DETERMINANTES DE LA GRAVEDAD DE LAS INFECCIONES RESPIRATORIAS POR RINOVIRUS EN POBLACIÓN PEDIÁTRICA. APLICABILIDAD DE LOS PANELES RESPIRATORIOS

María Isabel Sánchez Códez. Hospital Universitario Puerta del Mar (Cádiz).
Programa de Doctorado de Ciencias de la Salud
Tutor: Dr. D *Alfonso Mª Lechuga Sancho*
Directoras: ***Dr.Dña Isabel Benavente Fernández - Dra. Dña Asunción Mejías***

VI sesión 21/02/2023

APLICABILIDAD DE LOS PANELES RESPIRATORIOS

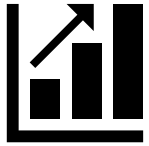
MANEJO PACIENTE
(VRS)

DISMINUCIÓN HOSPITALIZACIÓN

DESCENSO INFECCIONES NOSOCOMIALES
(cohortes)

USO ADECUADO ANTIBIOTERAPIA
(PROA)

TRATAMIENTOS PRECOCES
(asma)

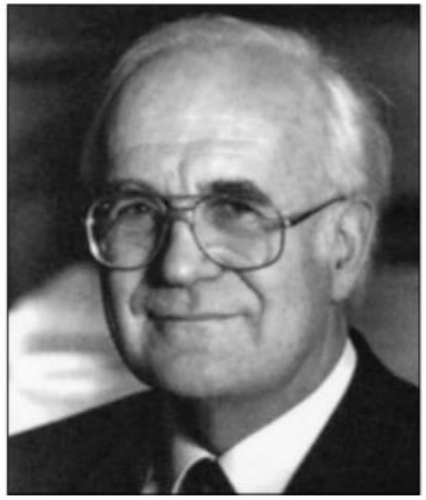


TENDENCIA EPIDEMIOLÓGICA
(Palivizumab)

VI sesión 21/02/2023

- Impact of multiplex molecular assay turn-around-time on antibiotic utilization and clinical management of hospitalized children with acute respiratory tract infections. J Clin Virol. 2019.
- Syndromic Multiplex Polymerase Chain Reaction (mPCR) Testing and Antimicrobial Stewardship: Current Practice and Future Directions. Curr Infect Dis Rep. 2021.

GENERALIDADES



David Tyrrell

Researcher who led efforts at the UK's Common Cold Unit from 1957 to 1990. Born on June 19, 1925, in Ashford, UK, he died in Salisbury, UK, on May 2, 2005, aged 79 years.

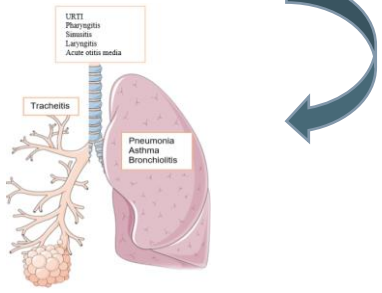
THE LANCET

Rinovirus es la causa más frecuente de infección respiratoria en niños y adolescentes

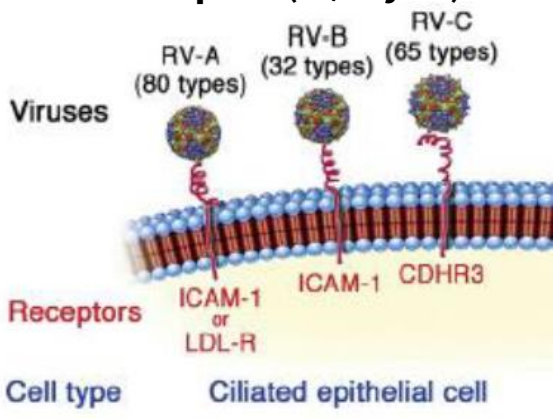
Common Cold Unit - Salisbury (1946-1989)

Thirty volunteers were required every fortnight during trial periods. The unit advertised in newspapers and magazines for volunteers, who were paid a small amount. A stay at the unit was presented in these advertisements as an unusual holiday opportunity. The volunteers were infected with preparations of cold viruses and typically stayed for ten days. They were housed in small groups of two or three, with each group strictly isolated from the others during the course of the stay. Volunteers were allowed to go out for walks in the countryside south of Salisbury, but residential areas were out of bounds.

- Familia pico**RNA**viridae/ **Género enterovirus**
- **Temperatura replicación variable** (32-35ºC)

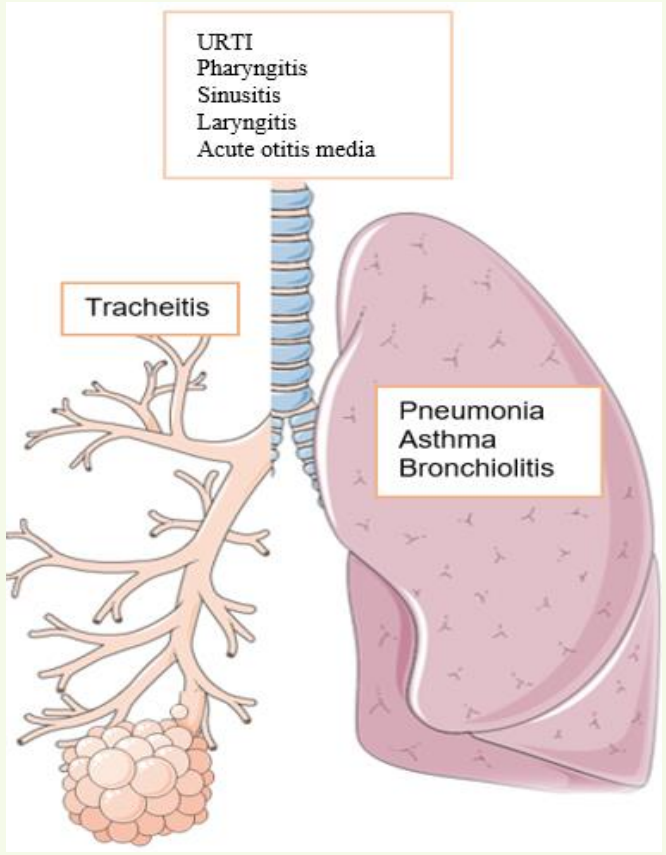


- **Genotipos** (**A**,**B** y C):



Role of viral infections in the development and exacerbation of asthma in children

MANIFESTACIONES CLÍNICAS



Elaboración propia

- **Rinovirus** produce predominantemente **manifestaciones respiratorias**: complicaciones bacterianas (**OMA**)
- **Fiebre** como síntoma aislado
- Clínica **digestiva**
- **Puede** detectarse en pacientes **asintomáticos (15-50%)**

> J Clin Virol. 2018 May;102:93-94. doi: 10.1016/j.jcv.2018.03.002. Epub 2018 Mar 5.

