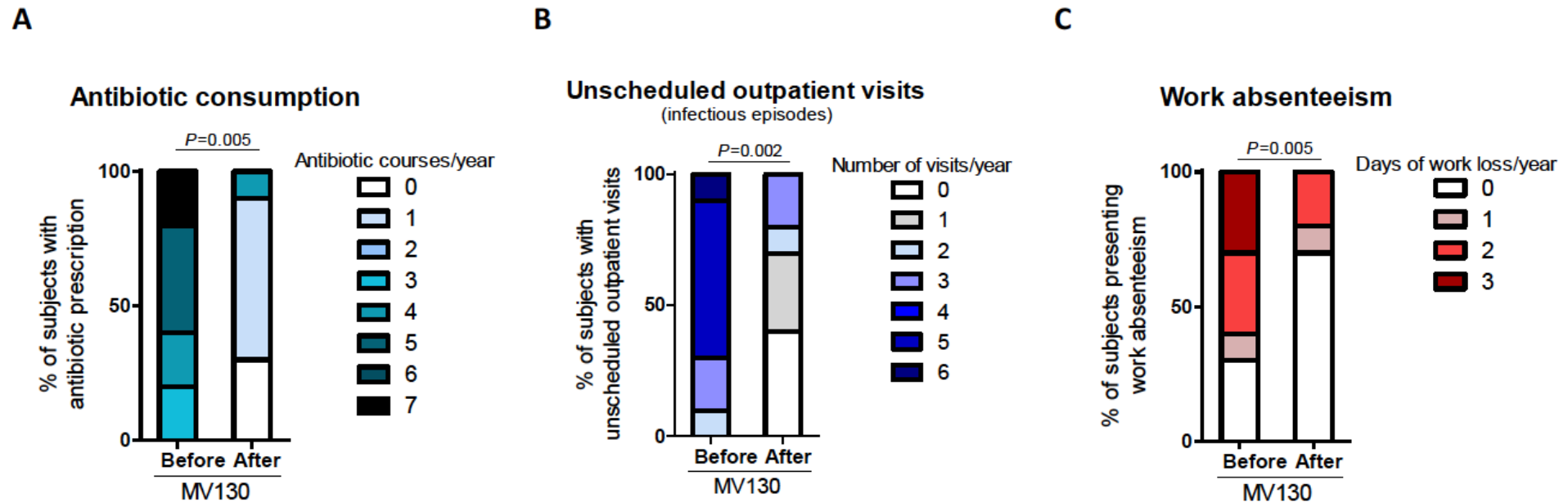
B



C



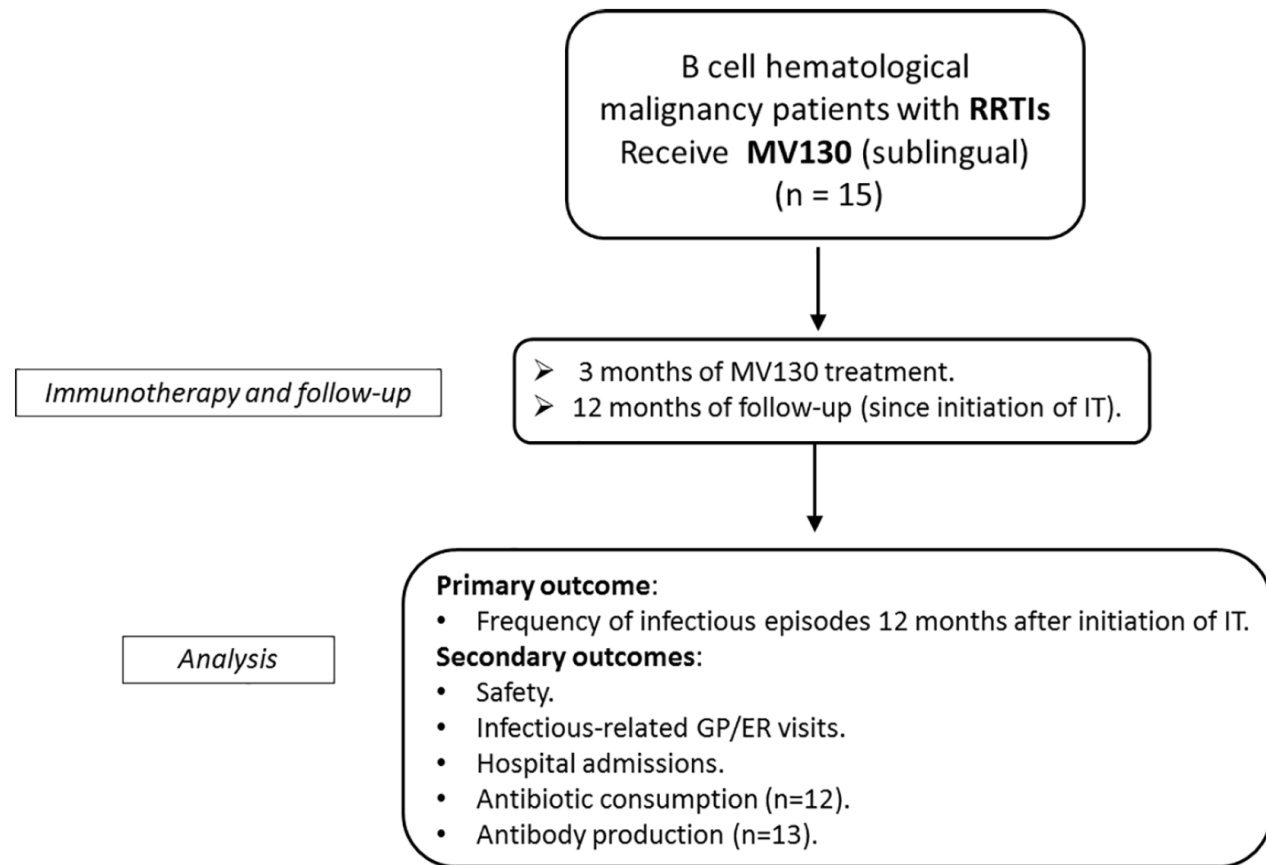
T1bV reduced antibiotic consumption, emergency room visits and lost work days.



