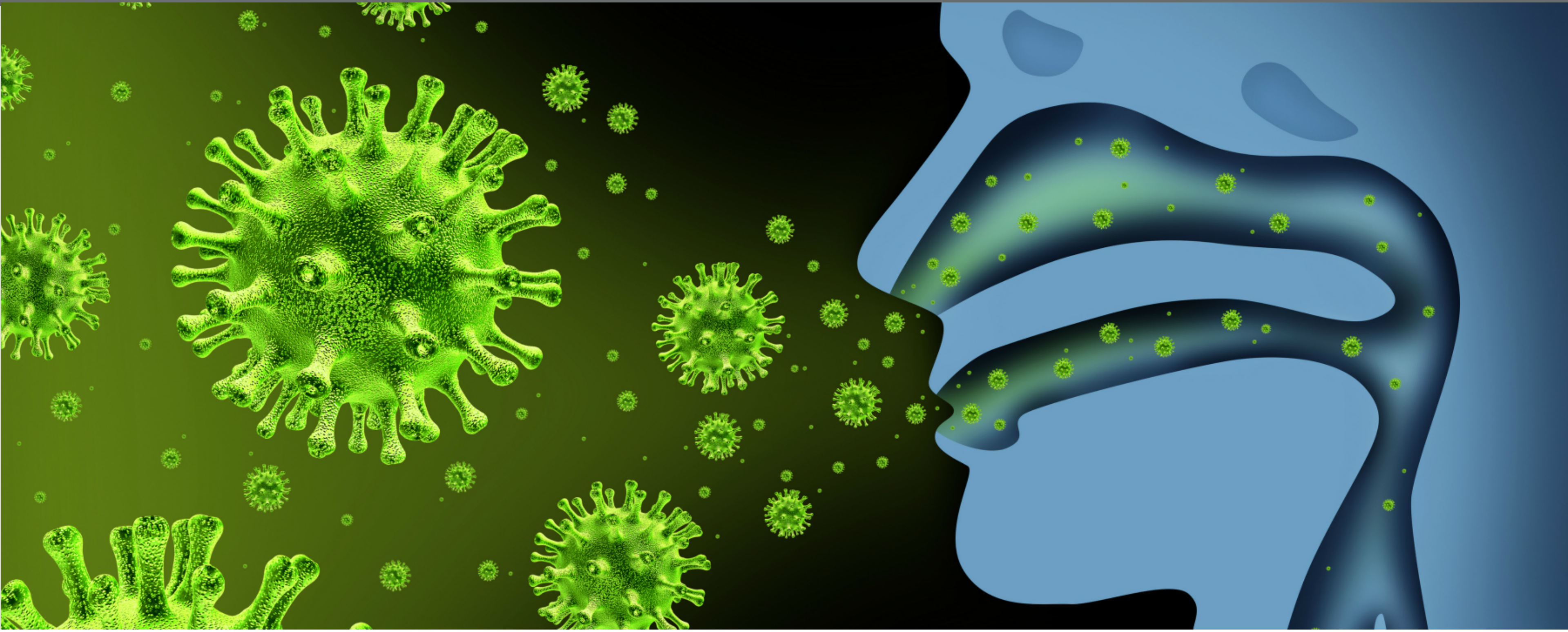
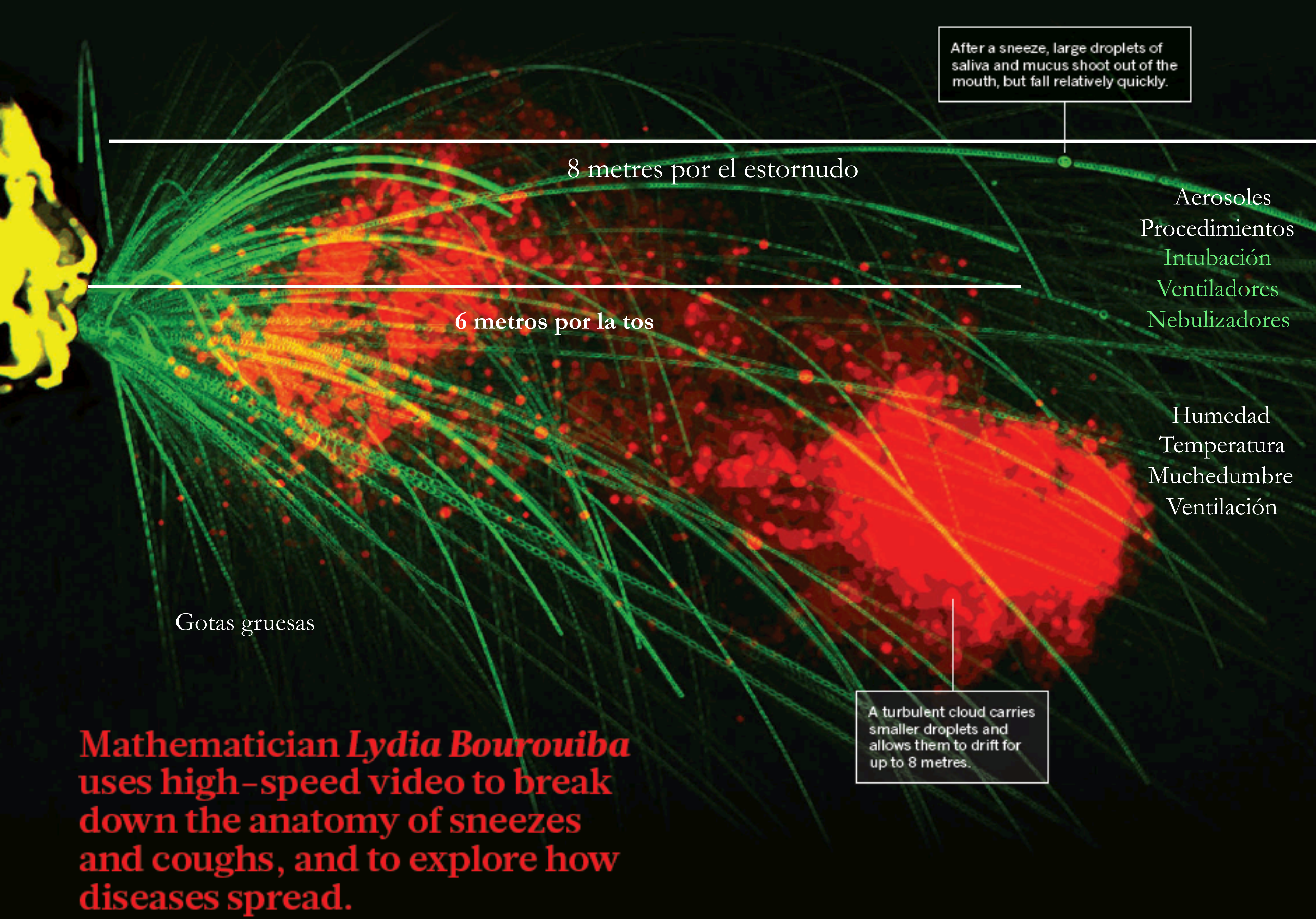
Universidad Nacional de Colombia
Departamento de Microbiología
Facultad de Medicina
Sede Bogotá



Aspectos básico-clínicos del nuevo coronavirus: SARS-CoV-2, COVID-19.

Fundamentos básicos de Biología Molecular

Manuel Antonio Vargas Córdoba
Profesor Titular



http://www.nature.com.ezproxy.unal.edu.co/polopoly_fs/1.19996!/menu/main/topColumns/topLeftColumn/pdf/534024a.pdf
https://www.youtube.com/watchv=bFxgVkslD-k

Rutas de transmisión de los virus respiratorios

Transmission route	Particles involved and particle characteristics	Characteristics/definition of transmission
Contact		Self-inoculation of mucous membranes by contaminated hands.
Direct	Deposited on persons.	Virus transfer from one infected person to another.
Indirect	Deposited on objects.	Virus transfer through contaminated intermediate objects (fomites).
Airborne		
Droplet	Droplets (>5 μm). Remain only shortly in air (<17 min) [116]. Dispersed over short distances (<1 m).	Short range transmission. Direct inoculation of naïve person through coughing/sneezing/breathing of infected person. Deposition mainly on mucous membranes and upper respiratory tract.
Aerosol	Aerosols, droplet nuclei (<5 μm), Remain in air for an almost infinite amount of time. Dispersed over long distances (>1 m).	Long range transmission. Inhalation of aerosols in respirable size range. Deposition along the respiratory tract, including the lower airways.

Current Opinion in Virology 2018;28:142-151

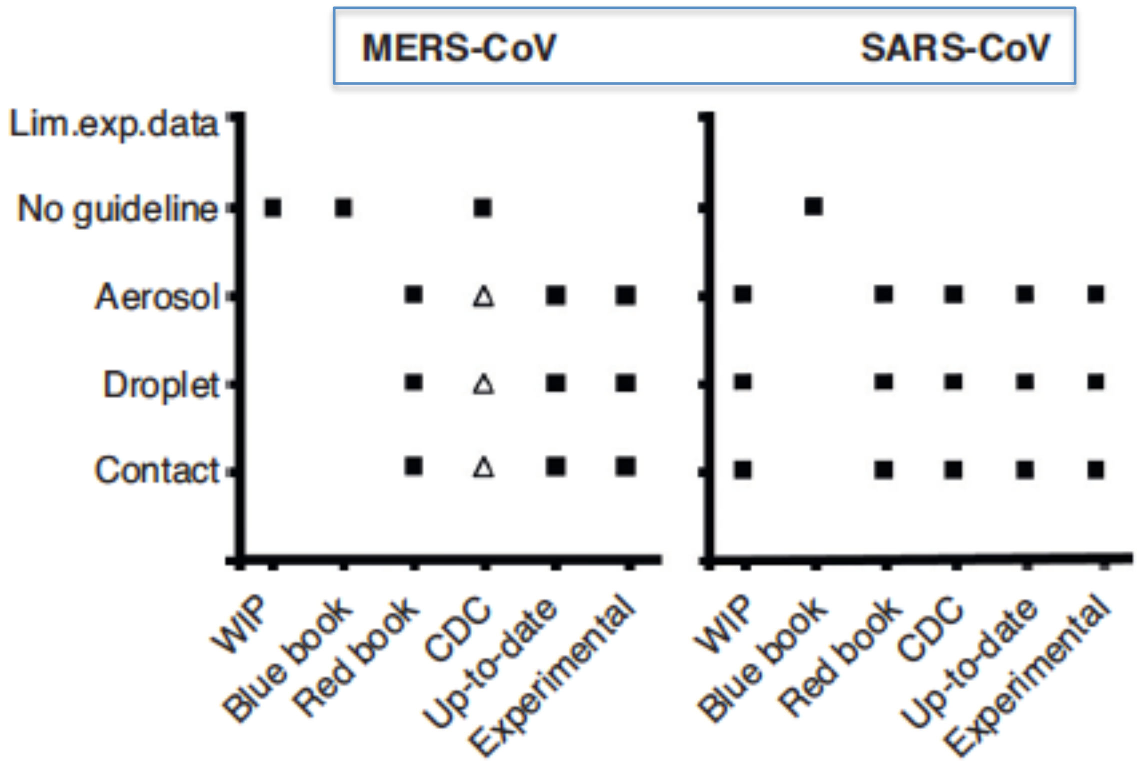
Evidencia al respecto de las rutas de transmisión

Virus	Virus family[a]	Transmission route	
		Experimental and observational data	Guidelines[b]
Measles virus	*Paramyxoviridae*	Aerosol [75–77,78•,79•].	Contact [3,110], droplet [3,109–111], aerosol [3,109–111].
Parainfluenza virus	*Paramyxoviridae*	Limited data, contact (by fomite) [83,84] [e].	Contact [3,109–111], droplet [3,109–111], aerosol [3,109].
HMPV	*Pneumoviridae*	Limited data, contact (by fomite)[e] [30]	Contact [3,110,111], droplet [3,110,111].
RSV	*Pneumoviridae*	Contact [89,88], droplet [88], aerosol [90,91••].	Contact [3,109–111], droplet [3,109,110], aerosol [109,111].
HCoV	*Coronaviridae*	Limited data, contact (by fomite) [65–67] [e].	Contact [3,110,111], droplet [3,110,111].
MERS-CoV	*Coronaviridae*	Contact [84] [e] [89] [c] [91••], droplet [89] [c], aerosol [91••].	Contact [111], droplet [3,111]
SARS-CoV	*Coronaviridae*	Contact [70] [e] [73,79,101], droplet [73,78•,79•,117], aerosol [76,118] [c] [82] [c,d].	Contact [3,110,111], droplet [3,110,111], aerosol [3,110,111].
Rhinovirus	*Picornaviridae*	Contact [35,36,42], aerosol [37,40,119].	Contact [109–111], droplet [109,111], aerosol [109–111].
Adenovirus	*Adenoviridae*	Contact [100] [e] [100,101], droplet [103•], aerosol [102,103•].	Contact [3,109–111], droplet [3,109,110], aerosol [110,111].
Influenza virus	*Orthomyxoviridae*	Droplet/aerosol [55,56,57•,59]	Contact [109–111], droplet [3,109–111], aerosol [3,109–111].

[a] Taxonomy was based on [62], airborne transmission is seemingly linked to:
[b] WIP [108], 'Blue Book' [109], 'Red Book' [110], CDC [3] and Up-To-Date [111]. The conclusions on experimental data as presented in this table reflect the conclusions from the authors.
[c] Superspreader events.
[d] Aerosol-generating procedures (in a nosocomial situation).
[e] Conclusions were drawn based on stability experiments.

Current Opinion in Virology 2018;28:142-151

Evidencia al respecto de las rutas de transmisión



Current Opinion in Virology 2018;28:142-151

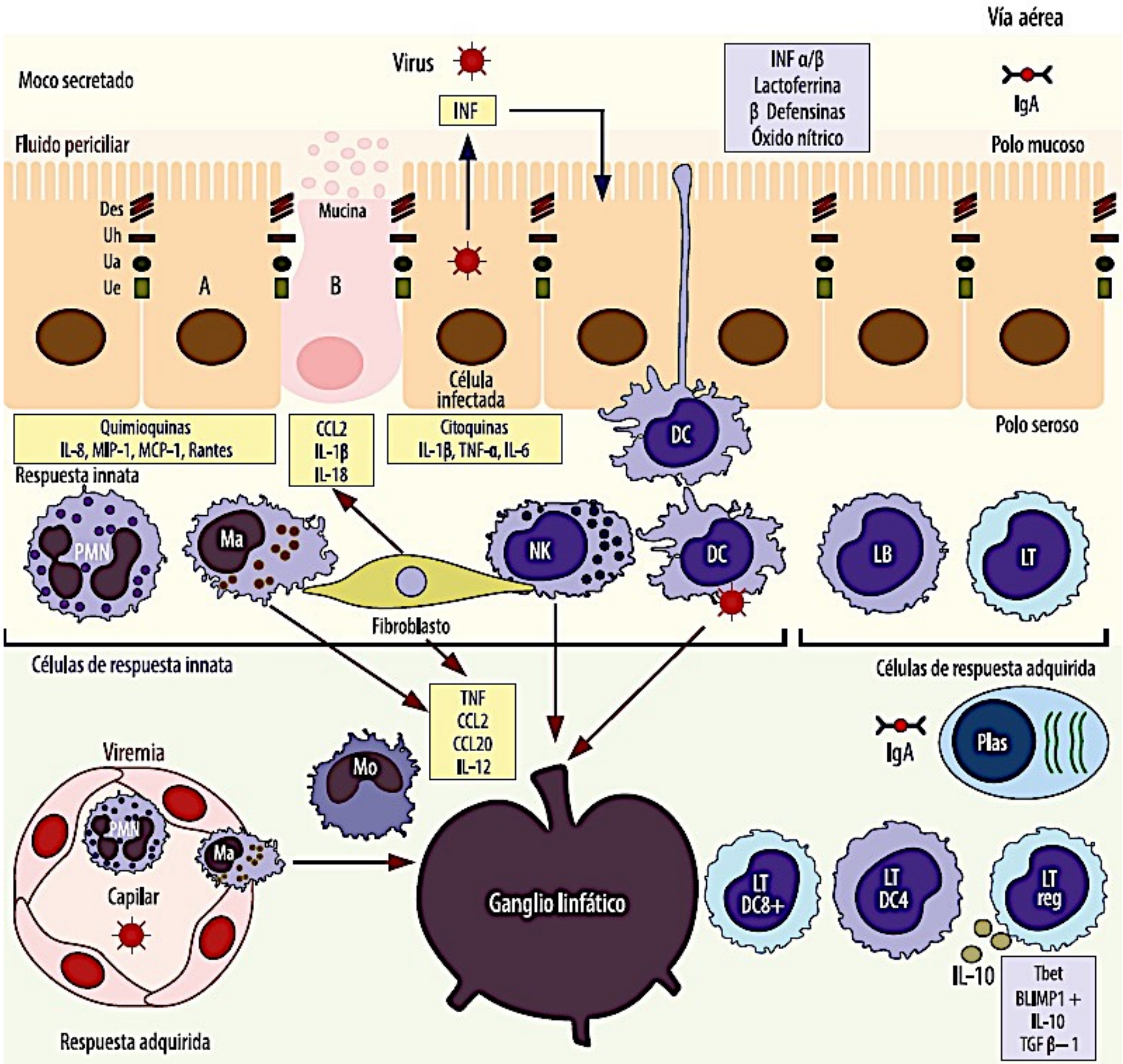
Super-transmisores

Factors	Categories	Examples
Host	Physiological	Compared to other avian species, American robins appear to be responsible for the majority of West Nile virus-infected mosquitoes, and act as a species equivalent of a super-spreader
	Behavioral	Contact length and contact frequency between hosts were implicated in shaping the Sin Nombre virus transmission among deer mice
	Immunological	Decreased immunity in a patient receiving hemodialysis was linked to a super-spreading event in the Amoy Gardens, Hong Kong SARS outbreak
Pathogen	Virulence	*Salmonella enterica* serovar Typhimurium SPI1 and SPI2 pathogenicity islands were associated with super-spreading
	Co-infection	'Cloud babies' and 'cloud adults' are individuals who, after rhinovirus infection, efficiently spread *S. aureus* that they are colonized with, and infect others in their environment. HIV shedding is higher in people co-infected with other sexually transmitted diseases, and treatment of those diseases often reduces shedding
Environment	Crowding	A study of the Beijing SARS outbreak revealed that in three super spreading events, the average number of contacts was 24
	Unrecognized/misdiagnosed disease	In a patient admitted to a Beijing hospital, SARS was initially misdiagnosed for tuberculosis
	Inter-hospital transfers	During the SARS outbreak, several patients with previous SARS contacts were admitted for unrelated complaints and were subsequently transferred between hospitals, infecting others
	Building ventilation/airflow dynamics	In the Amoy Gardens residential complex, building ventilation was one of the factors thought to have facilitated the initial SARS transmission to at least 187 individuals

Modelo 20/80: un 20% de los individuos en una población contribuyen al 80% de la transmisión de los patógenos

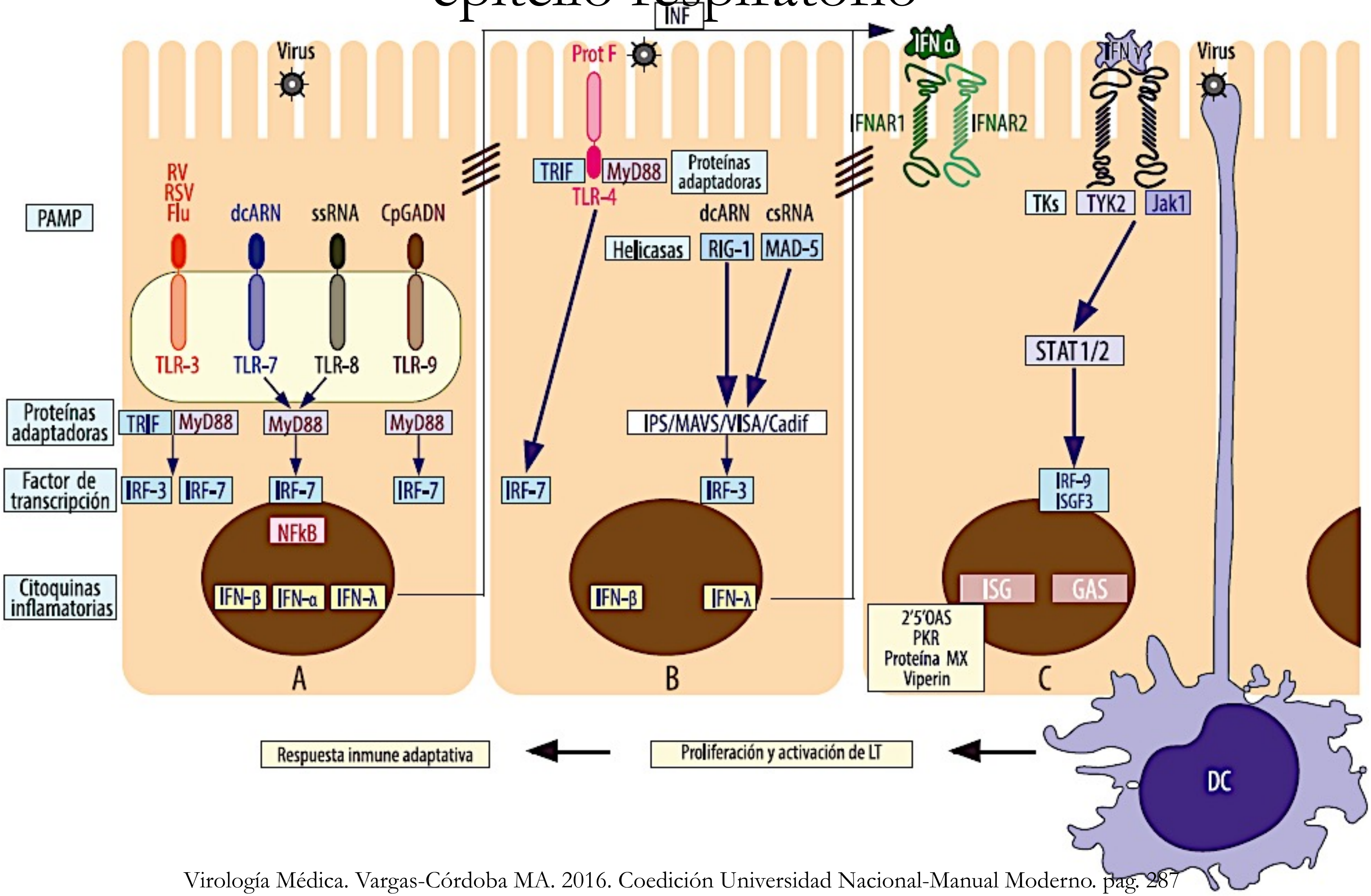
International Journal of Infectious Diseases 15 (2011) e510–e513

Estructura funcional del epitelio respiratorio



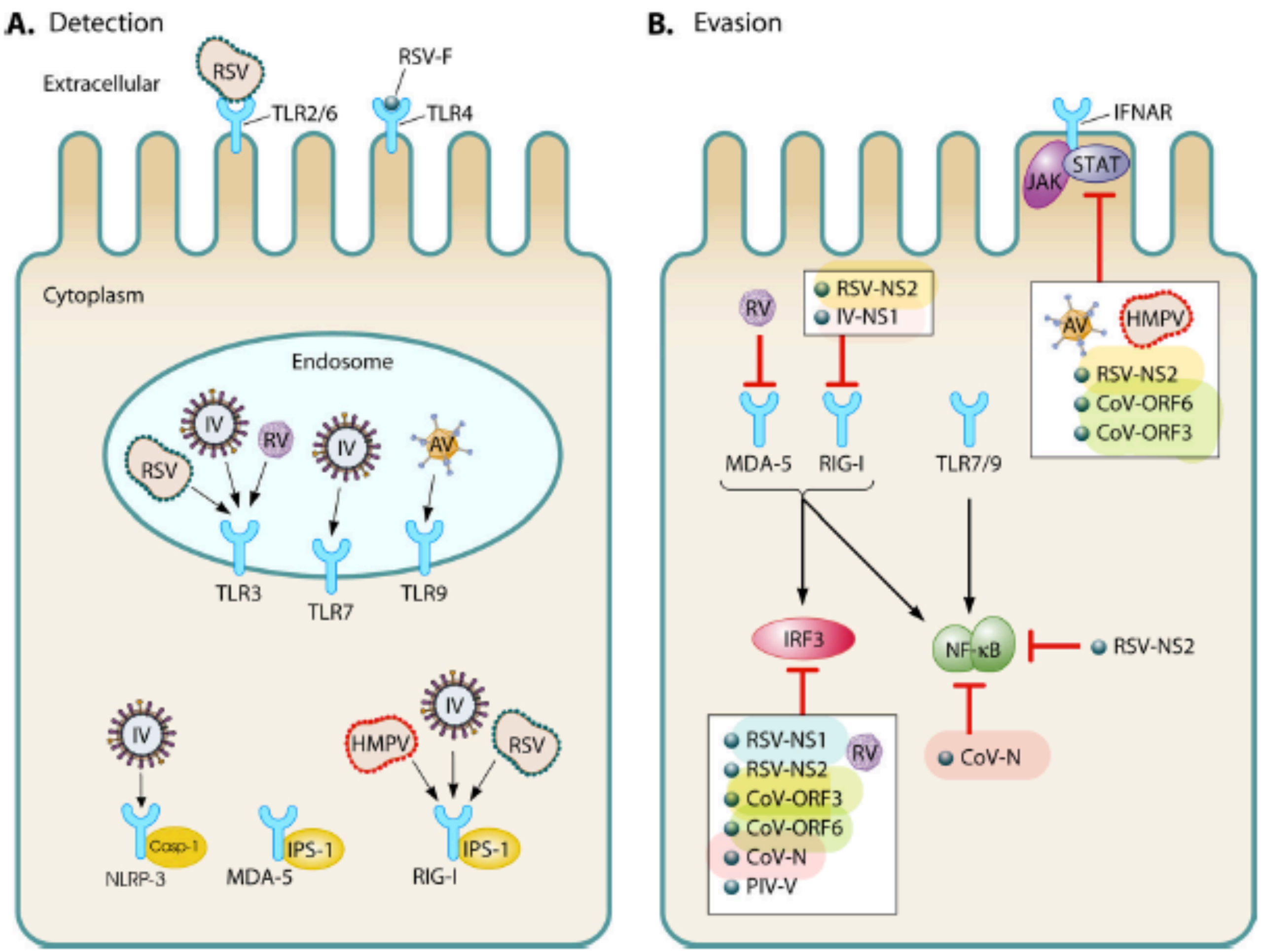
Virología Médica. Vargas-Córdoba MA. 2016. Coedición Universidad Nacional-Manual Moderno. pag. 285

Vías de señalización inducidas por virus en el epitelio respiratorio



Virología Médica. Vargas-Córdoba MA. 2016. Coedición Universidad Nacional-Manual Moderno. pag. 287

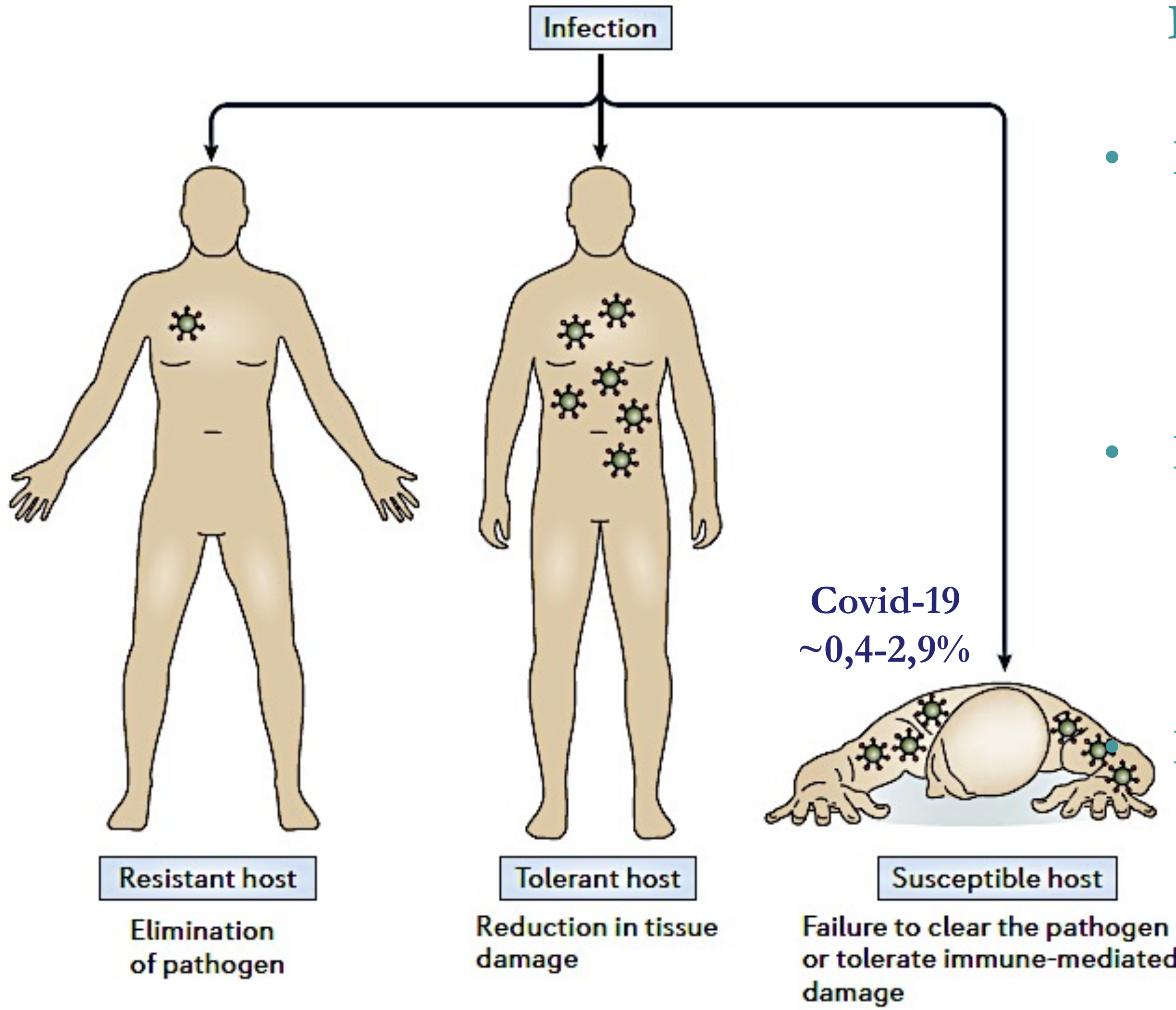
Detección y evasión viral



TLR: Toll Like Receptors.
MDA-5 (melanoma differentiation-associated gene 5)
NLRP3 (NLR family, pyrin domain-containing

Clinical Microbiology Reviews, Jan. 2010, p. 74–98

Virus respiratorios: resistencia antiviral y tolerancia a la enfermedad



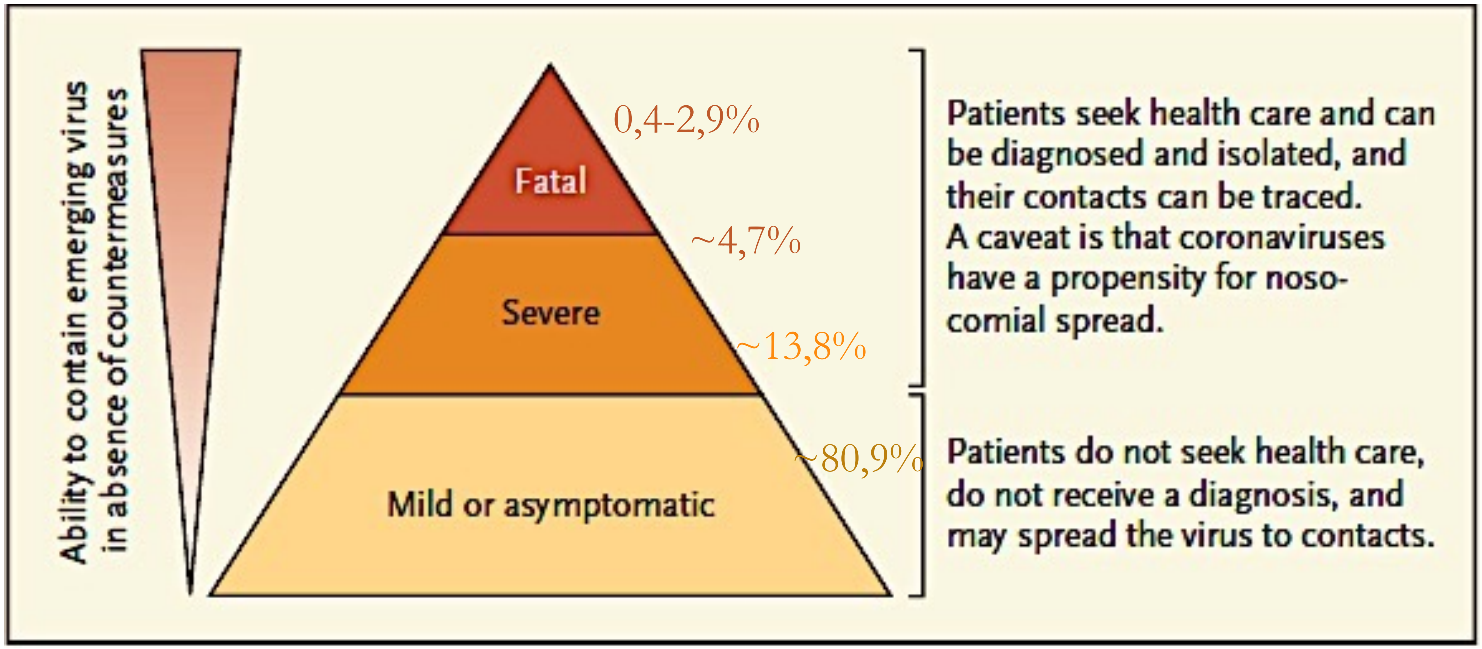
Nature Reviews Immunology **2014:14; 315**

Factores que determinan el curso clínico

- **Factores del virus**
  - Tipo de virus
  - Virulencia
  - Dosis infectante
- **Factores del huésped**
  - Edad
  - Susceptibilidad genética
  - Estado inmunológico
- **Factores del medio**
  - Temperatura
  - Humedad
  - Polución ambiental

The Pediatric Infectious Disease Journal • *2005; 11(1):*

Pirámide de la vigilancia epidemiológica



The proportion of **mild** and **asymptomatic** cases versus **severe** and **fatal** cases of Covid-19 is recently reported, so we have more knowledge of the virus's epidemic potential and the outbreak response.

The New England Journal of Medicine, Jan 31 2020

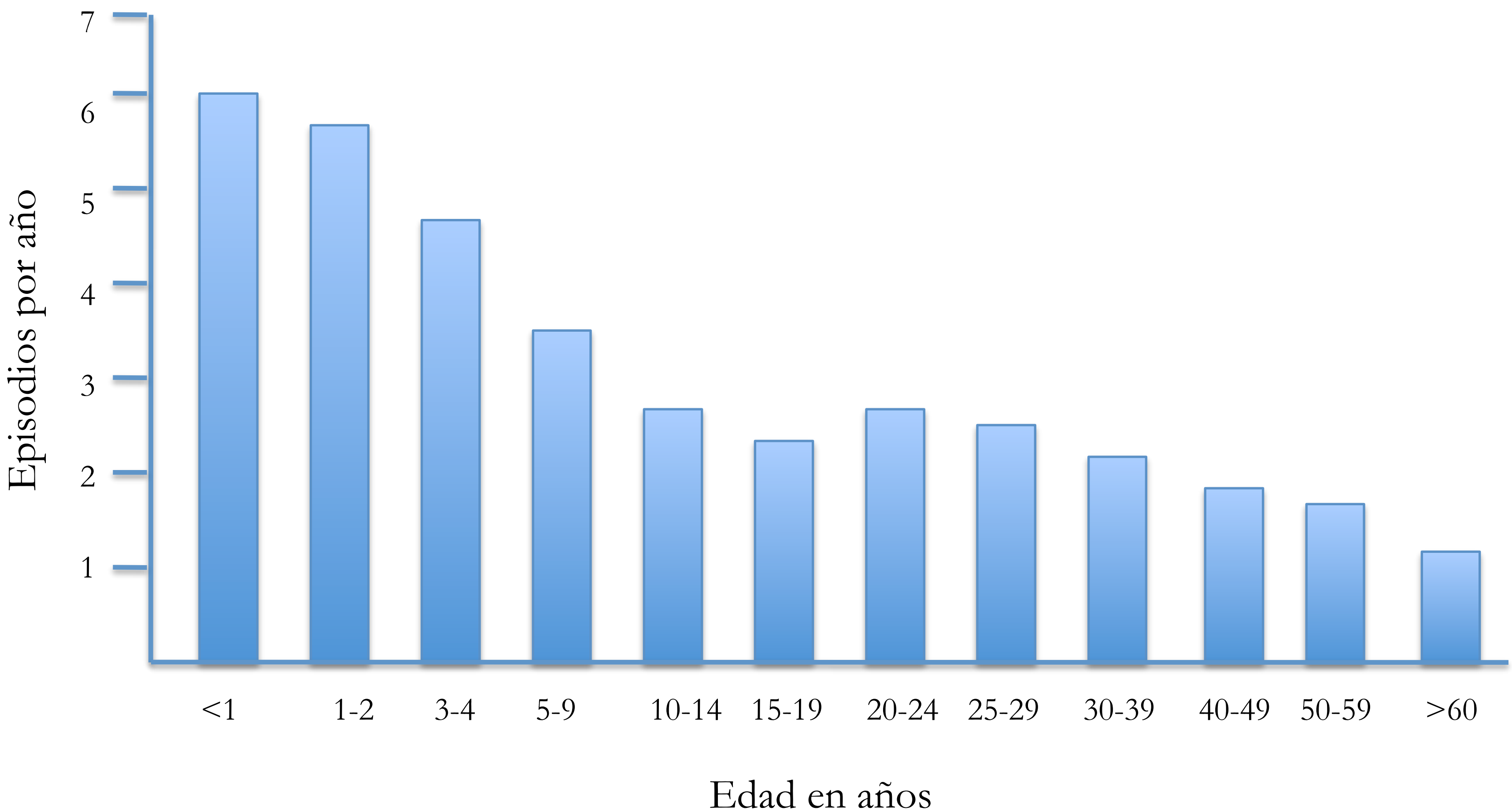
Patogénesis y transmisibilidad

Virus	Case Fatality Rate (%)	R_0
2019-nCoV	3	1.4~5.5*
SARS-CoV	10	2~5
MERS-CoV	40	<1
Avian H7N9 (2013)	40	<1
H1N1 (2009)	0.03	1.2~1.6
H1N1 (1918)	3	1.4~3.8
Measles Virus	0.3	12~18
Rhinovirus	<0.01	6
Ebola Virus	70	2.3
HIV	80**	3.4
Small Pox Virus	17	5~7

** Without therapy

Microbes and Infection, https://doi.org/10.1016/ j.micinf.2020.01.004.

Infecciones respiratorias anuales por grupo etáreo



Infección respiratoria aguda viral: etiología

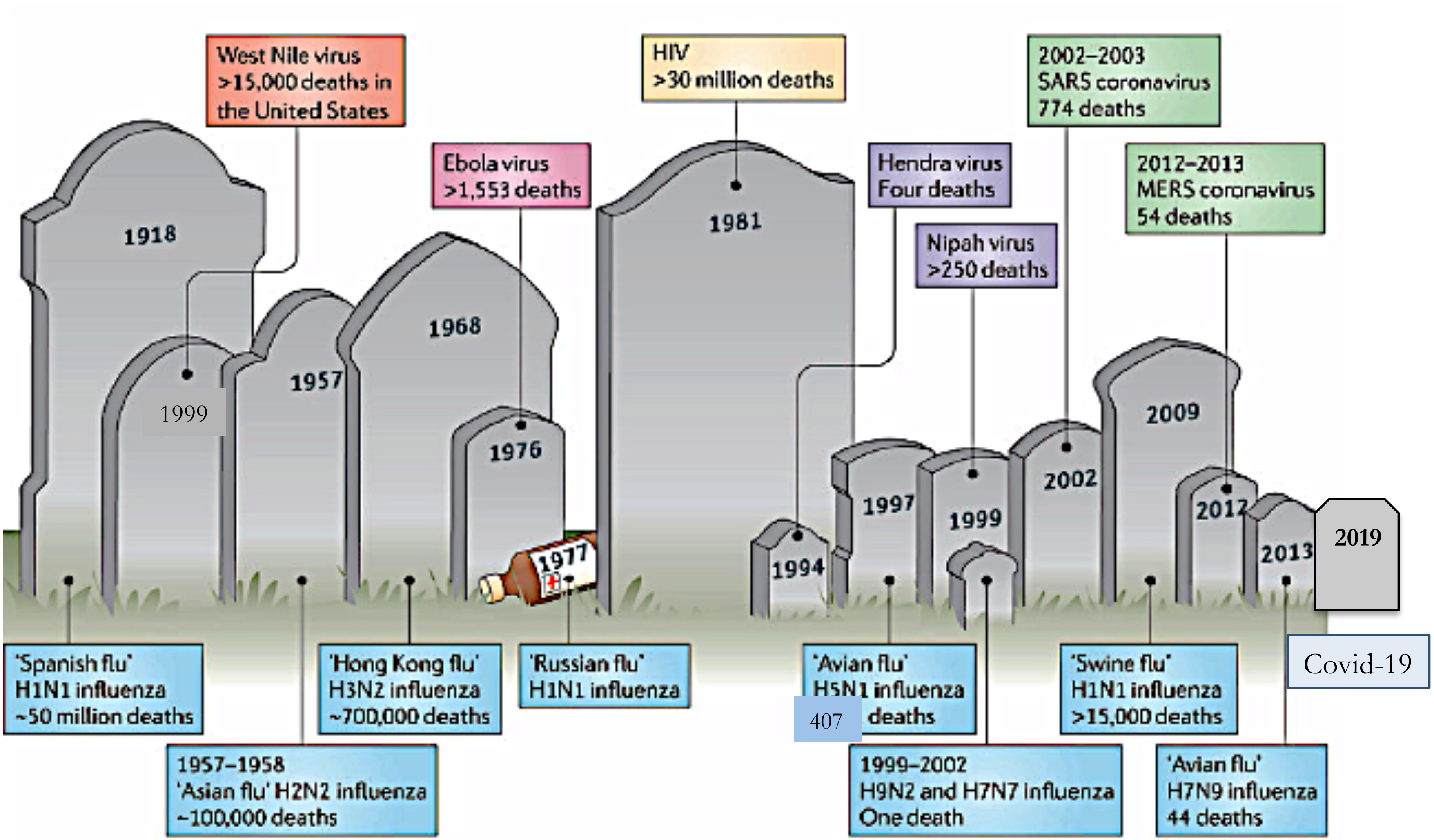
- Alta morbilidad.
- Causa pérdidas económicas por ausentismo laboral o estudiantil.
- Se han identificado más de 200 virus respiratorios que pertenecen al menos a 7 familias virales.
  - *Orthomyxoviridae*. Flu A, Flu B, Flu C
  - *Paramyxoviridae*. PIV 1-4
  - *Picornaviridae:* hRV más de 100 tipos antigénicos, varios EV
  - *Adenoviridae:* mas de 30 tipos antigénicos.
  - *Coronaviridae*. HCoV-OC43, HCoV-229, HCoV-NL63, HCoV-HKU1, Middle East respiratory syndrome coronavirus (MERS-CoV), SARS HCoV, Covid-19 (2019-nCoV).
  - *Herpesviridae*. HSV, VZV, CMV
  - *Parvoviridae*. hBoV (Bocavirus humano)
- Tres nuevos virus
  - MERS-CoV (al 8 de septiembre de 2015: 2.494 casos y 858 muertes)
  - Influenza H7N9 (al 12 de agosto de 2013 ha causado 135 casos-44 muertes)
  - Nuevo CoV en China Wuhan 2019-nCoV (a 15 Enero de 2020 se registraron 41 casos y una muerte, a 30 Enero de 2020 se reportan 7.700 casos y 170 muertes). 11-02-2020 Covid-19

Síndromes clínicos

Virus	Colds	Pharyngitis	Tracheobronchitis	Croup	Bronchiolitis	Pneumonia: Children[b]	Pneumonia: Adults	Pneumonia: Immuno-compromised
RNA viruses								
Influenza virus								
Type A	+[b]	++	+++	++	+	++	++++	++
Type B	+	++	++	+	+	+	++	+
Parainfluenza virus								
Type 1	+	++	+	++++	+			
Type 2	+	++	+	++	+			
Type 3	+	++	+	+++	++	+++	+	+
Respiratory syncytial virus	++	+		++	++++	++++	++	++
Human metapneumovirus	+				++	++	+	±
Measles virus			+	+		+	+	+
Rhinovirus	++++	++	+	+	+++	++	++	+
Enterovirus	++	++			+	+	±	
Coronavirus	++	+		++	+		+	+
DNA viruses								
Adenovirus		++	+	++	++	++	++	++
Herpes simplex virus		+	±		+	+		++
Varicella virus						+	+	+
Epstein-Barr virus		++					±	+
Cytomegalovirus		+				++	±	+++

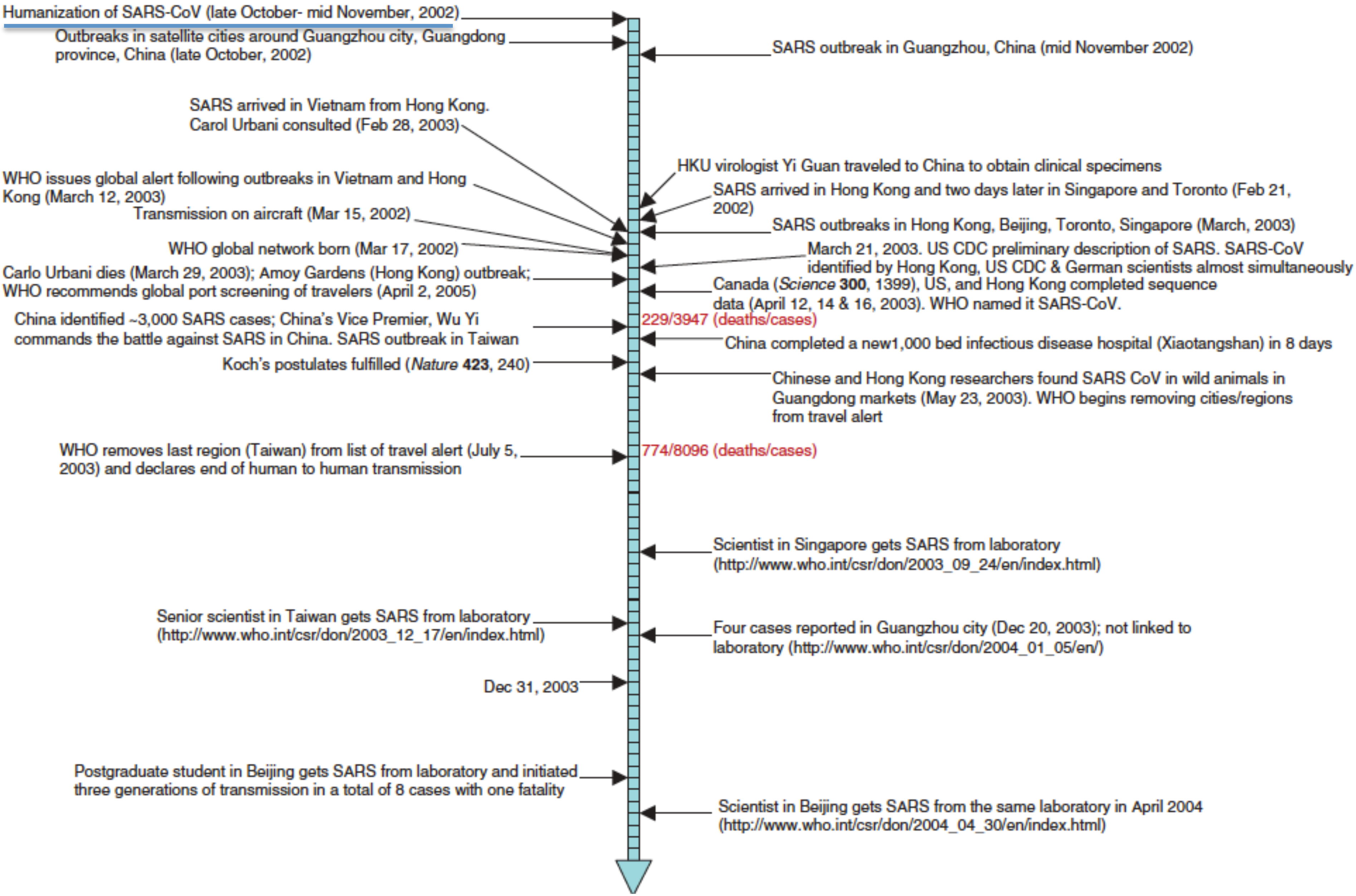
Richman DD, Whitley RJ, Hayden FG. Clinical Virology. ASM. Washintong. 2017. 4th Edition. pag 10.