Do asymptomatic respiratory viral infections occur?

Ryan H Tomlinson [1], Lisa G Harrison [1], Elizabeth A Meals [1], John P DeVincenzo [2]

- Pre-infección
- Post-infección
- Asintomático

¿ Papel RV en asintomáticos?
¿ Punto de corte de carga viral relevante?

VI sesión 21/02/2023

Impact of rhinovirus infections in children. Viruses 2019.
Molecular detection of gastrointestinal viral infections in hospitalized patients. Diagn Microbiol Infect Dis. 2012

SE DETECTA RINOVIRUS EN EL PANEL

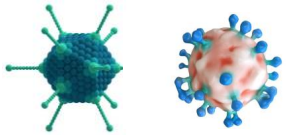
¿QUÉ NOS PUEDE AYUDAR A PREDECIR EL PRONÓSTICO?

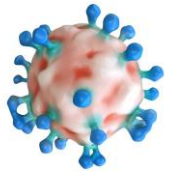
AGENTE

Genotipo viral

Cuantificación viral

Coinfecciones





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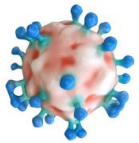
Factores demográficos-función pulmonar

Comorbilidades

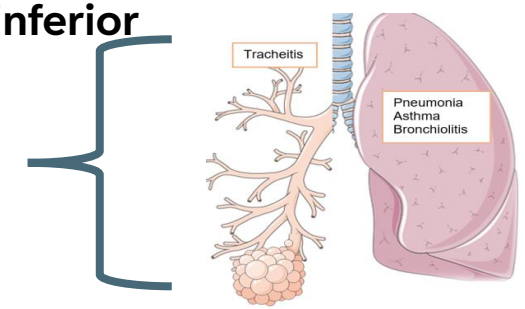
Factores genéticos, inmunológicos



AGENTE: GENOTIPO VIRAL

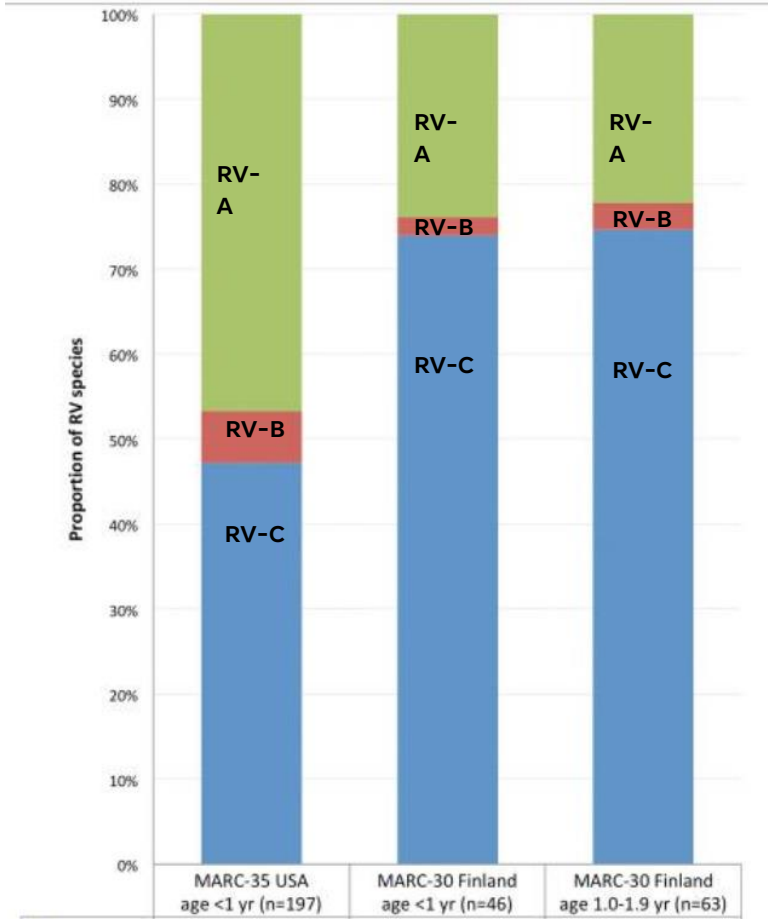
Genotipo A y C se relacionan con peor pronóstico:

- Prevalecen en **bronquiolitis** y otras **infecciones del tracto respiratorio inferior**



- Se relacionan con cuadro de mayor gravedad (estudios Urgencias y Cuidados Intensivos)

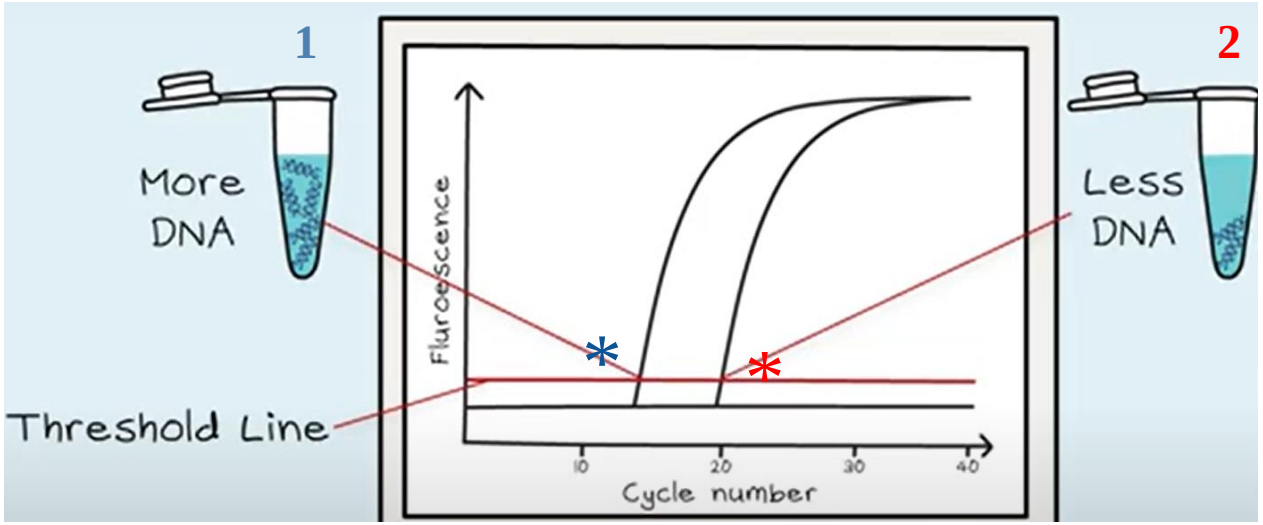
No hay diferencias en el perfil clínico según genotipo