MV130 reduced healthcare spending

Condition	Average # of Episodes before TibV MV130	Average # of Episodes after TibV MV130	Cost per Patient per Episode/ Day €	Annual Cost per Patient before TibV MV130 €	Annual Cost per Patient after TibV MV130 €	Annual Savings per Patient with TibV MV130 €
# of RRTIs	3.7	0.4	1656	6127	662	5464
# of physician/hospital/ ER visits	4.4	1.1	1288	5667	1416	4250
# Days Hospitalizations for RRTIs	7	3	792	5546	2377	3169
Cycles of antibiotics	4.8	1	259	1243	259	984
School/work days missed (Absenteeism)	1.6	0.5	14	22.4	7	15
Total per patient				18,606	4722	13,884
Annual cost TibV MV130 prophylaxis					190	13,694

Trained Immunity-Based Vaccine in B Cell Hematological Malignancies With Recurrent Infections: A New Therapeutic Approach



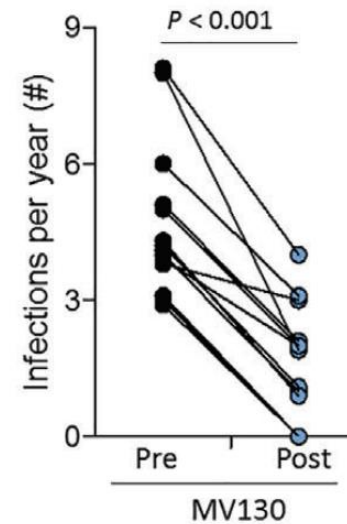
MV130 decreased the infection rate in MH

A

Patient	Number of infectious episodes		Improvement
	Pre MV130	Post MV130	
#1	3	0	100%
#2	5	2	60%
#3	5	2	60%
#4	4	1	75%
#5	4	2	50%
#6	3	0	100%
#7	8	2	75%
#8	4	2	50%
#9	8	4	50%
#10	4	1	75%
#11	4	3	25%
#12	3	0	100%
#13	6	3	50%
#14	3	0	100%
#15	4	1	75%