Zoonosis emergentes



Emerging Viral Diseases: The One Health Connection: Workshop Summary (2015)

hCoV-SARS: Cronología



Emerging Viruses in Human Populations. Editor Edward Tabor Rockville, MD, USA. 2007. Elsevier. First Edition

hCoV-MERS

September 2012

1st case: 20th Sept.
60-year old Saudi man admitted to hospital on 13/06/12 with severe pneumonia. No underlying conditions. He died of acute renal failure on 24/06/12.

2nd case: 22nd Sept.
49-year old Qatari man with history of travel to Saudi Arabia. Admitted to hospital in Doha with respiratory illness on 07/09/12. Transferred to UK on 11/09/12. Survived.

October 2012

November 2012

3th case: 4th Nov.
45-year old Saudi man admitted to hospital on 12/10/12 with severe respiratory illness. He was a heavy smoker and had underlying chronic conditions. He recovered from his illness and was discharged on 27/10/12.

4th case: 19th Nov.
A 70-year old Saudi man admitted to hospital with severe respiratory illness, but developed renal failure and died.

5th case: 23th Nov.
A Qatari man admitted to hospital in October with severe respiratory illness. Transferred to Germany. Discharged in the week beginning 18/11/12.

6th & 7th case: 23rd Nov.
Both cases were from one family and related to case 4. They presented with severe respiratory illness. One of the cases died.

8th & 9th case: 30th Nov.
Samples from two Jordanian healthcare workers (a 45-year old woman and a 25-year old man) who died of unexplained respiratory illness in April 2012 were confirmed to be positive for NCoV.

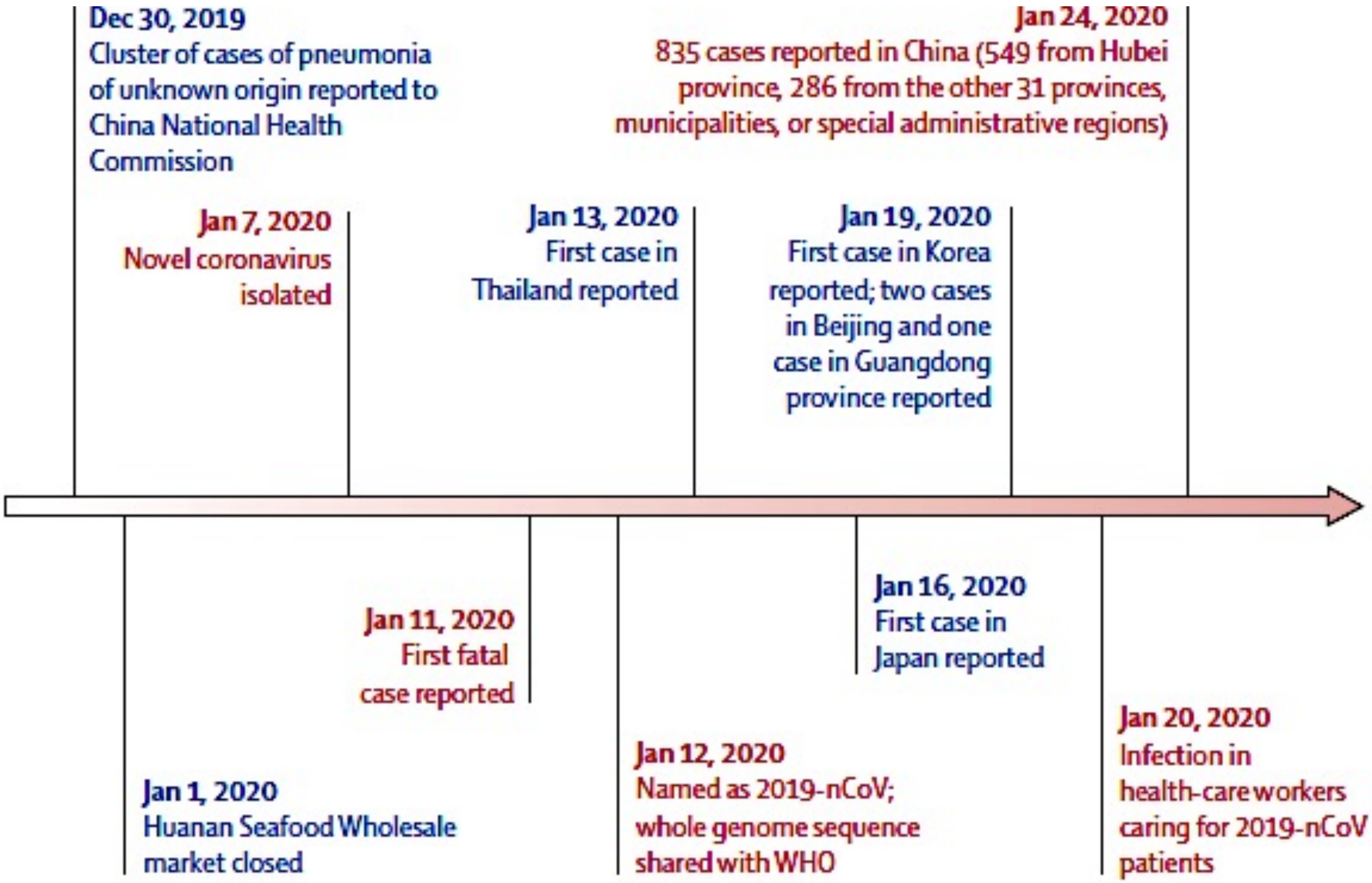
February 2013

10th case: 11th Feb.
A 60-year old UK resident, presented with respiratory illness on the 26/01/13. He had history of travel to Pakistan and Saudi Arabia. He was confirmed to be positive for influenza H1N1 2009 & NCoV. Currently In ICU.

11th case: 13th Feb.
A UK resident, family member of case 10. This patient has pre-existing medical conditions. He died from his illness (reported on 19/02/2013)

12th case: 15th Feb.
A UK resident, family member of case 10. No history of travel or pre-existing medical conditions.

Cronología temprana del Covid-19



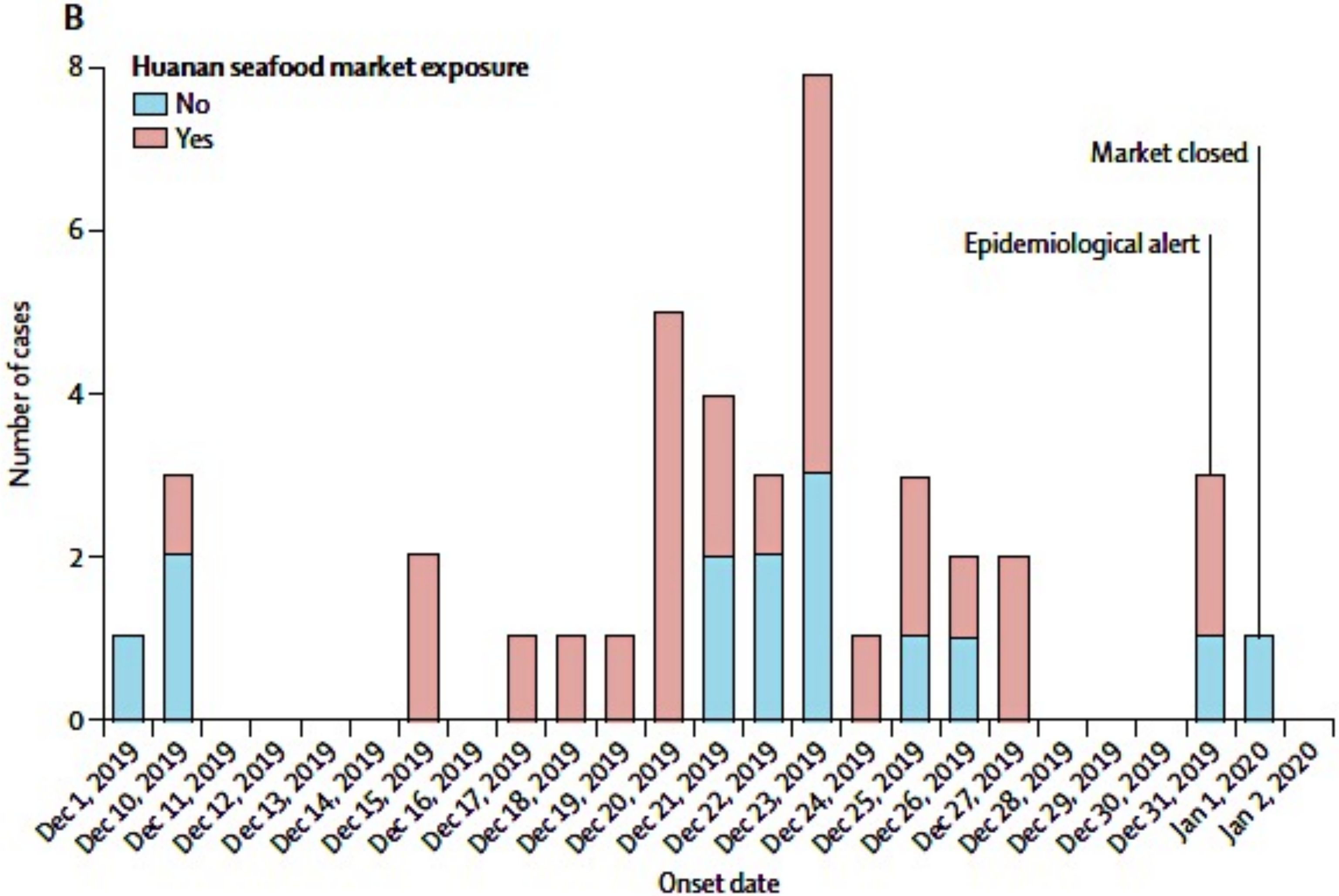
www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30185-9

Cronología del brote epidémico

- **31 de diciembre de 2019** - China alerta a la OMS de la erupción de casos de un tipo de neumonía en Wuhan
- **1 de enero de 2020** - Cierran el mercado de mariscos y animales que se cree es la fuente del brote
- **9 de enero** - La OMS dice que la infección es causada por un nuevo tipo de coronavirus
- **10 de enero** - China comparte el código genético del nuevo virus
- **11 de enero** - Los científicos empiezan a trabajar en una vacuna y se confirma la primera muerte.
- **13 de enero** - El virus se propaga en el exterior por primera vez, con un caso registrado en Tailandia.
- **30 de enero** - El virus afecta todas las regiones en China. Se reportan 7.711 casos y 170 muertes.

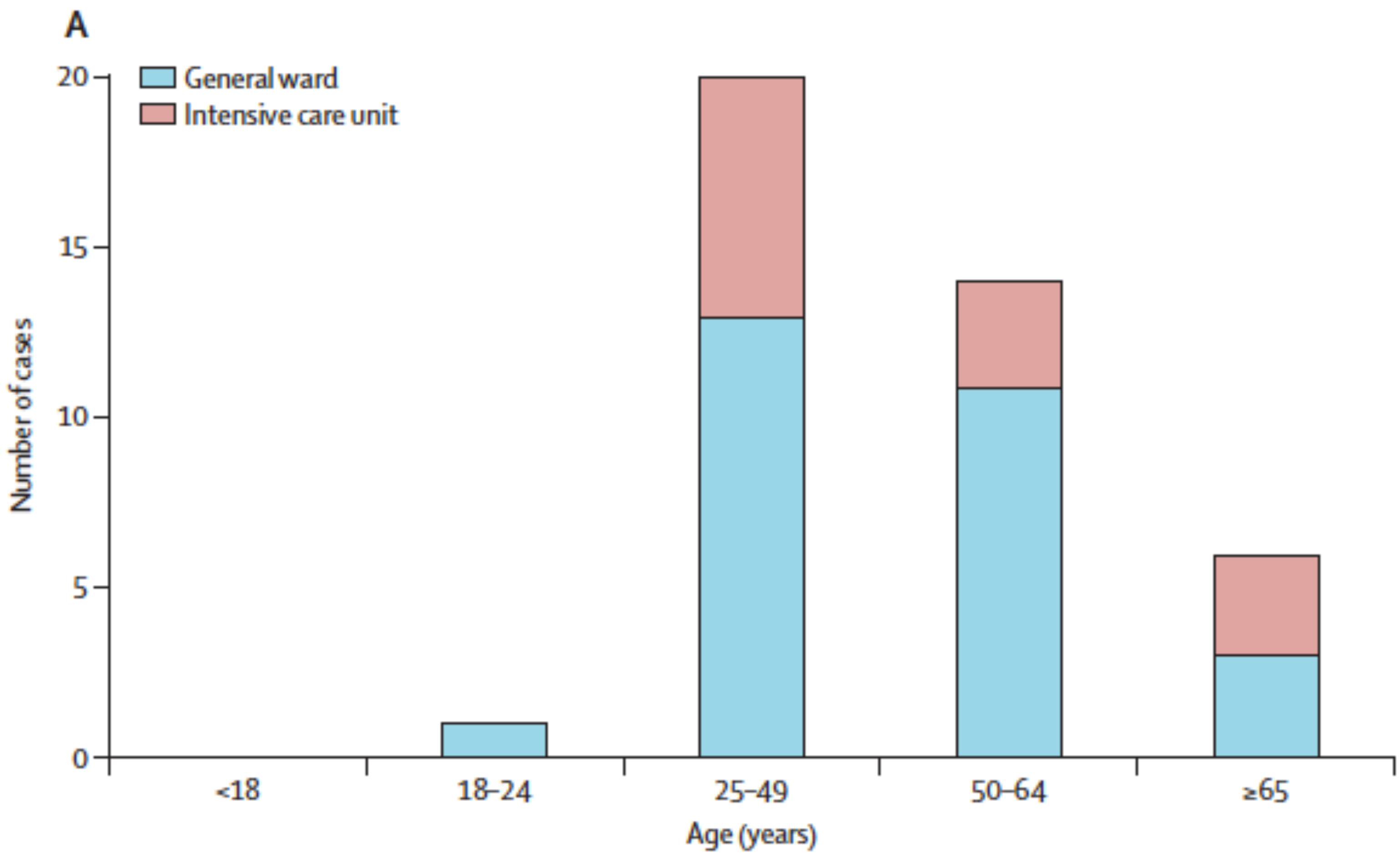
www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Cronología temprana del 2019-nCoV



www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Grupos afectados



Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

Reporte de caso

CASE REPORT

On January 19, 2020, a 35-year-old man presented to an urgent care clinic in Snohomish County, Washington, with a 4-day history of cough and subjective fever. On checking into the clinic, the patient put on a mask in the waiting room. After waiting approximately 20 minutes, he was taken into an examination room and underwent evaluation by a provider. He disclosed that he had returned to **Washington State** on January 15 after traveling to visit family in **Wuhan, China**. The patient stated that he had seen a health alert from the U.S. Centers for Disease Control and Prevention (CDC) about the novel coronavirus outbreak in China and, because of his symptoms and recent travel, decided to see a health care provider.

Apart from a history of **hypertriglyceridemia**, the patient was an otherwise healthy non-smoker. The physical examination revealed a body temperature of **37.2°C**, blood pressure of **134/87** mm Hg, pulse of **110 beats** per minute, respiratory rate of **16 breaths** per minute, and **oxygen saturation of 96**% while the patient was breathing ambient air.

Lung auscultation revealed **rhonchi**, and **chest radiography was performed, which was reported as showing no abnormalities**. A rapid nucleic acid amplification test (**NAAT**) for **influenza A and B** was **negative**. A **nasopharyngeal swab specimen was obtained and sent for detection of viral respiratory pathogens by NAAT; this was reported back within 48 hours as negative** for all pathogens tested, including influenza A and B, parainfluenza, respiratory syncytial virus, rhinovirus, adenovirus, and four common coronavirus strains known to cause illness in humans (HKU1, NL63, 229E, and OC43).

N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

Reporte de caso

CASE REPORT

Given the patient's travel history, the local and state health departments were immediately notified. Together with the urgent care clinician, the Washington Department of Health notified the CDC Emergency Operations Centre.

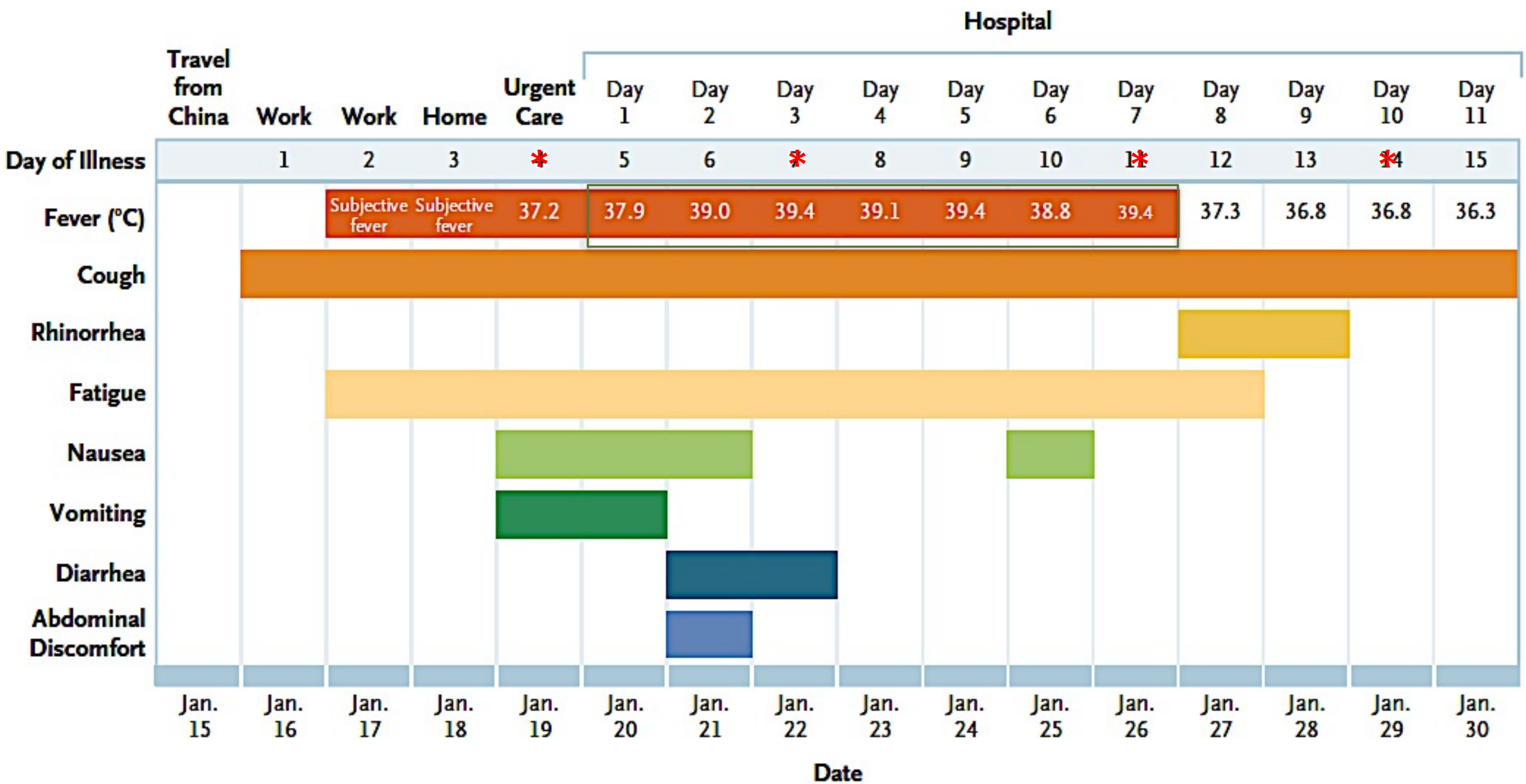
Although the patient reported that he **had not spent time at the Huanan seafood market** and reported **no known contact** with ill persons during his travel to China, CDC staff concurred with the need to test the patient for 2019-nCoV on the basis of current CDC "persons under investigation" case definitions. Specimens were collected in accordance with CDC guidance and included serum and **nasopharyngeal** and **oropharyngeal swab** specimens.

After specimen collection, the patient was discharged to **home isolation** with active monitoring by the local health department.

On January 20, 2020, the CDC confirmed that the patient's **nasopharyngeal and oropharyngeal swabs tested positive for 2019-nCoV by real-time reverse-transcriptase–polymerase-chain-reaction** (rRT-PCR) assay. In coordination with CDC subject- matter experts, state and local health officials, emergency medical services, and hospital leadership and staff, the patient was admitted to an airborne-isolation unit at Providence Regional Medical Centre for clinical observation, with health care workers following CDC recommendations for contact, droplet, and airborne precautions with eye protection.

N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

Reporte de caso: evolución de sintomatología



N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

Reporte de caso: diagnóstico

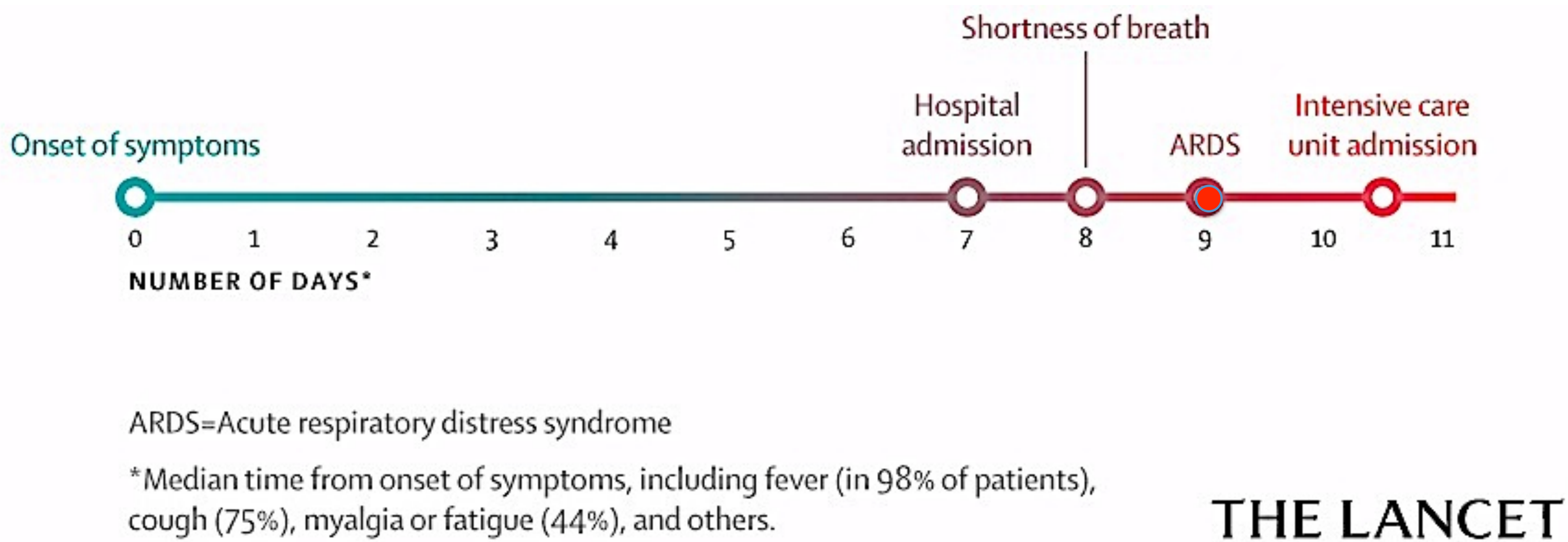
Table 2. **Results of Real-Time Reverse-Transcriptase–Polymerase-Chain-Reaction Testing for the 2019 Novel Coronavirus (2019-nCoV).***

Specimen	Illness Day 4	Illness Day 7	Illness Day 11	Illness Day 12
Nasopharyngeal swab	Positive (Ct, 18–20)	Positive (Ct, 23–24)	Positive (Ct, 33–34)	Positive (Ct, 37–40)
Oropharyngeal swab	Positive (Ct, 21–22)	Positive (Ct, 32–33)	Positive (Ct, 36–40)	Negative *
Serum	Negative	Negative	Pending	Pending
Urine	NT	Negative	NT	NT
Stool	NT	Positive (Ct, 36–38)	NT	NT

* Lower cycle threshold (Ct) values indicate higher viral loads. NT denotes not tested.

N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

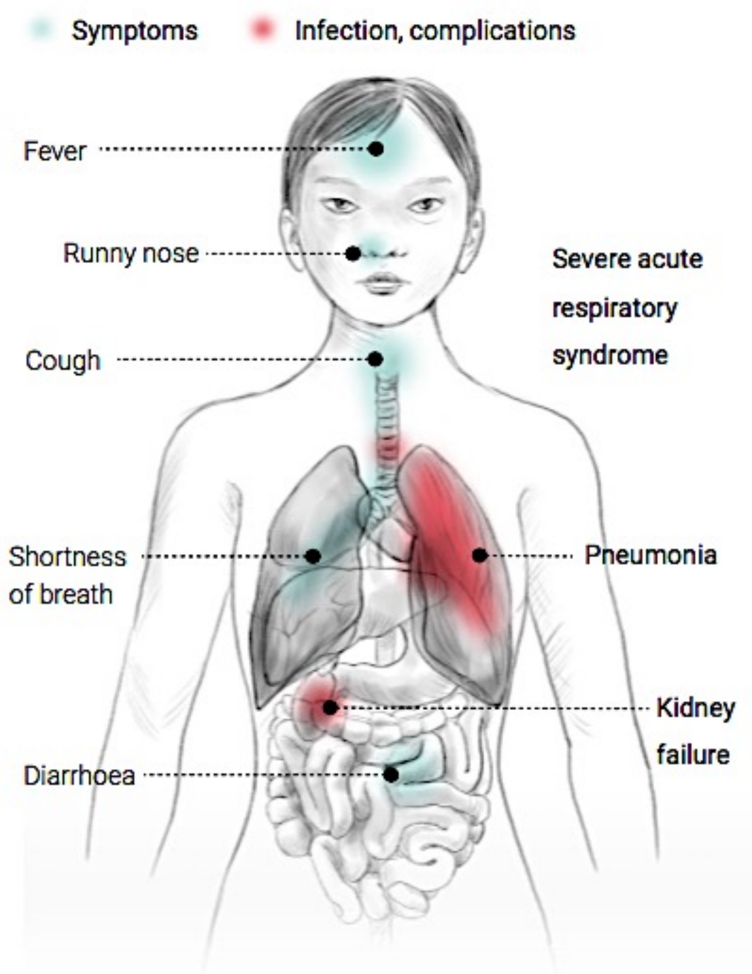
Evolución clínica de caso



https://www.thelancet.com/infographics/coronavirus

Symptoms and complications

Some infected people do not show any symptoms, while for others the symptoms can be severe, even fatal.



Children under two years old and people aged over 65, or with weak immune systems are particularly susceptible to developing severe complications such as **pneumonia**.

ADVICE FROM THE CDC:

- Avoid contact with sick people, animal markets, and live or dead animals (including uncooked meat).
- Wash hands often with soap and water for at least 20 seconds.
- If you feel sick with fever, cough, or difficulty breathing, seek medical care right away.
- Do not travel while sick.
- Cover your mouth and nose with a tissue or your sleeve when coughing or sneezing.

Source: CDC BUSINESS INSIDER

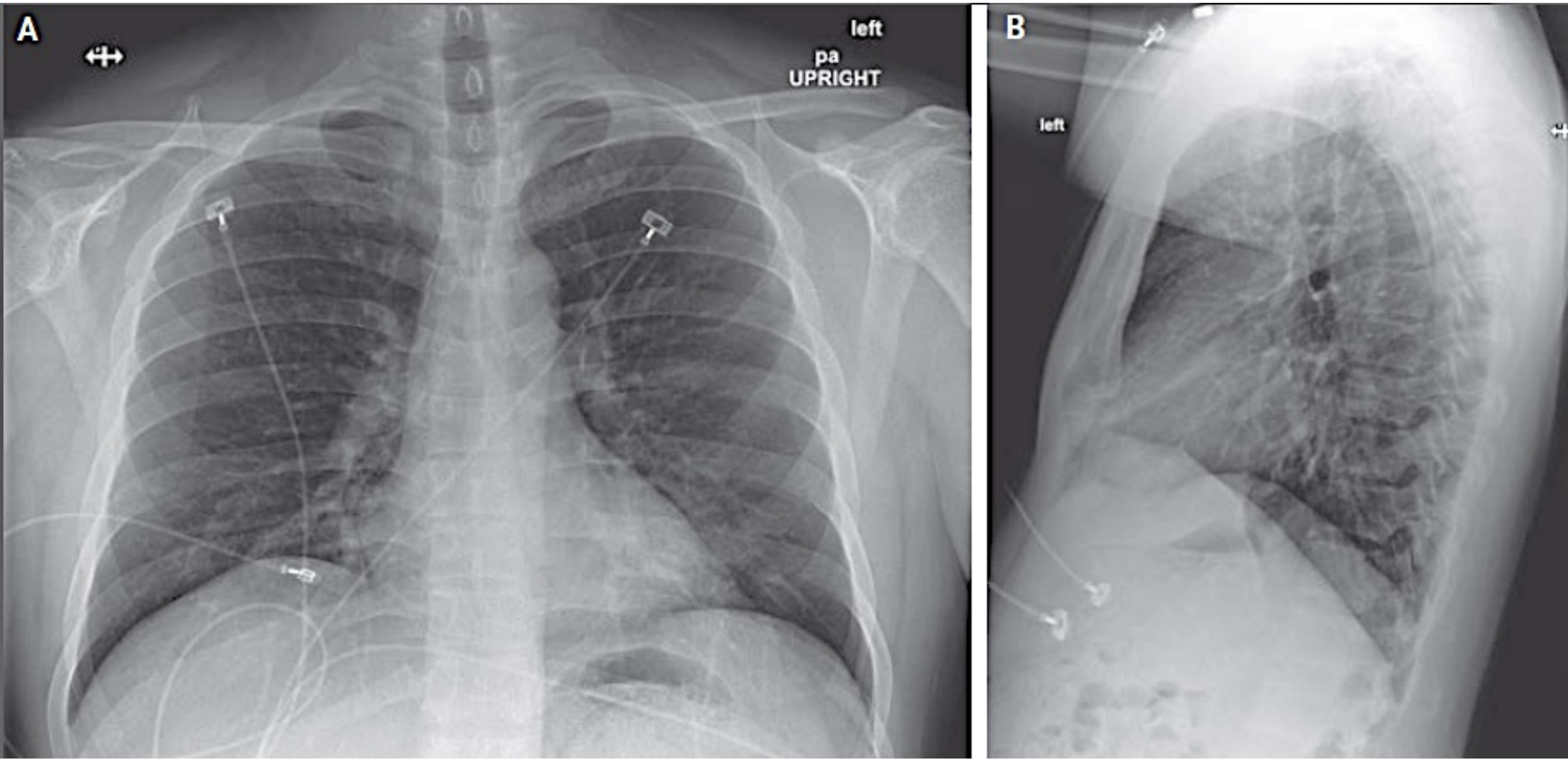
Exámenes paraclínicos en un caso

Table 1. Clinical Laboratory Results.*

Measure	Reference Range	Illness Day 6, Hospital Day 2†	Illness Day 7, Hospital Day 3	Illness Day 9, Hospital Day 5	Illness Day 11, Hospital Day 7	Illness Day 13, Hospital Day 9	Illness Day 14, Hospital Day 10
White-cell count (per μl)	3800–11,000	"Slight decrease"	3120‡	3300‡	5400	5600	6500
Red-cell count (per μl)	4,200,000–5,700,000	—	4,870,000	5,150,000	5,010,000	4,650,000	5,010,000
Absolute neutrophil count (per μl)	1900–7400	—	1750‡	1700‡	3700	3800	3200
Absolute lymphocyte count (per μl)	1000–3900	—	1070	1400	1400	1400	2100
Platelet count (per μl)	150,000–400,000	"Adequate"	122,000‡	132,000‡	151,000	150,000	239,000
Hemoglobin (g/dl)	13.2–17.0	12.2‡ o	14.2	14.8	14.8	13.5	14.2
Hematocrit (%)	39.0–50.0	36.0‡ o	42.0	43.0	43.0	39.3	42.0
Sodium (mmol/liter)	136–145	134‡ o	136	138	138	135‡	138
Potassium (mmol/liter)	3.5–5.1	3.3‡ o	3.6	3.4‡ o	3.6	4.1	3.9
Chloride (mmol/liter)	98–107	99	101	105	106	100	103
Calcium (mg/dl)	8.7–10.4	—	8.5‡	9.3	9.0	8.6‡	9.3
Carbon dioxide (mmol/liter)	20–31	—	26	24	25	23	36§
Anion gap (mmol/liter)	5–16	—	9	9	7	12	9
Glucose (mmol/liter)	65–140	104	103	120	96	148§	104
Blood urea nitrogen (mg/dl)	9–23	15	10	13	13	22§	18
Creatinine (mg/dl)	0.7–1.3	1.0	1.06	1.06	0.88	1.08	0.84
Total protein (g/dl)	5.7–8.2	—	6.9	7.1	6.8	6.9	6.8
Albumin (g/dl)	3.2–4.8	—	4.2	4.7	4.5	2.9‡	4.4
Total bilirubin (mg/dl)	0.3–1.2	—	1.0	1.1	1.5§ *	0.8	1.0
Procalcitonin (ng/ml)	<0.05	—	—	<0.05	<0.05	—	—
Alanine aminotransferase (U/liter)	10–49	—	68§ *	105§ *	119§ *	219§ *	203§ *
Aspartate aminotransferase (U/liter)	≤33	—	37§ *	77§ *	85§ *	129§ *	89§ *
Alkaline phosphatase (U/liter)	46–116	—	50	68§ *	88§ *	137§ *	163§ *
Fibrinogen (mg/dl)	150–450	—	477§	—	—	—	—
Lactate dehydrogenase (U/liter)	120–246	—	250§ *	465§ *	—	—	388§ *
Prothrombin time (sec)	12.2–14.6	—	11.9‡ o	11.9‡ o	—	—	12.7
International normalized ratio	0.9–1.1	—	0.9	0.9	—	—	1.0
Creatine kinase (U/liter)	62–325	—	353§ *	332§ *	—	—	—
Venous lactate (mmol/liter)	0.4–2.0	—	1.3	1.7	—	—	—

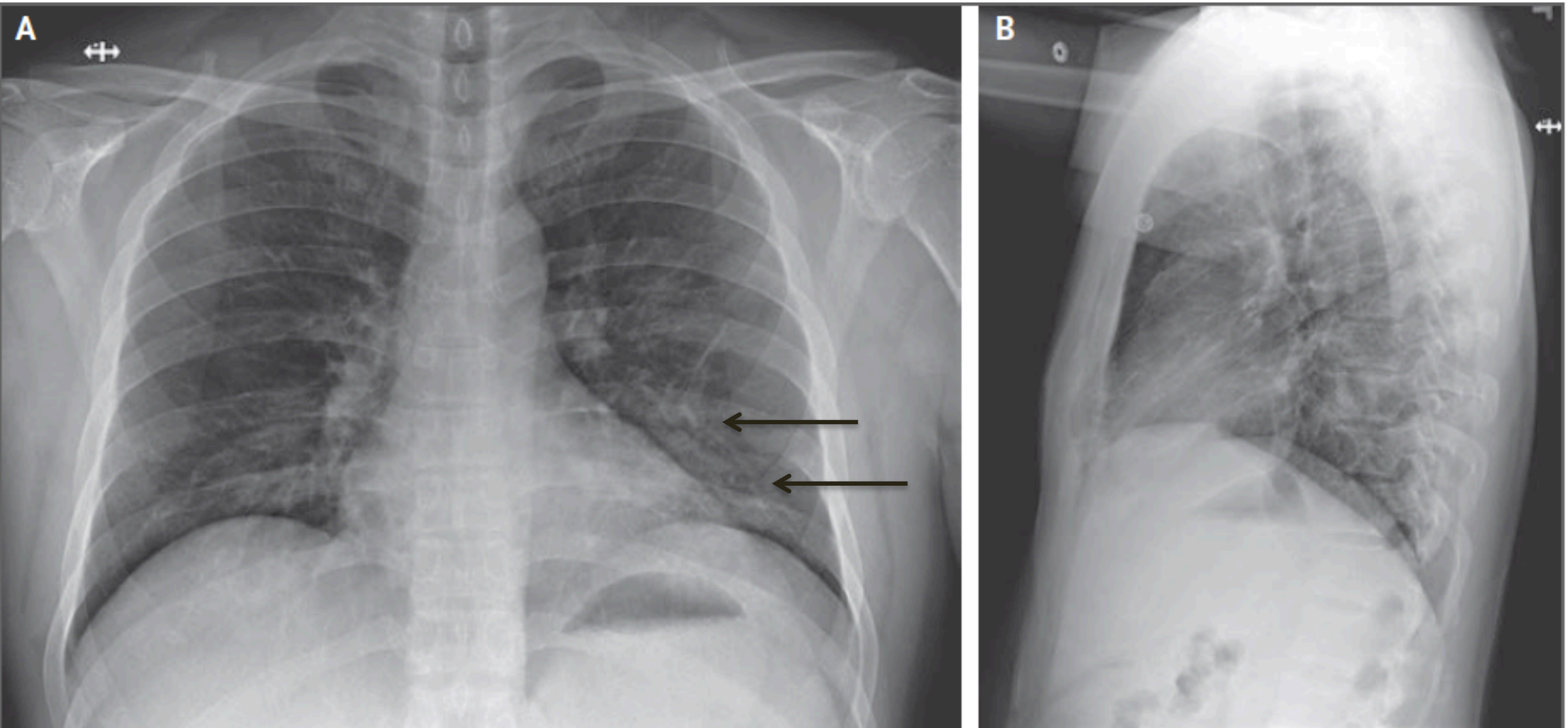
N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

RX de tórax 7ºdía enfermedad 3º hospitalización



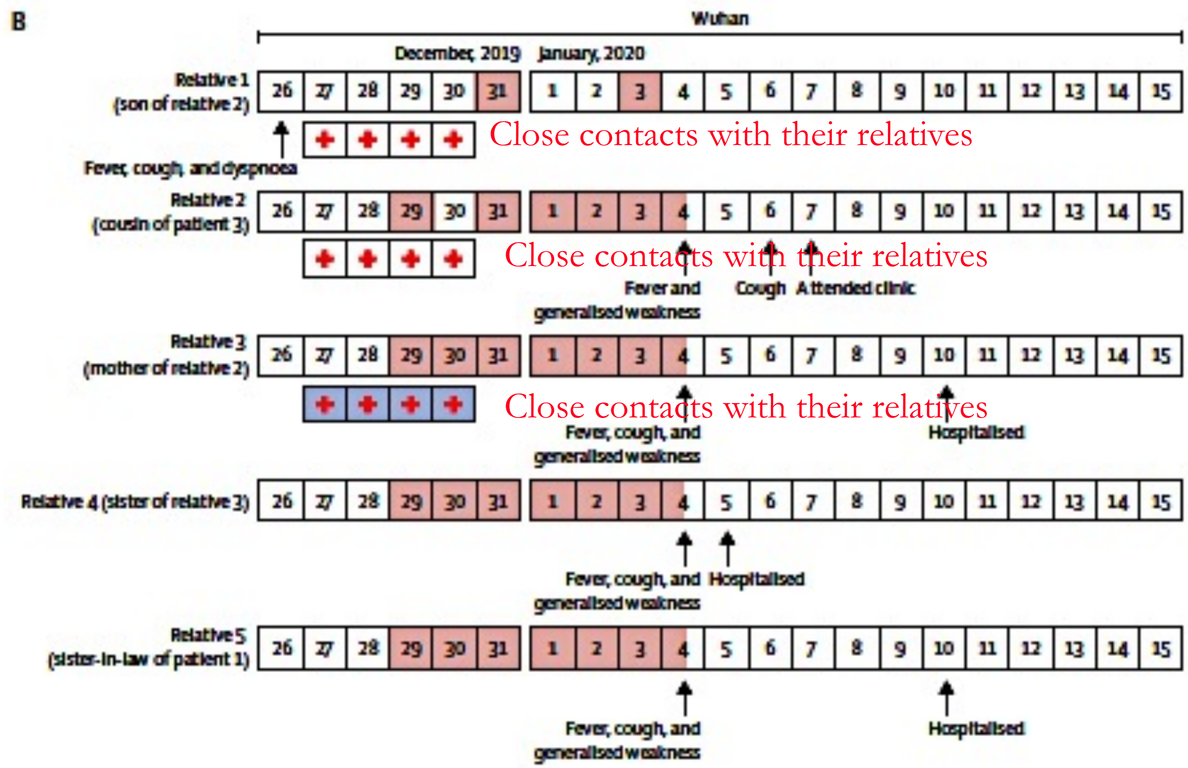
N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

RX de tórax 10ºdía enfermedad 6º hospitalización



N Engl J Med 2020. Jan 31 DOI: 10.1056/NEJMoa2001191

Cronología de síntomas en un grupo familiar en Shenzhen



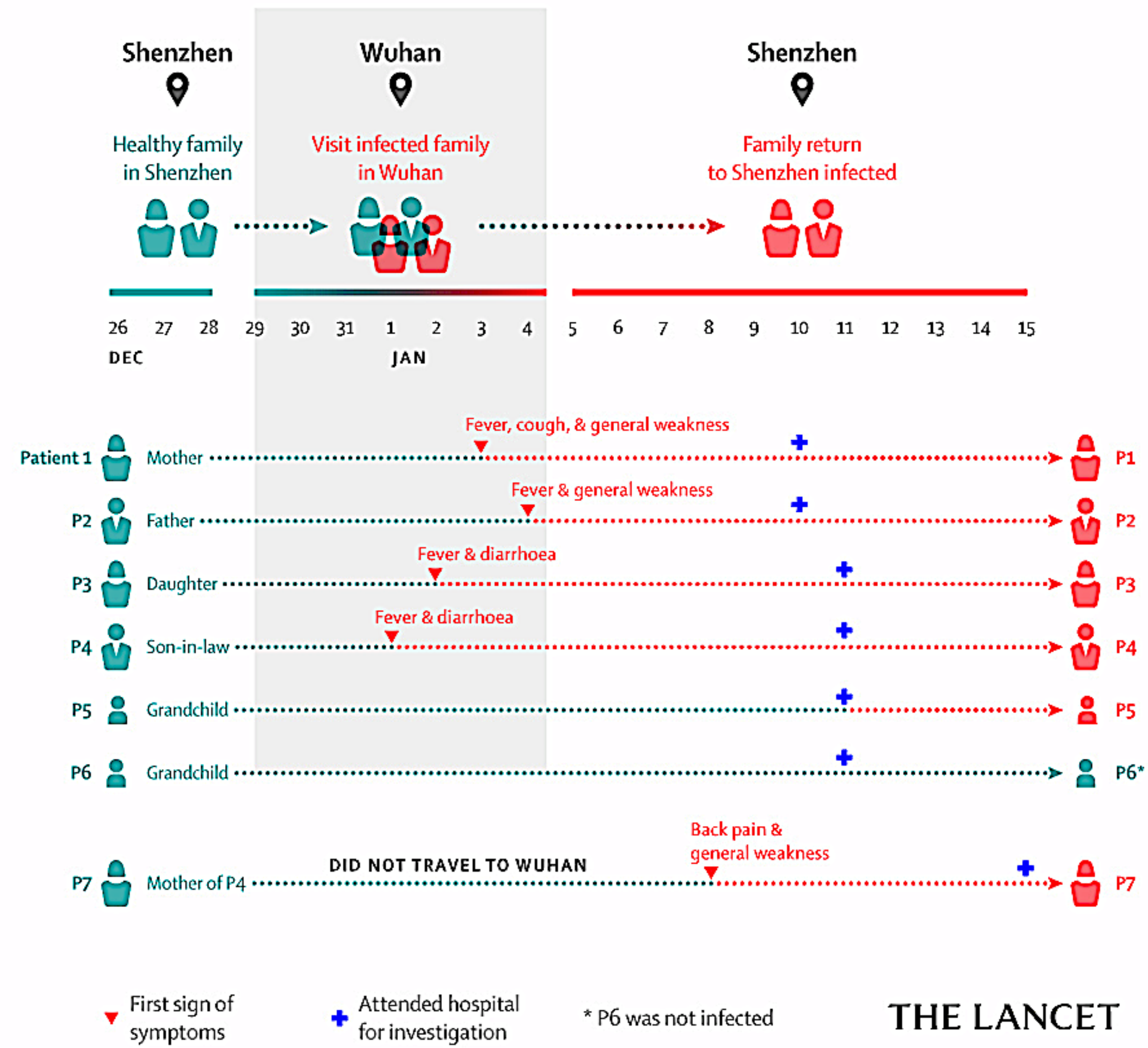
www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

Cronología de síntomas en un grupo familiar

Older patients (aged >60 years) had more systemic symptoms, extensive radiological ground-glass lung changes, lymphopenia, thrombocytopenia, and increased C-reactive protein and lactate dehydrogenase levels.