Proporción de especies de RV en distintas cohortes de bronquiolitis grave

Impact of Human Rhinovirus Types and Viral Load on the severity of illness in hospitalized children with lower respiratory tract infections. Pediatr Infect Dis J. 2015.
Rhinovirus species in children and severe bronchiolitis: multicenter cohort studies in the US and Finland. Pediatr Infect Dis J. 2019.
Molecular epidemiology of human rhinovirus infections in the pediatric emergency department. Journal of Clinical Virology. 2015.

AGENTE: CUANTIFICACIÓN VIRAL



Menor Ct= Carga viral más elevada

AGENTE: CUANTIFICACIÓN VIRAL

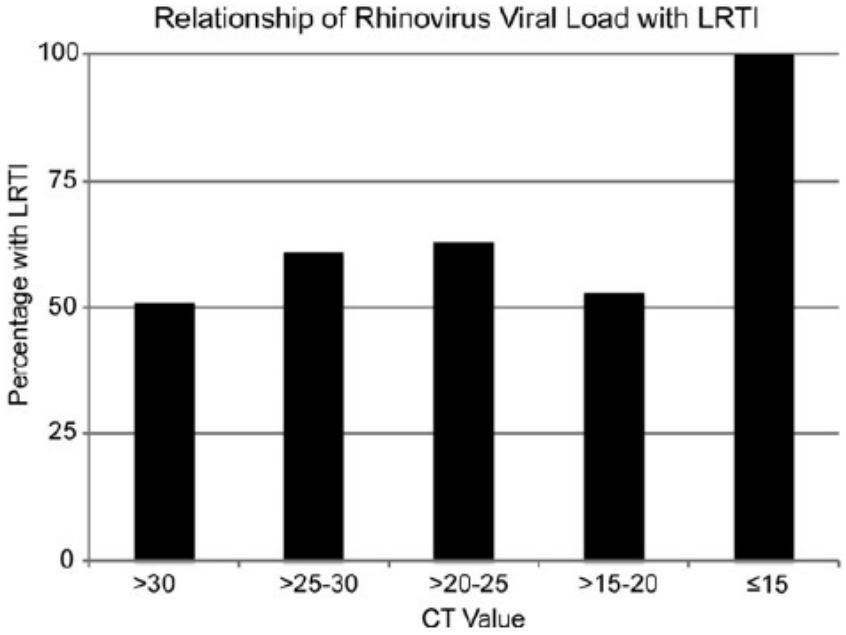
CV más alta = más gravedad

*n= **186** single detection

	HRV-A		
	Mild	Severe	*P*
Total			
N	84	17	
Median age (months)	10 (1–160)	5 (1–23)	0.011
Viral load, median (log_{10} copies/mL)	4.69 (1.52–7.45)	5.67 (3.88–6.84)	0.007
Age ≤ 23 months			
N	58	17	
Median age (months)	7 (1–20)	5 (1–23)	0.465
Viral load, median (log_{10} copies/mL)	4.91 (1.52–7.45)	5.67 (3.88–6.84)	0.042

Menores de 23 meses y RV-A, CV elevada: + gravedad

n= **445



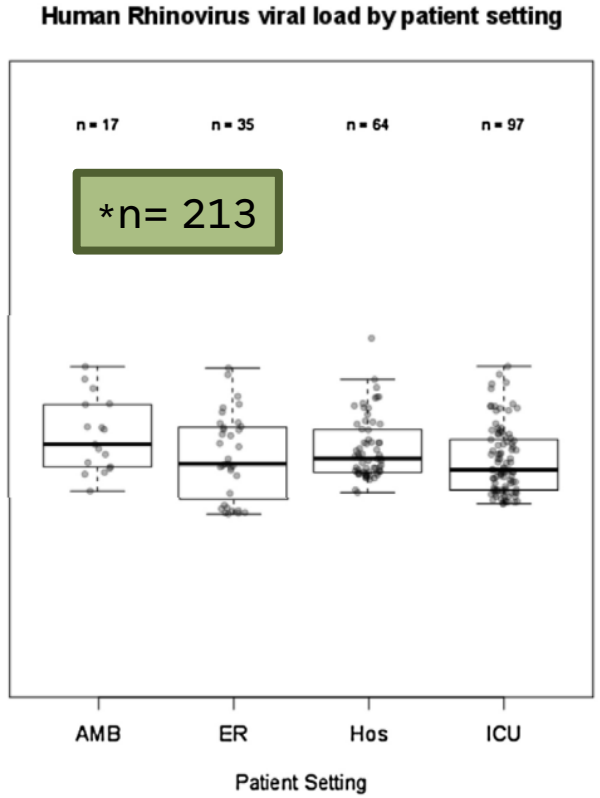
Ct≤30 relacionado con **LRTI;** (OR **2,11**;95% CI,1.24-3.58)

*Impact of Human Rhinovirus Types and Viral Load on the severity of illness in hospitalized children with lower respiratory tract infections. Pediatr Infect Dis J. 2015.