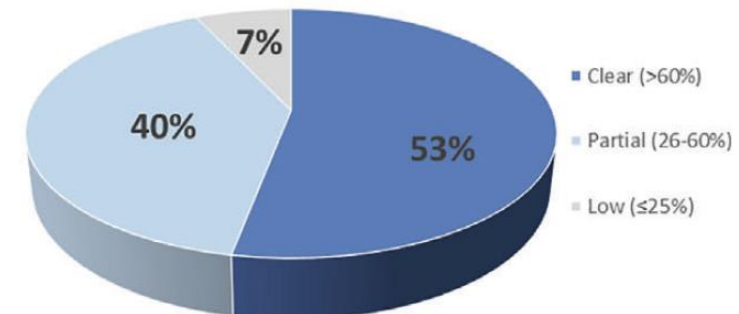
B

Respiratory tract infections

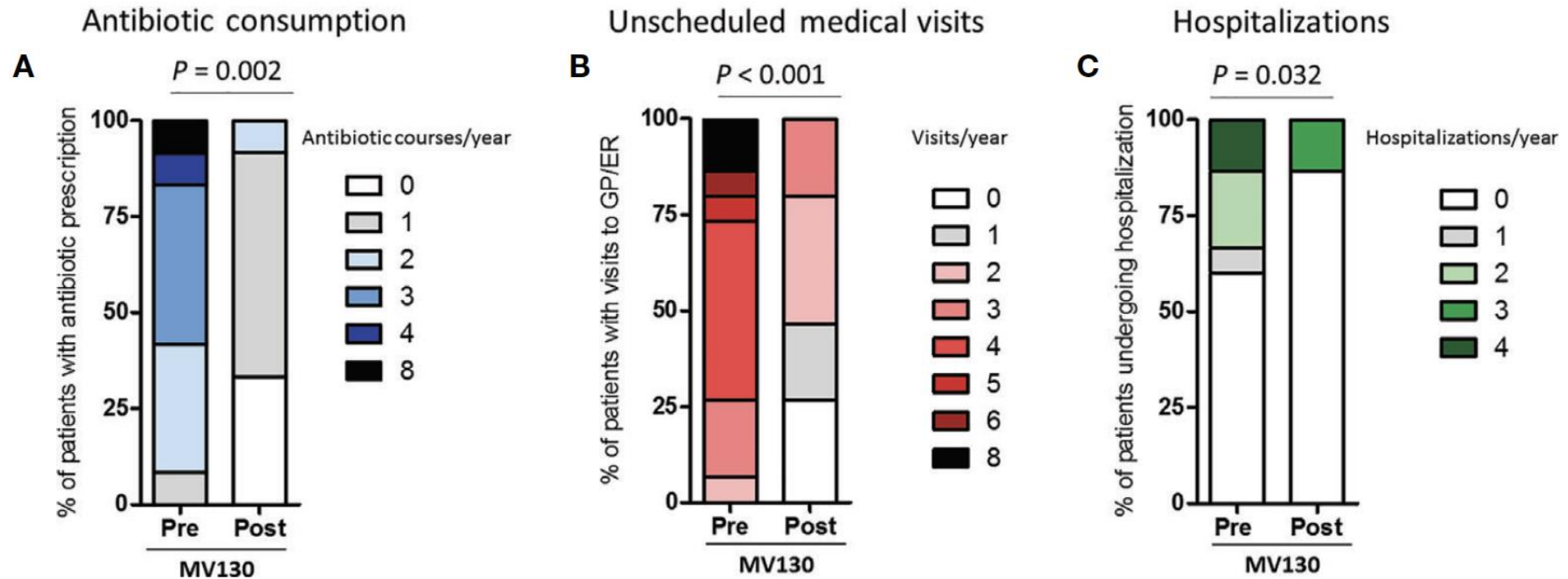


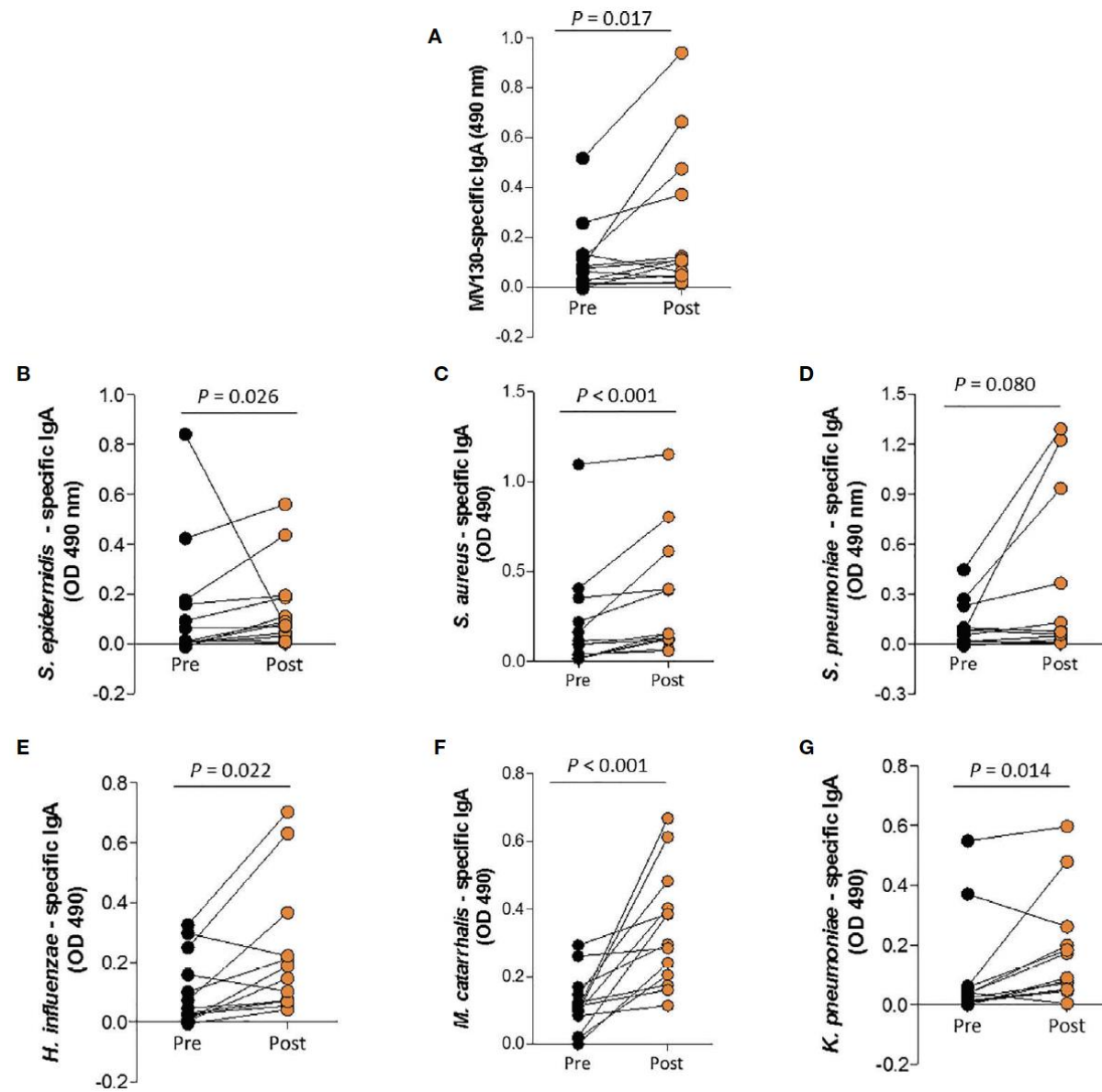
Improvement on infection rate (%)

C



Lower antibiotics, Emergencies, hospitalizations





Conclusiones

- ❑ PID patients are a risk group for antimicrobial resistance because they use AB extensively.
- ❑ There is little evidence on the spectrum of AMR in PID
- ❑ Antimicrobial resistance appears to be higher in IDP patients vs. immunocompetent patients
- ❑ No prophylaxis protocols in PID: TMP-SMX seems to be the ideal AB for prophylaxis in PID
- ❑ AB combinations do not seem to decrease ADR
- ❑ New adjuvant/alternative strategies: inhaled Ig (still experimental); immunity-trained vaccines; targeted cellular therapy



Thank you!

Perspectiva de representantes de pacientes

Patient organisation: How can NMOs get involved in the topic?

Leire Solis, España
Leire Solis, Spain

Why getting active on antimicrobial resistance?

1. Antibiotics are key to treat a wide variety of bacterial infections.
2. Antibiotics are an integral part of the treatment regiment of some patients with PIDs.
3. Antimicrobial resistance* is becoming a real concern for doctors, industry, healthcare systems, politicians, International organisations.

*Antimicrobial resistance – infections growing resistant to the use of antibiotics

Why getting active on antimicrobial resistance?

- In this context, PID patient organisations need to take a position to inform:
- their members;
 - physicians;
 - policy makers
- } about the specificities of PIDs and the perspective of patients with PIDs

Getting active on antimicrobial resistance: key messages

- Patients must be able to fight off infections throughout their lives, with the treatment prescribed by their treating physician.
- Patients need therapies that can do it successfully.
- A major area of concern is antimicrobial resistance.
- Patients with PIDs support campaigns on rationale use of antibiotics – it's on their own interest!

How do we get started?

- Think about the objective of your campaign / action:
 - Is it to inform the wider public / policy makers / doctors / reimbursement agencies?
 - Is it to influence a law in the making?
- Think about the message
- Think about potential hooks

Lo mejor contra la gripe
es echarse la siesta
abrazado a un tronco



¿Absurdo?

Tan absurdo como
usar antibióticos
contra la gripe, la
fiebre o el dolor.