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

Transmisión en un grupo familiar



www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

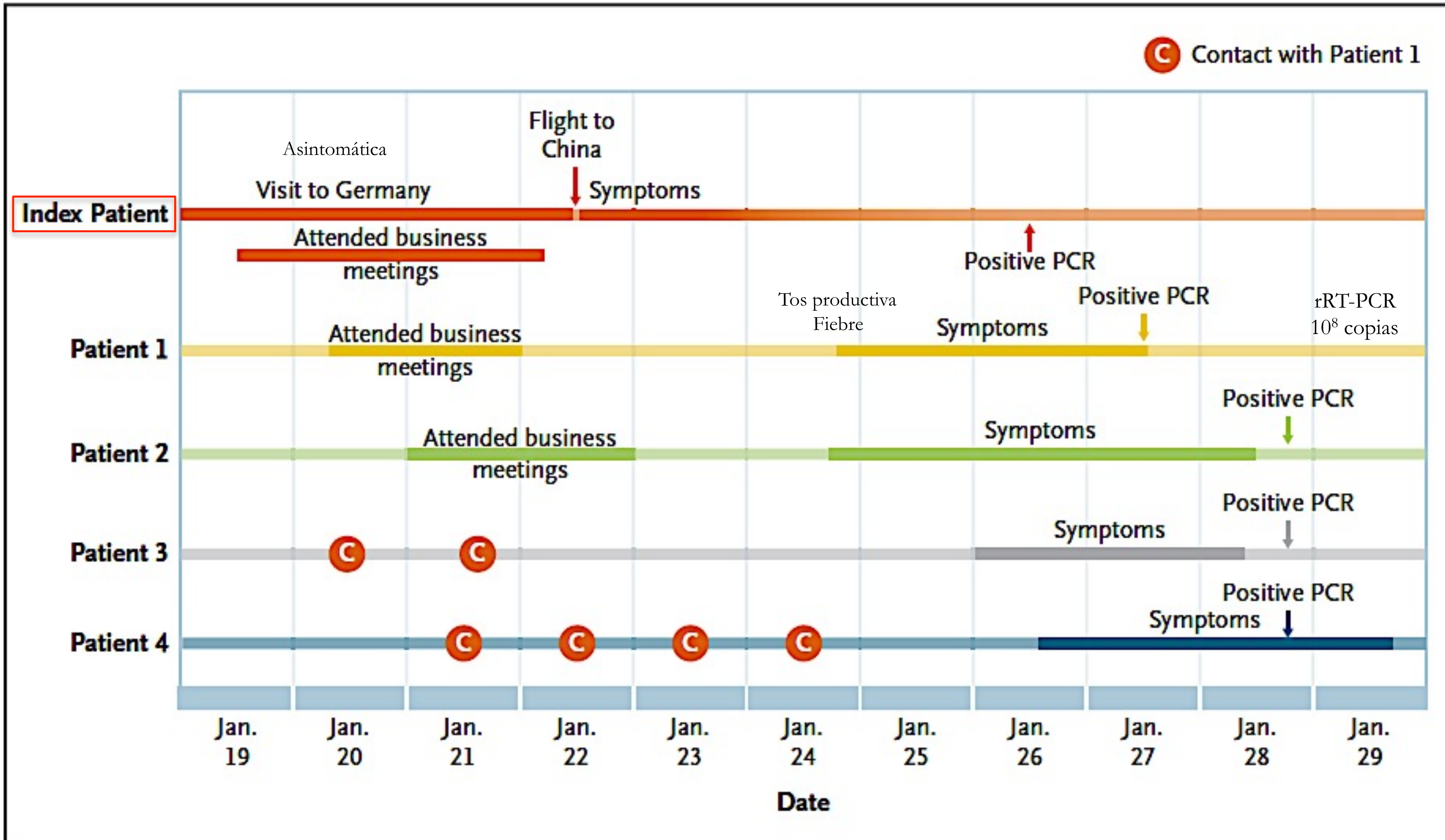
Cronología de síntomas en un grupo familiar

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 7
Body temperature (°C)	39·0	39·0	36·2	36·5	36·5	39·0
Oximetry saturation (%)	94%	96%	NA	NA	NA	NA
Haemoglobin (g/dL); (male normal range 13·3–17·1; female normal range 11·5–14·8)	13·1	15·6	15·0	15·2	14·6	13·0
White blood cell count (x 10⁹ cells per L); (normal range 3·9–9·9)	4·8	4·2	5·6	11·4 (↑)	6·5	4·3
Neutrophil count (x 10⁹ cells per L); (normal range 2·0–7·4)	4·0	3·2	3·1	8·1 (↑)	3·2	2·7
Lymphocyte count (x 10⁹ cells per L); (normal range 1·1–3·6)	0·6 (↓) o	0·7 (↓) o	2·2	2·7	2·8	1·2
Platelet count (x 10⁹ cells per L); (normal range 162–341)	157 (↓) o	118 (↓) o	224	196	197	205
Prothrombin time (s); (normal range 11·0–14·5)	12·6	12·5	13·0	13·0	13·1	12·9
International normalised ratio	1·0	1·0	1·0	1·0	1·0	1·0
Activated partial thromboplastin time (s); (normal range 26·0–40·0)	45·4 (↑) *	45·3 (↑) *	36·0	31·4	34·0	35·8
D-dimer (μg/mL); (normal range 0·0–0·5)	0·6 (↑)	0·3	NA	NA	NA	0·6 (↑) *
Fibrinogen (g/dL); (normal range 2·0–4·0)	6·2 (↑)	5·1 (↑)	3·8	3·8	2·9	4·5 (↑) *
C-reactive protein (mg/L); (normal range 0·0–5·0)	55·6 (↑) *	34·2 (↑) *	0·5	4·9	0·2	44·9 (↑) *
Albumin (g/L); (normal range 35·0–52·0)	39·4	38·5	50·4	48·1	49·1	41·2
Bilirubin (μmol/L); (normal range 0·0–21·0)	6·9	5·9	9·3	8·9	3·6	10·4
Alkaline phosphatase (U/L); (normal range 35–105)	68	56	56	48	211 (↑) *	66
Alanine aminotransferase (U/L); (normal range 0·0–33·0)	14·2	13·9	25·9	20·2	23·9	17·3
Aspartate aminotransferase (U/L); (normal range 0·0–32·0)	20·5	23·3	27·4	18·1	28·2	27·6
Urea (mmol/L); (normal range 2·8–8·1)	3·5	5·7	3·1	5·2	5·6	4·9
Creatinine (μmol/L); (normal range 44–80)	53	93 (↑) *	67	87 (↑) *	51	55
Sodium (mmol/L); (normal range 136–145)	136	133 (↓) o	142	141	141	139
Potassium (mmol/L); (normal range 3·5–5·1)	3·2 (↓) o	3·7	3·7	3·7	3·9	3·8
Creatine kinase (U/L); (normal range 0–170)	42	109	50	137	78	143
Lactate dehydrogenase (U/L); (normal range 135–214)	286 (↑) *	232 (↑) *	192	176	194	252 (↑) *
Amylase (U/L); (normal range 28–100)	NA	NA	70	61	61	NA

NA=not available. +=positive. –=negative. ↑=above normal range. ↓=below normal range.

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

Covid-19: transmisión de caso índice (Alemania)



DOI: 10.1056/NEJMc2001468

JAMA Network

From: **Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China**

JAMA. Published online February 14, 2020. doi:10.1001/jama.2020.2131

Table. Characteristics of 9 Hospitalized Infants Infected With Coronavirus Disease 2019

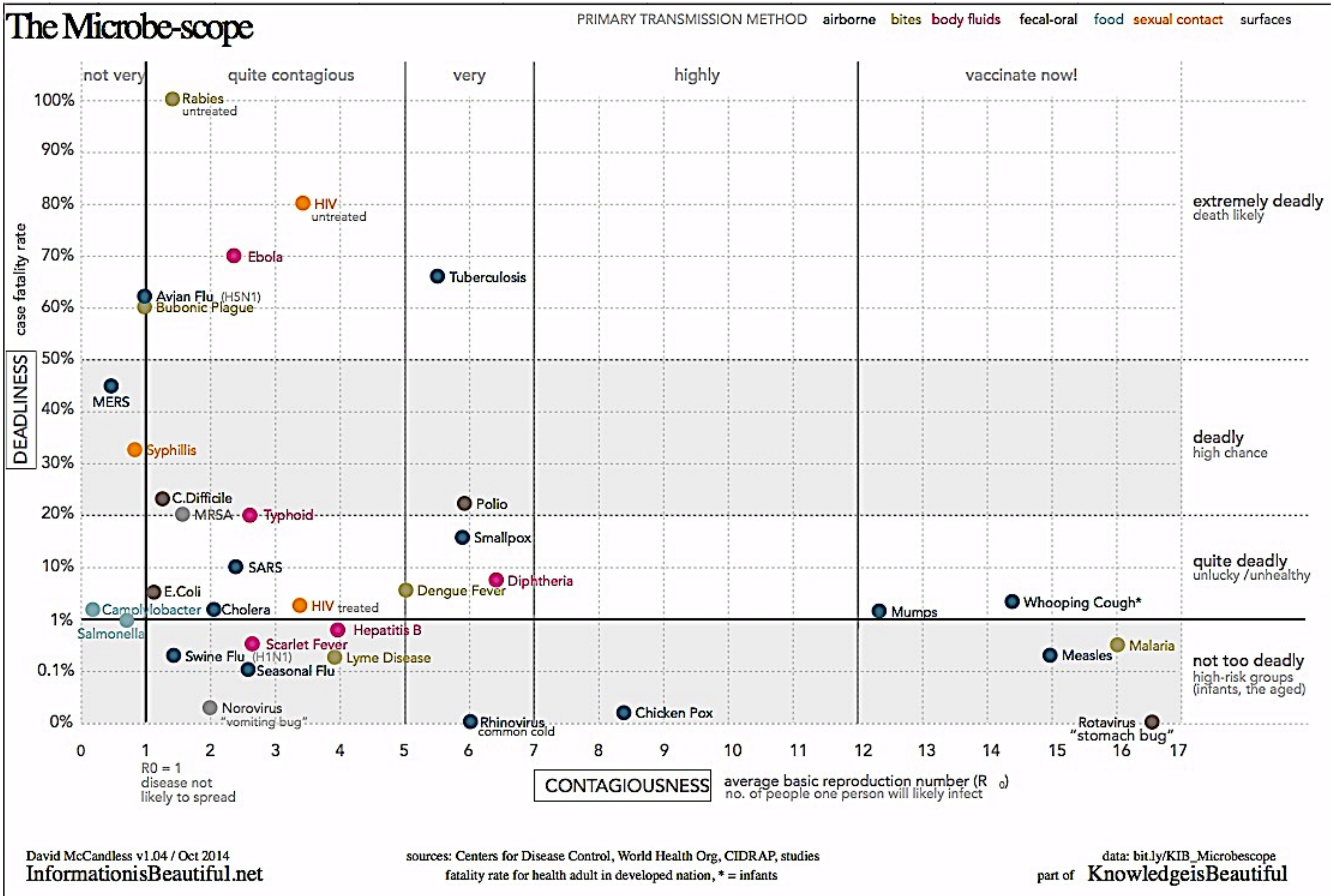
Characteristic	Patient 1	2	3	4	5	6	7	8	9
Demographics									
Age	9 mo	11 mo	8 mo	10 mo	7 mo	1 mo 26 d	3 mo	3 mo 22 d	6 mo
Sex	Female	Female	Female	Male	Female	Female	Female	Female	Male
Symptoms at onset	Fever, peaking at 38.8 °C	Mild fever	None	NA	Fever	Runny nose; cough	Cough; sputum production	Fever	NA
Time between admission and diagnosis, d	1	1	3	3	1	1	1	1	2
Epidemiologic history									
No. of family members infected	2	1	5	1	2	2	2	1	1
Linkage to Wuhan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Treatment									
Intensive unit care	No	No	No	No	No	No	No	No	No
Mechanical ventilation	No	No	No	No	No	No	No	No	No
Severe complications	No	No	No	No	No	No	No	No	No

Abbreviation: NA, not available.

Table Title:

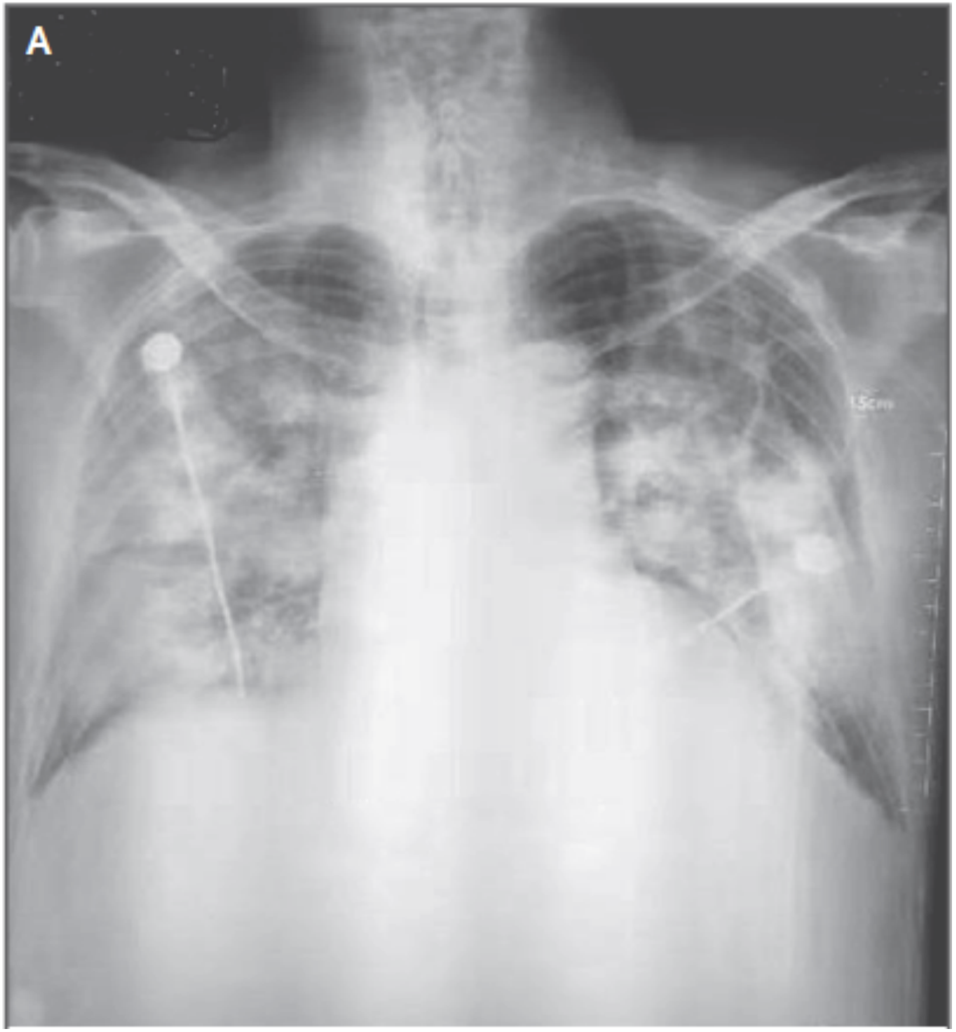
Characteristics of 9 Hospitalized Infants Infected With Coronavirus Disease 2019

Covid-19: Ro

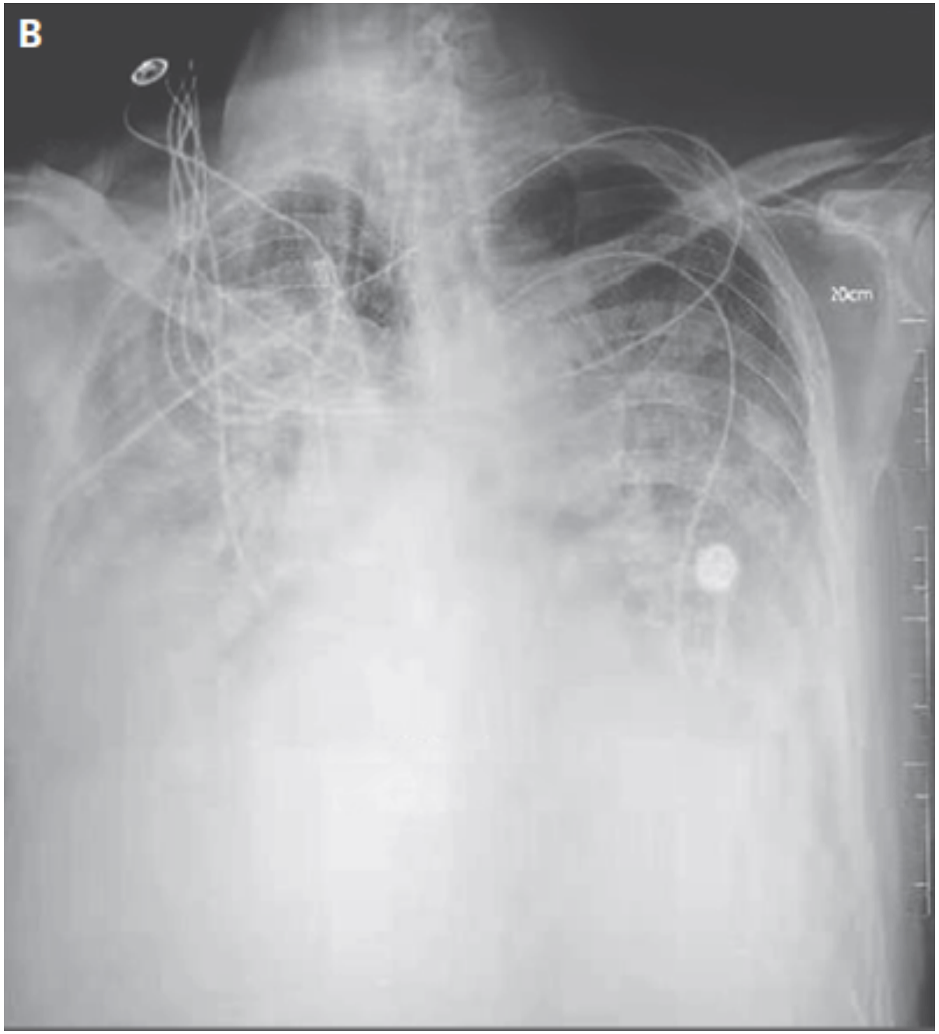


R0: Cambio en el número de personas susceptibles por infección. Cambios en los hábitos y medidas de control. Tiempos de eliminación (excresión) viral.

Radiografía de tórax 2019-nCoV 61y-man



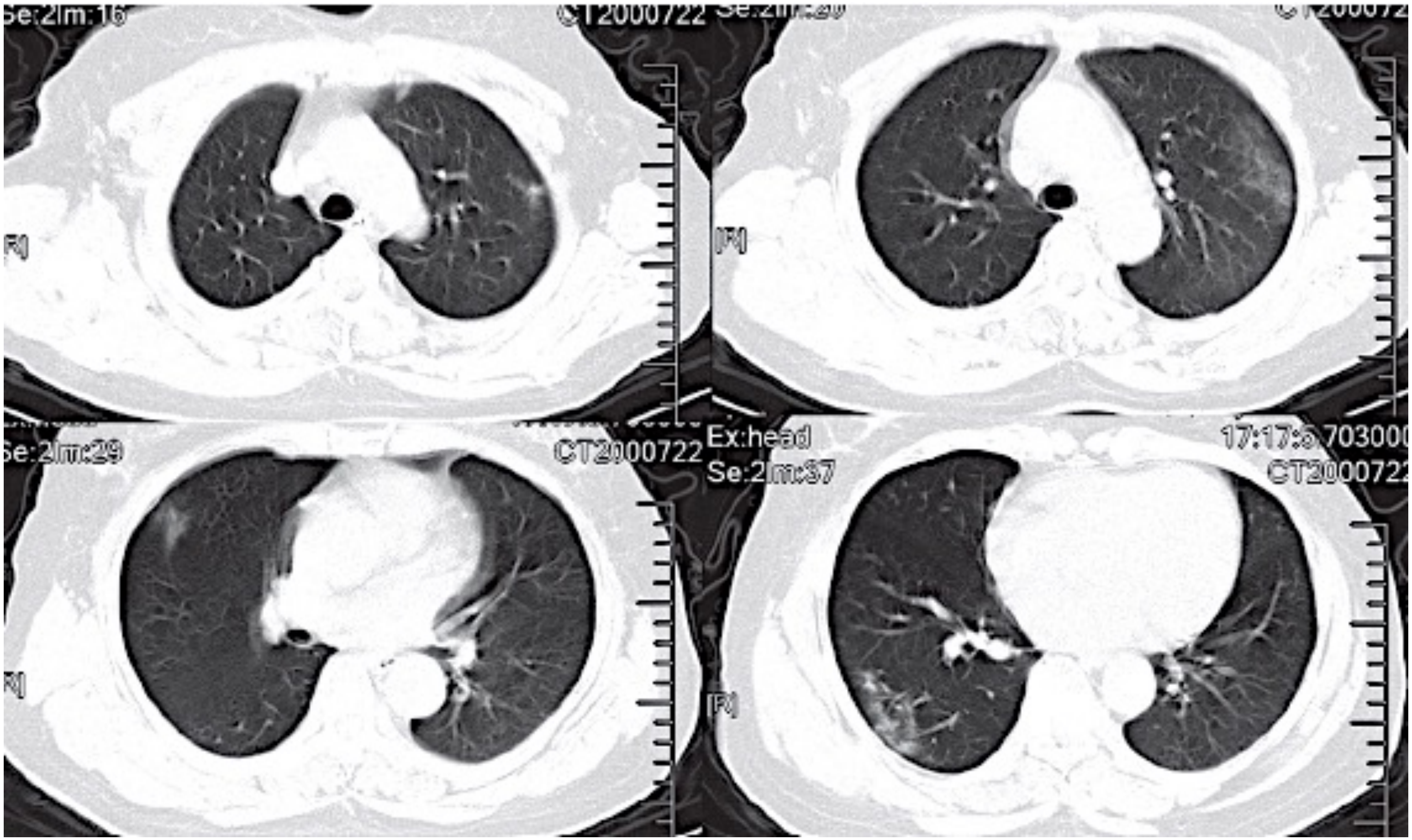
Día 8



Día 11

DOI: 10.1056/NEJMoa2001017

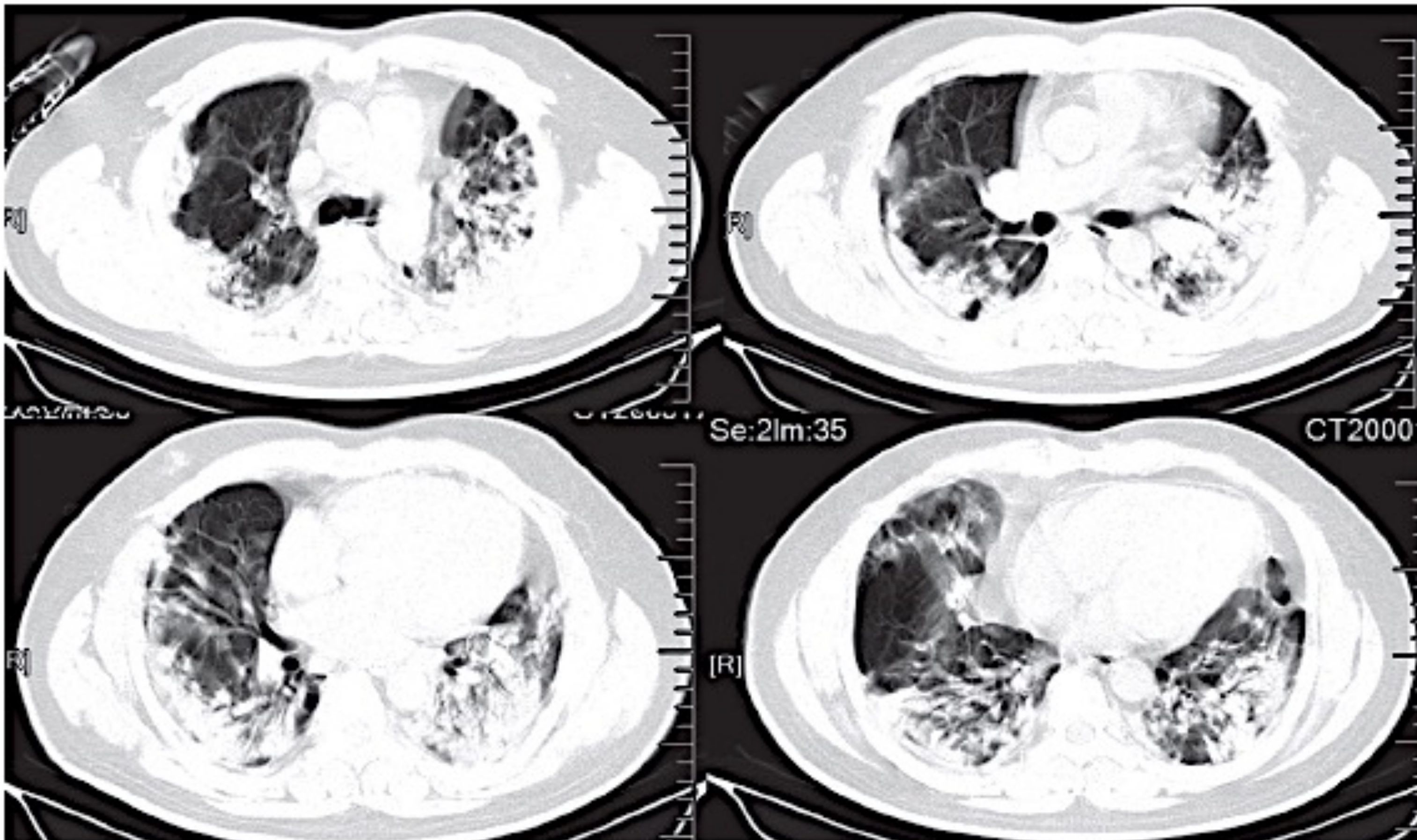
Imagenología de tórax



Bilateral ground-glass opacity on day 12 after symptom onset

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Imagenología de tórax



(A) Transverse chest CT images from a 40-year-old man showing bilateral multiple lobular and subsegmental areas of consolidation on day 15 after symptom onset.

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Li Wenliang MD

https://www.bbc.com/mundo/noticias-internacional-51400608

Últimas publicaciones

CORRESPONDENCE

DOI: 10.1056/NEJMc2001899

Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China

In this effort to evacuate 126 people from Wuhan to Frankfurt, a symptom-based screening process was ineffective in detecting SARS-CoV-2 infection in 2 persons who later were found to have evidence of SARS-CoV-2 in a throat swab.

CORRESPONDENCE

DOI: 10.1056/NEJMc2001621

Journey of a Thai Taxi Driver and Novel Coronavirus

On January 20, 2020, a 51-year-old male taxi driver had fever, cough, and myalgia and went to a local pharmacy to get unspecified over-thecounter medications. At the time, he was not aware of the emergence of SARS-CoV-2 or the illness it causes (Covid-19). Throat and nasopharyngeal swabs that were obtained from the patient tested positive for SARS-CoV-2 on real-time reverse transcriptase– polymerase-chain-reaction (RT-PCR)

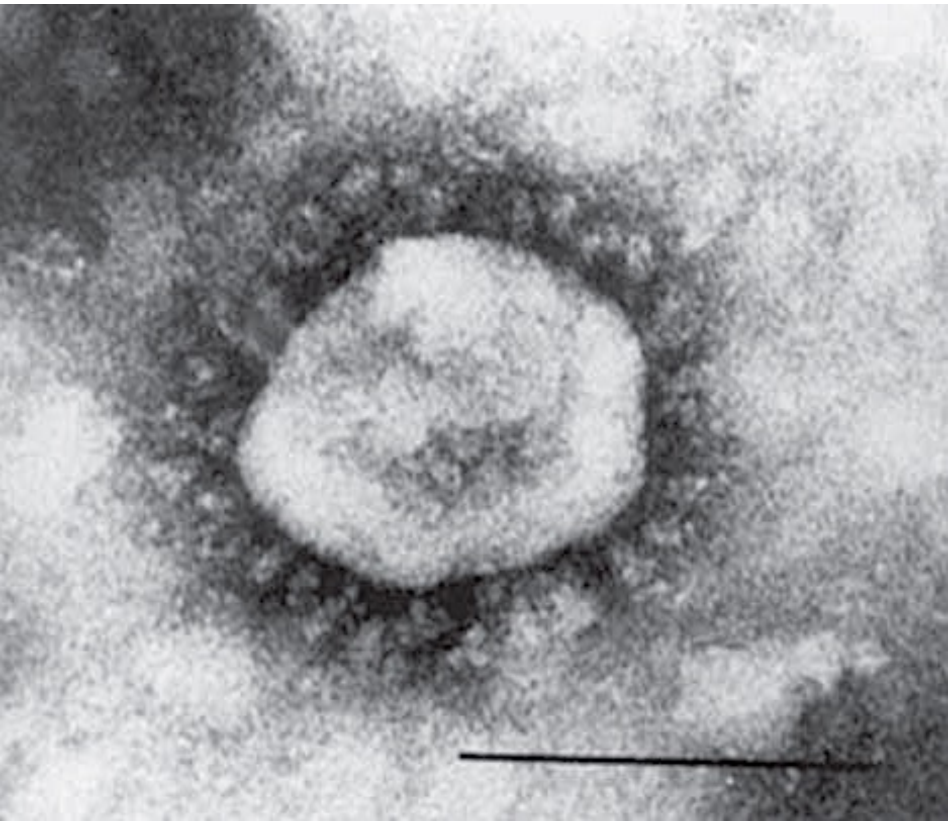
https://www.bbc.com/mundo/noticias-internacional-51400608

Coronavirus: el agente infeccioso

- Orden: *Nidovirales*
- Familia: *Coronaviridae*.
- Subfamilia: *Coronavirinae*.
- Géneros: *Alphacoronaovirus, Betacoronaovirus, Gammacoronaovirus, Deltacoronaovirus,*
- Especies: OC43, 229E, HKU1, NL63, SARS-CoV, MERS-CoV, 2019-nCoV
- Virus cubierto esférico de 120 nm de diámetro.
- Nucleocápside de simetría helicoidal.
- Genoma ARN linear de cadena sencilla de 27-32 kpb, sentido positivo.
- Envoltura con glicoproteínas S.
- Otras proteínas: NP, M, E.
- Interacciones con células
  - CoV-OC42: ácido siálico
  - CoV-229E: ANPEC
  - SARS-CoV: ACE2

http://viralzone.expasy.org/all_by_species/178.html

Coronavirus: generalidades



hCoV-OC46

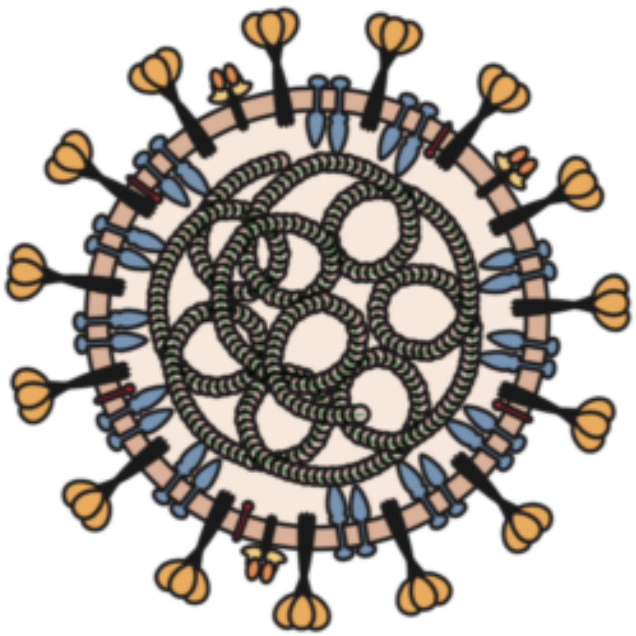
- Los Coronavirus son agentes cubiertos con material genético de tipo ARN (+) de 27-32 Kb, ampliamente prevalentes en humanos, mamíferos, aves y son responsables de infecciones respiratorias, entéricas, hepáticas y neurológicas.
- Se conocen siete especies de CoV en humanos.
- Cuatro: (**229E, OC43, NL63 y HKU1**) son las más prevalentes y son causa de resfriado común en pacientes sin alteraciones inmunes.
- Tres: **SARS**, **MERS**, **Covid-19** son de origen zoonótico

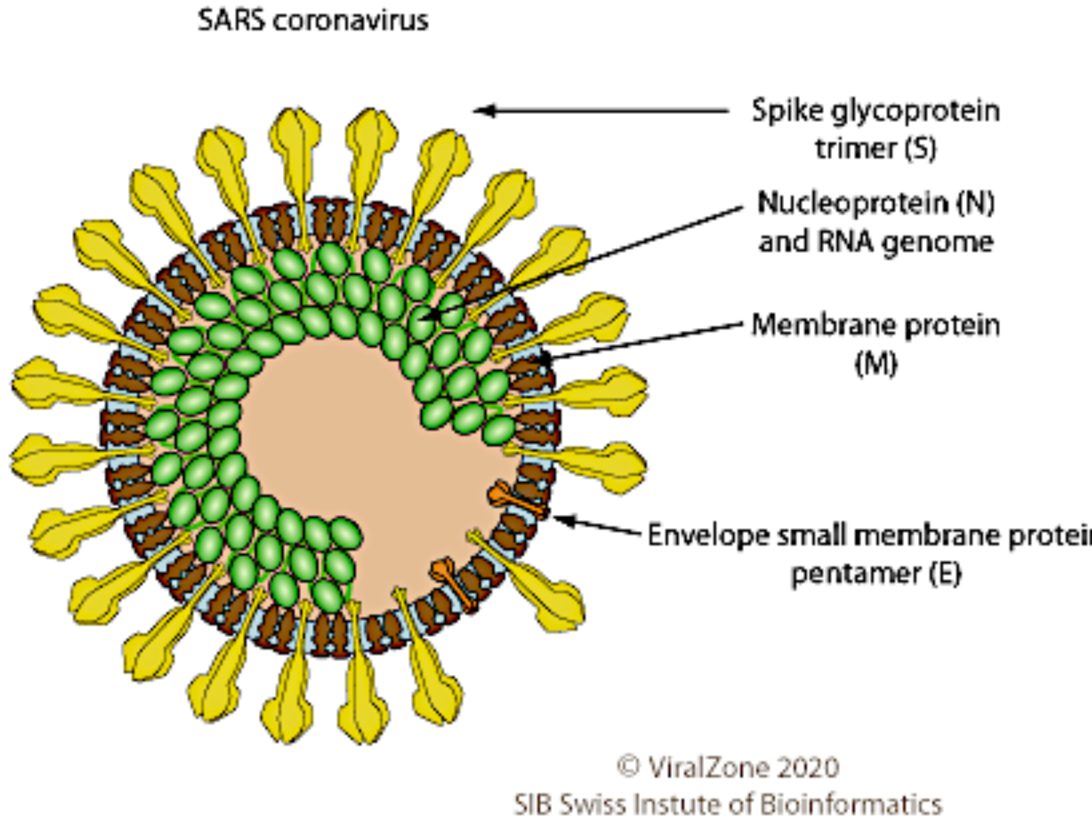
Coronavirus y enfermedad

- Los coronavirus son un grupo amplio y diverso de virus, muchos de los cuales afectan especies animales..
- Antes del descubrimiento del 2019-nCoV, se conocían seis coronavirus que infectaban humanos. Cuatro de estos (HKU1, NL63, OC43, and 229E) causan enfermedades leves o moderadas del tracto respiratorio alto y se estima que son responsables del **10-30% de los resfriados comunes**.
- **Ocasionalmente causan neumonía viral** y pueden ser detectados por los páneles de diagnóstico molecular múltiple.
- Otros coronavirus han causado brotes **de infección respiratoria aguda severa**.
- El SARS apareció en China en 2002 y el MERS en el medio oriente en 2012. Éste último aún causa casos esporádicos.
- El brote actual es causado por el denominado Covid-19 (2019-nCoV), un beta coronavirus hasta hace poco desconocido. Este agente es muy relacionado con virus de murciélagos (~**96**%) y comparte un **80**% de homología con el SARS CoV y tan solo un 50% de homología con MERS-CoV.
- La identidad entre aislamientos es del 99.98%

DOI: 10.1056/NEJMc2001468 y Lancet https://doi.org/10.1016/ S0140-6736(20)30251-8

SARS-CoV: estructura

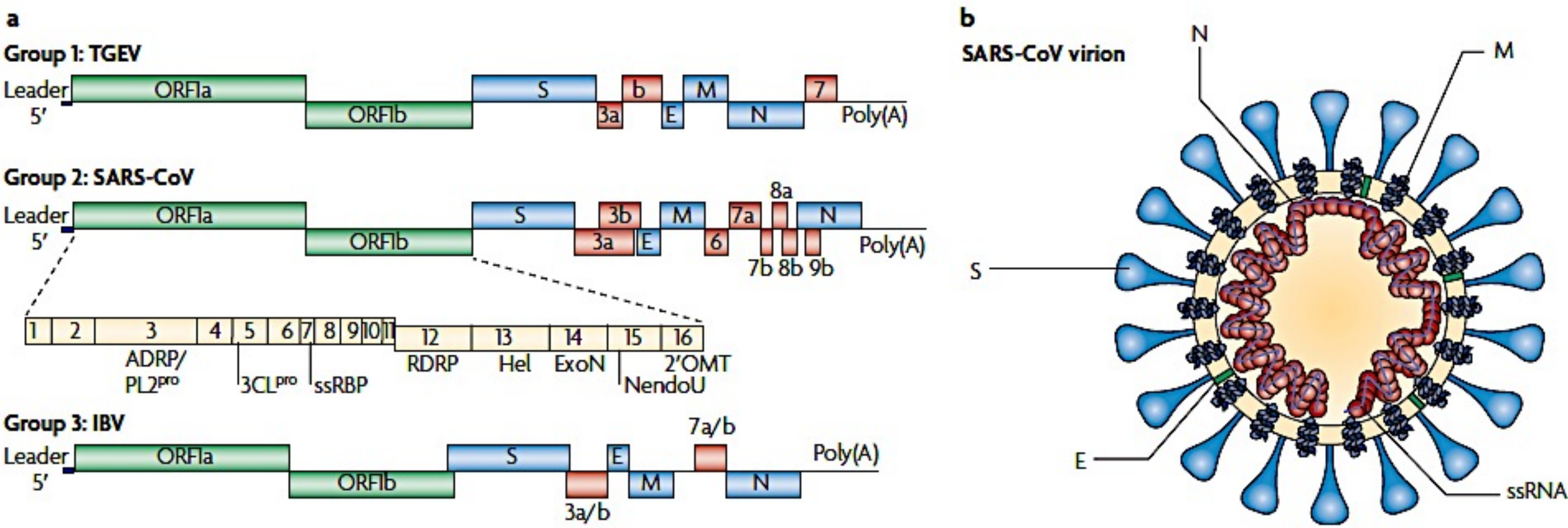




Flint. Principles of Virology. 4th Edition. 2015. ASM Press.