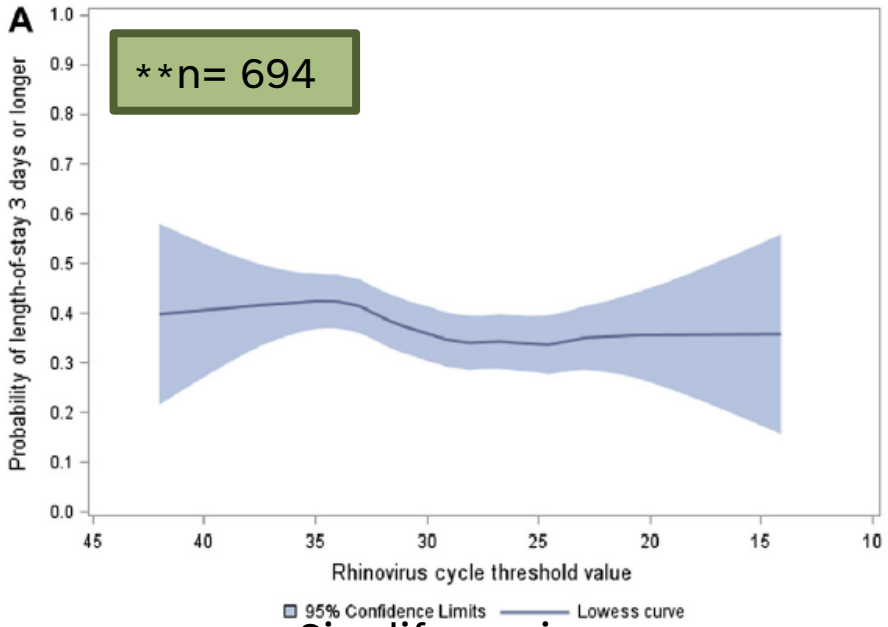
** Rhinovirus Disease in Children Seeking Care in a Tertiary Pediatric Emergency Department. J Pediatric Infect Dis Soc.2016.

AGENTE: CUANTIFICACIÓN VIRAL

CV más alta ≠ más gravedad



Sin diferencias de CV entre pacientes ambulatorios Vs. UCI



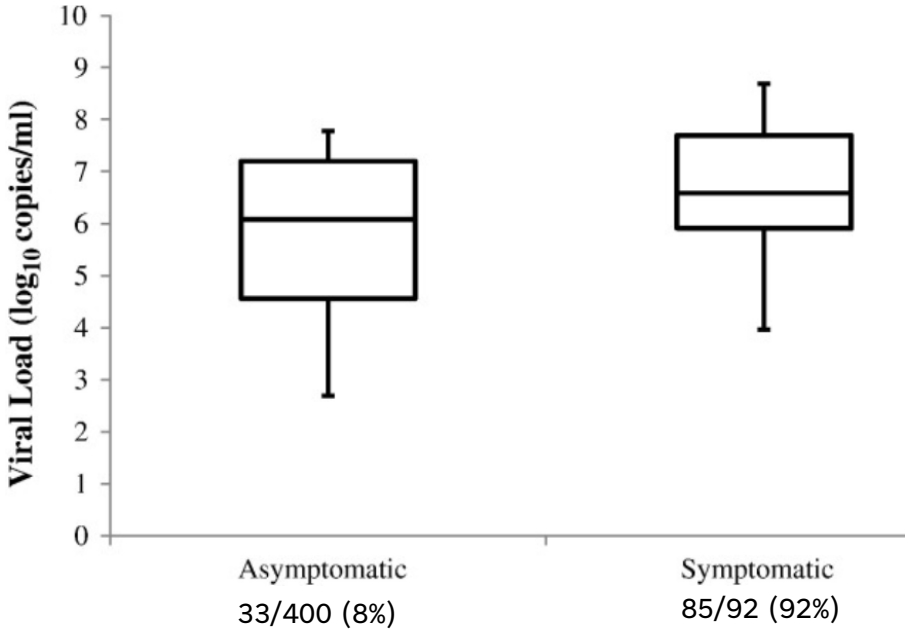
Sin diferencias en duración de estancia o necesidad de UCIP **según CV**

*Influenza and rhinovirus viral load and disease severity in upper respiratory tract infections. Journal of Clinical Virology. 2017.
** Rhinovirus-induced bronchiolitis: lack of association between virus genomic load and short-term outcomes. J Allerg IClin Immunol.2015

AGENTE: CUANTIFICACIÓN VIRAL

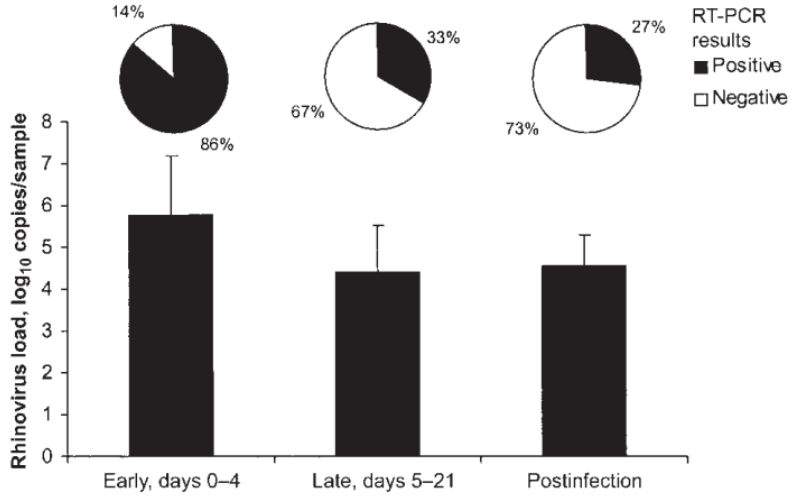
CV más alta en sintomáticos

*n= 502



CV más alta ≠ en sintomáticos

groups were made. A trend toward lower pathogen load was observed in asymptomatic compared with symptomatic subjects, but the difference was not statistically significant for any of the three pathogens (data not shown). Among the 35 symptom-