ANTIBIÓTICOS
TÓMATELOS EN SERIO



Plan Nacional
Resistencia
Antibióticos



OPS



Organización
Panamericana
de la Salud



Organización
Mundial de la Salud
SECRETA REGIONAL PARA LAS Américas



10 October 2023 | Departmental news

**WHO announces the
members of the first
Taskforce of Antimicrobial
Resistance survivors**



24 November 2022

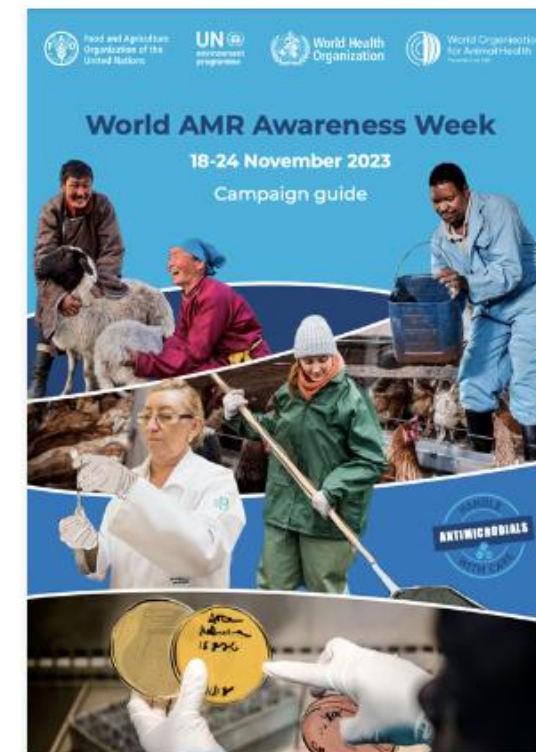
**Uruguay: National action plan
against antimicrobial
resistance 2018 (Spanish)**

[Download](#)

[Read More](#)

**PLAN NACIONAL
CONTRA LA RESISTENCIA
A LOS ANTIMICROBIANOS
CHILE 2021-2025**

an IPOPI event



Semana Mundial de Concientización sobre el Uso de los Antimicrobianos 2022

How do we get started?

- Make friends along the way.
- Start small and get bigger with time.

20th PID Forum

Anti-Microbial Resistance and the PID

Virtual Event
17th May 2022 11:00
Co-hosted by MEPs
Sarah Wiener (Greens/EFA, Austria)



an IPOPI event

Programme

Welcome & Opening Remarks

MEPs [Juozas Olekas](#) (S&D, Lithuania) and [Sarah Wiener](#) (Greens/EFA, Austria)

Setting the Scene: PIDs and AMR

[Martine Perqent](#), IPOPI President

Patients

[Representative](#)

[Infants Malades University Hospital, Paris \(France\)](#)

Innovation

[Representative](#)

on AMR and PID Medical Care

[Lithuania](#) and [Sarah Wiener](#) (Greens/EFA, Austria)

European Antibiotic Awareness Day 2022

02:22

Request control

Pop out

People

Chat

Reactions

More

Camera

Mic

Share

Leave

ting

rk week

archest

Gorayeb

A & C

Catalin Bercaru (External)

RES# Brussels Zaventem

ICSPP steering committee meeting - GBS

IPOPI Webinar Livestorm NATALIE HELENA

RES# 76167245 - Brussels Zaventem

2021 activities

Lorenzo CC

11°C

ENG BEFR

09:26

04/10/2022

EAAD 2022 – from 17 November and onwards

- **Annual Epidemiological Reports** and ECDC publication on the health burden of AMR in the EU/EEA, published on the ECDC website on 17 November.
- Highlights of **European Commission's outputs** (preliminary) e.g. proposal for a new Council Recommendation, results of the Eurobarometer on AMR, information about the new Joint Action on AMR. And OECD's data on economic burden.
- **Digital campaign**
Videos answering 5 to 10 top misconceptions about AMR and antibiotics.
Collaboration with 40 social media ambassadors from EU/EEA countries.
Interactive map on ECDC website showcasing national resources and social media ambassadors.
- **Digital events**
Press conference on 17 November in the morning.
High-level launch event on 17 November in the afternoon.
Event targeting the scientific community on 17 November in the afternoon.
Event targeting the general public and/or communicators on 22 November.
- **Social media** activities including Global social media relay with international partners, and focused content sharing.
- **Media release** highlighting the latest data.
- **Web updates** on the ECDC website and EAAD website.

In conclusion

- Antimicrobial resistance is a topic worth engaging in: from its relevance to patients with PIDs, to the whole society and its increasing political attention.
- There are many ways of engaging – use the hooks!
- IPOPI would be happy to support you – just get in touch.

Q&A

COLLABORATION



SUPPORTED BY

GRIFOLS



INTERVALO COFFEE BREAK

30 min

COLLABORATION



SUPPORTED BY