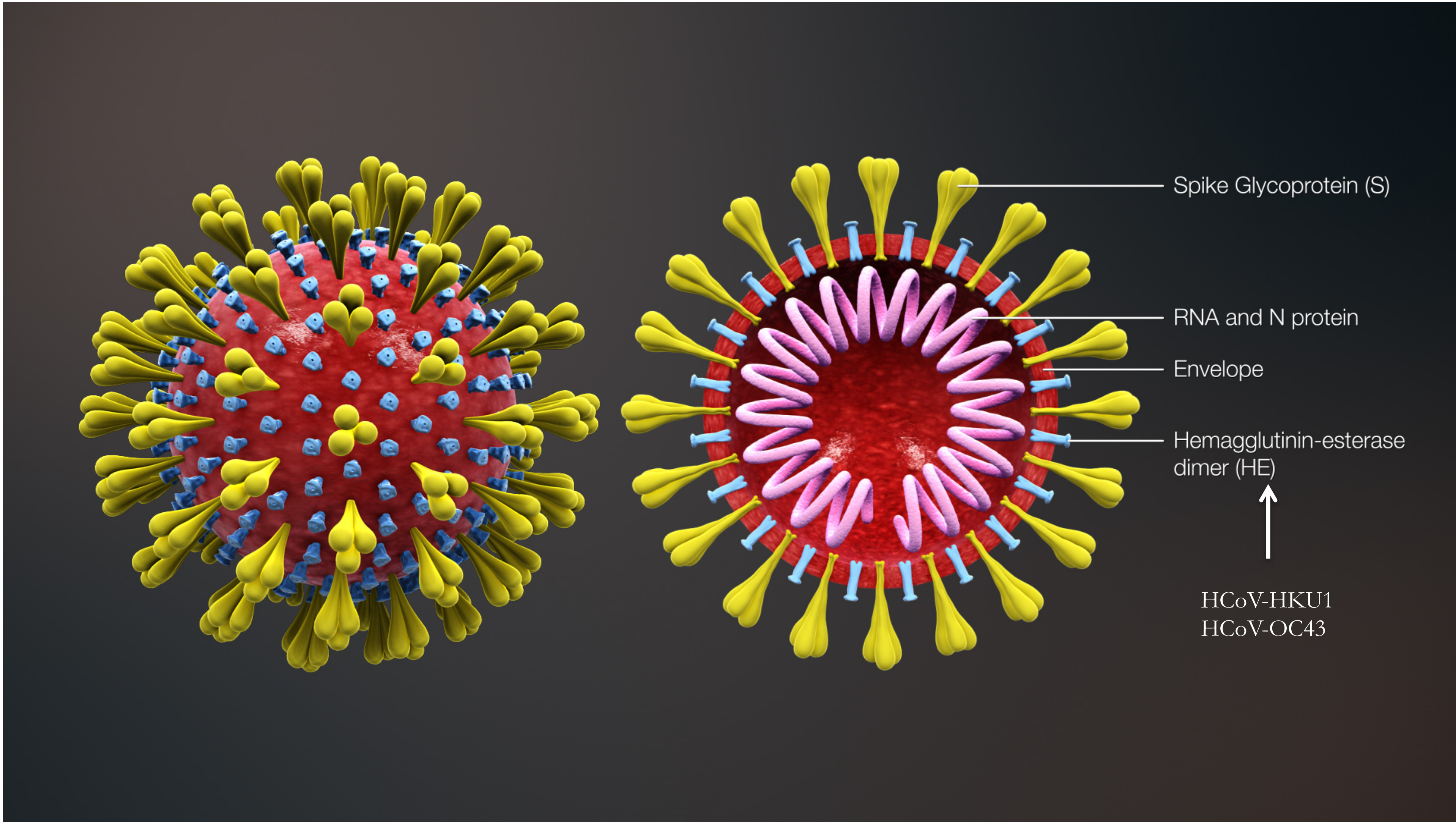
https://viralzone.expasy.org/764outline=all_by_protein

hCoV: estructura



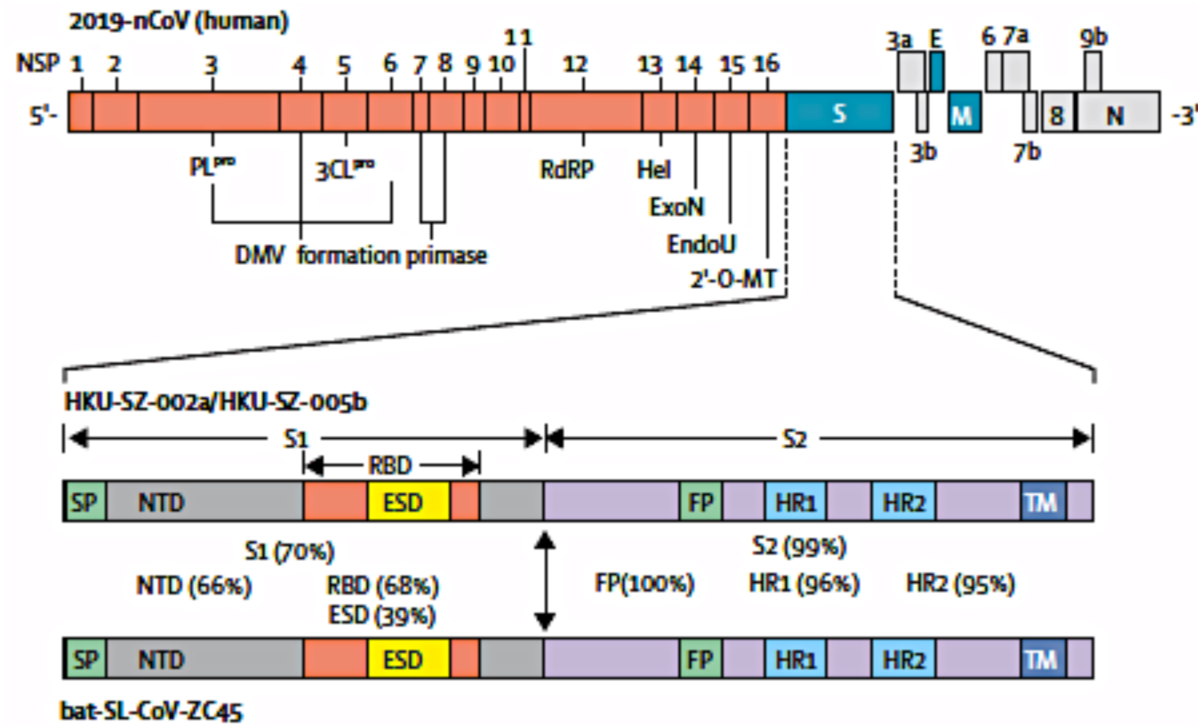
Nat Rev Microbiol 2009; 7: 439-451

Covid-19: estructura



https://www.eluniverso.com/sites/default/files/styles/powgallery_1280/public/fotos/2020/01/-_coronavirus-eeuu_34636035.jpgitok=Y7SArwki

Organización genómica Covid-19

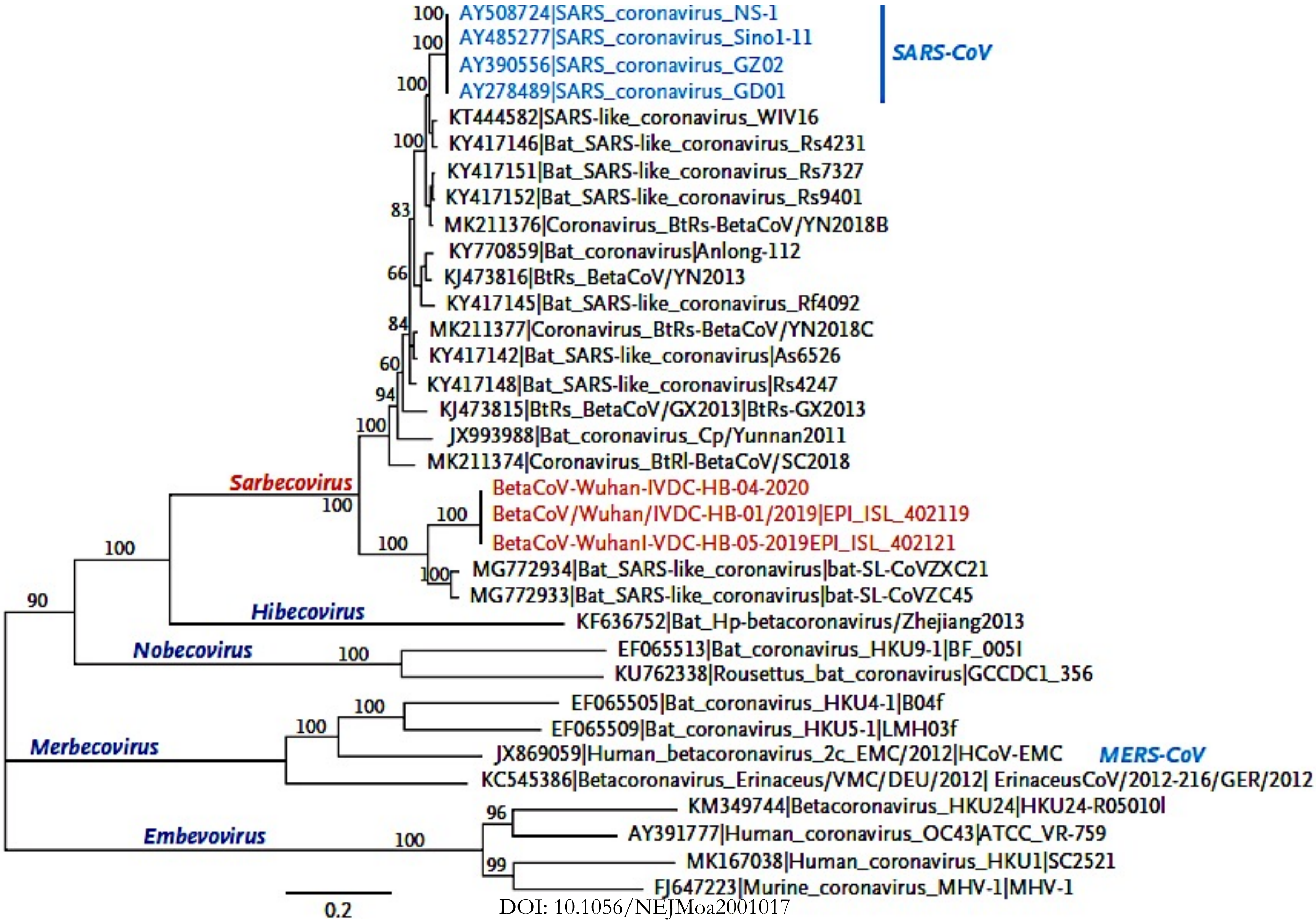


Asilamientos

Genome	Position (nucleotide)	Gene	Amino acid
HKU-SZ-002a HKU-SZ-005b	9529 (TCA) 9577 (TTA)	NSP4 NSP4	Ser336 Leu336
HKU-SZ-002a HKU-SZ-005b	15575 (TTA) 15623 (CTA)	NSP12 NSP12	Leu723 Leu723

https://doi.org/10.1016/ S0140-6736(20)30184-7, and https://doi.org/10.1016/ S0140-6736(20)30185-9

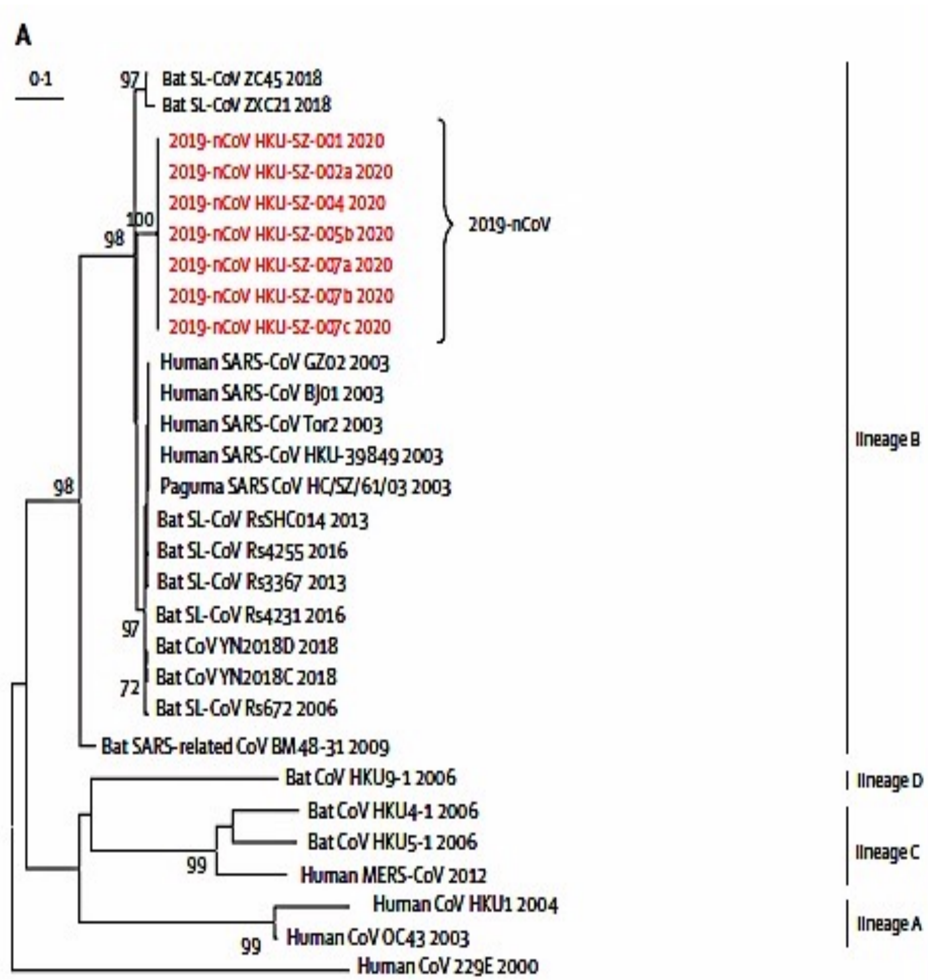
Árbol filogenético 2019-nCoV



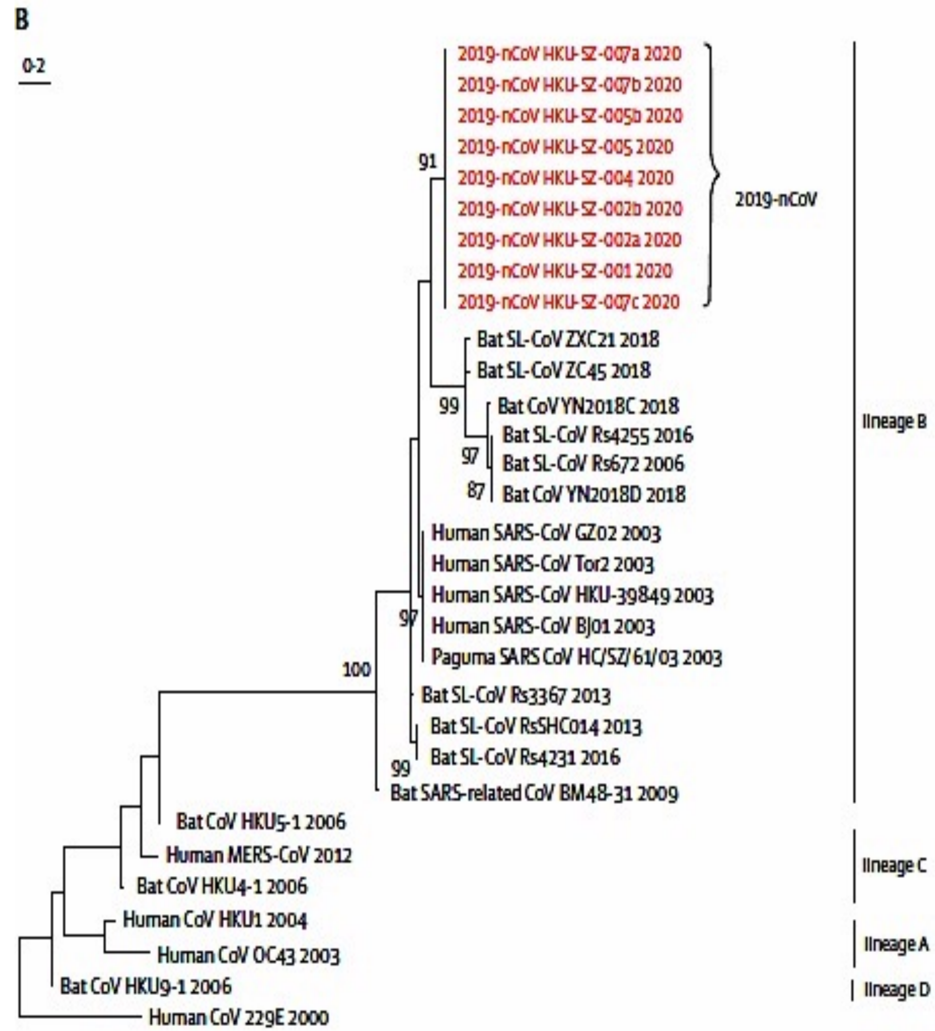
DOI: 10.1056/NEJMoa2001017

Árbol filogenético 2019-nCoV

RNA polymerase



Spike gene



https://doi.org/10.1016/ S0140-6736(20)30184-7, and https://doi.org/10.1016/ S0140-6736(20)30185-9

Proteína S y su receptor

- First, the sequence of Covid-19 RBD, including its **receptor-binding motif** (RBM) that directly contacts **ACE2**, is **similar to that of SARS-CoV**, strongly suggesting that Covid-19 uses ACE2 as its receptor.
- Second, several critical residues in 2019-nCoV RBM (particularly **Gln493**) provide **favourable interactions with human ACE2**, consistent with Covid-19's capacity for human cell infection.
- Third, several other critical residues in Covid-19 RBM (particularly **Asn501**) are compatible with, but not ideal for, binding human ACE2, suggesting that Covid-19 **has acquired some capacity for human-to-human transmission**.
- Last, while phylogenetic analysis indicates a bat origin of **2019-nCoV**, also potentially recognizes **ACE2** from a diversity of animal species (except mice and rats), implicating these animal species as **possible intermediate hosts** or **animal mod**els for Covid-19infections.
- These analyses provide insights into the **receptor usage**, **cell entry**, **host cell infectivity** and **animal origin** of Covid-19, and may help epidemic surveillance and preventive measures against Covid-19.

Journal of Virology 2020. **DOI:** 10.1128/JVI.00127-20

Secuencia de aminoácidos dominio RBD-proteína S

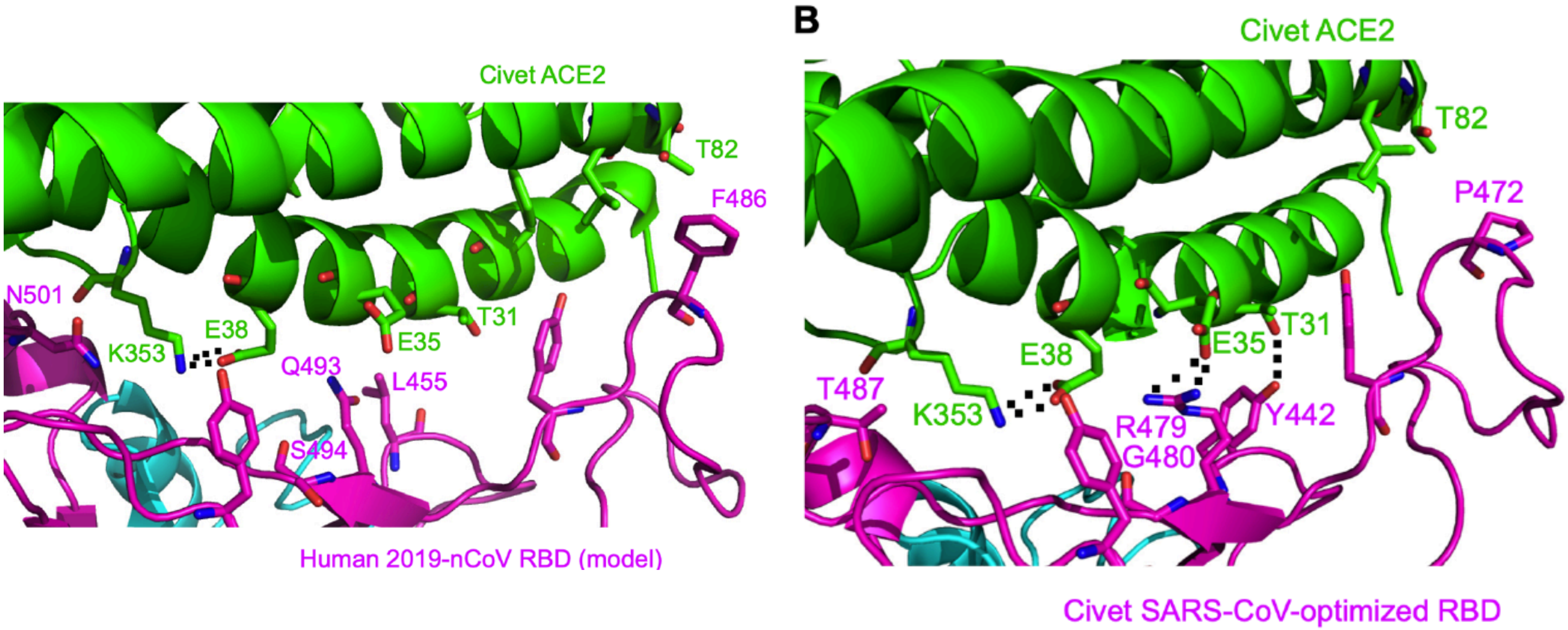
A

```
Human-SARS-2002   306 RVVPS GDVVRFPNIT NLCPFGEVFN ATKFPSVYAW ERKKISNCVA DYSVLYNSTF 360
Civet-SARS-2002   319 RVVPS GDVVRFPNIT NLCPFGEVFN ATKFPSVYAW ERKRISNCVA DYSVLYNSTS 373
Bat-SARS-2013     319 RVAPS KEVVRFPNIT NLCPFGEVFN ATTFPSVYAW ERKRISNCVA DYSVLYNSTS 373
2019-nCoV         319 RVQPT ESIVRFPNIT NLCPFGEVFN ATRFASVYAW NRKRISNCVA DYSVLYNSAS 373
                      ** *:  .:******* ********** ** * ***** :**:****** ********:

Human-SARS-2002   FSTFKCYGVS ATKLNDLCFS NVYADSFVVK GDDVRQIAPG QTGVIADYNY KLPDDFMGCV 420
Civet-SARS-2002   FSTFKCYGVS ATKLNDLCFS NVYADSFVVK GDDVRQIAPG QTGVIADYNY KLPDDFMGCV 433
Bat-SARS-2013     FSTFKCYGVS ATKLNDLCFS NVYADSFVVK GDDVRQIAPG QTGVIADYNY KLPDDFTGCV 433
2019-nCoV         FSTFKCYGVS PTKLNDLCFT NVYADSFVIR GDEVRQIAPG QTGKIADYNY KLPDDFTGCV 433
                  **********  ********: ********:: **:******* *** ****** ****** ***

Human-SARS-2002   LAWNTRNIDA TSTGNYNYKY RYLRHGKLRP FERDISNVPF SPDGKPCTP-P ALNCYWPLND 480
Civet-SARS-2002   LAWNTRNIDA TSTGNYNYKY RYLRHGKLRP FERDISNVPF SPDGKPCTP-P ALNCYWPLKD 493
Bat-SARS-2013     LAWNTRNIDA TQTGNYNYKY RSLRHGKLRP FERDISNVPF SPDGKPCTP-P AFNCYWPLND 493
2019-nCoV         IAWNSNNLDS KVGGNYNYLY RLFRKSNLKP FERDISTEIY QAGSTPCNGVE GFNCYFPLQS 494
                  :***:.*:*:  .   ***** * * :*:.:*:* ******.  :  . ...**.     .:***:**:.

Human-SARS-2002   YGFYTTTGIG YQPYRVVVLS FELLNAPATV CGPKL 515
Civet-SARS-2002   YGFYTTSGIG YQPYRVVVLS FELLNAPATV CGPKL 528
Bat-SARS-2013     YGFYITNGIG YQPYRVVVLS FELLNAPATV CGPKL 528
2019-nCoV         YGFQPTNGVG YQPYRVVVLS FELLHAPATV CGPKK 529
                  ***  *.*:* ********** ****:***** ****
```

RBD: Receptor binding domain

Journal of Virology 2020. **DOI:** 10.1128/JVI.00127-20

Dominio RBD-proteína S



Journal of Virology 2020. **DOI:** 10.1128/JVI.00127-20

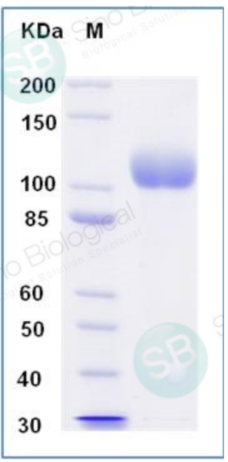
Covid-19: función del receptor

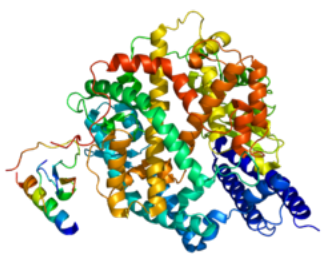
ACE2: Carboxipeptidasa que convierte la angiotensina I en angiotensin 1-9.

Se localiza predominantemente en células del tracto respiratorio bajo meas que en el tracto respiratorio alto.

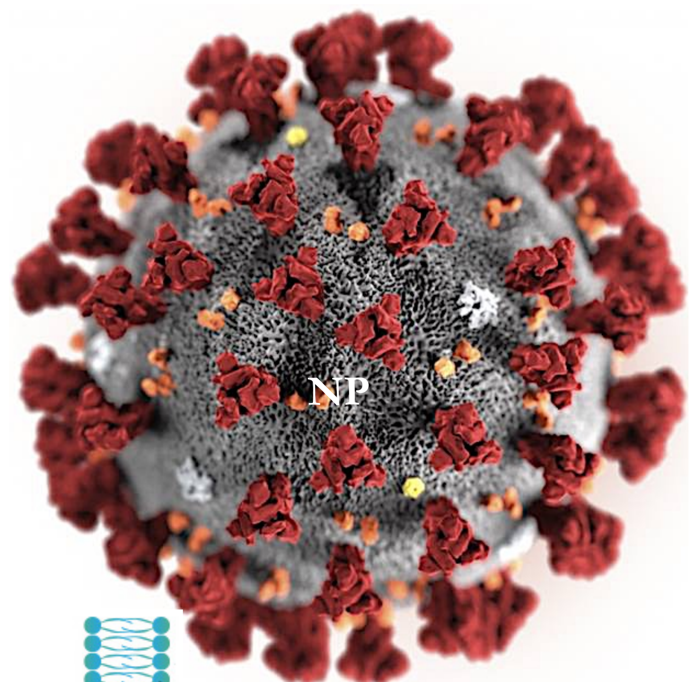
Esto permite comprender porqué los síntomas respiratorios altos son escasos y por que la mayor eliminación del virus se observa hacia el 10 día.

Por homología genética Covid-19 debe usar **ACE2** como receptor y esto permita su adaptación al humano, facilitando la infección.





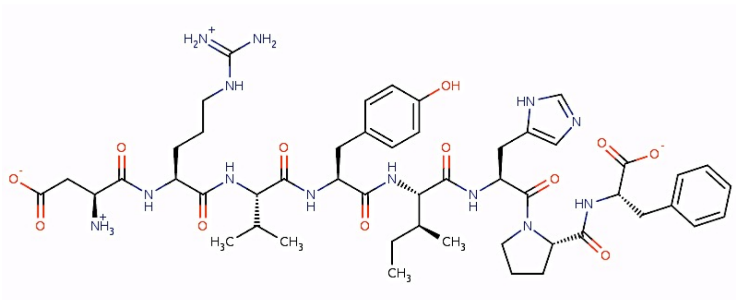
ACE2



https://www.eluniverso.com/sites/default/files/styles/powgallery_1280/public/fotos/2020/01/-_coronavirus-eeuu_34636035.jpgitok=Y7SArwki

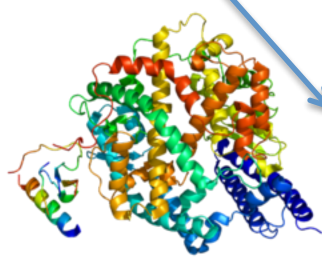
Covid-19: receptor ACE2

Función desconocida.



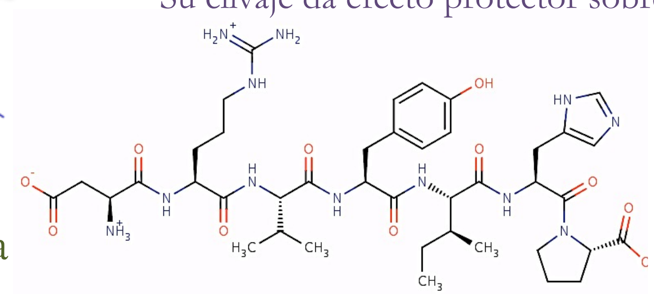
Angiotensina I

+H_2O



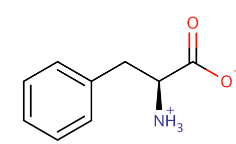
ACE2
Carboxipeptidasa

Vasodilatador, regulador de la función cardiaca.
Su clivaje da efecto protector sobre el daño pulmonar agudo



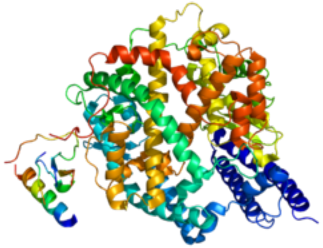
Angiotensina II

+

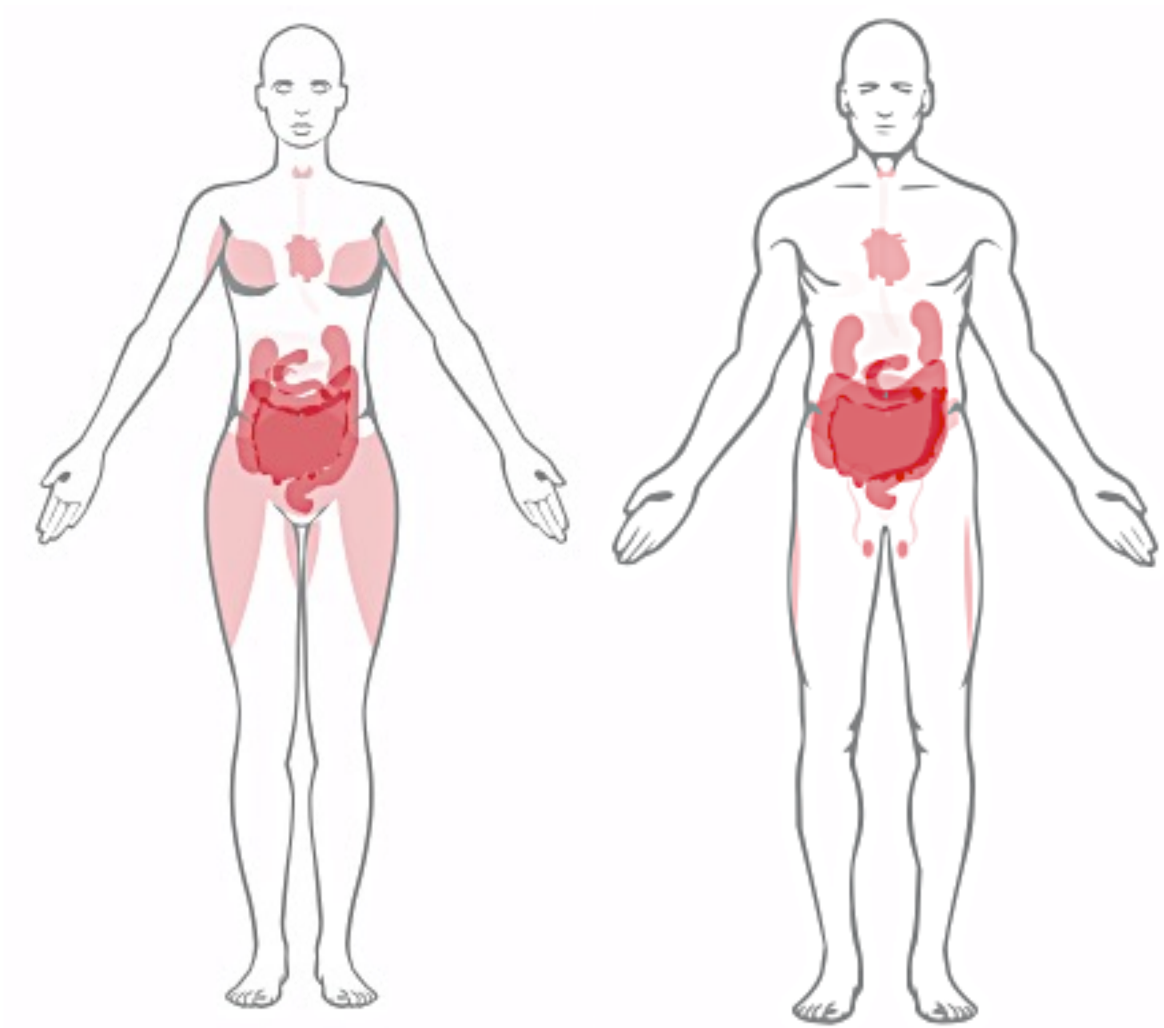


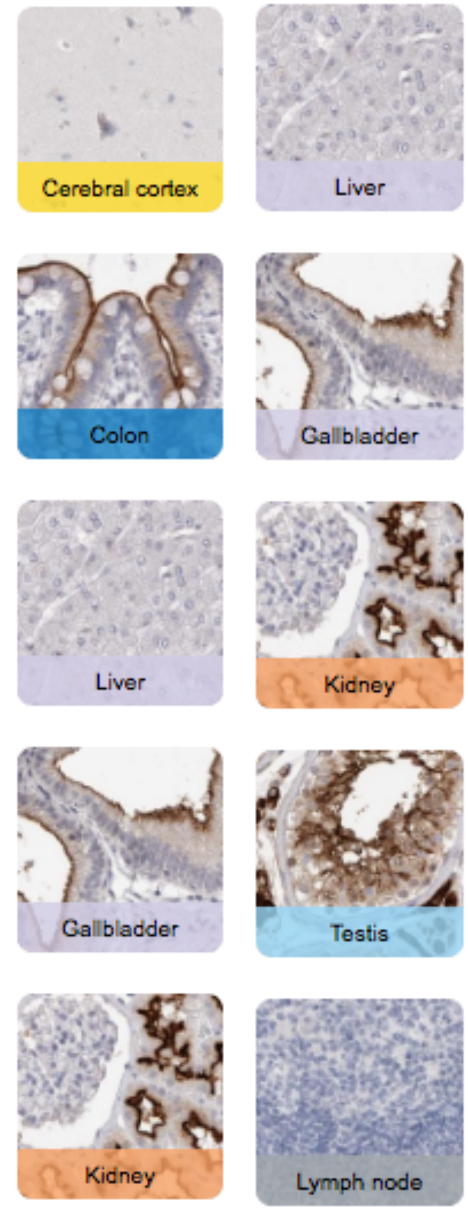
L-fenilalanina

https://www.uniprot.org/uniprot/Q9BYF1



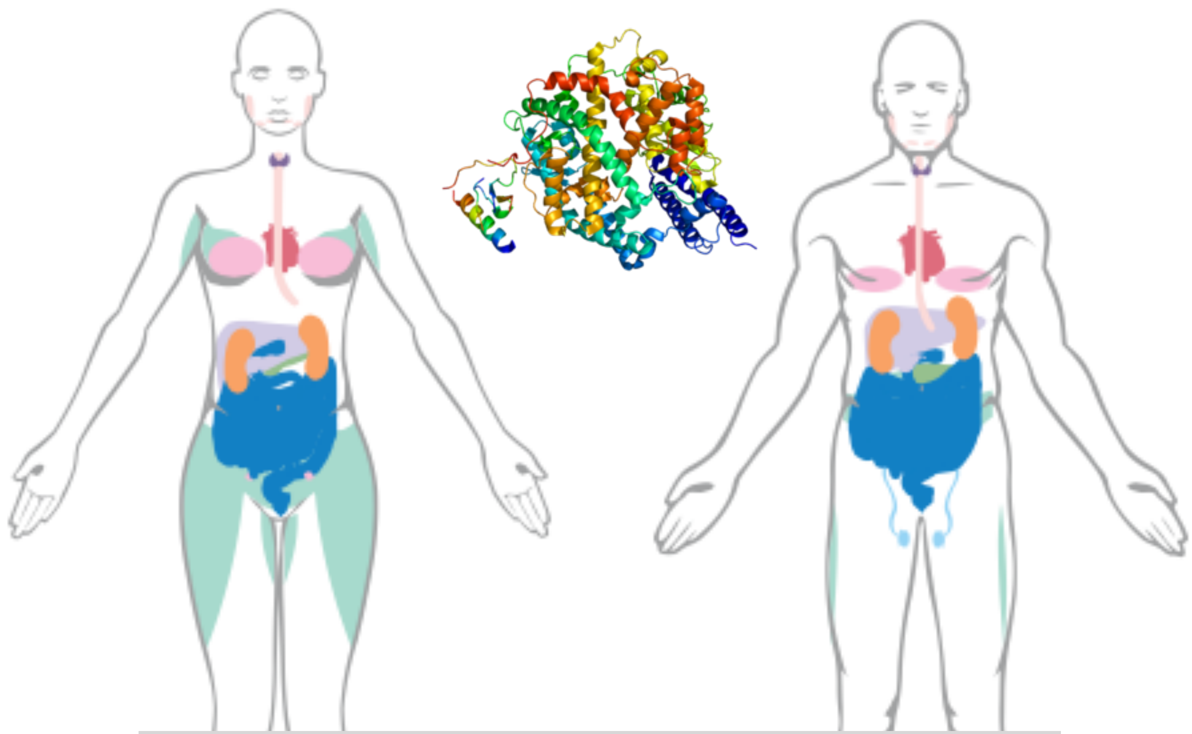
ACE2: expresión tisular

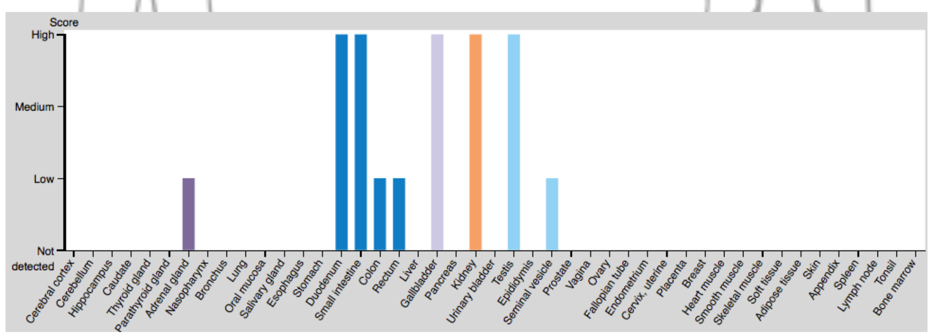




https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue

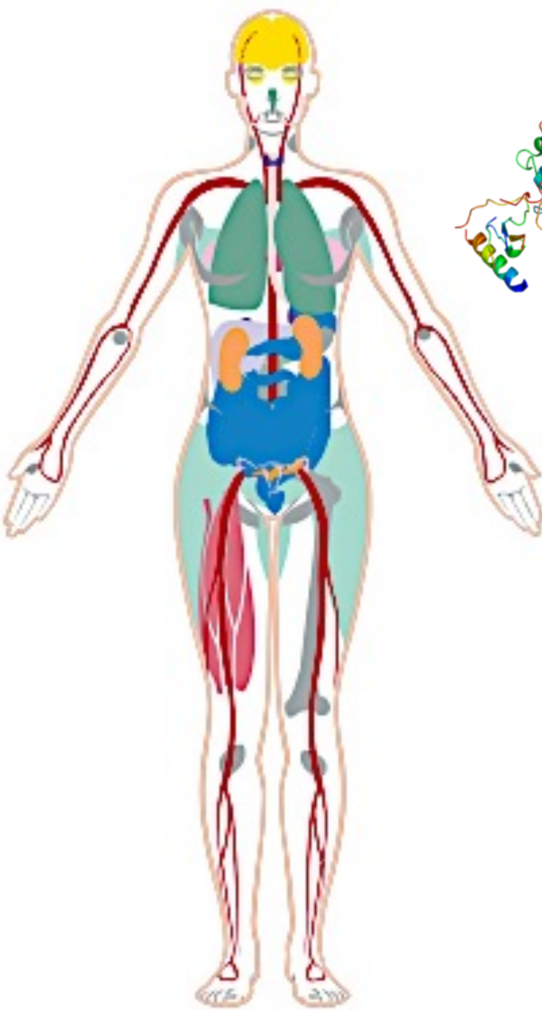
ACE2: detección tisular

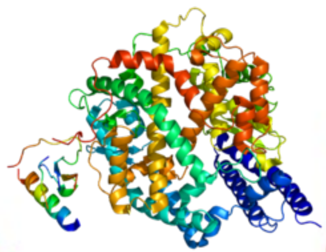


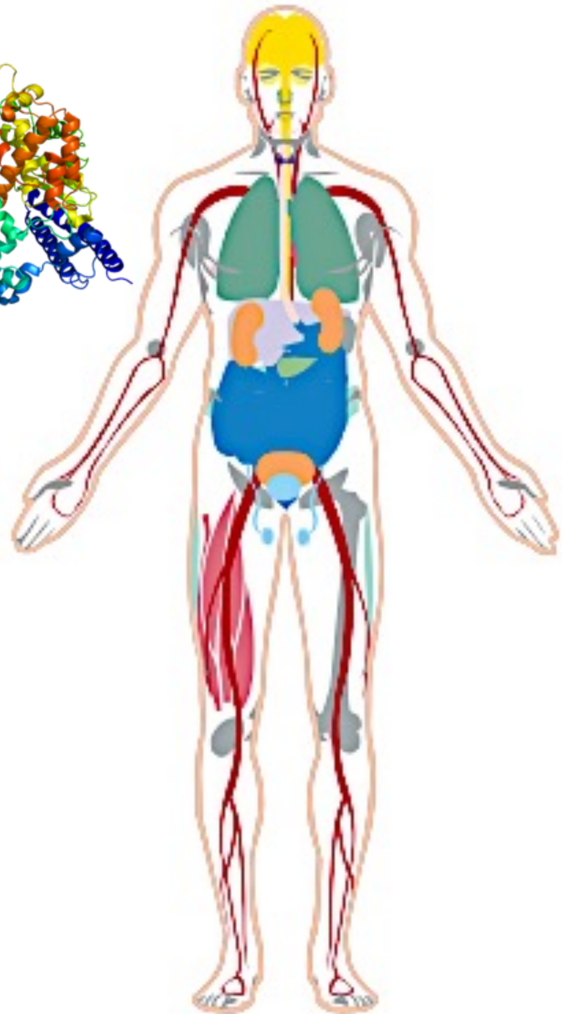


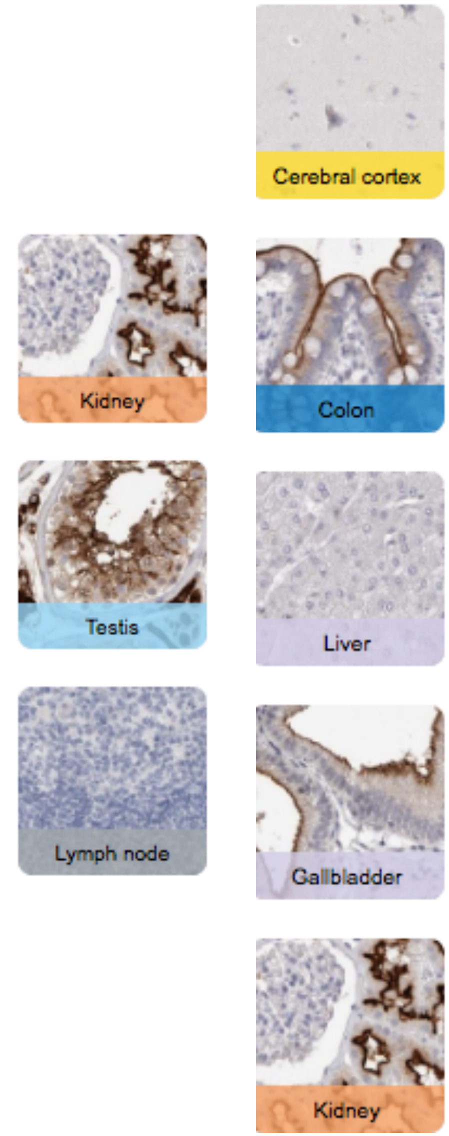
https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue

ACE2: todos los tejidos

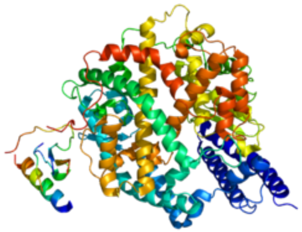




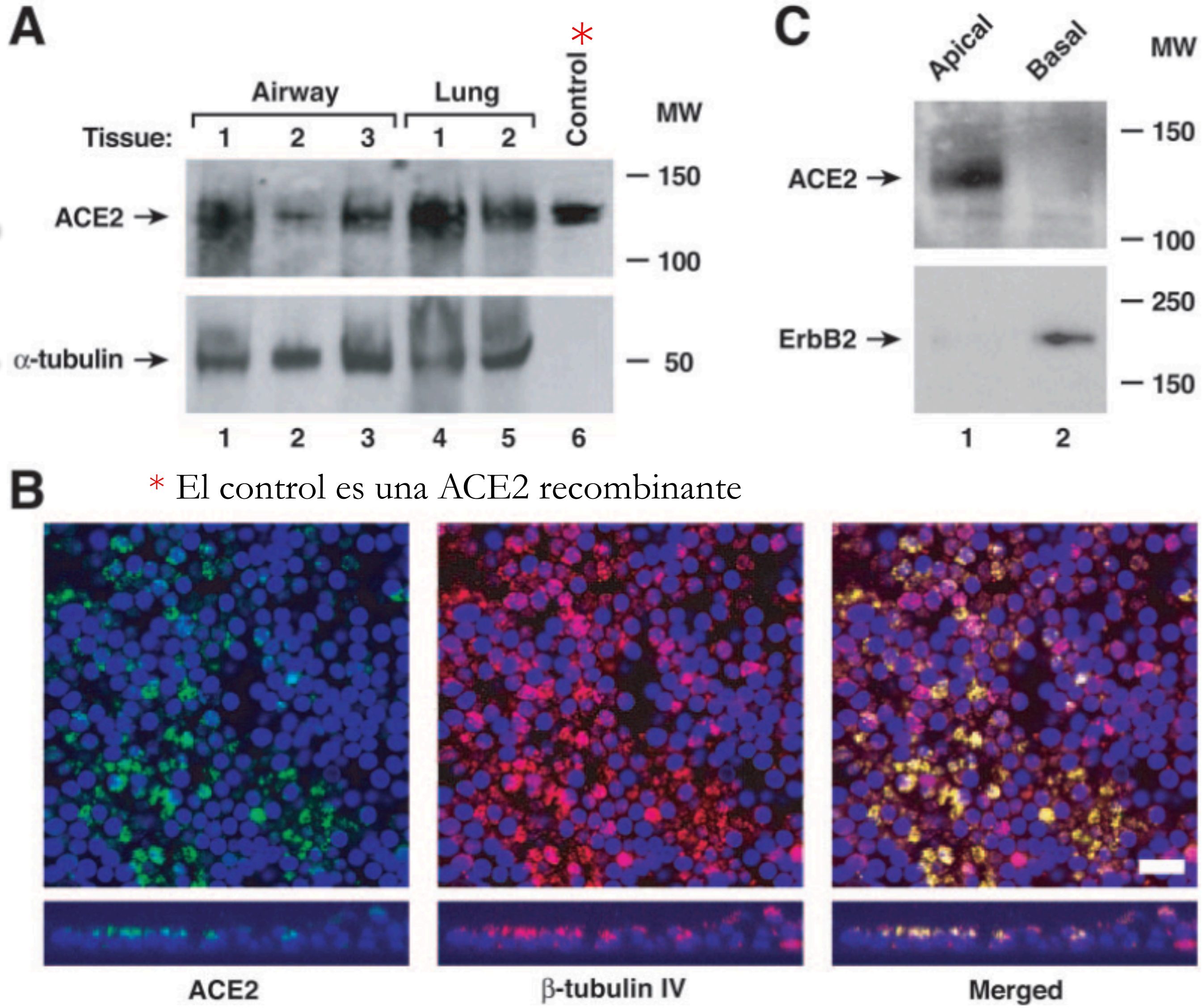




https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue



ACE2: expresión tisular

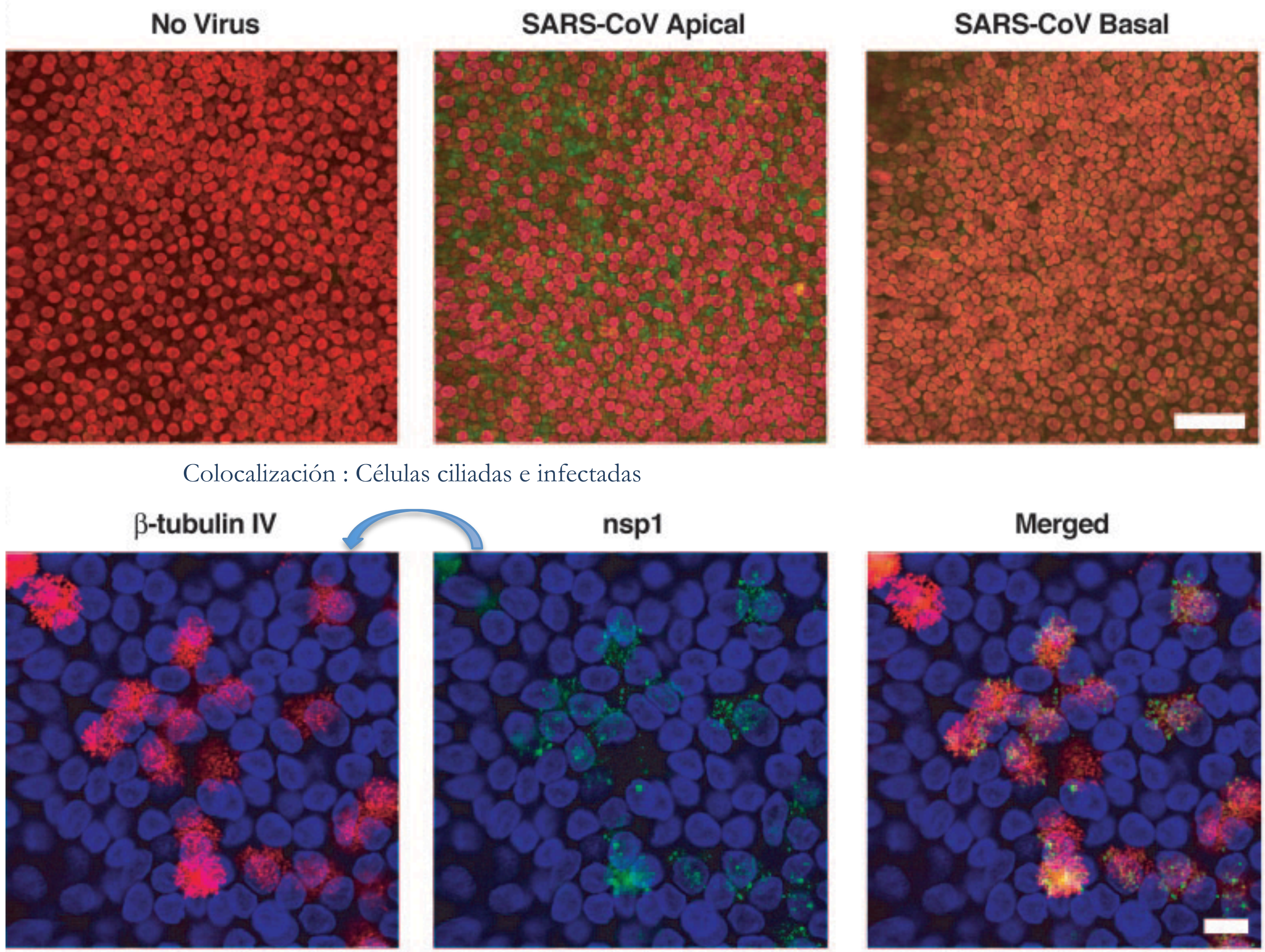


Colocalización
Células ciliadas

* El control es una ACE2 recombinante

Journal of Virology, Dec. 2005;79(23) p. 14614–14621

Infección de células epiteliales diferenciadas



Journal of Virology, Dec. 2005;79(23) p. 14614–14621

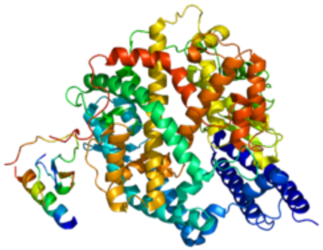
ACE-2: resumen metabólico

METABOLIC SUMMARY[i]

ACE2 is associated with 8 reactions in 3 different subsystems: Boundary, Cytosol, Endoplasmic reticulum, Extracellular, Inner mitochondria, Lysosome, Mitochondria, Nucleus, Peroxisome.