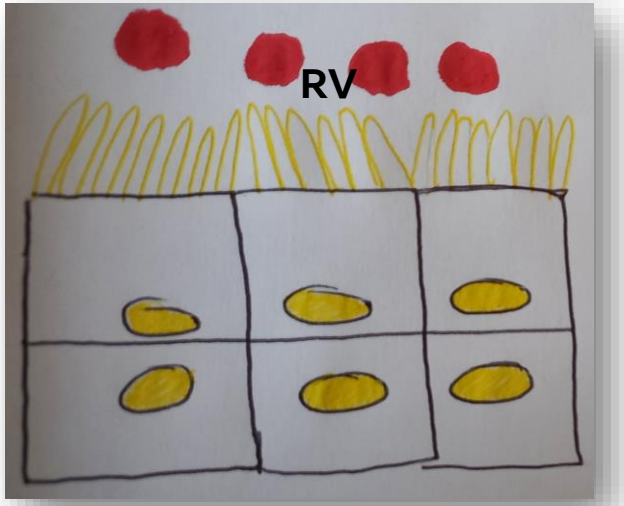


CV depende de la fase de infección

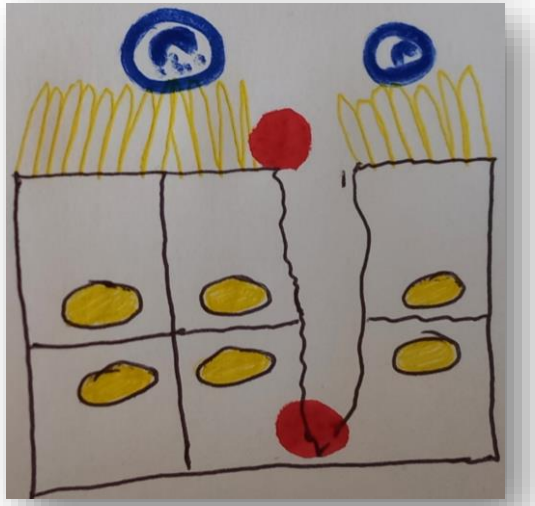
*Comparison of asymptomatic and symptomatic rhinovirus infections in university students:incidence,species diversity, and viral load. Diagnostic Microbiology and Infectious Disease.2015.
Comparison of viral load in individuals with and without Asthma during infections with rhinovirus. Am J Respir Crit Care Med. 2014.
PCR detection of respiratory pathogens in asymptomatic and symptomatic adults. Journal of Clinical Microbiology. 2019.
Rhinovirus transmisión within families with children: incidence of symptomatic and asymptomatic infections.J Infect Dis.2008.

AGENTE: PAPEL DE LAS COINFECCIONES

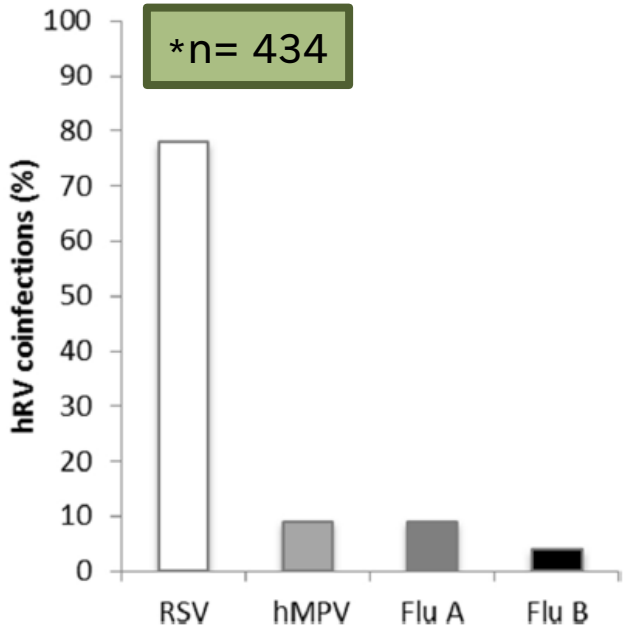
Las coinfecciones (Virales y Bacterianas) pueden determinar el pronóstico de las infecciones por rinovirus



Epitelio intacto



Epitelio dañado



Disrupción del epitelio→ **adhesión**→ **internalización** neumocitos

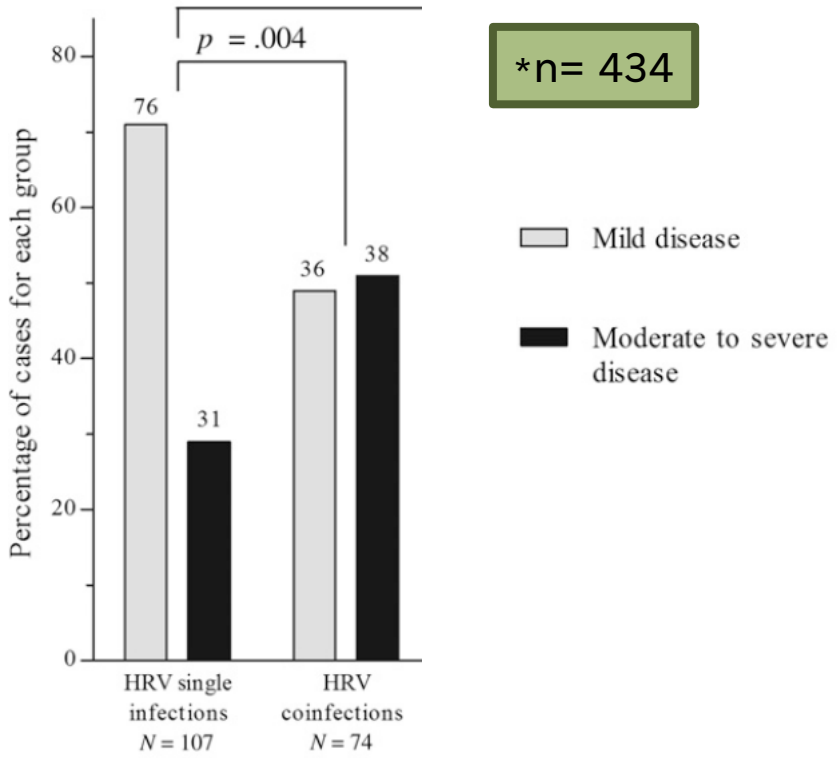
Coinfección viral variable (≈50%)

Infrecuente codetección gripe

The ABCs of Rhinoviruses,Wheezing, and Asthma. J Virol. 2010.
*Epidemiological characteristics and clinical outcomes of human rhinovirus infections in hospitalized population.Severity is independently linked to RSV coinfection and comorbidities. J Clin Virol. 2020.
Impact of Human Rhinovirus Types and viral load on the severity of illness in hospitalized children with lower respiratory tract infections. Pediatri Infect Dis J.2015.

AGENTE: COINFECCIONES

Coinfecciones = peor pronóstico



*n= 434

Coinfecciones ≠ peor pronóstico

**n= 340

than for HRV-C among children aged 6–23 months. Children with codetections and those with other viruses only had similar clinical courses.

***n= 434

hRV was the most common virus found, and one third of hRV infections in hospitalized patients were severe. Remarkably, we showed that coinfection with RSV and a history of asthma were important determinants of severity among patients under two years. These results

*Human Rhinovirus and disease severity in children. Pediatrics. 2014.
**Human Rhinovirus Species Associated with hospitalizations for acute respiratory illness in Young US Children.The Journal of Infections Diseases.2011.
***Epidemiological characteristics and clinical outcomes of human rhinovirus infections in hospitalized population.Severity is independently linked to RSV coinfection and comorbidities. J Clin Virol. 2020.
Impact of Human Rhinovirus Types and viral load on the severity of illness in hospitalized children with lower respiratory tract infections. Pediatri Infect Dis J.2015.