Provided by metabolicatlas.org

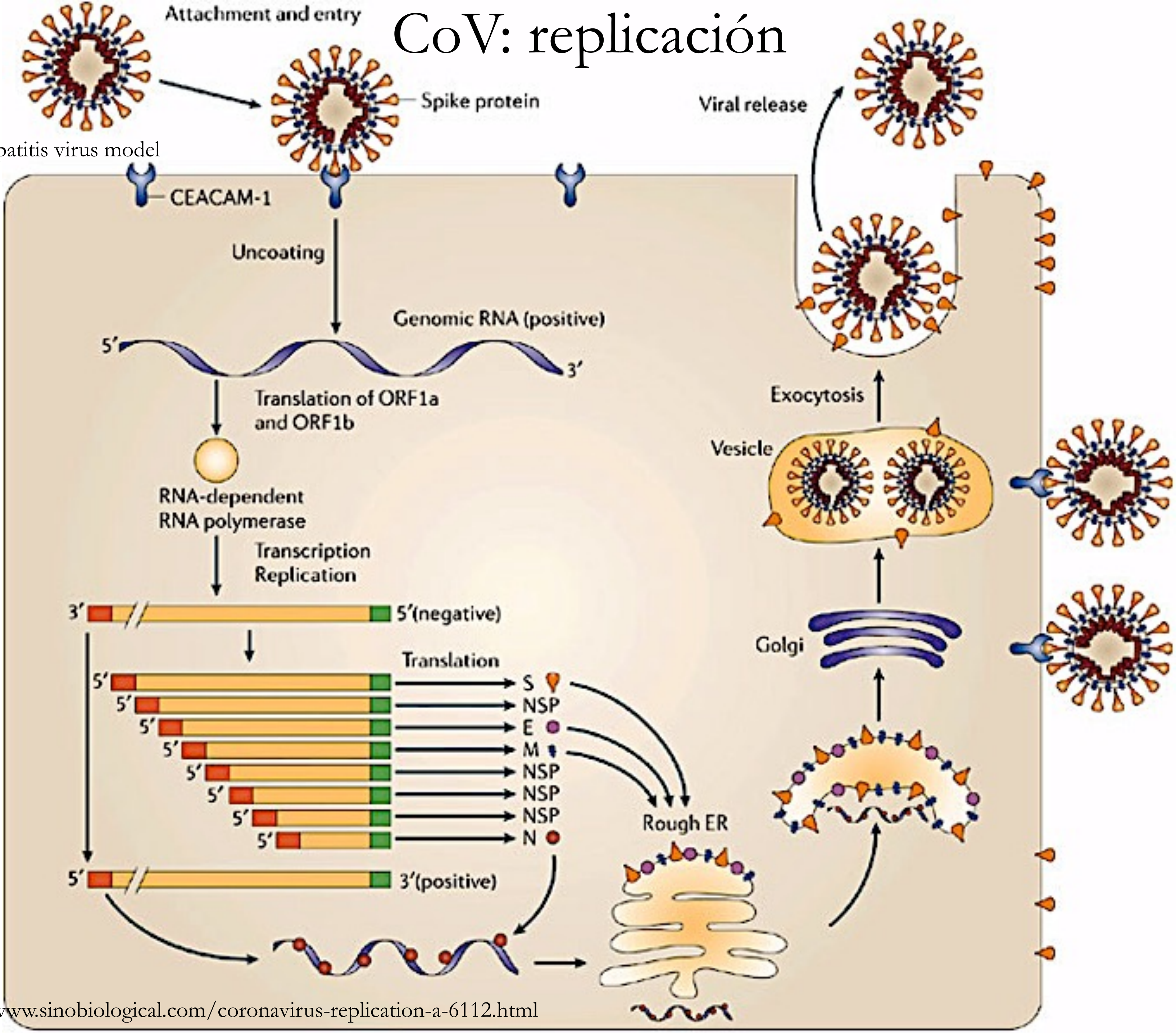
Pathway / Subsystem	Compartments	# proteins	# metabolites	# reactions for this protein
Miscellaneous	Boundary, Cytosol, Endoplasmic reticulum, Extracellular, Inner mitochondria, Lysosome, Mitochondria, Nucleus, Peroxisome	102	173	4
Isolated	Cytosol, Endoplasmic reticulum, Extracellular, Mitochondria, Nucleus, Peroxisome	981	310	3
Transport reactions	Boundary, Cytosol, Endoplasmic reticulum, Extracellular, Golgi apparatus, Inner mitochondria, Lysosome, Mitochondria, Nucleus, Peroxisome	594	1600	1



https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue

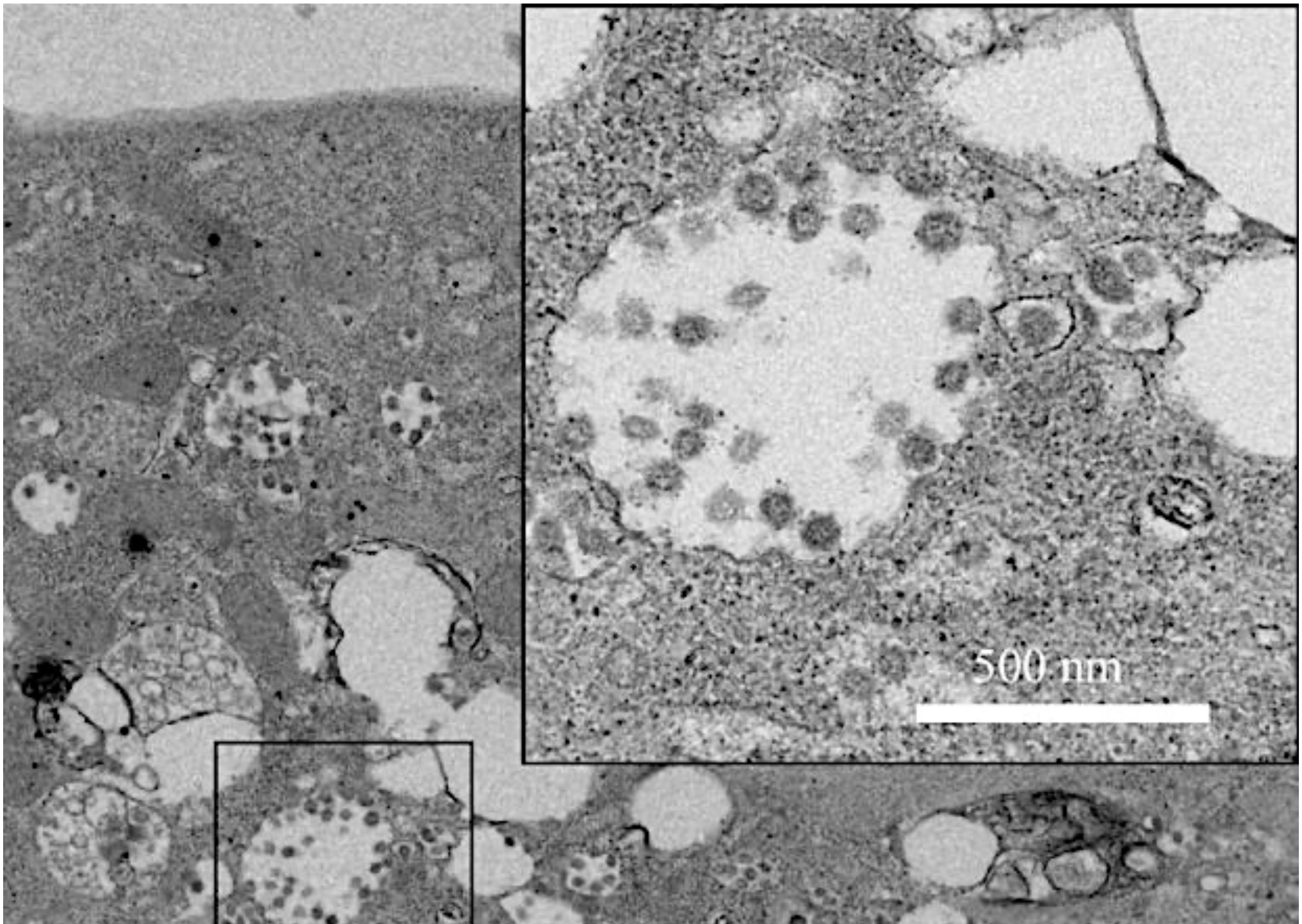
CoV: replicación

Mouse hepatitis virus model

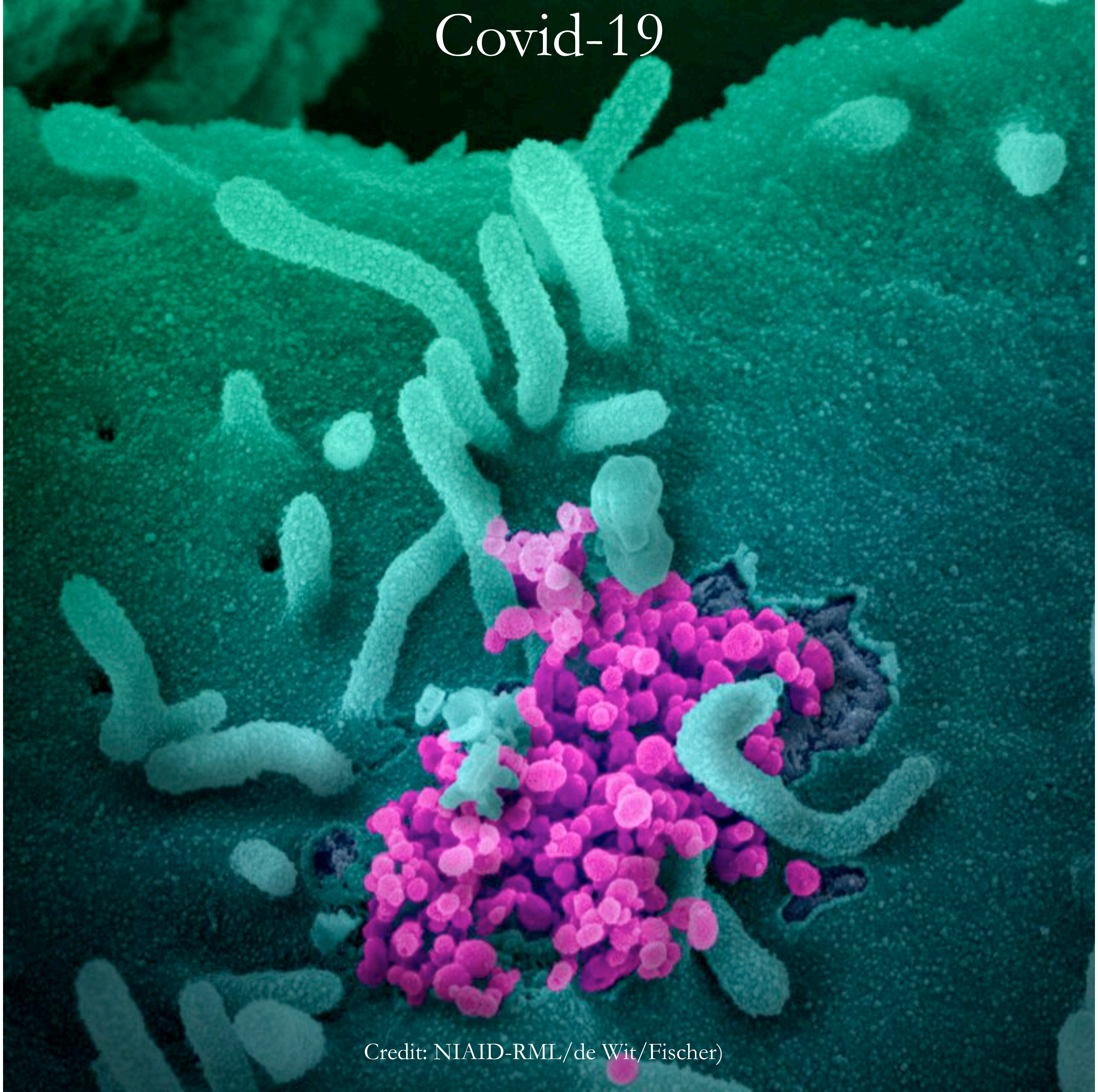


https://www.sinobiological.com/coronavirus-replication-a-6112.html

hCoV



Covid-19



Credit: NIAID-RML/de Wit/Fischer)

Betacoronavirus interacción con el hospedero

Host-virus interaction

Host gene expression shutoff

SARS-CoV nsp1 protein mediates host mRNA decay.

Apoptosis modulation

Human coronavirus induces neuronal apoptosis via mitochondrial apoptosis-inducing factor and cyclophilin D.

Cell-cycle modulation

SARS-CoV Nsp15 has a retinoblastoma protein-binding motif (LXCXE/D) and seems to interact with host retinoblastoma protein resulting in an increased proportion of cells in the S phase of the cell cycle. This probably involves G1/S host cell cycle checkpoint dysregulation by the virus.

Murine coronavirus and SARS-CoV may also induce G0/G1 checkpoint dysregulation.

Innate immune response inhibition

SARS-CoV Protein 3a, which has a viral channel activity, may cause endoplasmic reticulum stress and inhibition of the type 1 interferon receptor.

SARS-CoV PL-Pro mediates ISG15 inhibition and inhibition of host IRF3.

SARS-CoV M protein mediates the inhibition of host TRAF3

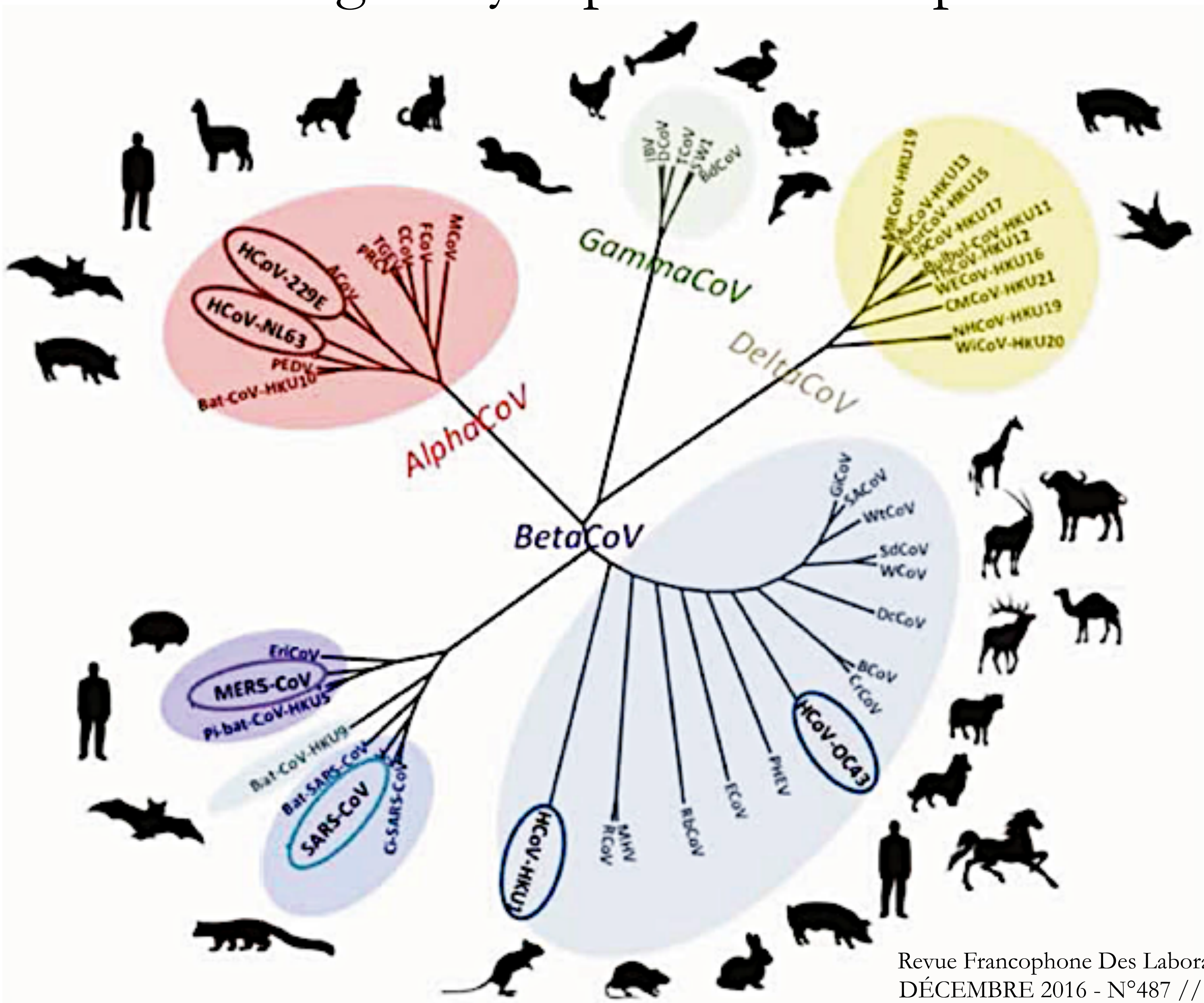
https://viralzone.expasy.org/764outline=all_by_species#tab2

Emergencia viral

- The broad-scale factors responsible for viral emergence have been well documented and include human population growth, increased frequency and reach of travel, changing patterns of land use, changing diets, wars and social upheaval and climate change.
- These factors increase interactions between humans and reservoir hosts, facilitating exposure to zoonotic viruses and spillover infections in people, and allow emerging viruses to spread more easily through human populations.
- The interactions between virus genetics, ecology and the host factors that determine virus emergence are so complex that it is impossible to predict what virus will cause the next epidemic, making it essential that our response is scientifically informed, robust and efficient.

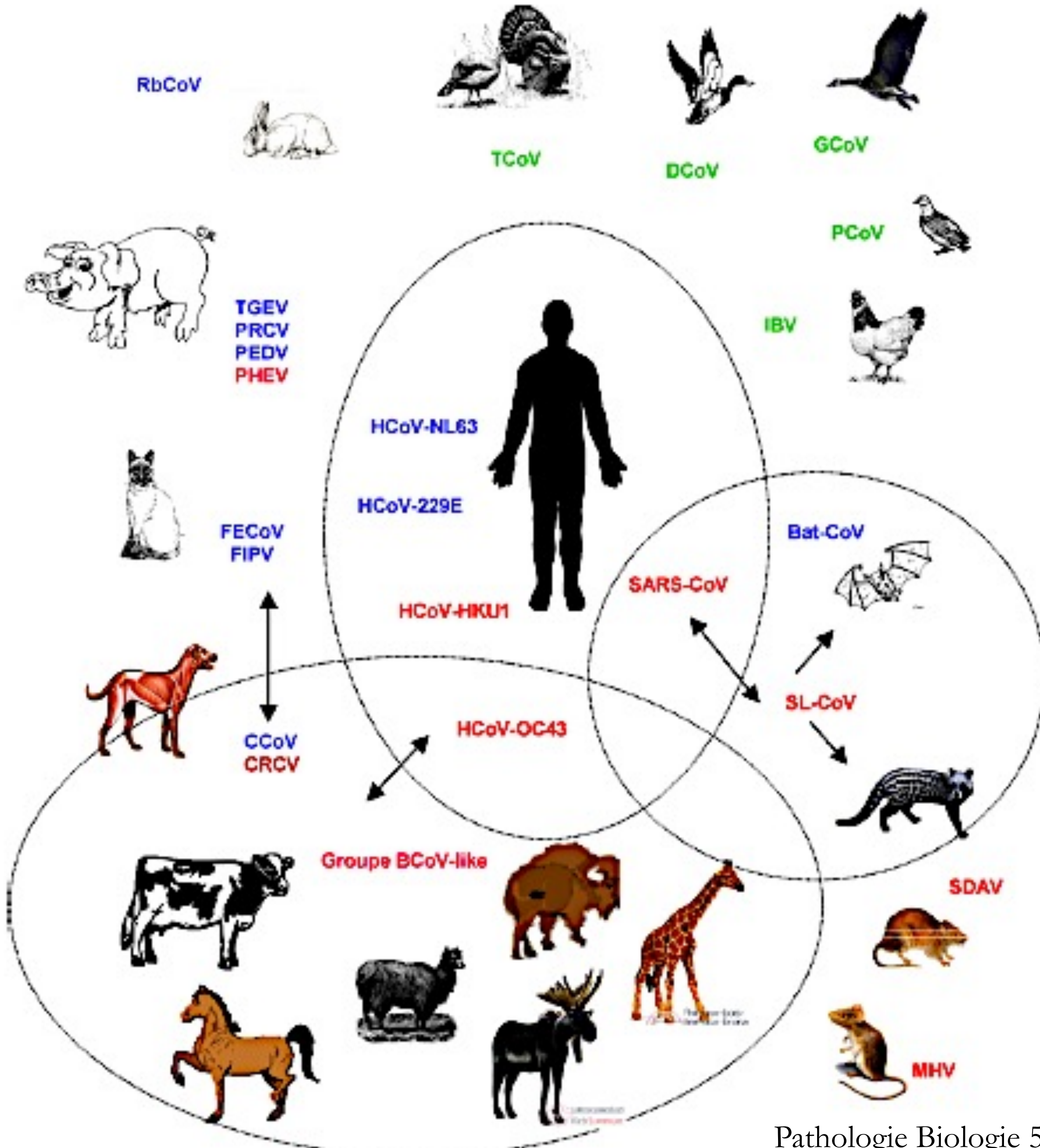
Grubaugh, N.D., Ladner, J.T., Lemey, P. *et al.* Tracking virus outbreaks in the twenty-first century. *Nat Microbiol* **4,** 10–19 (2019). https://doi.org/10.1038/s41564-018-0296-2

hCoV: filogenia y espectro de hospederos



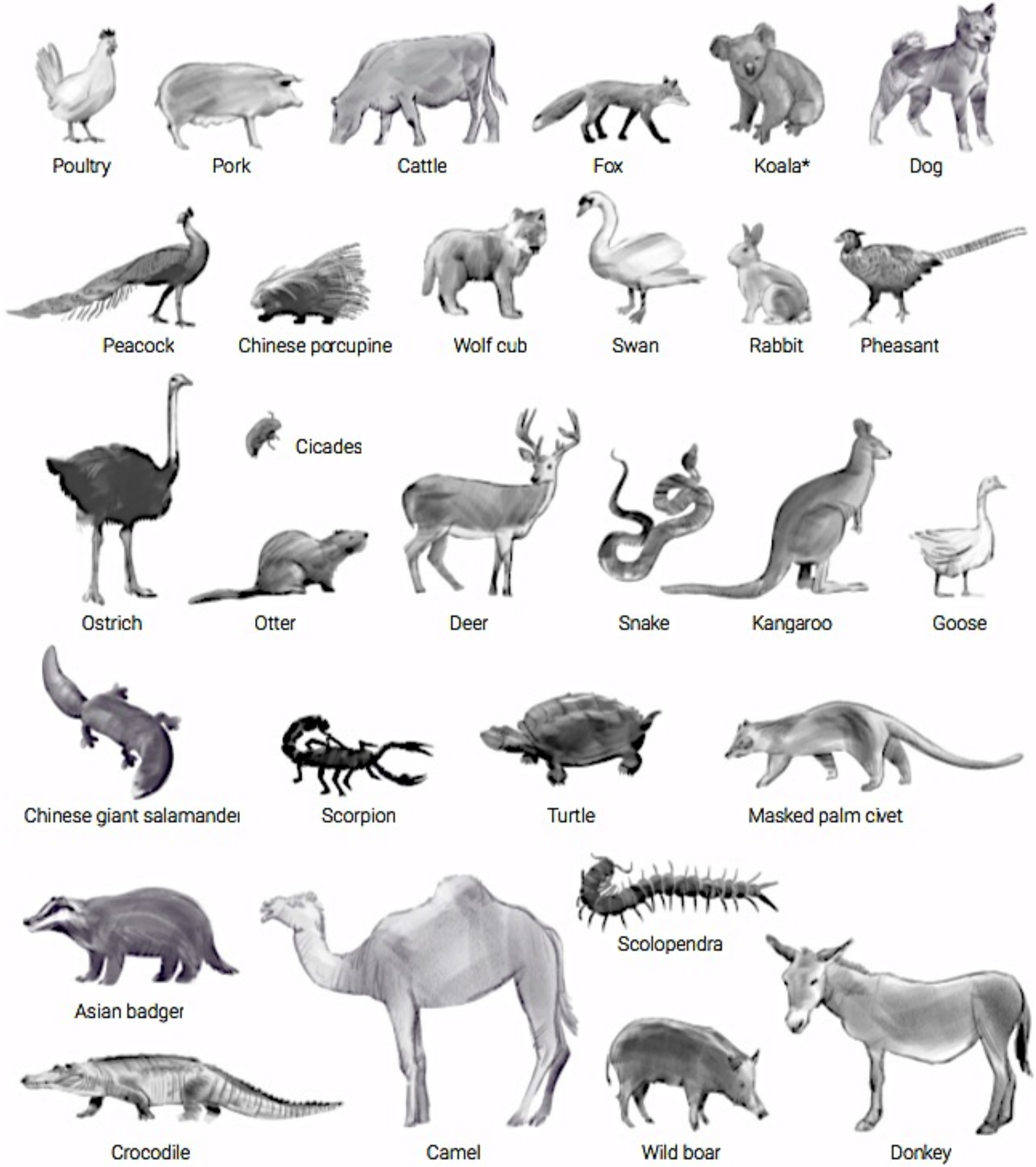
Revue Francophone Des Laboratoires
DÉCEMBRE 2016 - N°487 // 25-34

hCoV: zoonosis



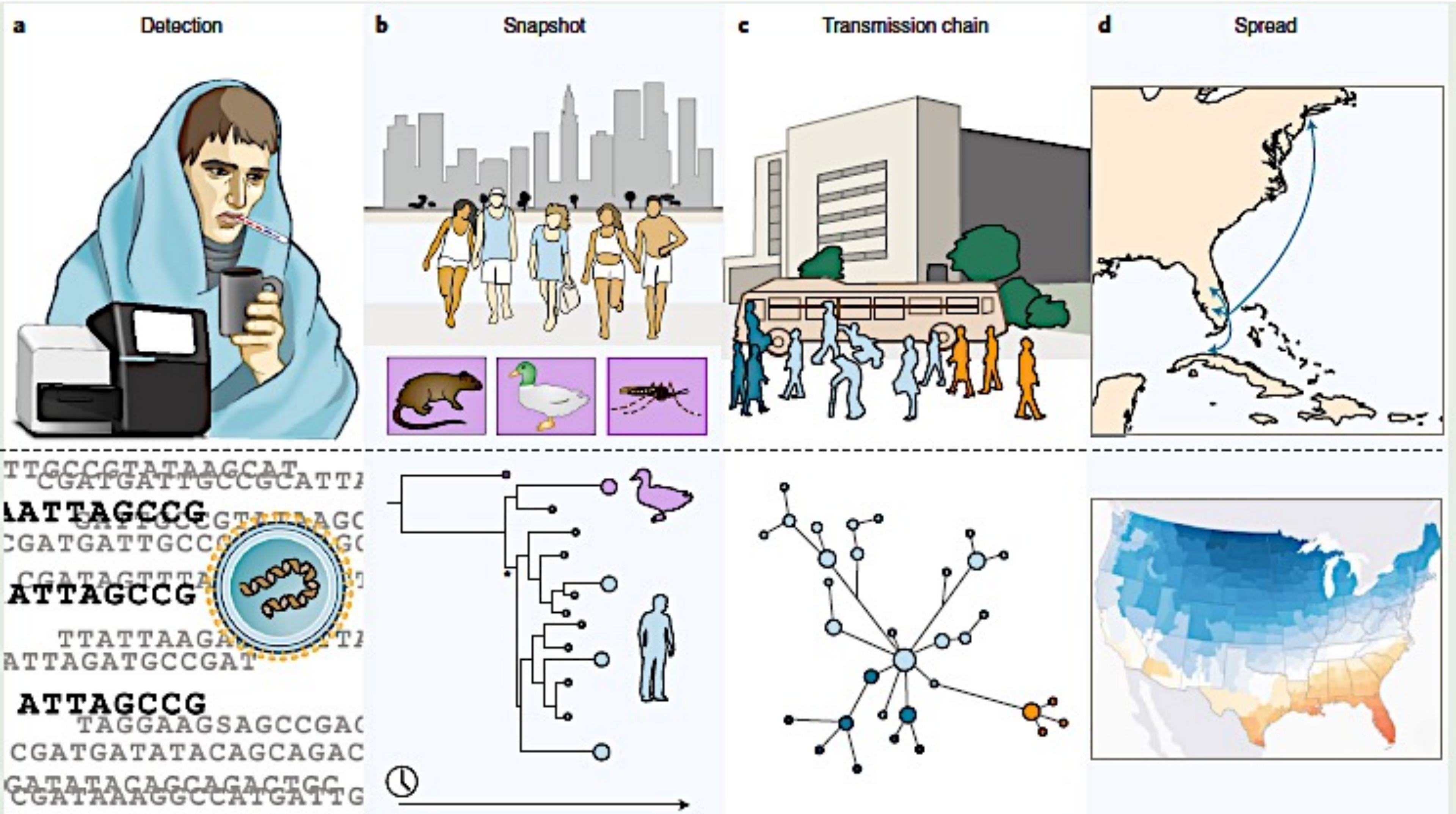
Pathologie Biologie 57 (2009) 149–160

Meat Market



*The Chinese character for koala seems to be used to deliberately mislead and likely refers to beavers.

Investigación genómica en tiempo real



Grubaugh, N.D., Ladner, J.T., Lemey, P. *et al.* Tracking virus outbreaks in the twenty-first century. *Nat Microbiol* **4,** 10–19 (2019).
https://doi.org/10.1038/s41564-018-0296-2

Murciélagos e infecciones emergentes

1.200 especies
20% mamíferos

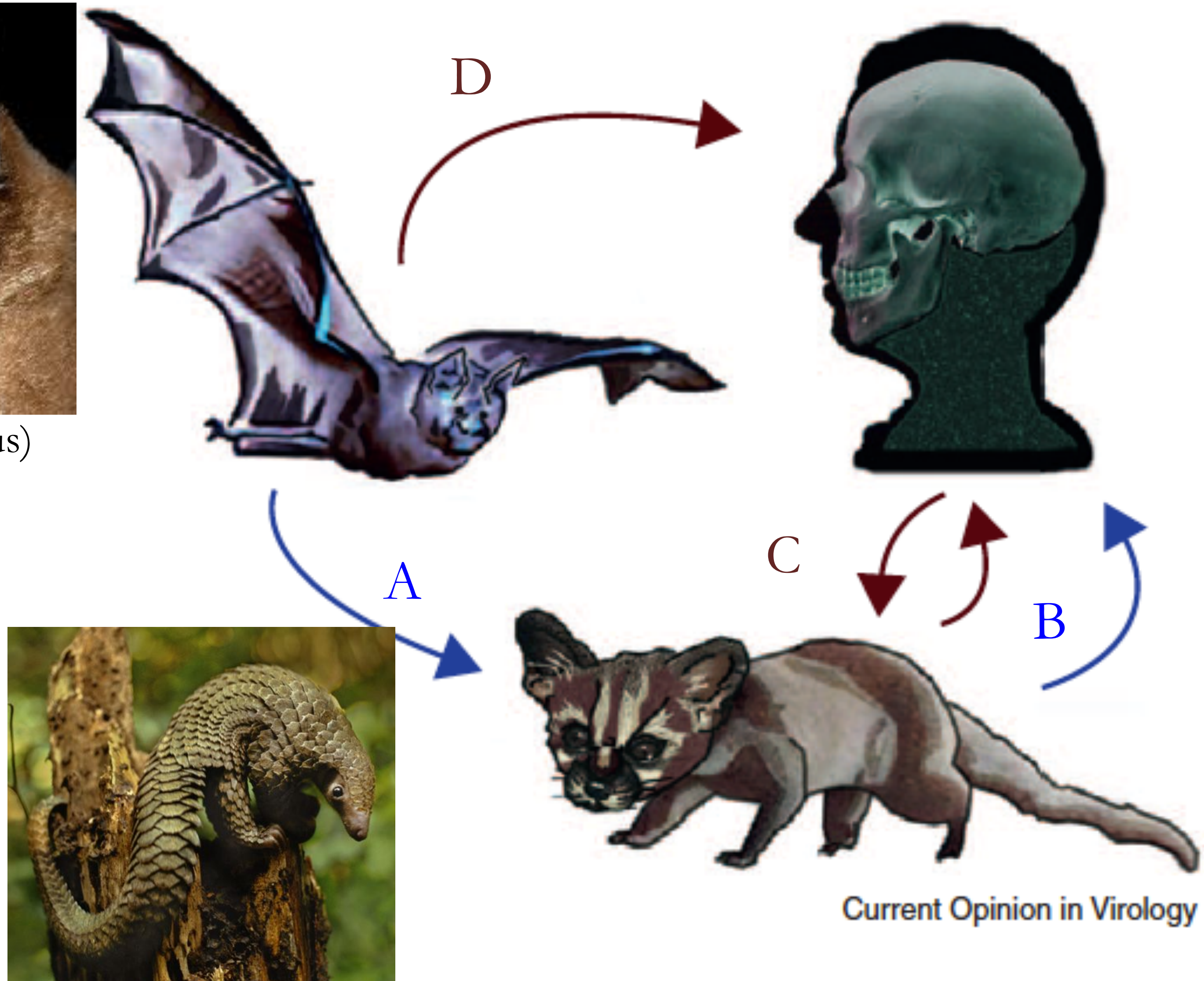
Rabia
SARS
Hendra
Nipah
Ébola

Emerging Viral Diseases: The One Health Connection: Workshop Summary (2015)

SARS-CoV/Covid-19: modelos de emergencia

Rhinolophus sinicus)

bio.bris.ac..uk



Pangolín

Current Opinion in Virology 2011:26: p. 264-76

CoV que han emergido por adaptación genética

Resulting CoV/host	Suspected original CoV/host	Genomic modification	References
HCoV-OC43/human	BCoV/cow	290-nt deletion (corresponding to the absence of BCoV nsp 4.9 kDa and nsp 4.8 kDa)	Vijgen et al., 2005
HECV-4408/human	BCoV/cow	Not known	
SARS-CoV/human	Bat and civet SARS-CoV/ horseshoe bat and civet cats	29-nt deletion in ORF8 and substitutions in spike gene and ORF3	Lau et al., 2005

Emerging Viral Diseases: The One Health Connection: Workshop Summary (2015)

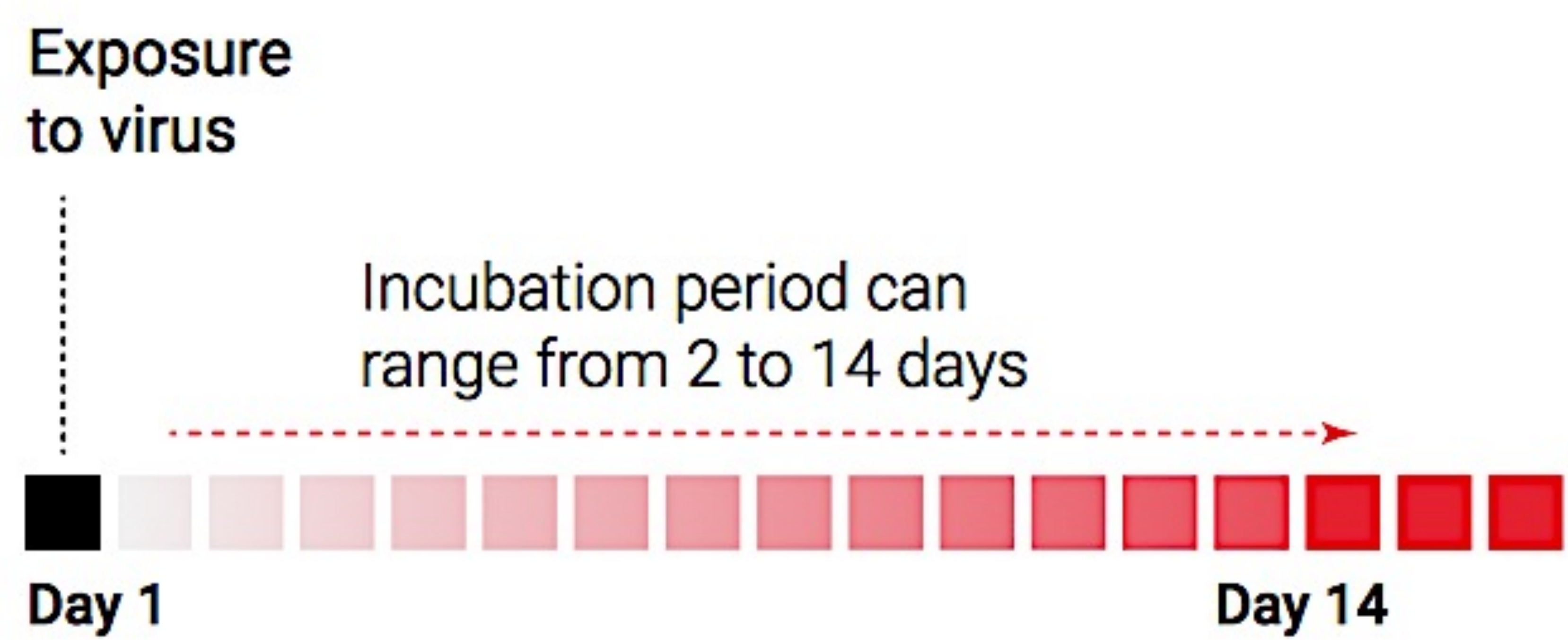
SARS-CoV: patogénesis

SARS-CoV Protein	Innate Immune Function
nsp1	Antagonizes IFN; inactivates host translation; degrades host mRNA; blocks phosphorylation of STAT1
PLP	Antagonizes IFN; interacts with STING; blocks IRF Phosphorylation; blocks NF- κB signaling
nsp7	Antagonizes IFN by undescribed mechanism
nsp14	Guanine-N7-methyltransferase activity part of viral RNA capping machinery for evading host detection
nsp15	Antagonizes IFN by undescribed mechanism
nsp16	2'-O-methlytransferase activity modifies the cap of viral RNAs for evading host detection
ORF3b	Antagonizes IFN signaling induced by MAVS/RIG-I
Membrane	Antagonizes IFN signaling through kinases TBK1/IKKε
ORF6	Antagonizes IFN by blocking nuclear import of STAT1
Nucleocapsid	Antagonizes IFN by unknown mechanism

Cognate receptors

Current Opinion in Virology 2012:26: p. 264-76

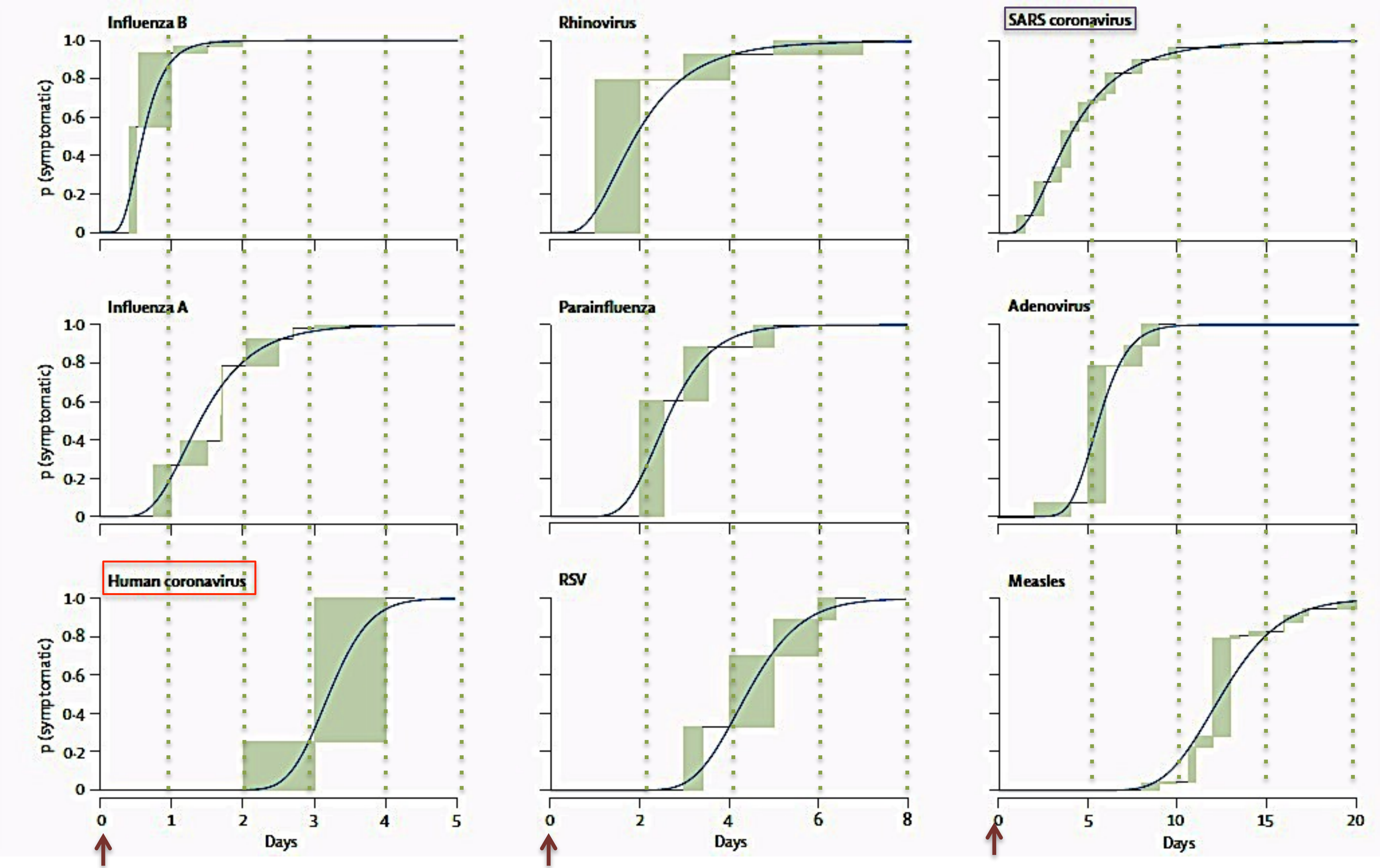
Periodo de incubación



https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

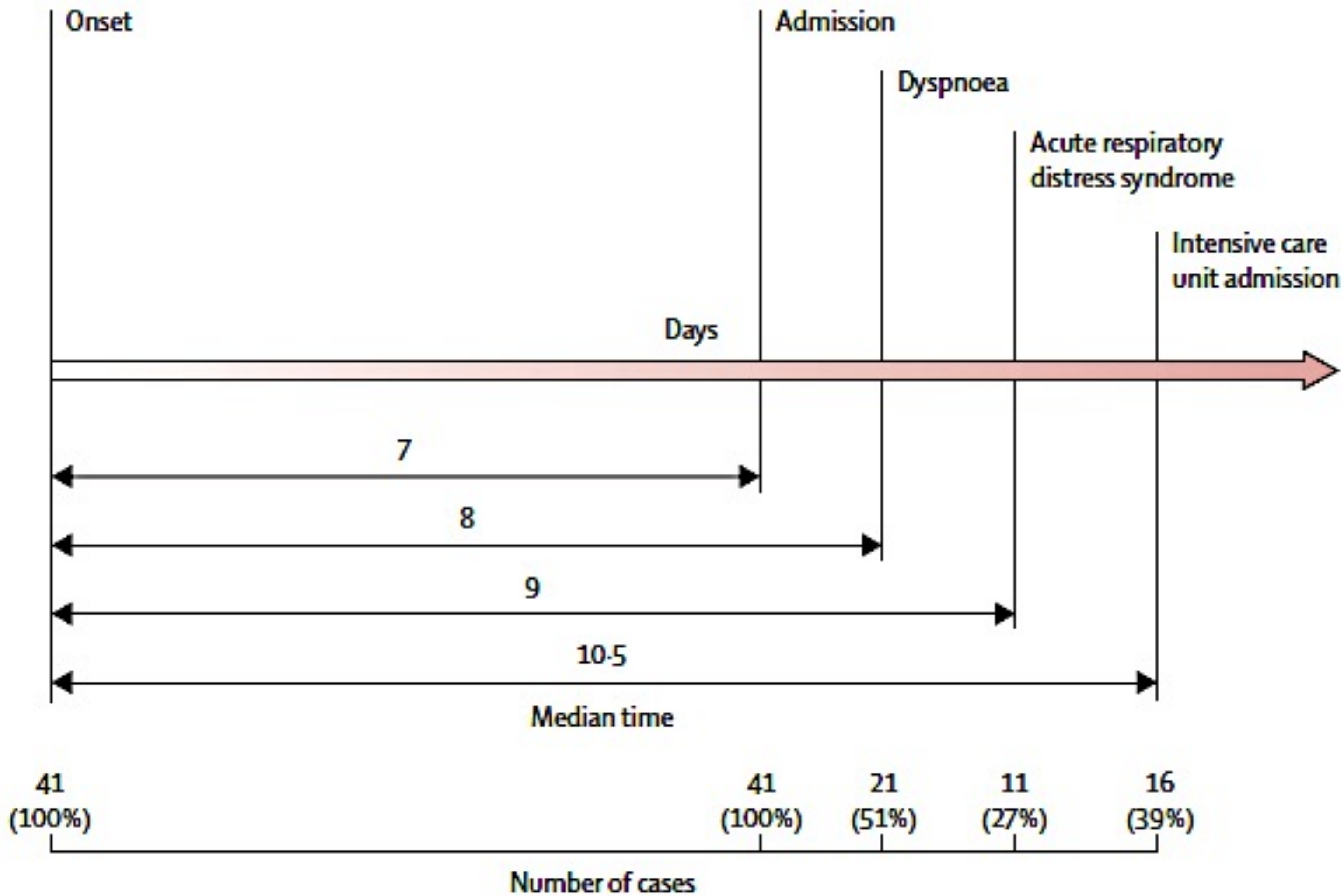
IRA: períodos de incubación

Cumulative percentage of cases developing symptoms



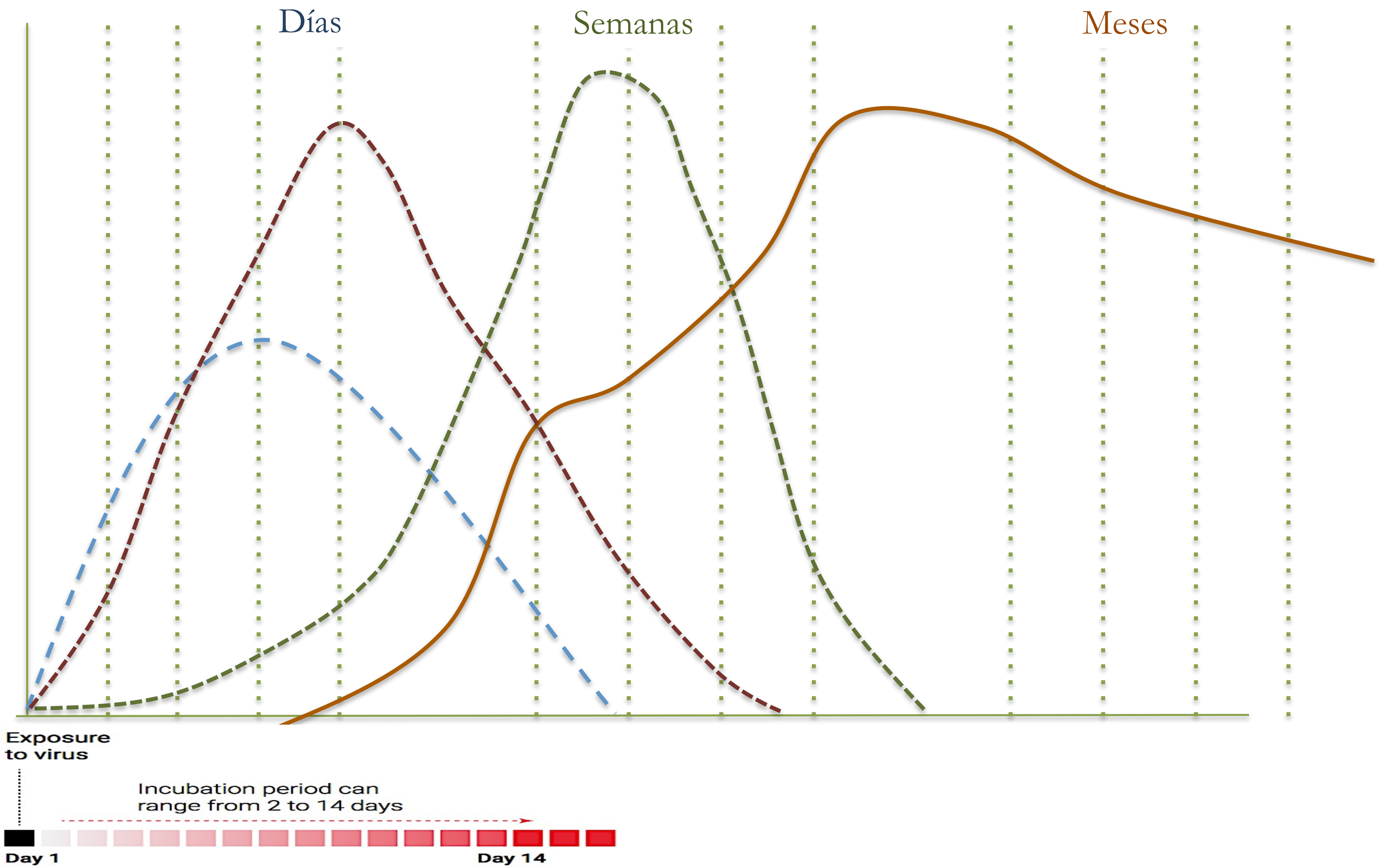
Lancet Infect Dis 2009;9: 291–300

Cronología de eventos desde el inicio de la sintomatología

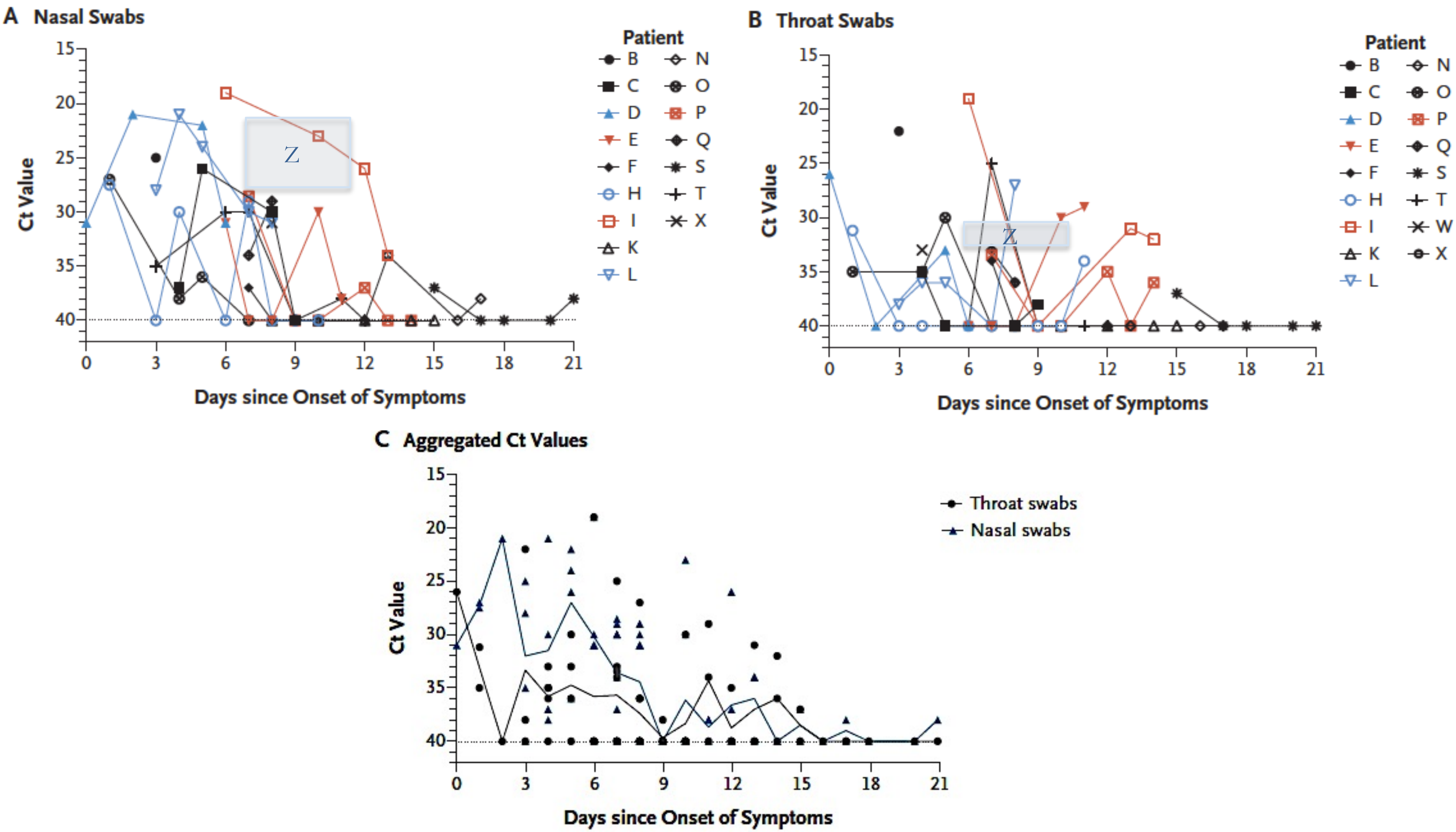


www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Covid-19: dinámica de replicación viral



SARS-CoV-2: dinámica de replicación viral



NEJM February 19, 2020 DOI: 10.1056/NEJMc2001737

Covid-19 y gestación

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Clinical characteristics										
Date of admission	Jan 20	Jan 25	Jan 27	Jan 26	Jan 27	Jan 27	Jan 28	Jan 29	Jan 30	29.88
Age (years)	33	27	40	26	26	26	29	28	34	..
Gestational age on admission	37 weeks, 2 days	38 weeks, 2 day	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	..
Epidemiological history	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)*	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)†	9 (100%)
Other family members affected	No	Yes	Yes	No	No	Yes	No	Yes	No	4 (44%)
Onset to delivery (days)	1	6	4	3	1	4	2	2	7	..
Complications	Influenza	None	Gestational hypertension	Pre-eclampsia	Fetal distress	None	PROM	Fetal distress	PROM	..
Signs and symptoms										
Fever on admission	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7 (78%)
Post-partum fever	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	6 (67%)
Myalgia	No	Yes	No	No	Yes	Yes	No	No	No	3 (33%)
Malaise	No	No	No	No	Yes	Yes	No	No	No	2 (22%)
Rigor	No	No	No	No	No	No	No	No	No	0
Cough	Yes	Yes	Yes	No	No	Yes	No	No	No	4 (44%)
Dyspnoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Sore throat	No	No	No	No	No	Yes	Yes	No	No	2 (22%)
Diarrhoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Chest pain	No	No	No	No	No	No	No	No	No	0

www.thelancet.com Published online February 12, 2020 https://doi.org/10.1016/S0140-6736(20)30360-3

Covid-19 y gestación/laboratorio clínico

Laboratory characteristics										
White blood cell count ($\times 10^9$ cells per L)	6·15	5·07	8·78	7·63	9·34	5·57	10·61	9·96	7·08	..
Low or normal leukocyte count ($<9·5\times10^9$ cells per L)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	7 (78%)
Lymphocyte count ($\times 10^9$ cells per L)	1·59	0·56	0·46	2·83	0·69	0·66	0·87	1·53	1·47	..
Lymphopenia ($<10^9$ cells per L)	No	Yes	Yes	No	Yes	Yes	Yes	No	No	5 (56%)
C-reactive protein concentration (mg/L)	20·3	14·4	33·4	3·3	28·2	18·2	NA	6·2	24·9	..
Elevated C-reactive protein (>10 mg/L)	Yes	Yes	Yes	No	Yes	Yes	NA	No	Yes	6 (75%)‡
Elevated ALT (>45 U/L) or AST (>35 U/L)	Yes	No	Yes	Yes	No	No	No	No	No	3 (33%)
ALT (U/L)	2093	9	62	54	18	14	6	16	12	..
AST (U/L)	1263	24	71	67	24	23	15	22	21	..
Confirmatory test done (SARS-CoV-2 quantitative RT-PCR)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (100%)

www.thelancet.com Published online February 12, 2020 https://doi.org/10.1016/S0140-6736(20)30360-3

Covid-19 y gestación/laboratorio clínico

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
(Continued from previous page)										
CT evidence of pneumonia										
Typical signs of viral infection	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8 (89%)
Delivery										
Method of delivery	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	C-section	..
Indication for C-section	Severely elevated ALT or AST; COVID-19 pneumonia	Mature; COVID-19 pneumonia	History of C-section (×2); COVID-19 pneumonia	Pre-eclampsia; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	History of stillbirth (×2); COVID-19 pneumonia	PROM; COVID-19 pneumonia	Fetal distress; COVID-19 pneumonia	PROM; COVID-19 pneumonia	..
Treatment after delivery										
Oxygen support (nasal cannula)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	→ 9 (100%)
Antiviral therapy	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	→ 6 (67%)
Antibiotic therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	→ 9 (100%)
Use of corticosteroid	No	No	No	No	No	No	No	No	No	0

PROM=premature rupture of membrane. NA=not applicable. ALT=alanine transaminase. AST=aspartate transaminase. COVID-19=2019 novel coronavirus disease. C-section=caesarean section. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Exposure to Hankou, the area in Wuhan where the epidemic was first detected. †A university where the patient works, and a gathering of people. ‡Data missing for one patient.

www.thelancet.com Published online February 12, 2020 https://doi.org/10.1016/S0140-6736(20)30360-3

Covid-19 y gestación/recién nacidos

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Gestational age at delivery	37 weeks, 2 days	38 weeks, 3 days	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	..
Birthweight (g)	2870	3730	3820	1880	2970	3040	2460	2800	3530	..
Low birthweight (<2500 g)	No	No	No	Yes	No	No	Yes	No	No	2 (22%)
Premature delivery	No	No	Yes	Yes	No	Yes	Yes	No	No	4 (44%)
Apgar score (1 min, 5 min)	8, 9	9, 10	9, 10	8, 9	9, 10	9, 10	9, 10	9, 10	8, 10	..
Severe neonatal asphyxia	No	No	No	No	No	No	No	No	No	0
Neonatal death	No	No	No	No	No	No	No	No	No	0
Fetal death or stillbirth	No	No	No	No	No	No	No	No	No	0

www.thelancet.com Published online February 12, 2020 https://doi.org/10.1016/S0140-6736(20)30360-3

Resumen de síntomas en seis pacientes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 7
Relationship	Mother of patient 3	Father of patient 3	Daughter of patients 1 and 2	Son-in-law of patients 1 and 2	Grandson of patients 1 and 2	Mother of patient 4 in Shenzhen
Age (years)	65	66	37	36	10	63
Sex	Female	Male	Female	Male	Male	Female
Occupation	Retired	Retired	Office worker	Architect	Student	Retired
Chronic medical illness	Hypertension; benign intracranial tumour treated by gamma knife	Hypertension	None	Chronic sinusitis	None	Diabetes
Interval between symptom onset and arrival at Wuhan (days)	5 (hospital exposure)	6	4 (hospital exposure)	3	NA	NA
Interval between admission to hospital and symptom onset (days)	7	6	9	10	NA	7
Presenting symptoms and signs	..	..	..	..	..	..
Fever	+	+	+	+	–	+
Cough	+ (dry)	+ (dry)	–	+ (productive)	–	+ (dry)
Generalised weakness	+	+	–	–	–	+
Nasal congestion	–	–	+	–	–	–
Rhinorrhoea	–	–	–	+	–	–
Sneezing	–	–	–	+	–	–
Sore throat	–	–	+	–	–	–
Pleuritic chest pain	–	–	+	–	–	–
Diarrhoea	–	–	+ (3 days, 5–6 times per day)	+ (4 days, 7–8 times per day)	–	–

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

Tratamientos y resultados

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Duration from illness onset to first admission	7·0 (4·0–8·0)	7·0 (4·0–8·0)	7·0 (4·0–8·5)	0·87
Complications				
Acute respiratory distress syndrome	12 (29%)	11 (85%)	1 (4%)	<0·0001
RNAaemia	6 (15%)	2 (15%)	4 (14%)	0·93
Cycle threshold of RNAaemia	35·1 (34·7–35·1)	35·1 (35·1–35·1)	34·8 (34·1–35·4)	0·3545
Acute cardiac injury*	5 (12%)	4 (31%)	1 (4%)	0·017
Acute kidney injury	3 (7%)	3 (23%)	0	0·027
Secondary infection	4 (10%)	4 (31%)	0	0·0014
Shock	3 (7%)	3 (23%)	0	0·027
Treatment				
Antiviral therapy	38 (93%)	12 (92%)	26 (93%)	0·46
Antibiotic therapy	41 (100%)	13 (100%)	28 (100%)	NA
Use of corticosteroid	9 (22%)	6 (46%)	3 (11%)	0·013
Continuous renal replacement therapy	3 (7%)	3 (23%)	0	0·027

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Tratamientos y resultados

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Duration from illness onset to first admission	7·0 (4·0–8·0)	7·0 (4·0–8·0)	7·0 (4·0–8·5)	0·87
Oxygen support	..	..	..	<0·0001
Nasal cannula	27 (66%)	1 (8%)	26 (93%)	..
Non-invasive ventilation or high-flow nasal cannula	10 (24%)	8 (62%)	2 (7%)	..
Invasive mechanical ventilation	2 (5%)	2 (15%)	0	..
Invasive mechanical ventilation and ECMO	2 (5%)	2 (15%)	0	..
Prognosis	..	..	..	0·014
Hospitalisation	7 (17%)	1 (8%)	6 (21%)	..
Discharge	28 (68%)	7 (54%)	21 (75%)	..
Death	6 (15%)	5 (38%)	1 (4%)	..

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Patogenia y transmisibilidad

Table 1. Pathogenicity and Transmissibility Characteristics of Recently Emerged Viruses in Relation to Outbreak Containment.

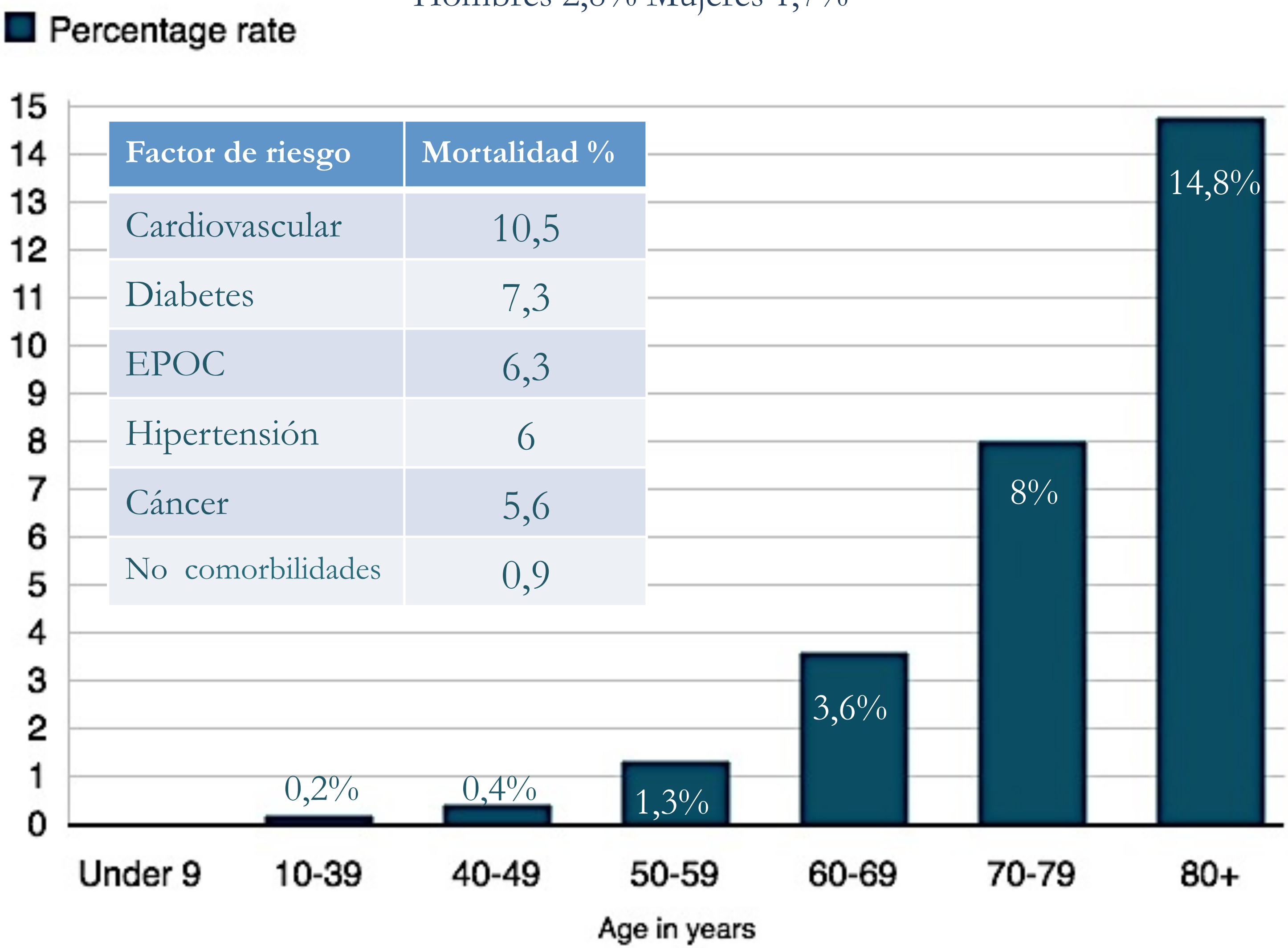
Virus		Case Fatality Rate (%)	Pandemic	Contained	Remarks
2019-nCoV	~2%	Unknown*	Unknown	No, efforts ongoing	
pH1N1		0.02–0.4	Yes	No, postpandemic circulation and establishment in human population ←	
H7N9		39	No	No, eradication efforts in poultry reservoir ongoing	
NL63		Unknown	Unknown	No, endemic in human population	
SARS-CoV		9.5	Yes	Yes, eradicated from intermediate animal reservoir	58% of cases result from nosocomial transmission
MERS-CoV		34.4	No	No, continuous circulation in animal reservoir and zoonotic spillover	70% of cases result from nosocomial transmission
Ebola virus (West Africa)		63	No	Yes	

* Number will most likely continue to change until all infected persons recover. ~2%

The New England Journal of Medicine, Jan 31 2020

Tasa de mortalidad

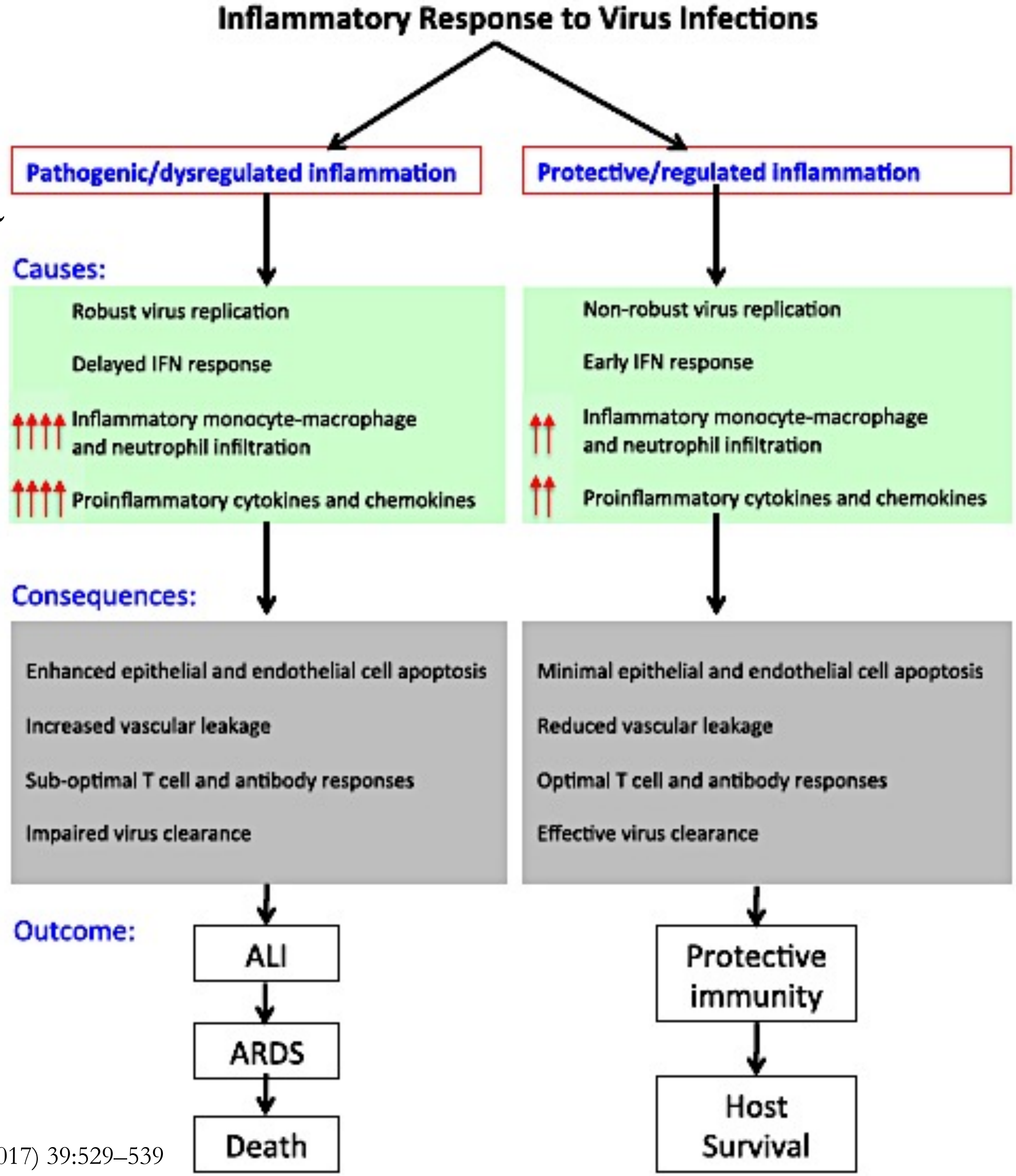
Hombres 2,8% Mujeres 1,7%



Factor de riesgo	Mortalidad %
Cardiovascular	10,5
Diabetes	7,3
EPOC	6,3
Hipertensión	6
Cáncer	5,6
No comorbilidades	0,9

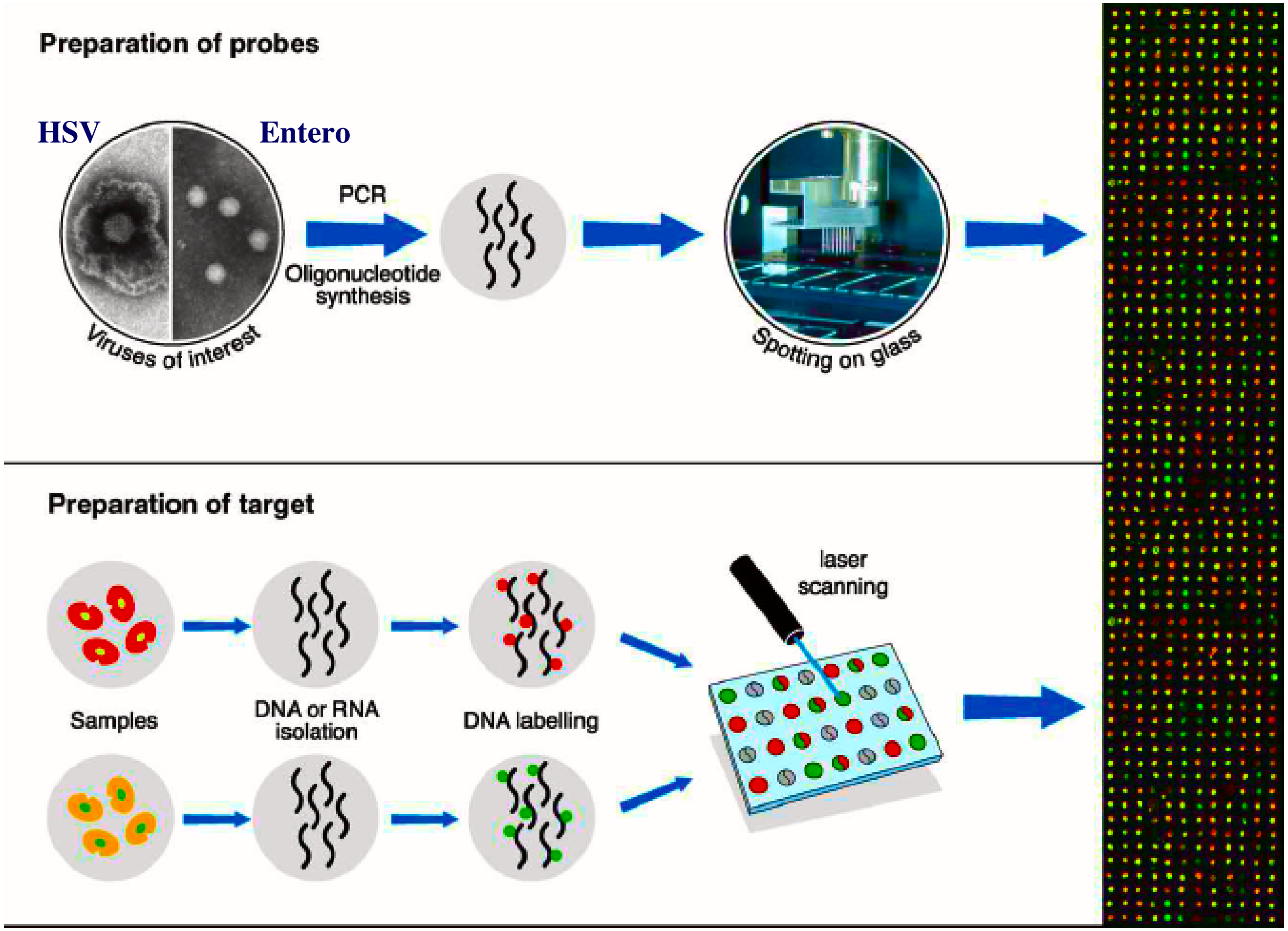
www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30154-9

hCoV: respuesta inmune



Semin Immunopathol (2017) 39:529–539

Patogenómica



Rúbrica de la expresión de genes en I.R.A.

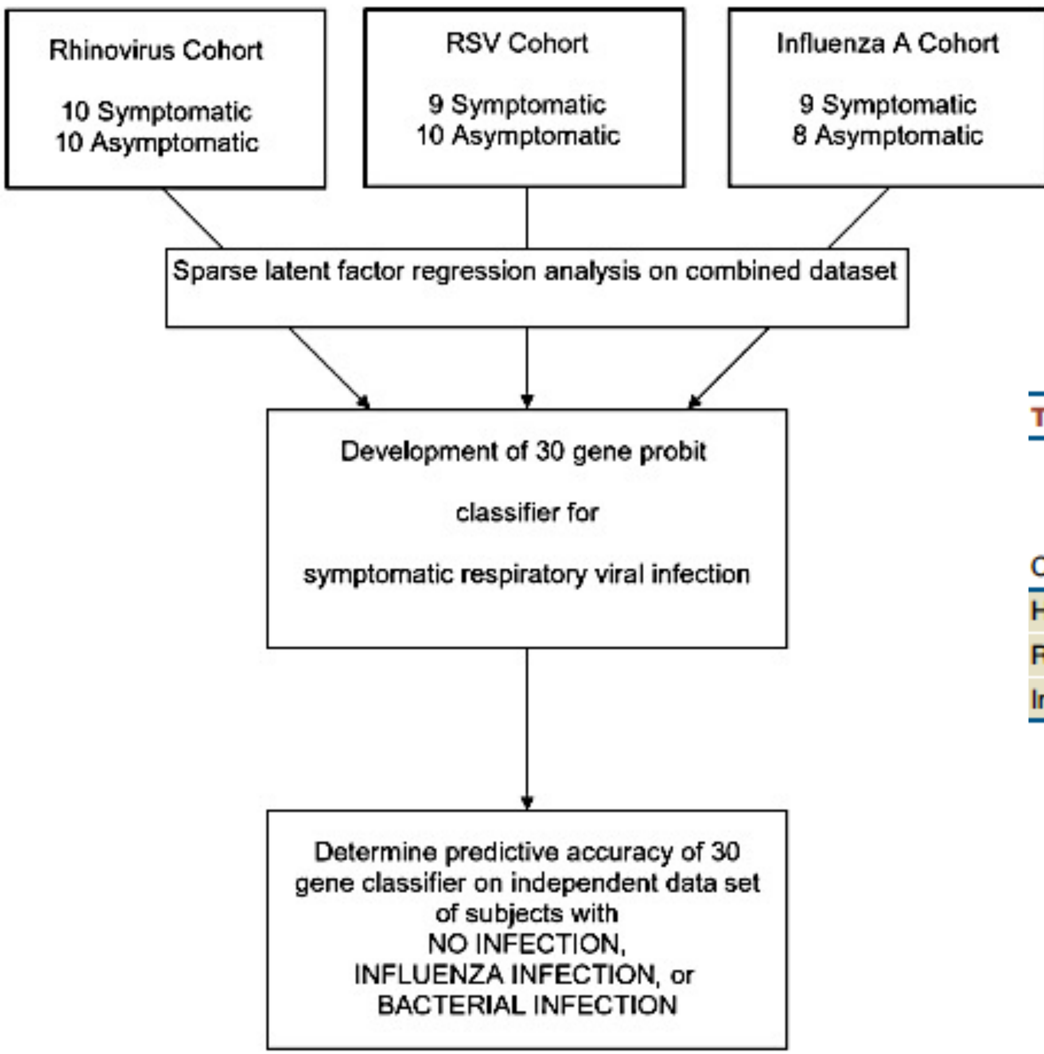
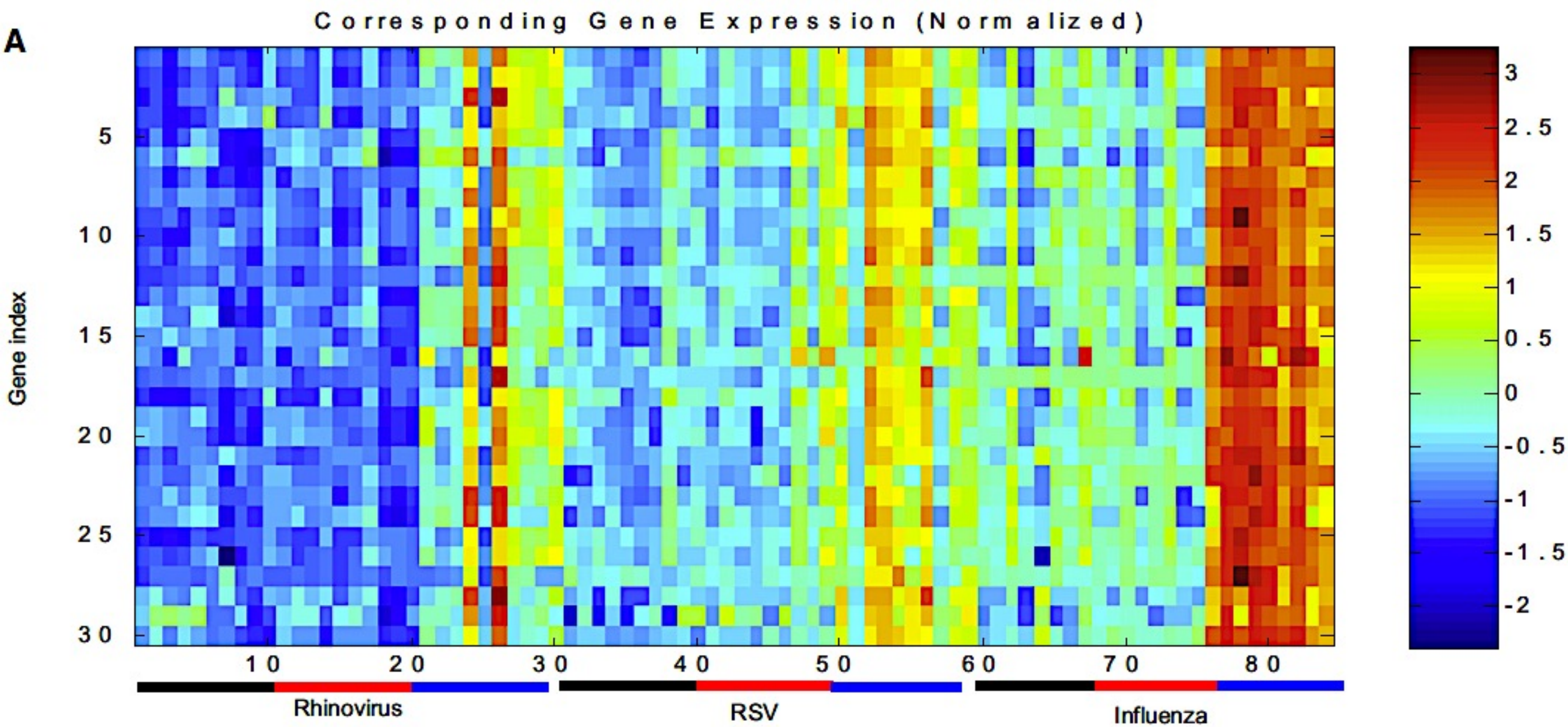


Table 1. Description of Experimental Cohorts

Cohort	Number exposed	Number symptomatic	Median time to peak symptoms (T)	Corresponding time used for asymptomatic subjects
HRV	20	10	72 hr	72 hr
RSV	20	9	141.5 hr	141.5 hr
Influenza	17	9	80 hr	86 hr

Cell Host & Microbe 6, 207–217, September 17, 2009

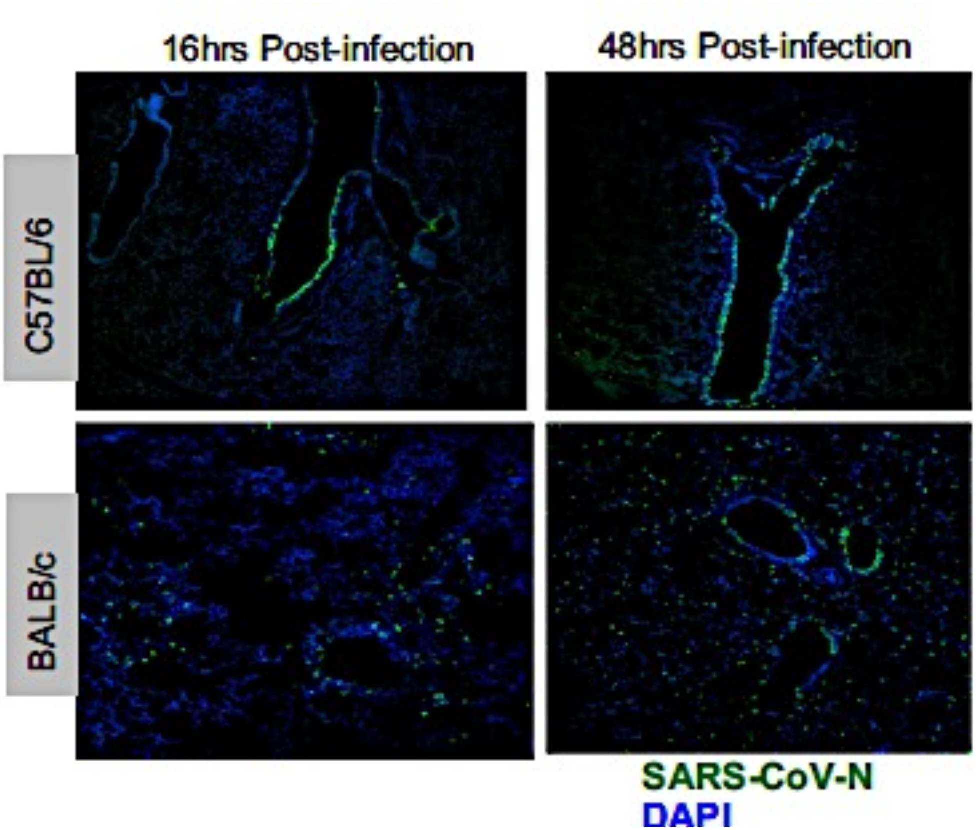
Rúbrica de la expresión de genes en pacientes con IRA sintomática: Rhinovirus/RSV/Influenza



Genes unique to an individual virus factor include the following: **SOCS1** (HRV) and **FCGR1A, GBP1, LAP3, ETV7, and FCGR1B** (RSV).