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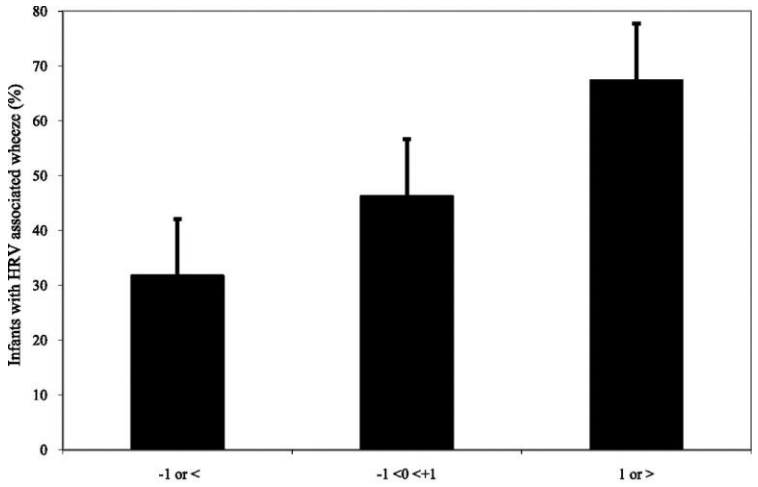
Factores **demográficos y función pulmonar**

- **Varones**
- Menores de **un año**

} Calibre **inferior** de vía respiratoria



Resistencia vía respiratoria

Comorbilidades

Prematuridad (DBP, bajo peso)
Asma
Cardiopatías congénitas

Conclusions: This study showed that total lung resistance is clearly associated with HRV-associated wheeze. Moreover, HRV-associated wheeze might be the first sign to recognize infants with reduced neonatal lung function.

Tabaquismo materno→ desarrollo pulmonar

Characteristics of Hospitalized rhinovirus.associated community-acquired pneumonia in children, Finland, 2003-2014. Front Med.2019
The Influence of Neonatal Lung Function on rhinovirus-associated Wheeze.American Journal of respiratory and critical care medicine.2009.
Human rhinovirus and disease severity in children. Pediatrics.2014.

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Factores genéticos

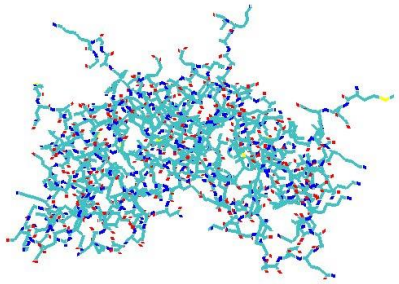
Estudios **COAST** & **COPSAC**

n~300

n ~410

cohort. We observed significant interactions between 17q21 genotypes and HRV wheezing illness with respect to the subsequent risk of asthma (P≤0.01 for interaction) (Fig. 1C, and Table S3

Susceptibilidad inmunológica



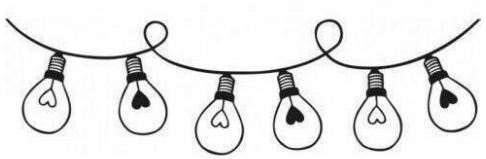
INT-λ (LT y NK)
Prematuridad y asmáticos

has been shown that atopic asthmatics have deficient type III interferon-λ responses to RV infection when compared with healthy controls.[31]

Prematurely born infants are also particularly susceptible to RV infections.[12] Those who develop RV LRTI, compared

Rhinovirus-not just the Common Cold.Am J Respir Crit Care Med.2017.
Rhinovirus wheezing illness and genetic risk of childhood-onset Asthma. The New England Journal of Medicine. 2013.

OBJETIVOS:



Gravedad de las infecciones por RV

1. Manifestaciones clínicas
2. Codetecciones
3. Carga viral
4. Comorbilidades

viruses

Article

Viral Loads and Disease Severity in Children with Rhinovirus-Associated Illnesses

IMPORTANCE OF VIRAL QUANTITATION IN CHILDREN RHINOVIRUS (RV) INFECTIONS: INTEREFERENCE WITH OTHER RESPIRATORY VIRUSES AND DISEASE SEVERITY

Nationwide Children's — When your child needs a hospital, everything matters.™ — The Ohio State University College of Medicine

María Isabel Sánchez Códez[1], Katherine Moyer[2], Isabel Benavente Fernández[3,4,5], Amy L. Leber[6]
Octavio Ramilo[7], Asuncion Mejias[7]

EAPS October 7-11, 2022 Barcelona

DISEÑO DEL ESTUDIO

(28/07/11- 31/12/13)

Estudio retrospectivo

Menores de 21 años

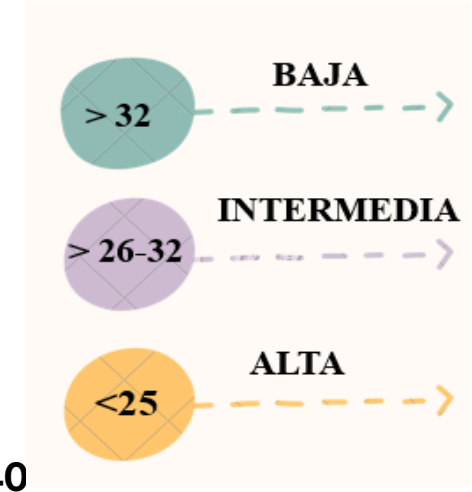
Hospitalizados & ambulatorios

CRITERIOS DE EXCLUSIÓN

Datos incompletos-duplicados

Mayores de 21 años

PARÁMETROS MICROBIOLÓGICOS*



- CV medida por Ct
- Se considera positivo: Ct≤40
- Panel respiratorio: **RV, VRS,PIV, IV-A, IV-B, adenovirus y hMPV**

PARÁMETROS DE GRAVEDAD

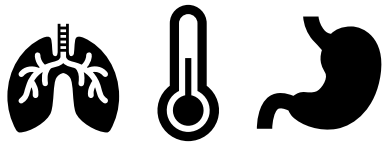
- Hospitalización (ingreso)
- Necesidad oxigenoterapia (duración)
- UCI (duración)

REDCap Research Electronic Data Capture

STATA 17

*Moyer, K.; Wang, H.; Salamon, D.; Leber, A.; Mejias, A. Enterovirus D68 in Hospitalized Children: Sequence Variation, Viral Loads and Clinical Outcomes. PLoS ONE 2016, 11, e0167111.

1 Manifestaciones clínicas- Población de estudio



Total patients included n=**2473**

Compatible symptoms **n=2383 (96.3%)**

Non-compatible symptoms **n=91 (3.7%)**

Diagnósticos (96.3%)

Diagnósticos

Comorbilidad más frecuente 745 (42%)

URTI	680 (29.62)	Cardiovascular	24 (26.37)
Bronchiolitis	483 (21.04)	GERD	19 (20.87)
Asthma exacerbation	454 (19.80)	Neurological disorders	13 (14.28)

- **+ Infección vías respiratorias inferior** (n=1274) vs**. Infección vías respiratorias superior** (n=680);
- **No diferencias de CV según localización** (infecciones respiratorias superior/inferior)

1 Manifestaciones clínicas- pronóstico

Coinfecciones **virales**

	RV Symptoms Group (n = 2382)	RV Incidental Group (n = 91)	p Value
Viral co-infections	532/2382 (22.33)	10/91(10.99)	0.010
Adenovirus	241 (10.12)	8 (8.79)	**0.679**
RSV	185 (7.77)	0 (0)	**0.006**
Parainfluenza	98 (4.12)	1 (1.10)	**0.150**
hMPV	53 (2.23)	2 (2.20)	**0.986**
Influenza A	9 (0.38)	0 (0)	**0.557**
Influenza B	6 (0.25)	0 (0)	**0.632**
RV viral loads	25.2 (22.05–29.04)	25.6 (22.09–29.07)	**0.934**

→ **Excepcional detección incidental VRS**

→ **No diferencias de CV** entre pacientes sintomáticos Vs detección incidental

Gravedad

	RV Symptoms Group (n = 2382)	RV Incidental Group (n = 91)	Odds Ratio (Upper-Lower CI)	p Value
Hospitalization	2048 (85.98)	51 (56.4)	4.80 (3.12–7.39)	0.0001
PICU	743 (31.19)	9 (9.89)	4.13 (2.06–8.26)	**0.0001**
Length of stay [a]	2.4 (1.5–4.7)	1.7 (1–3.1)	1.90 (1.14–3.17)	**0.013**
Length of stay in PICU [b]	2.4 (1.4–4.7)	1.6 (1.2–2.6)	3.30 (0.82–13.32)	**0.093**
Suplemental oxygen Requirement, n (%)	1278 (53.65)	8 (8.79)	12.01(5.78–24.92)	**0.0001**
Duration (days) [c]	2 (1–4)	2.5(1.5–6)	0.95 (0.19–4.74)	**0.953**

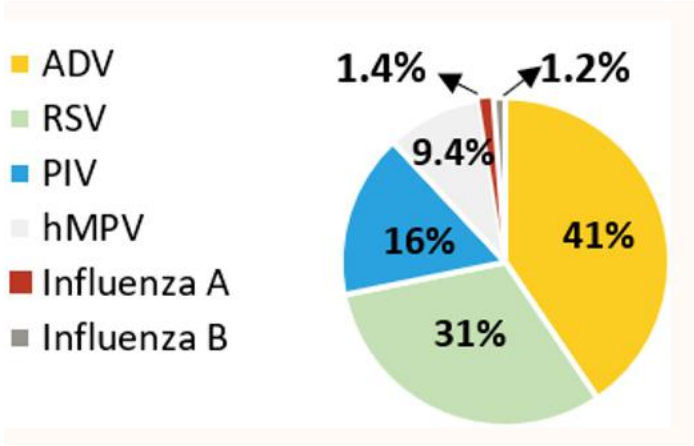
Pacientes **sintomáticos**: mayor riesgo de **hospitalización, estancia más prolongada**, ingreso en **UCI** y necesidad de **oxigenoterapia**

2 Codetecciones víricas- Población de estudio y pronóstico

Total patients included n=**1899**

Single RV infection **n=1440 (75.8%)**

RV viral co-infection **n=459 (24.2%)**



Gravedad

	RV single detection (*n*=1440)	RV Co-infection group (*n*=459)	*p* value
Age, (months)	14.95 (3.5-57.5)	9.5 (3.7-21.6)	0.0001
RV viral loads (Ct)	24.74 (21.7-28.49)	26.62 (22.1-29.03)	0.0001
Hospitalization, n (%)	1231 (85.49)	365 (79.52)	0.002
Length of stay in PICU [b]	2.2 (1.3-3.9)	2.6(1.4-5.9)	0.030

b Prolonged pediatric intensive care unit (PICU) stay if greater than the median length of PICU stay, which was 1.9 days. PICU, pediatric intensive care unit.

Los pacientes con **mono-infección** tienen **CV más alta, son de mayor edad** e **ingresan más**

3 Carga viral- pronóstico

Ct más bajo = CV más alta

Gravedad

	Hospitalization (OR,95% CI) *p*-value	PICU (OR,95% CI) *p*-value	Length of stay (OR,95% CI) *p*-value	Supplemental oxygen (OR,95% CI) *p*-value
Genomic load category (Ct)				
Low	Reference	Reference	Reference	Reference
Intermediate	1.22 (0.83-1.79) 0.292	1.09 (0.78-1.51) 0.591	1.23 (0.91-1.67) 0.173	1.05 (0.78-1.41) 0.739
High	1.26 (0.87-1.82) 0.214	**1.49 (1.09-2.05) 0.012**	1.30 (0.96-1.75) 0.081	1.20 (0.90-1.60) 0.210

Los pacientes con **CV más alta** tienen ingresan más en **Cuidados Intensivos**

	Ct≤25 (n=920)	Ct 26-32 (n=713)	Ct >32 (n=266)	*p* value
Viral co-infections	**178 (19.35)**	**197 (27.63)**	**84 (31.58)**	**0.0001**

Los pacientes con **CV más alta** tienen **menos coinfecciones víricas**

4 Comorbilidades- pronóstico

Gravedad

	Chronic Medical Conditions (CMC; *n*=1477)	Previously healthy (*n*=422)	*p* value
Demographic characteristics			
Age, (months)	**15.8 (4.9-52.9)**	**4.7 (1.5-19.9)**	**0.0001**
Sex, n (%) male	894 (60.5)	243 (57.58)	0.28
Management/Outcomes of care			
Steroids, n (%)	**672 (45.50)**	**87 (20.72)**	**0.0001**
Hospitalization	**1271 (86.05)**	**325 (77.01)**	**0.0001**
Supplemental O2			
Administration	**848 (57.41)**	**149 (35.31)**	**0.0001**
Duration (days) [a]	2 (1-4)	2 (1-3)	0.38
PICU			
Admission	**508 (34.39)**	**71 (16.82)**	**0.0001**
Length ICU of stay [b]	2.3 (1.3-3.9)	2.7 (1.2-6.1)	0.25
Mechanical ventilation	**138 (9.3)**	**19 (4.5)**	**0.0001**
Length of stay [c]	**2.6 (1.7-4.5)**	**1.9 (1.3-3)**	**0.0001**

c Prolonged duration of supplemental oxygen if greater than median O2 supplementation that was 4 days.d Values expressed as median [interquartile range]. NIV, non-invasive ventilatory support.

Los pacientes con **comorbilidades son mayores.** Precisan **más hospitalizaciones, UCI, Oxigenoterapia (VM) e ingreso más prolongado**

CONCLUSIONES- PARA SEGUIR APRENDIENDO

APLICABILIDAD DE PANELES RESPIRATORIOS

Nos permite establecer **clasificación detallada** de los pacientes desde Urgencias y determinar **fenotipos clínicos**

CLÍNICA

Sin diferencias en la CV en función de presentación.
La presencia de síntomas: mayor gravedad

1

COINFECCIONES

Gravedad similar
Menos riesgo de hospitalización.

2

CARGA VIRAL

CV más alta: Mayor **riesgo de ingreso en UCI**.
Menor porcentaje de coinfección viral

3

COMORBILIDADES

En general**, peor pronóstico** por presentar enfermedades de base

4

DETERMINANTES DE LA GRAVEDAD DE LAS INFECCIONES RESPIRATORIAS POR RINOVIRUS EN POBLACIÓN PEDIÁTRICA. APLICABILIDAD DE LOS PANELES RESPIRATORIOS

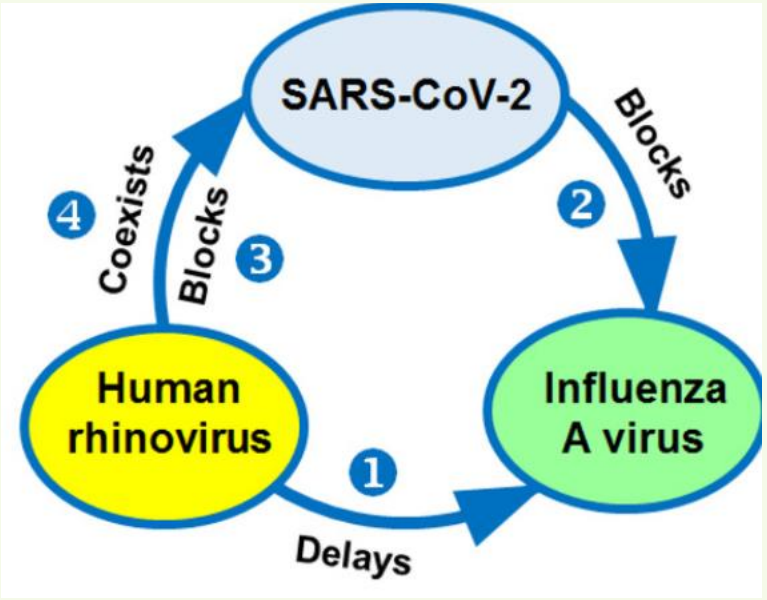
MUCHAS GRACIAS

María Sánchez Códez

mscodez1990@gmail.com

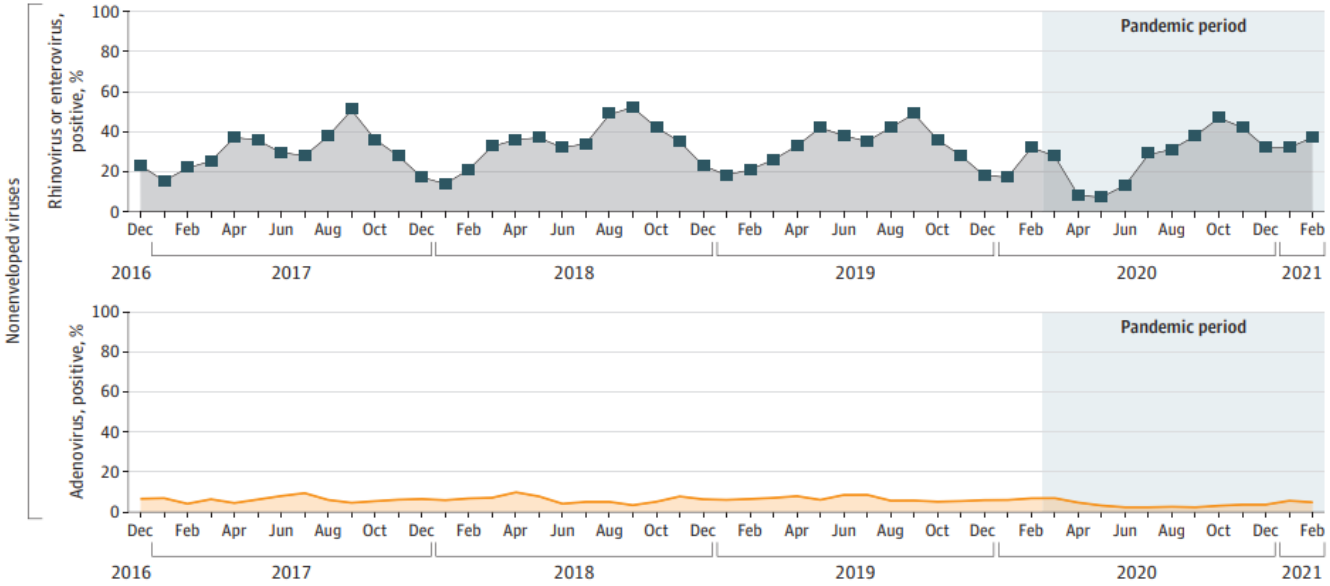
VI sesión 21/02/2023

¿Qué hemos aprendido?



Open Access Review

COVID-19 Shuts Doors to Flu but Keeps Them Open to Rhinoviruses



JAMA Network | Open

Original Investigation | Pediatrics

Circulation of Rhinoviruses and/or Enteroviruses in Pediatric Patients With Acute Respiratory Illness Before and During the COVID-19 Pandemic in the US