Cell Host & Microbe 6, 207–217, September 17, 2009

SARS-CoV: antígeno en pulmón



Semin Immunopathol (2017) 39:529–539

SARS-CoV: antígeno en pulmón

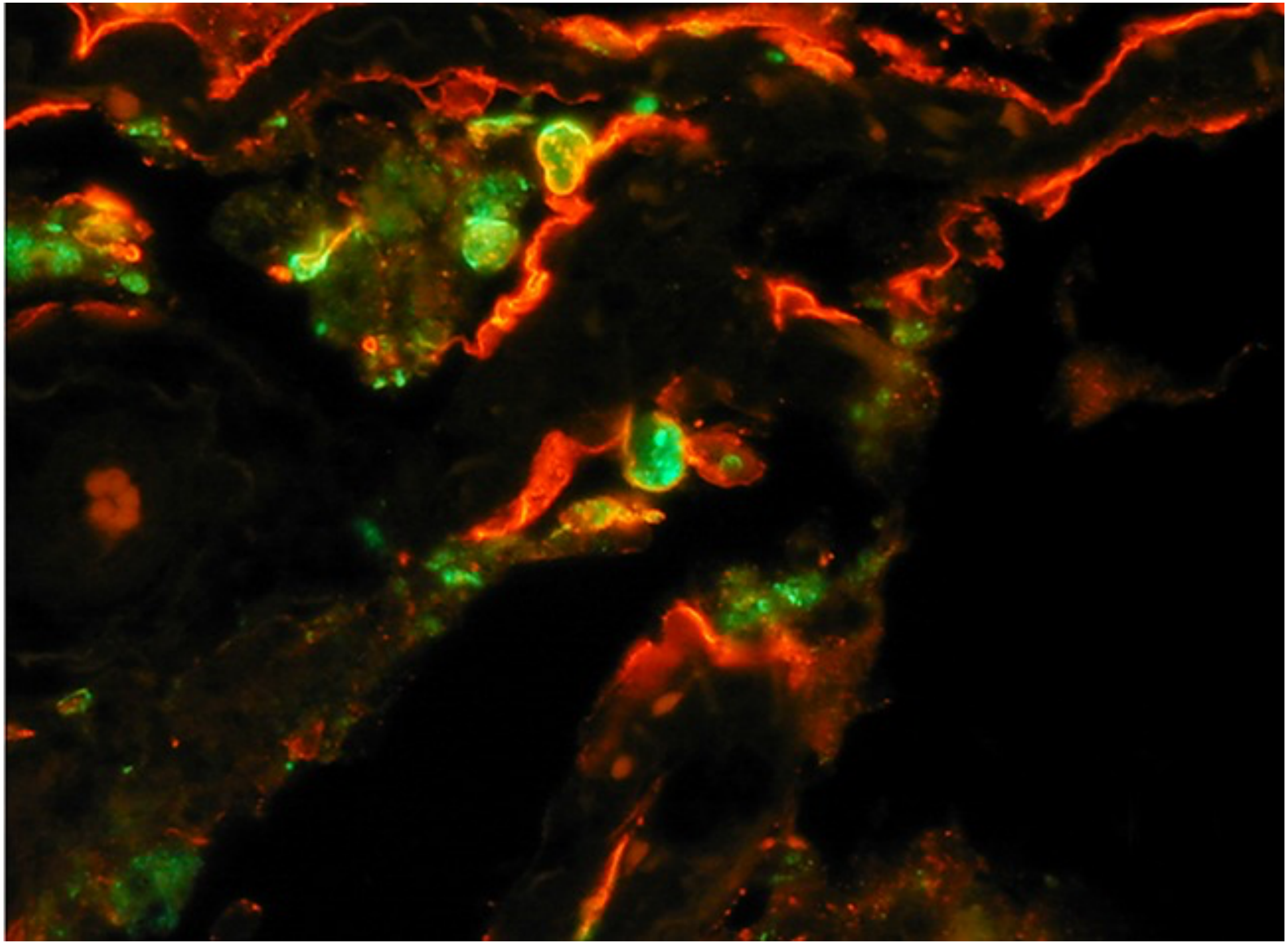
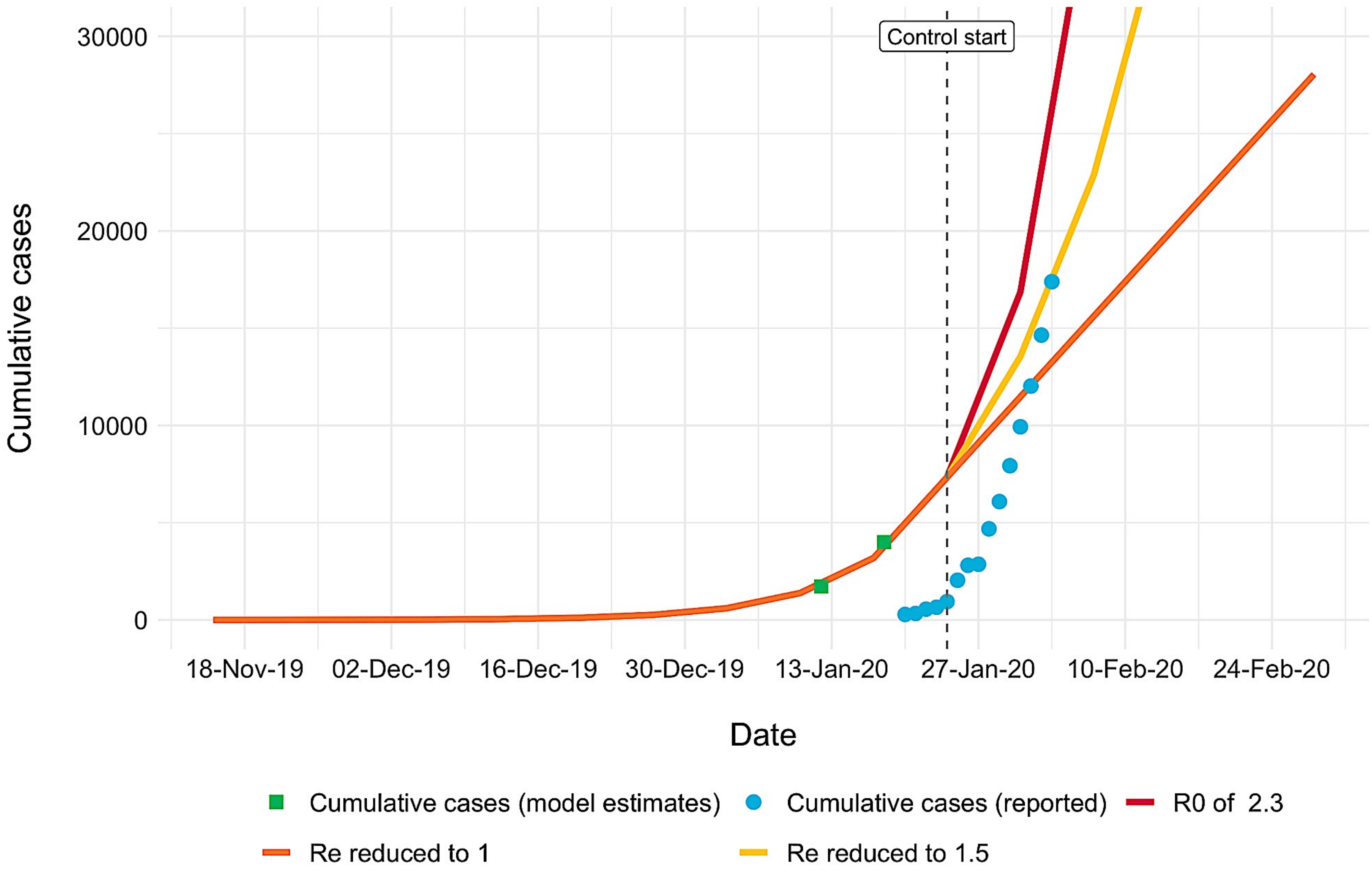


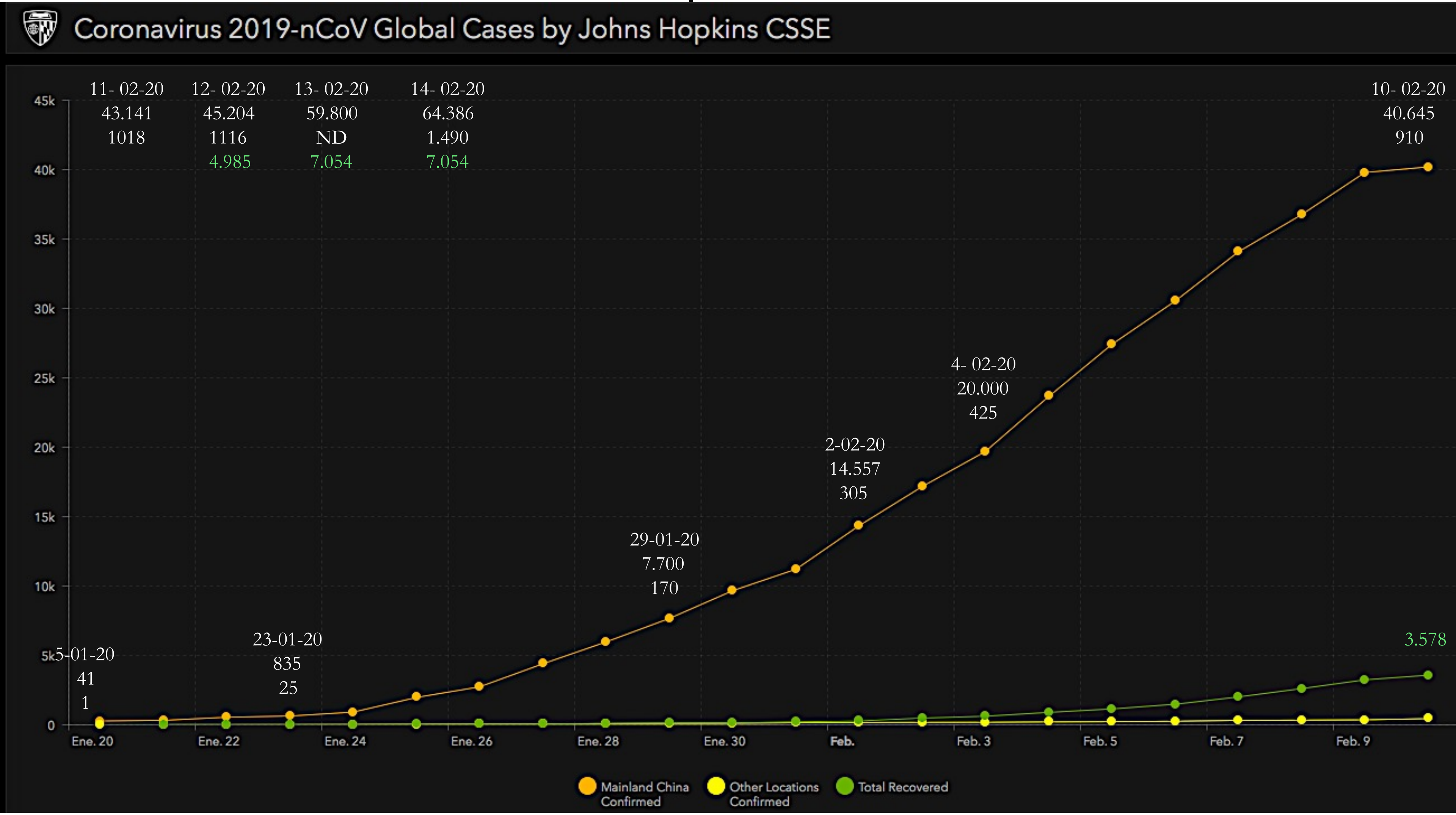
Figure posted on 03.01.2006, 08:15 by The PLOS Medicine Staff

Prospectiva de la epidemia



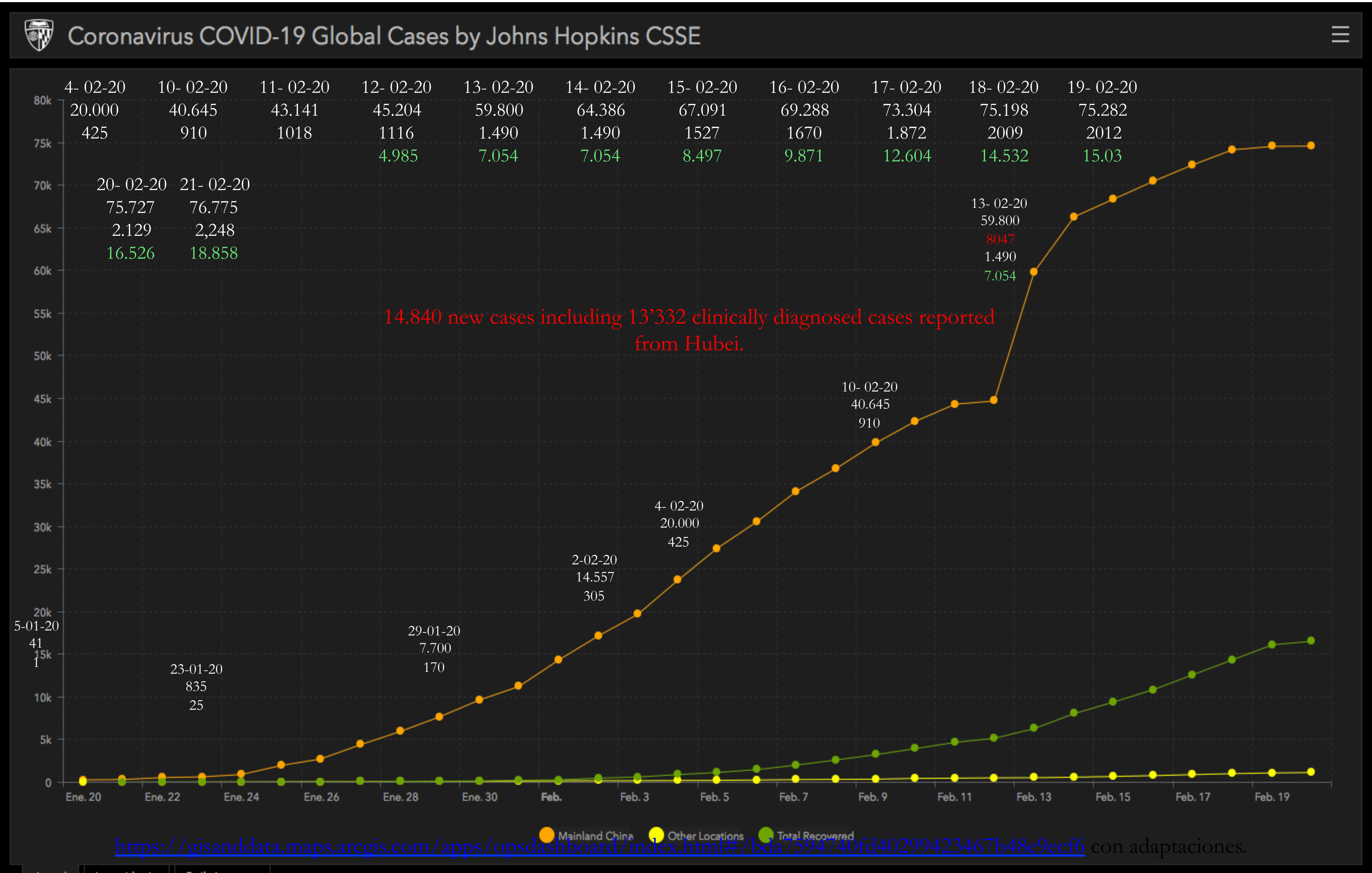
https://figshare.com/articles/nCoV_Reporting_and_Control/11788932

Covid-19: casos confirmados/defunciones/ recuperados



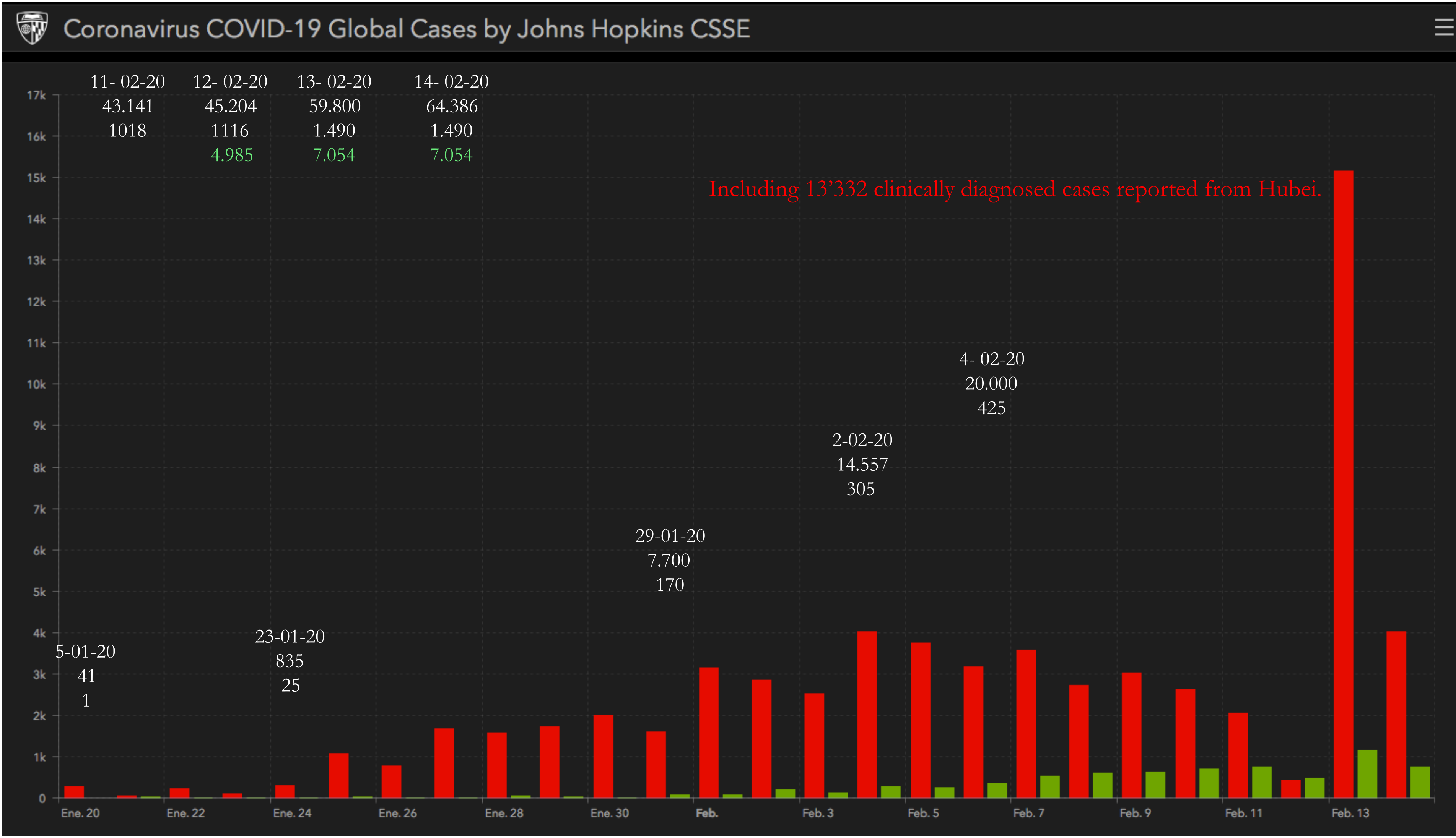
https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

Covid-19: Nuevos casos/recuperados



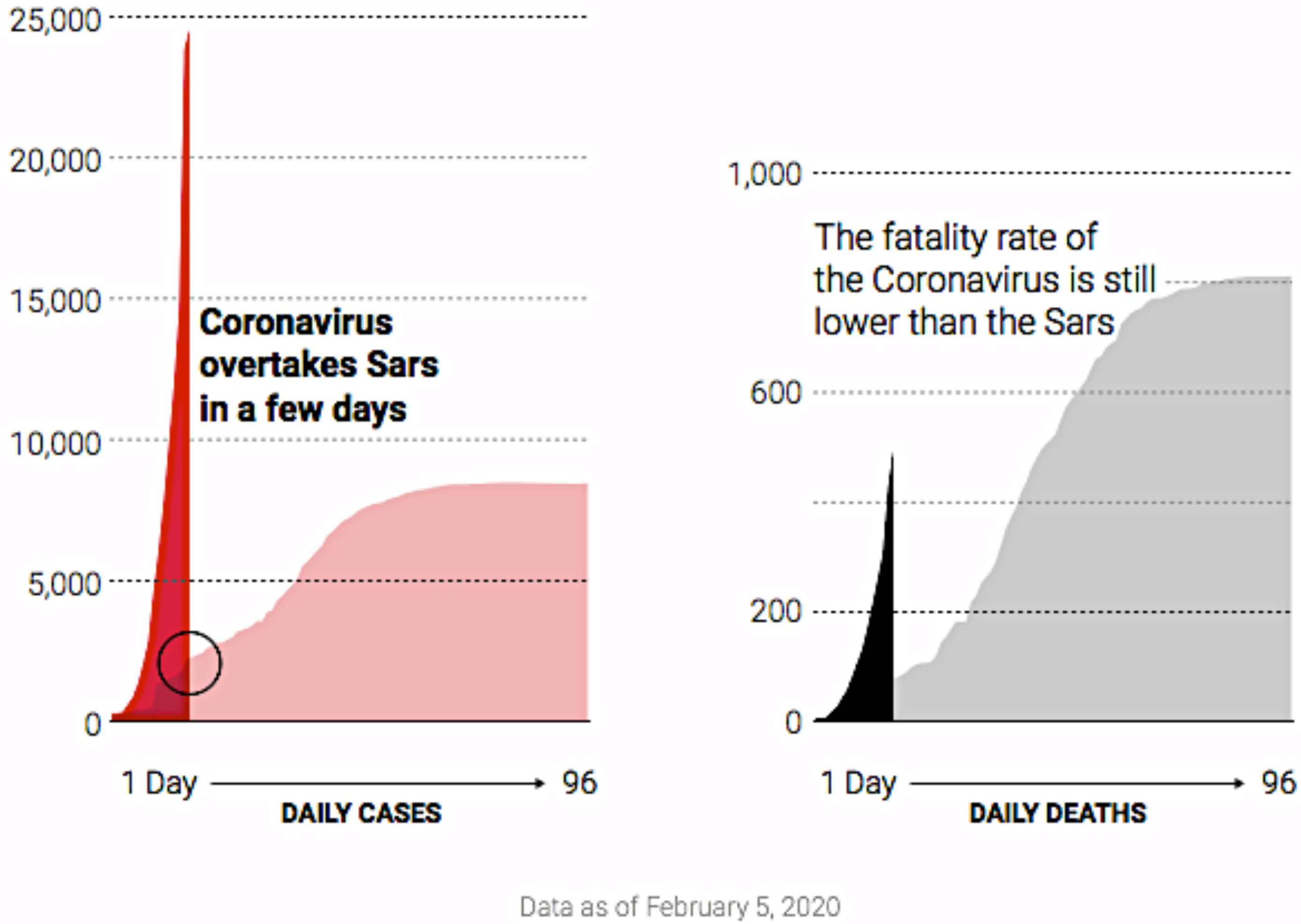
https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 con adaptaciones.

Covid-19: Nuevos casos/recuperados



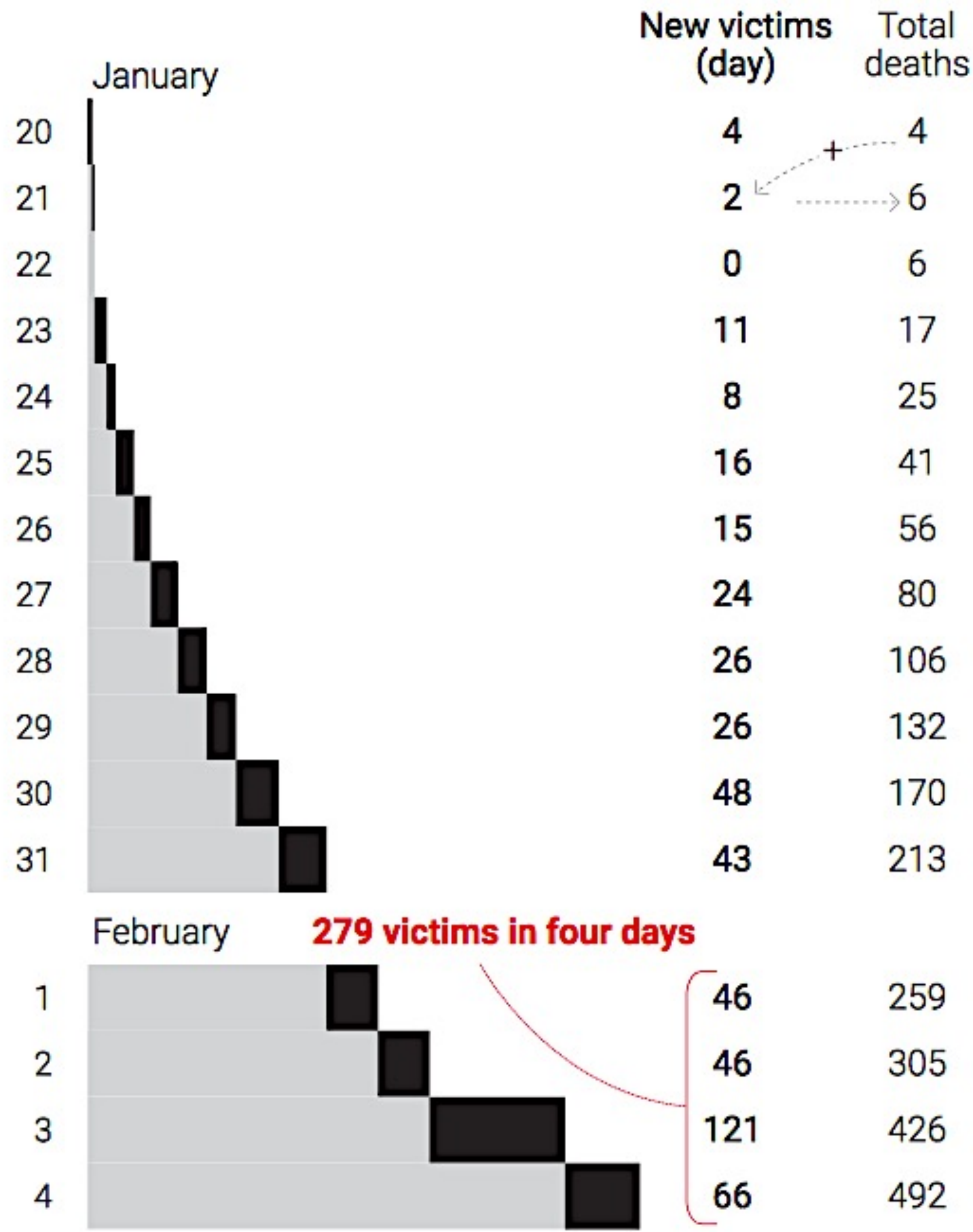
https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. , con adaptaciones.

SARS-CoV vs Covid-19



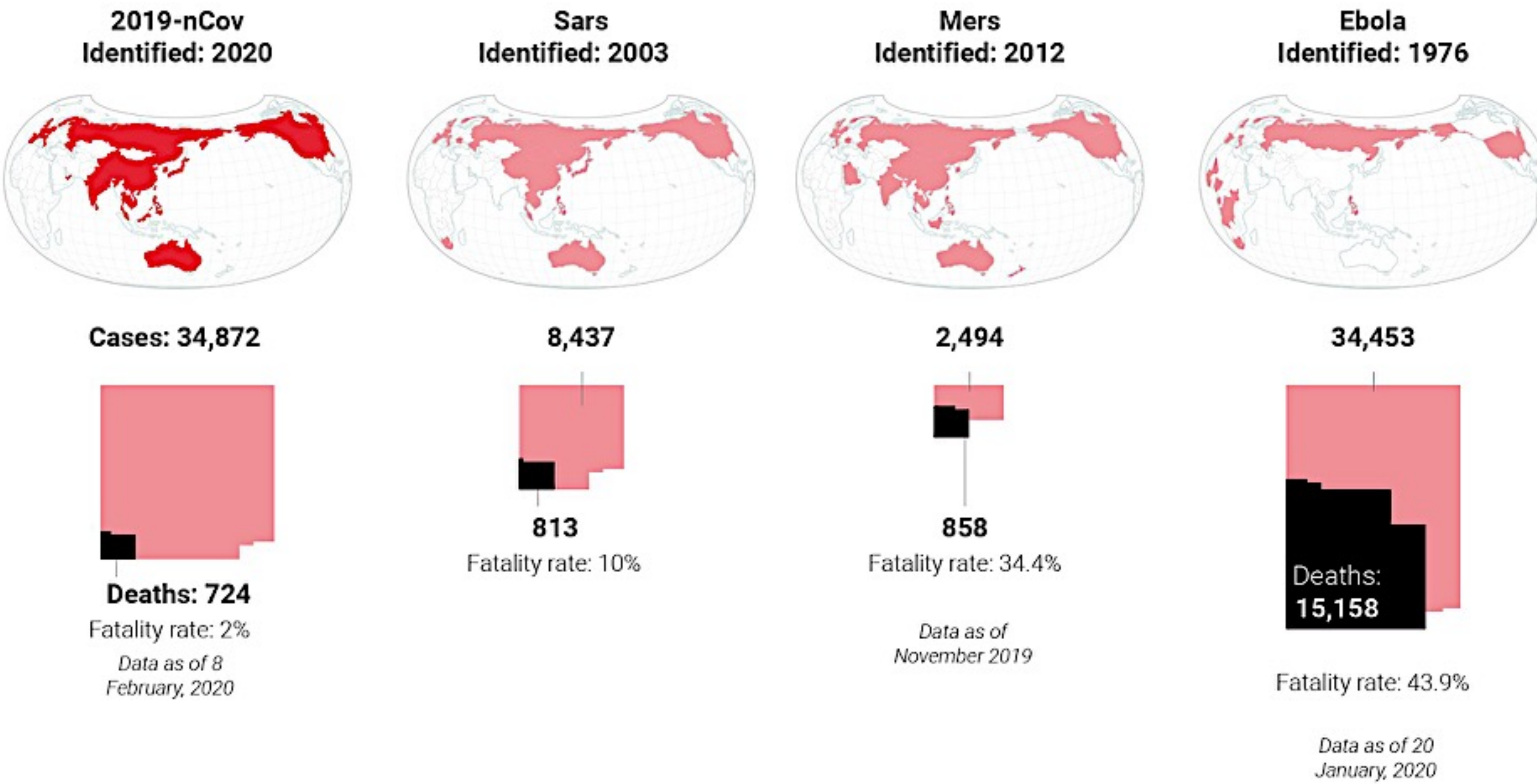
https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

Covid-19
Mortalidad



ml

Covid-19: Mortalidad



https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

SARS-CoV: cambios genéticos durante la epidemia

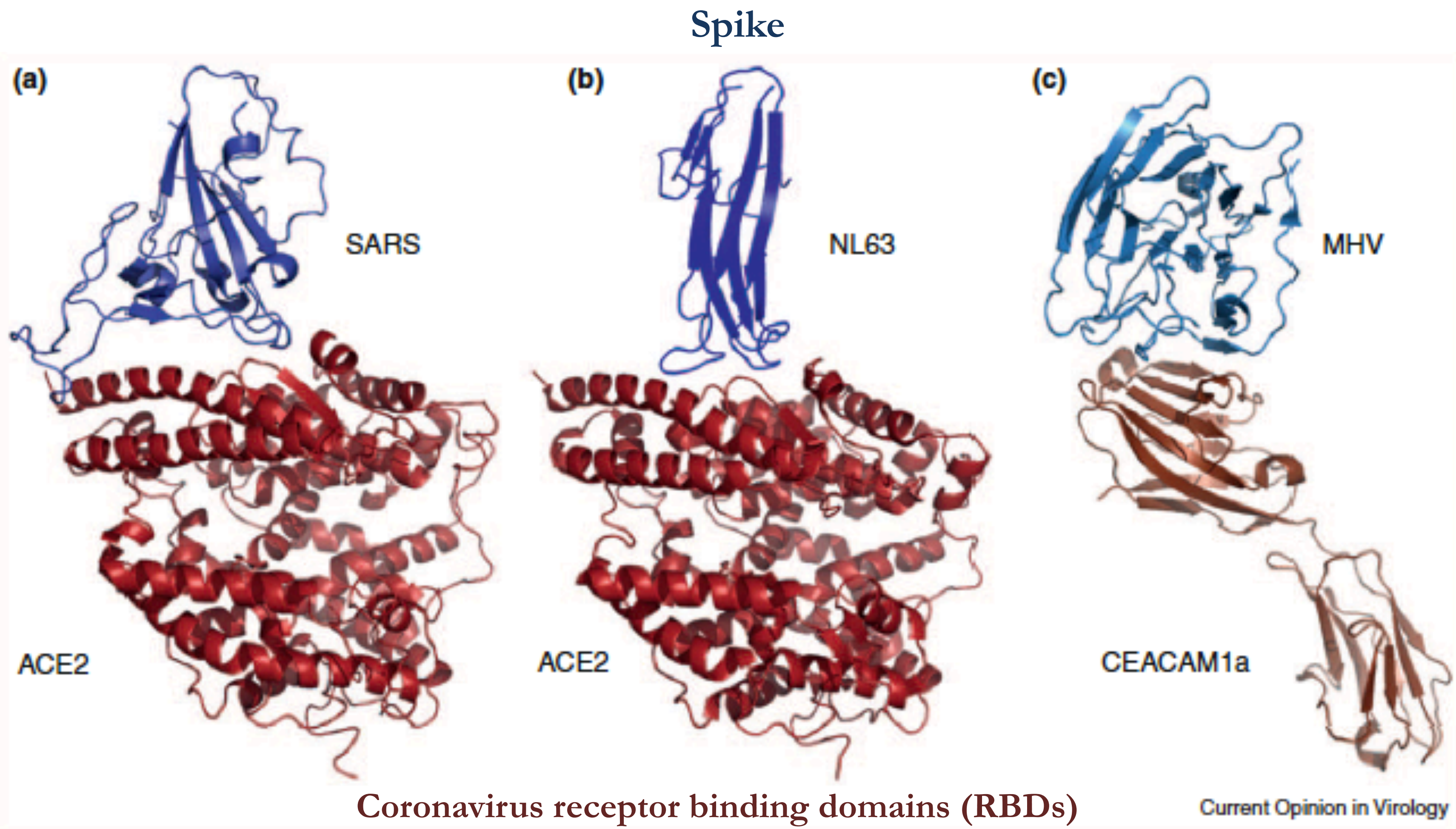
	Gene	ORF 1A												1B		Spike																	M	X1			
Phase	STRAIN	594	1021	1121	1136	1663	2116	2222	2269	2746	2971	3047	3072	1389	2532	77	227	239	244	261	344	360	479	487	607	665	701	743	754	778	849	1163	M4	X1-7	X1-81	X1-93	X1-121
Animal strains	SZ16	S	A	T	L	I	F	Y	S	W	A	A	A	E	K	D	K	L	T	K	R	S	K	S	P	S	L	A	A	D	A	E	S	I	S	Y	G
	HC/SZ/63	A	V	T	P	I	L	C	L	C	A	A	A	E	R	D	K	S	T	T	R	S	R	S	S	S	S	T	V	D	T	E	S	I	S	H	G
Early isolates	ZS-A	A	A	T	P	I	L	Y	L	W	A	A	A	E	K	D	N	L	T	T	R	F	N	T	S	L	S	T	V	D	T	K	G	F	C	H	C
	ZS-B	A	V	T	P	I	L	Y	L	W	A	A	A	E	K	D	N	L	T	T	R	F	N	T	S	L	S	T	V	D	T	K	G	F	C	H	C
	GZ02	A	V	T	P	I	F	Y	L	W	A	A	A	E	K	D	N	L	T	T	R	F	N	T	S	L	S	T	V	D	T	E	G	F	C	H	C
	GD01	A	V	T	P	L	F	Y	L	C	A	A	A	E	R	D	N	L	T	T	R	F	N	T	S	L	S	T	V	D	T	K	G	F	C	H	C
	HSZ	A	V	I	P	L	L	C	L	C	V	A	A	E	R	D	N	S	T	T	K	F	N	T	S	L	S	T	V	D	T	E	G	F	C	H	C
Middle isolates	CUHK-W1	A	V	I	P	L	L	C	L	C	V	A	A	E	R	D	N	S	T	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C
	BJ01	A	V	I	P	L	L	C	L	C	V	A	V	E	R	D	N	S	T	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C
	HZS2-A	A	V	I	P	L	L	C	L	C	V	V	V	E	R	D	N	S	T	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C
	HZSZ-F	A	V	I	P	L	L	C	L	C	V	V	V	E	R	G	N	S	T	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C
	GZ-C	A	V	I	P	L	L	C	L	C	V	A	V	D	R	G	N	S	I	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C
Epidemic	Urbani	A	V	I	P	L	L	C	L	C	V	V	V	D	R	G	N	S	I	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C

Original residue
Civet to Human
Early to middle
Middle to late

Current Opinion in Virology

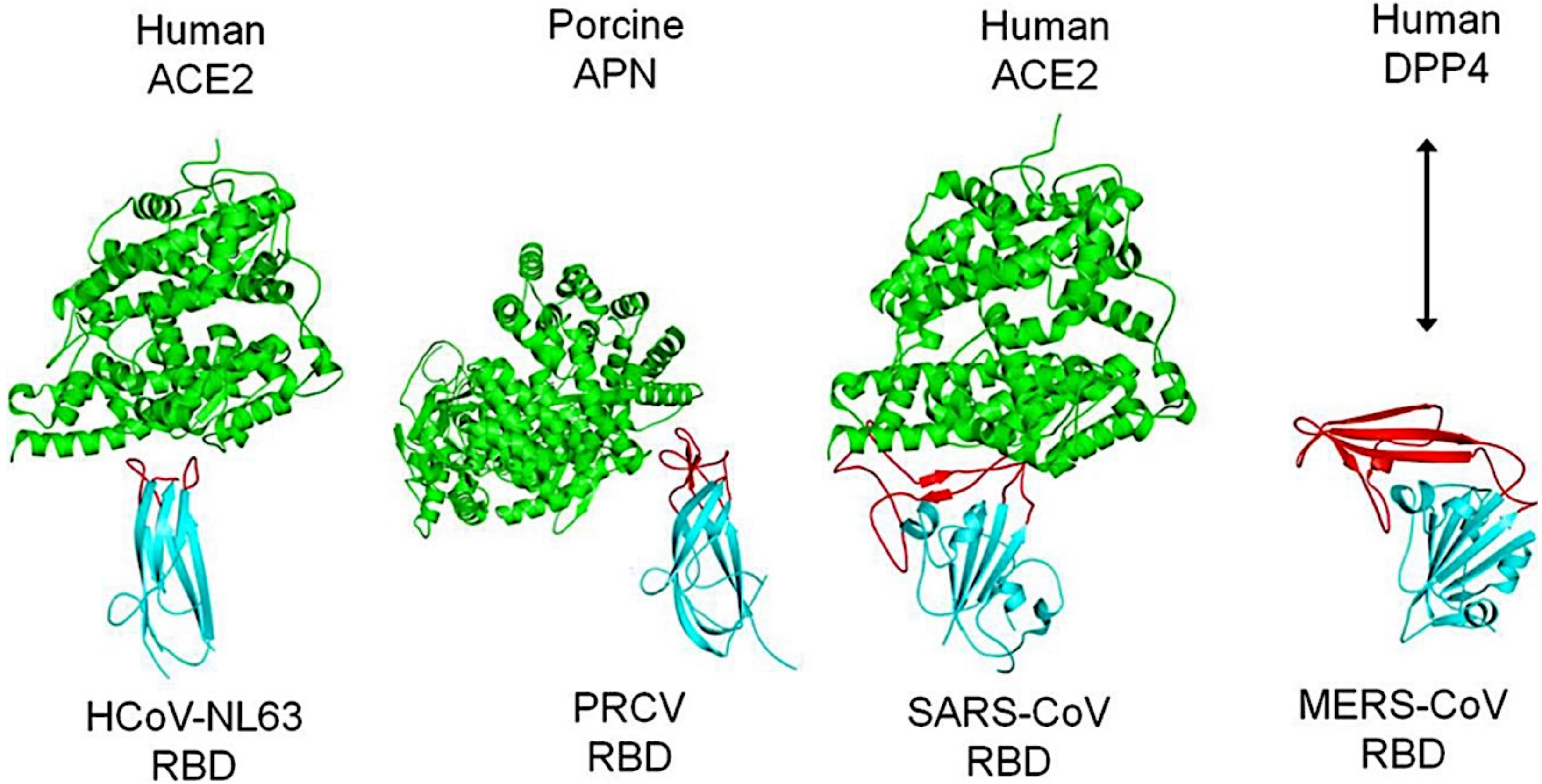
Current Opinion in Virology 2011:1: p. 624-634

hCoV: dominios de unión en los receptores



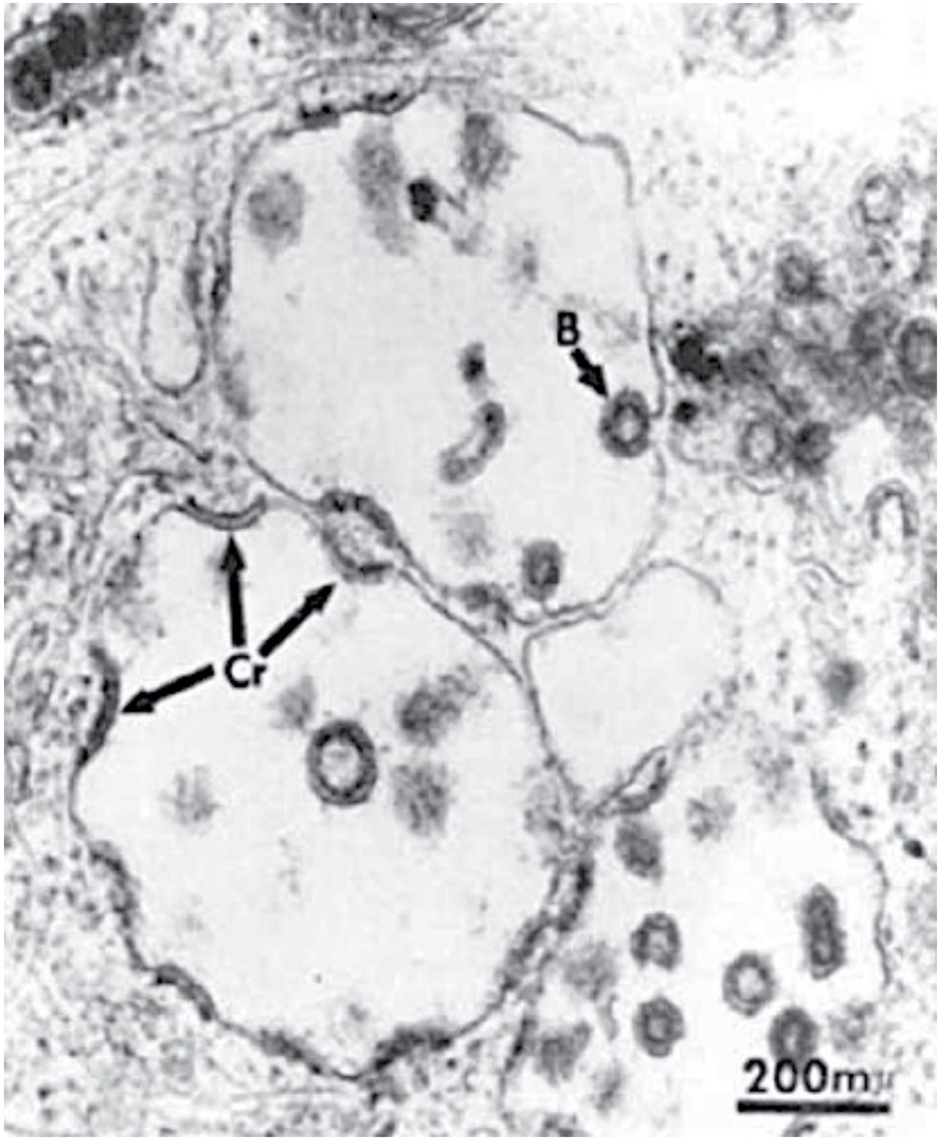
Current Opinion in Virology 2011:1: p. 624-634

Comparasion de los dominios de unión del receptor y los dominios S1 C

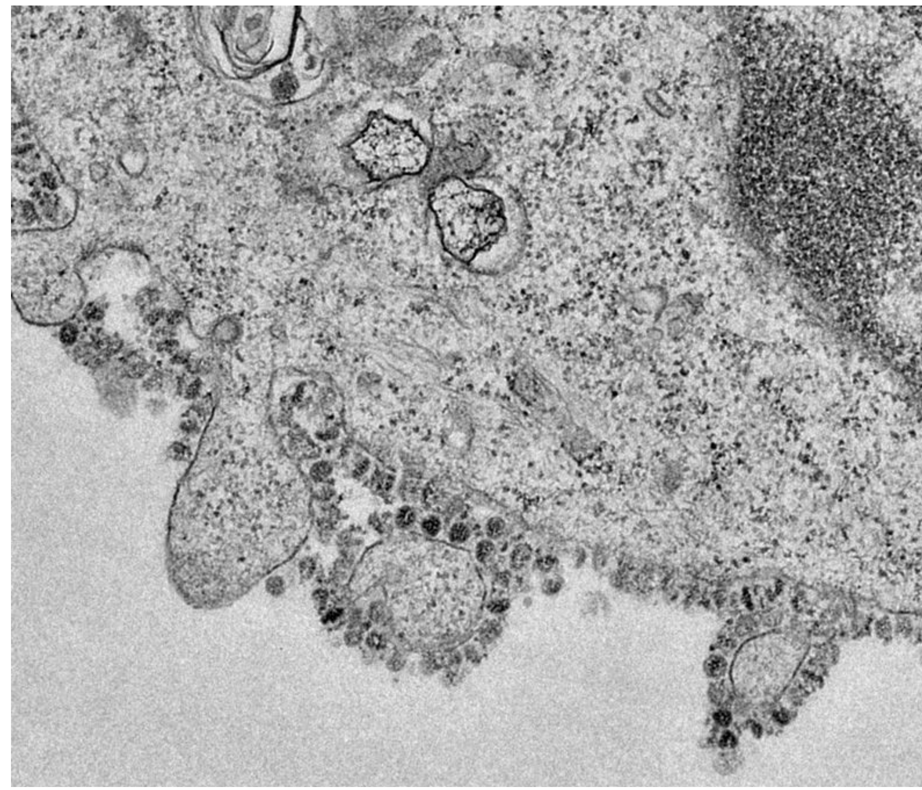


Yaoqing Chen et al. J. Virol. 2013; doi:10.1128/JVI.01756-13

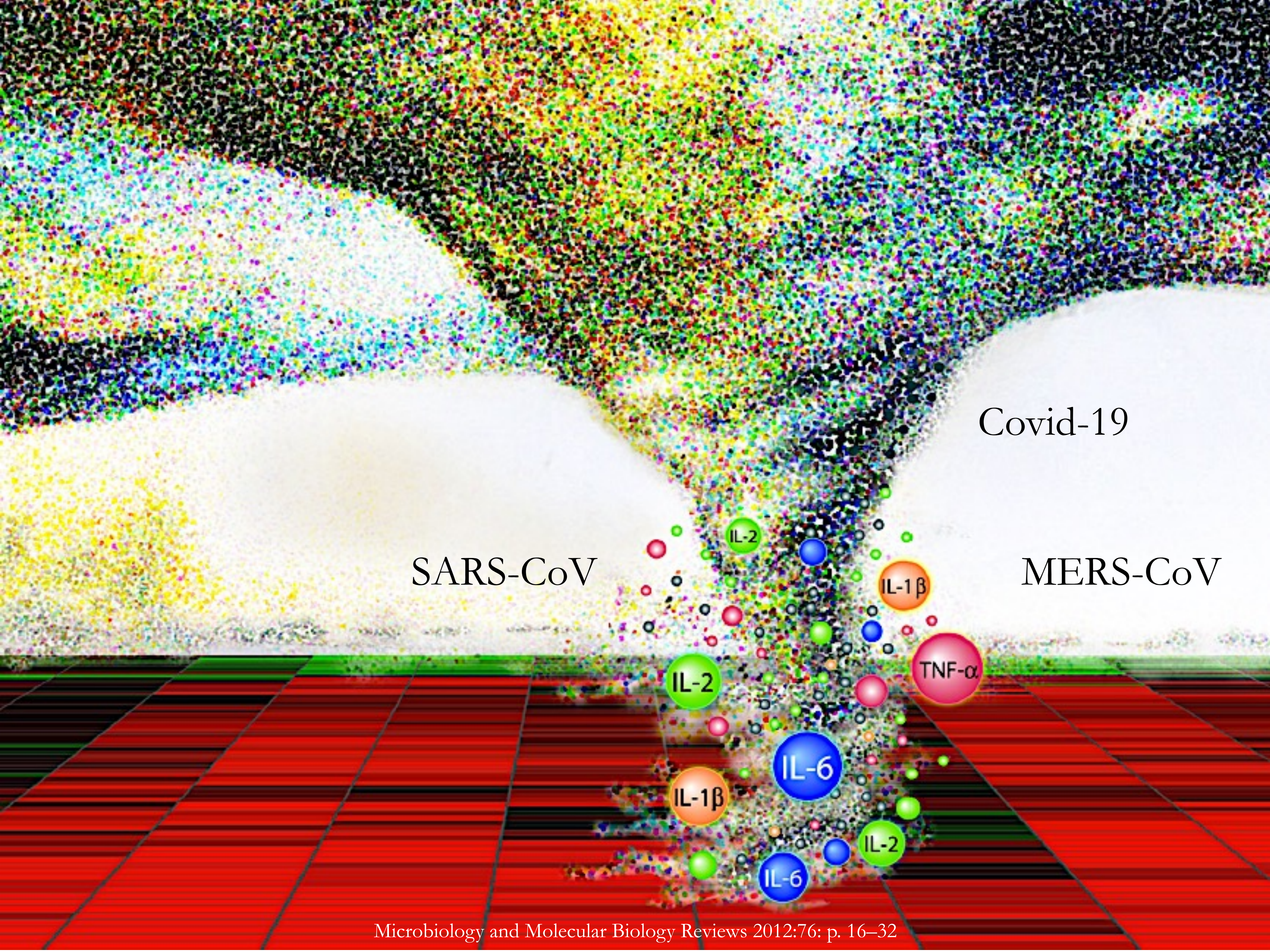
hCoV-229E en células WI38



Covid-19 en células



https://www.nature.com/articles/d41586-020-00154-w



Microbiology and Molecular Biology Reviews 2012:76: p. 16–32

Coronavirus: y tormenta de citoquinas

- Se caracteriza la producción de citoquinas y quimioquinas plasmáticas en la fase aguda de la enfermedad (IL-1B, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, I-L8 [CXCL8), IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, Eotaxina [CCL11], FGF2 básica, GCSF (CSF3), GMCSF (CSF2), IFN, IP10 (CXCL10), MCP1 (CCL2), MIP1A (CCL3), MIP1B (CCL4), PDGFB, RANTES (CCL5), TNF-α, y VEGFA usando una prueba Human Cytokine Standard 27-Plex Assays Bio-Plex 200 system®.
- En el plasma inicial los niveles de IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFN-γ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, y VEGF fueron mayores en pacientes que ingresaron o no a la UCI que en el grupo control (adultos jóvenes). Los niveles plasmáticos de IL-5, IL-12p70, IL-15, Eotaxin, y RANTES fueron similares en adultos jóvenes e infectados por Covid-19.
- Las comparaciones entre pacientes que fueron atendidos en UCI o no mostraron que la IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A y TNFα fueron mayores en pacientes de UCI que en pacientes no-UCI.

Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

Coronavirus: y tormenta de citoquinas

- Los pacientes infectados con Covid-19 tienen niveles elevados de IL-1B, IFN-γ, IP10, y MCP1, lo cual muestra una respuesta celular T-helper-1 (Th-1).
- Los pacientes que requirieron atención en UCI presentaron niveles mayores de GCSF, IP10, MCP1, MIP1A y TNFα que aquellos que no requirieron manejo en UCI, sugiriendo un posible evento de **tormenta de citoquinas** asociado con la gravedad de la enfermedad.
- Sin embargo, la infection por Covid-19 también presentó un incremento en la respuesta de citoquinas T-helper-2 (e.g. IL-4 and IL-10) que suprimen la respuesta inflamatoria en lo cual difiere con la infección por SARS-CoV.
- Esta tormenta de citoquinas desencadenada por la infección por coronavirus puede ser debida a una excesiva repliación viral y a un sistema inflamatorio descontrolado que puede llevar a **neumonitis**, **ARDS**, **falla respiratoria**, **falla orgánica**, **choque**, **infección bacteriana secundaria** y potencialmente la **muerte**.
- Ser equieren otros estudios para caracterizar las respuestas Th1 y Th2 y aclarar la patogénesis.

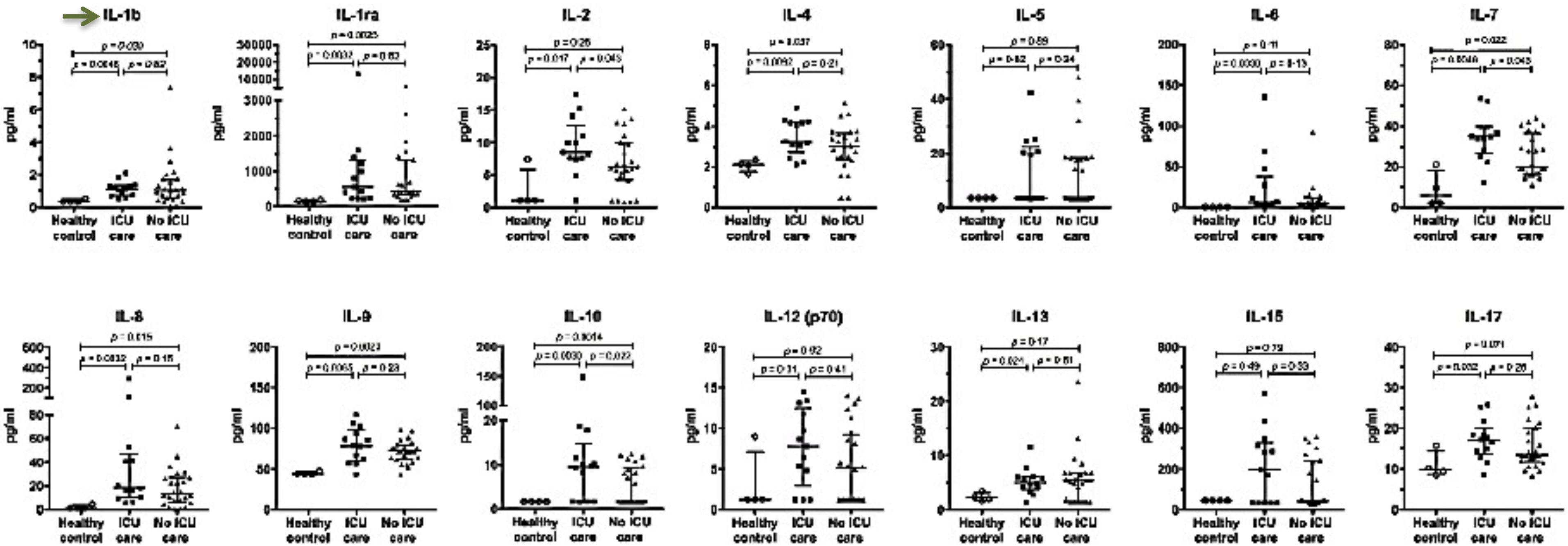
Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

Tormenta de citoquinas y Covid-19

- About a third of the 41 patients needed intensive care, and six of them died. Some of the patients with more serious illnesses suffered from a dangerous immune system overreaction called a cytokine storm, but the researchers said they still did not have a good understanding of how the virus affects the immune system.
- In view of the high amount of cytokines induced by SARS-CoV, MERS-CoV, and 2019-nCoV infections, corticosteroids were used frequently for treatment of patients with severe illness, for possible benefit by reducing inflammatory-induced lung injury. However, current evidence in patients with SARS and MERS suggests that receiving corticosteroids did not have an effect on mortality, but rather delayed viral clearance. Therefore, corticosteroids should not be routinely given systemically, according to WHO interim guidance.
- Further studies are necessary to characterise the Th1 and Th2 responses in 2019-nCoV infection and to elucidate the pathogenesis. Autopsy or biopsy studies would be the key to understand the disease.

Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

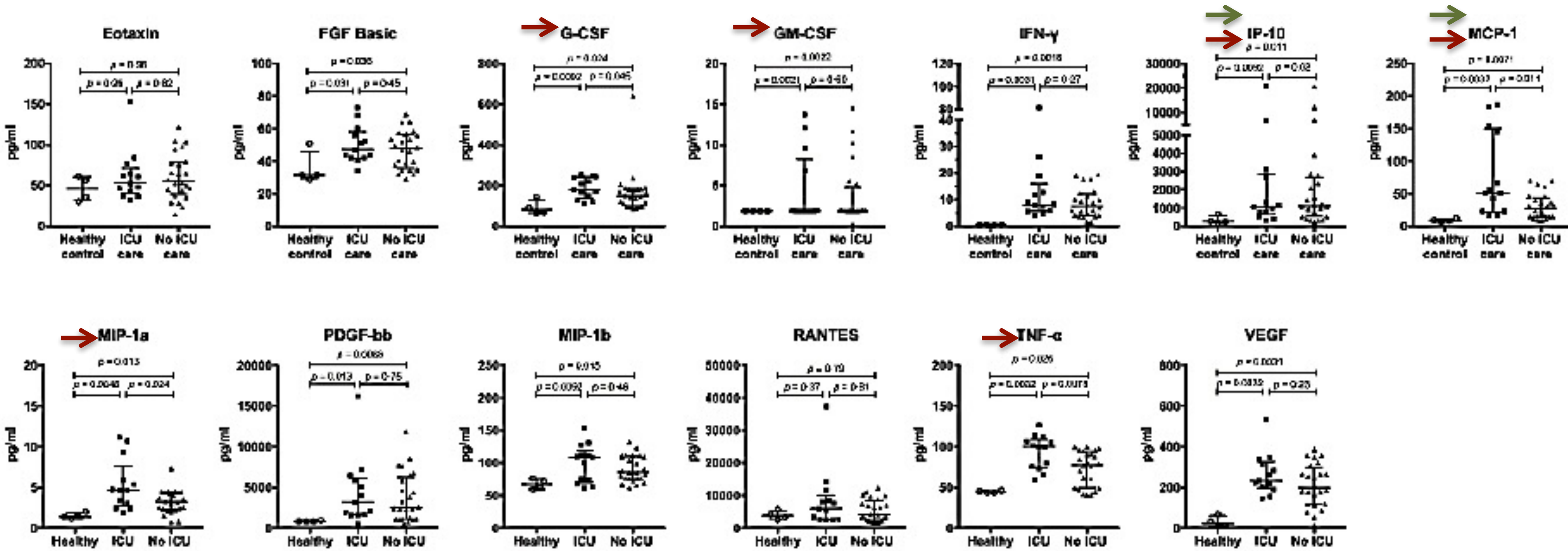
Citoquinas y Covid-19



They noted that patients infected with 2019-nCoV also had high amounts of IL-1B, IFN-γ, IP10, and MCP1, probably leading to activated T-helper-1 (Th-1) cell responses. Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα than did those not requiring I.C.U admission, suggesting that the cytokine storm was associated with disease severity

Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

Citoquinas y Covid-19



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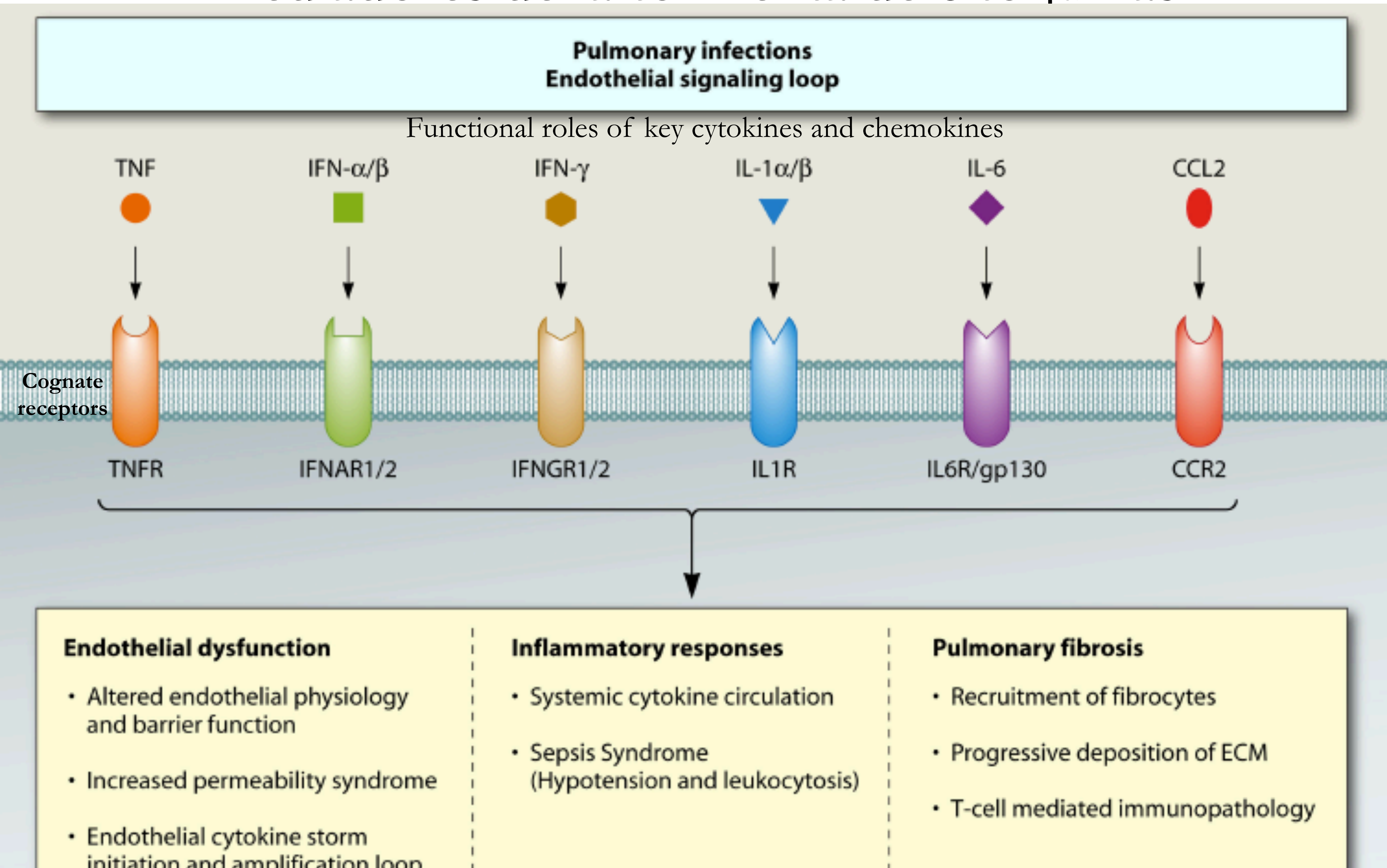
Mediadores de la tormenta de citoquinas



Microbiology and Molecular Biology Reviews 2012:76: p. 16–32

Tormenta de citoquinas y Covid-19

Implications of all the available evidence
2019-nCoV caused clusters of fatal pneumonia with clinical presentation greatly resembling SARS-CoV. Patients infected with 2019-nCoV might develop acute respiratory distress syndrome, have a high likelihood of admission to intensive care, and might die. The cytokine storm could be associated with disease severity. More efforts should be made to know the whole spectrum and pathophysiology of the new disease.

In 41 cases, higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MP1A and TNF α were found.
These data provide the rationale to potentially use CytoSorb®, the first specifically-approved extracorporeal cytokine adsorber in the European Union, in this setting.

Lancet https://doi.org/10.1016/ S0140-6736(20)30185-9

Comparación clínica de 2019-nCoV/MERS/SARS

29-01-20
7.700
170

	2019-nCoV*	MERS-CoV	SARS-CoV
Demographic			
Date	December, 2019	June, 2012	November, 2002
Location	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Age, years (range)	49 (21–76)	56 (14–94)	39·9 (1–91)
Male:female sex ratio	2·7:1	3·3:1	1:1·25
Confirmed cases	835†	2494	8096
Mortality	25† (2·9%)	858 (37%)	744 (10%)
Health-care workers	16‡	9·8%	23·1%
Symptoms			
Fever	40 (98%)	98%	99–100%
Dry cough	31 (76%)	47%	29–75%
Dyspnoea	22 (55%)	72%	40–42%
Diarrhoea	1 (3%)	26%	20–25%
Sore throat	0	21%	13–25%
Ventilatory support	9·8%	80%	14–20%

Data are n, age (range), or n (%) unless otherwise stated. 2019-nCoV=2019 novel coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. *Demographics and symptoms for 2019-nCoV infection are based on data from the first 41 patients reported by Chaolin Huang and colleagues (admitted before Jan 2, 2020).[8] Case numbers and mortalities are updated up to Jan 21, 2020) as disclosed by the Chinese Health Commission. †Data as of Jan 23, 2020. ‡Data as of Jan 21, 2020.[9]

www.thelancet.com Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30185-9

Paradigma molecular de las infecciones virales

Contagio

Tiempo

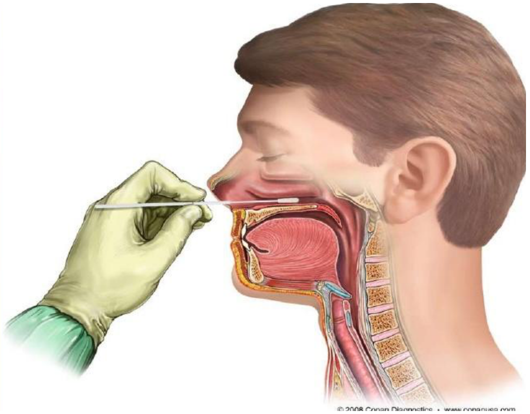
Aspecto	Área de estudio
Interactoma	Interacciones entre proteínas celulares y virales
Proteonoma	Proteinas en células, tejidos u organismo
Microbioma	Genomas de la comunidad de microorganismos que habitan en sistemas
Inmunoma	Perfil de respuesta inmune en el curso de la infección (IL, Citoquinas, IFN) o ARNm de estos.
Metaboloma	Colección de todos los metabolitos en células, tejidos u organismo
Metatranscriptoma	Todos los ARN codificados por un grupo de microorganismos en especímenes complejos
Transcriptoma	ARNm en células, tejidos u organismo ARNm, ARNr, ARNt, ARNnc
Epigenoma	Estructura del genoma, uniones a proteinas o ARN, estructuras alternativas de ADN, y modificaciones químicas del ADN
Genoma	Viral y del hospedero: estructura, función, evolución y mapeo.

Infección respiratoria baja: diagnóstico

- Métodos indirectos.
  - Serología (no es de utilidad clínica en I.R.A). Su única aplicación es epidemiológica.
- Métodos directos.

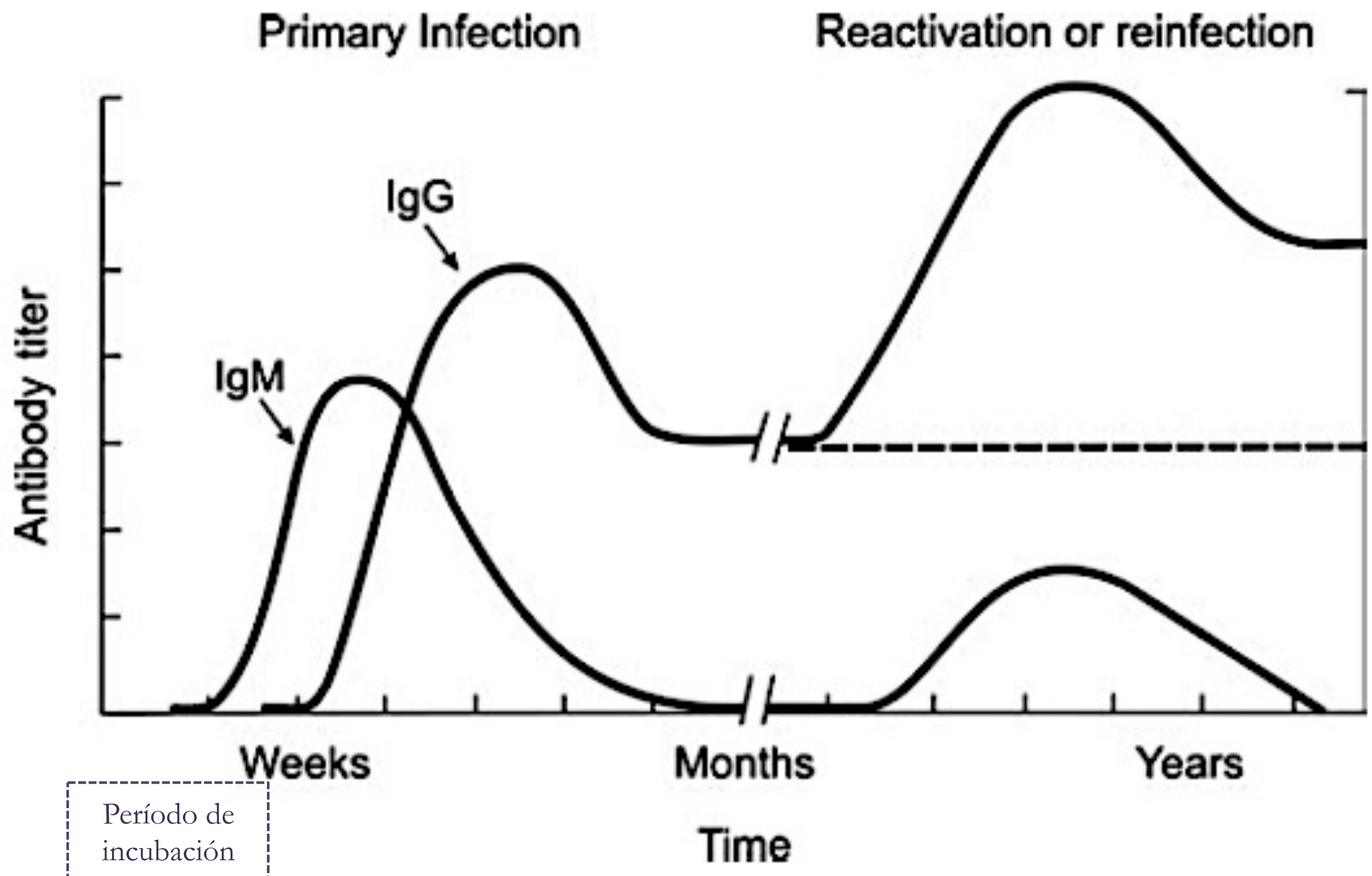
Toma de muestra nasofaríngea (células descamativas)

  - Aislamiento viral en cultivos celulares.
  - Detección de antígenos virales.
  - Biología molecular: detección de genoma viral.



https://www.youtube.com/watchv=ITwGb_NJY0M
https://vimeo.com/7697631

Serología en el diagnóstico viral



Período de incubación

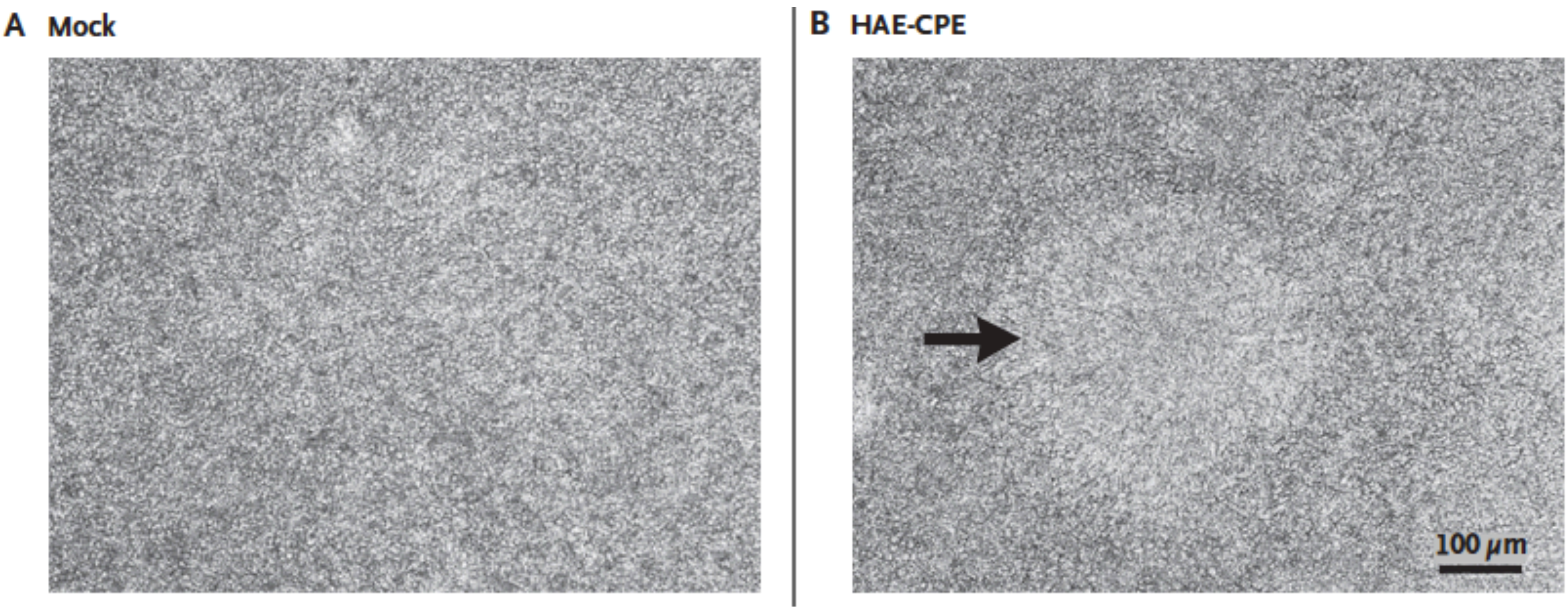
Lennette's laboratory diagnosis of viral infections / edited by Keith R. Jerome. – 4th ed. pag 135

Fase preanalítica

- Identificación
  - Paciente: Nombre, edad, género.
  - Del médico solicitante: nombre, mail, fax.
  - De la muestra: fecha, hora, tipo de espécimen.
- Transporte
  - Rápido +++
  - Medio de transporte (VTM).
  - Recipiente estéril
- Conservación antes de análisis
  - 2 a 6 ºC, -70ºC.

Efecto citopático Covid-19

HAE: Human airway epithelial



Human airway epithelial cells

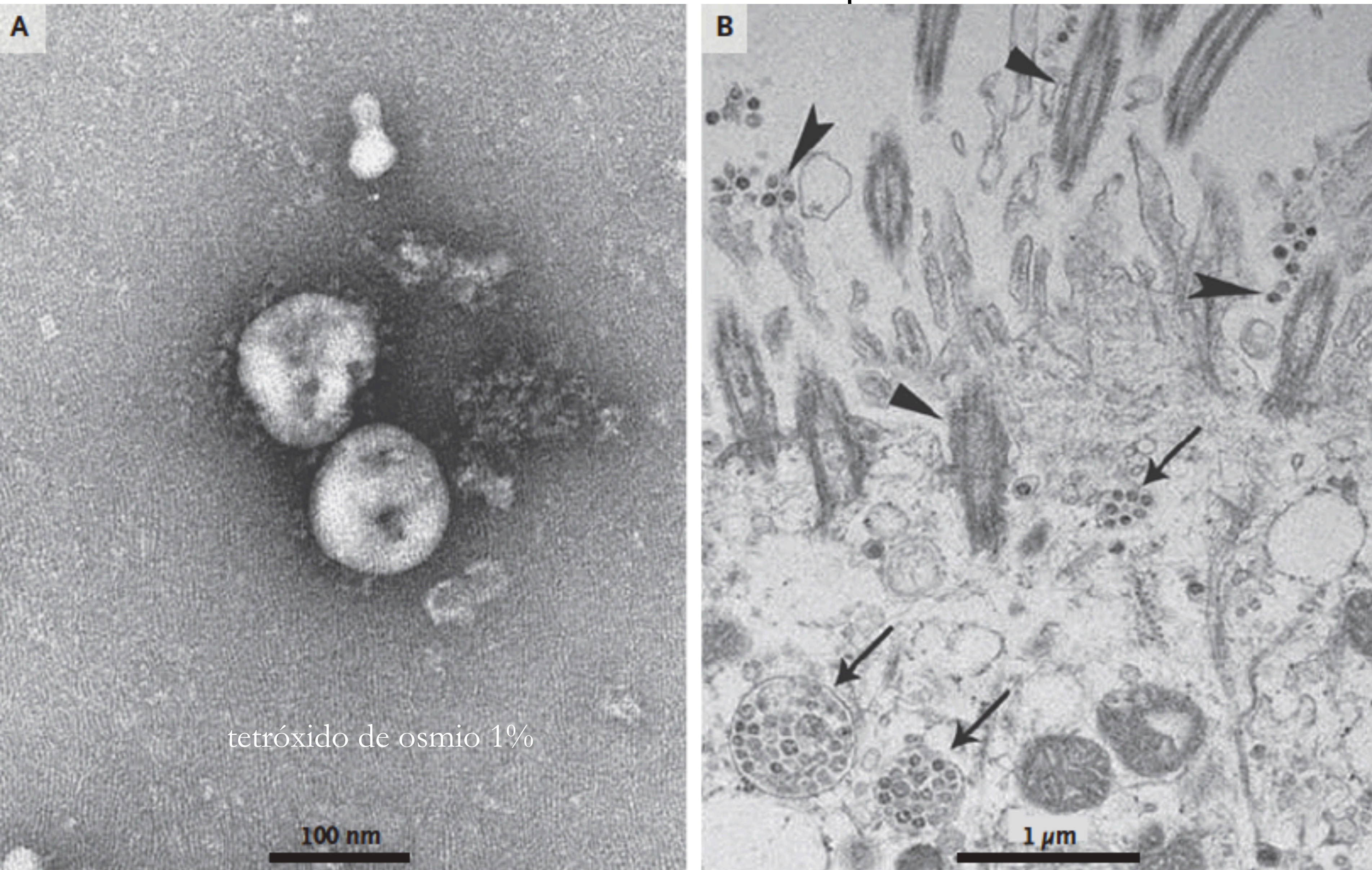
CPE: lack of cilium beating

Vero E6 cells

Huh-7 cell lines.

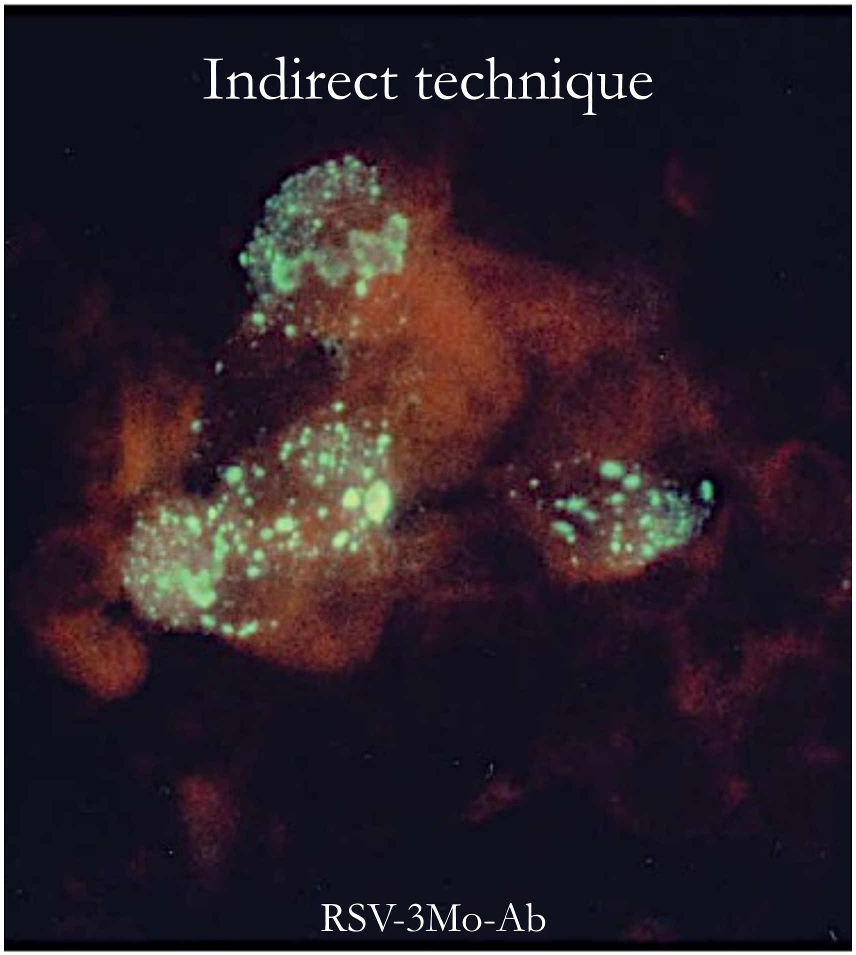
DOI: 10.1056/NEJMoa2001017

Covid-19en cultivo de células respiratorias humanas



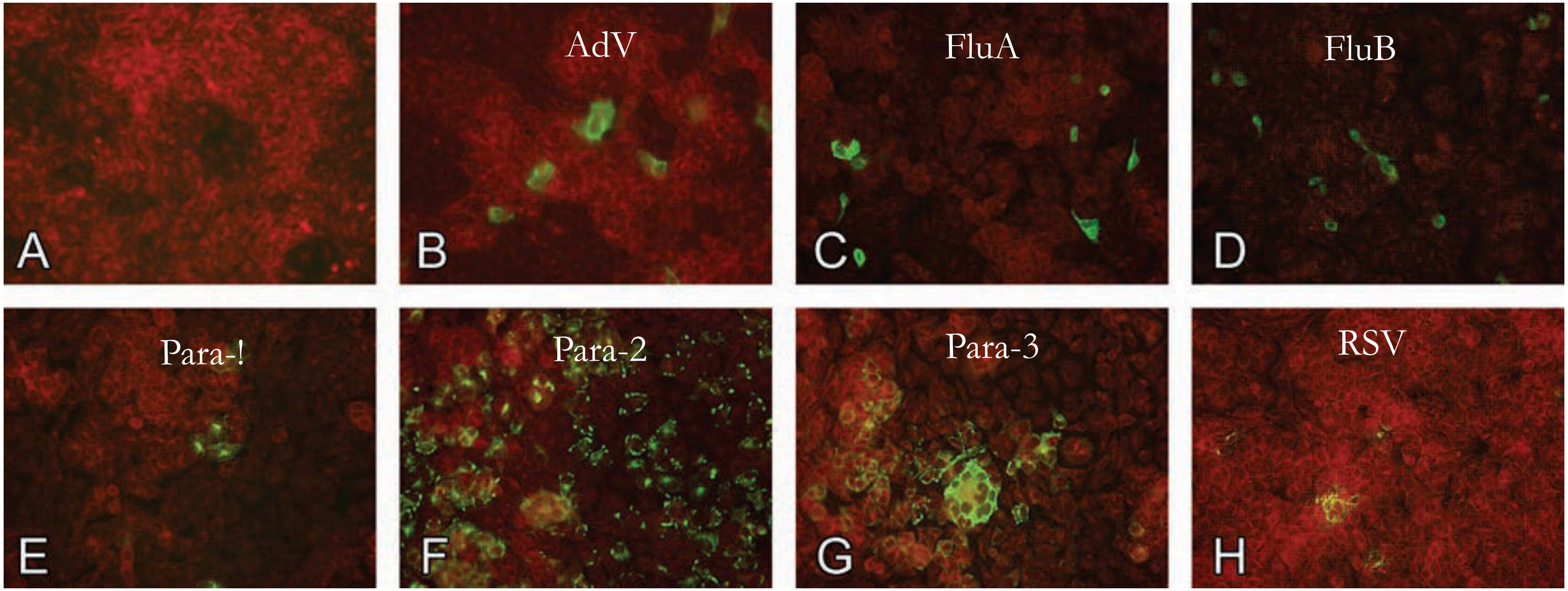
DOI: 10.1056/NEJMoa2001017

Métodos convencionales de diagnóstico virológico: inmunofluorescencia



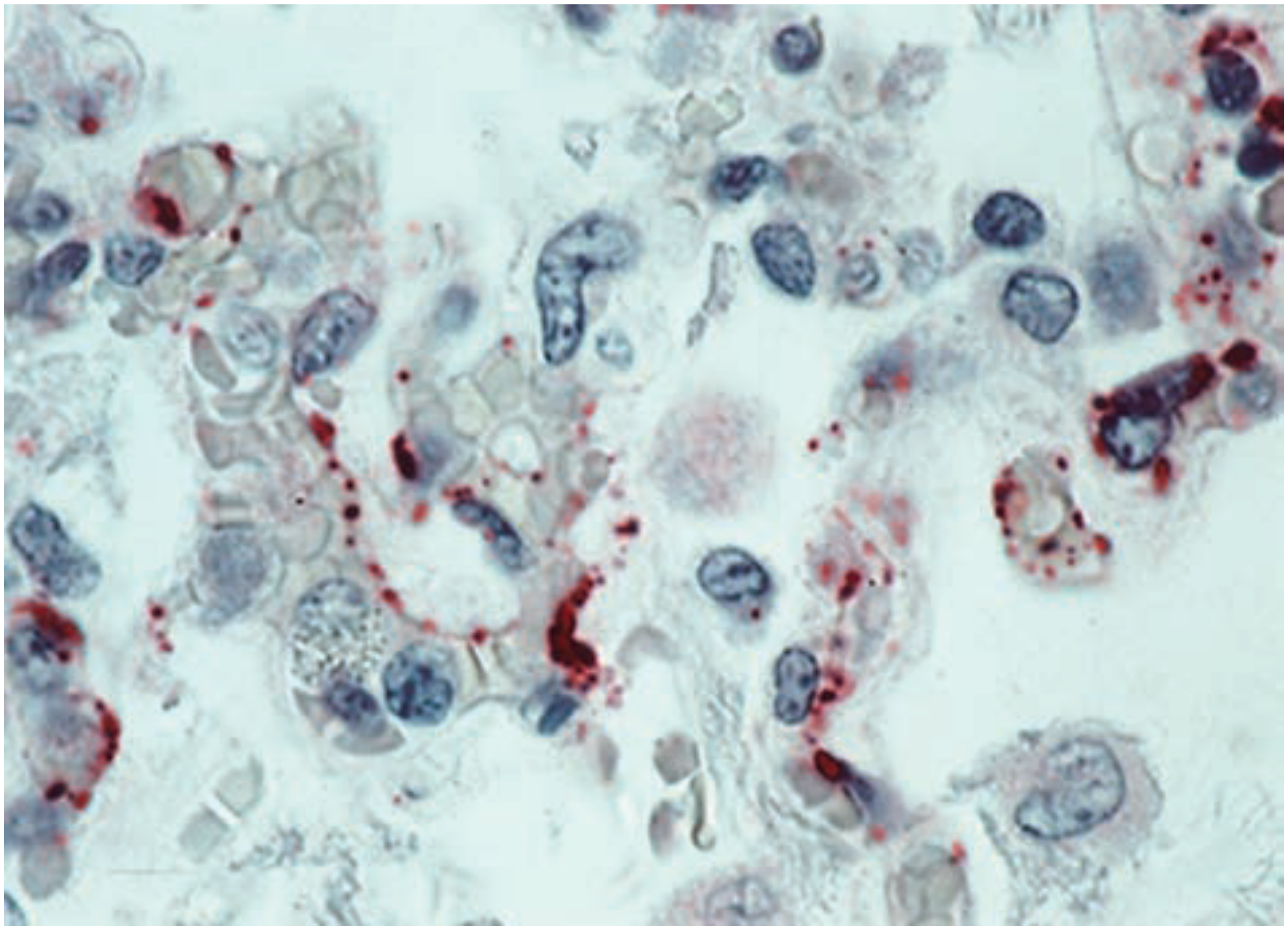
Journal of Clinical Virology 25 (2002) 121–134

IFI: detección de virus respiratorios



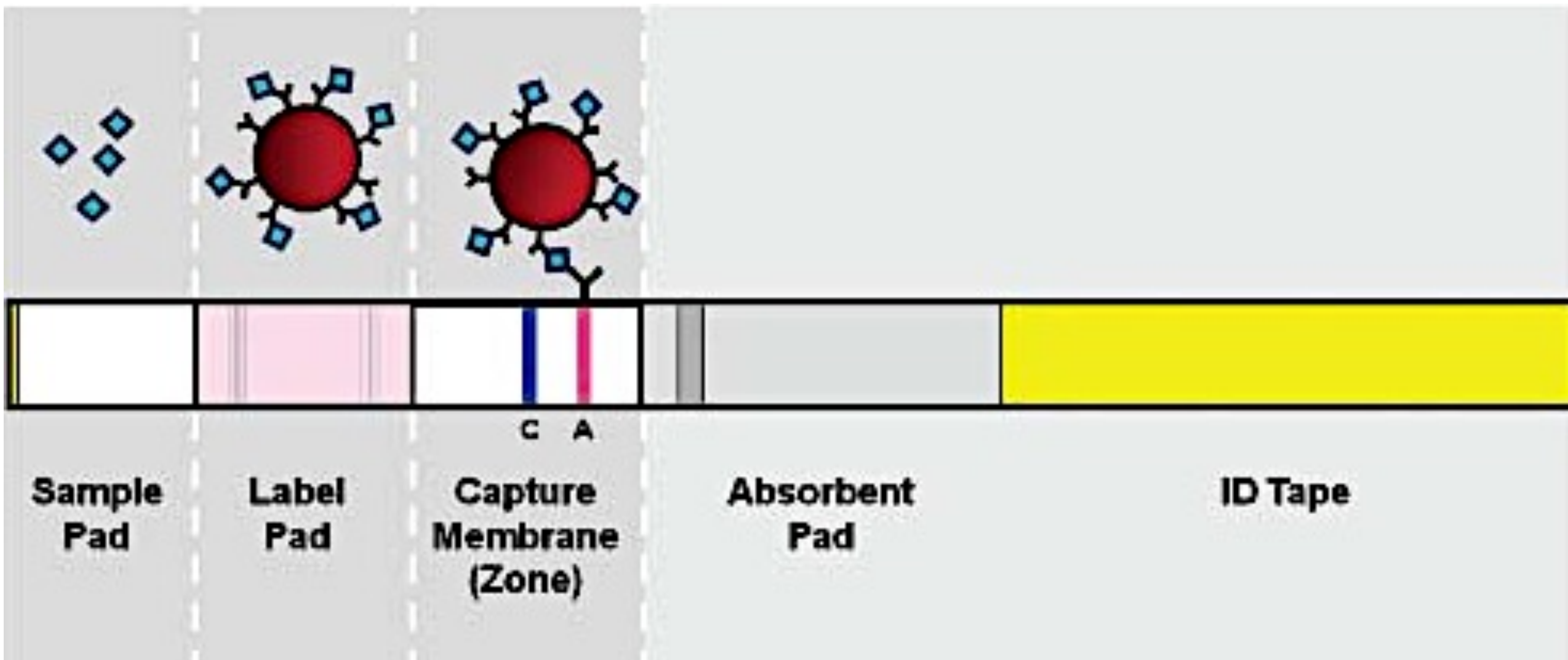
Manual of Clinical Microbiology-2015

Inmunohistoquímica: Hantavirus en pulmón



Manual of Clinical Microbiology-2015

Inmunocromatografía de flujo lateral

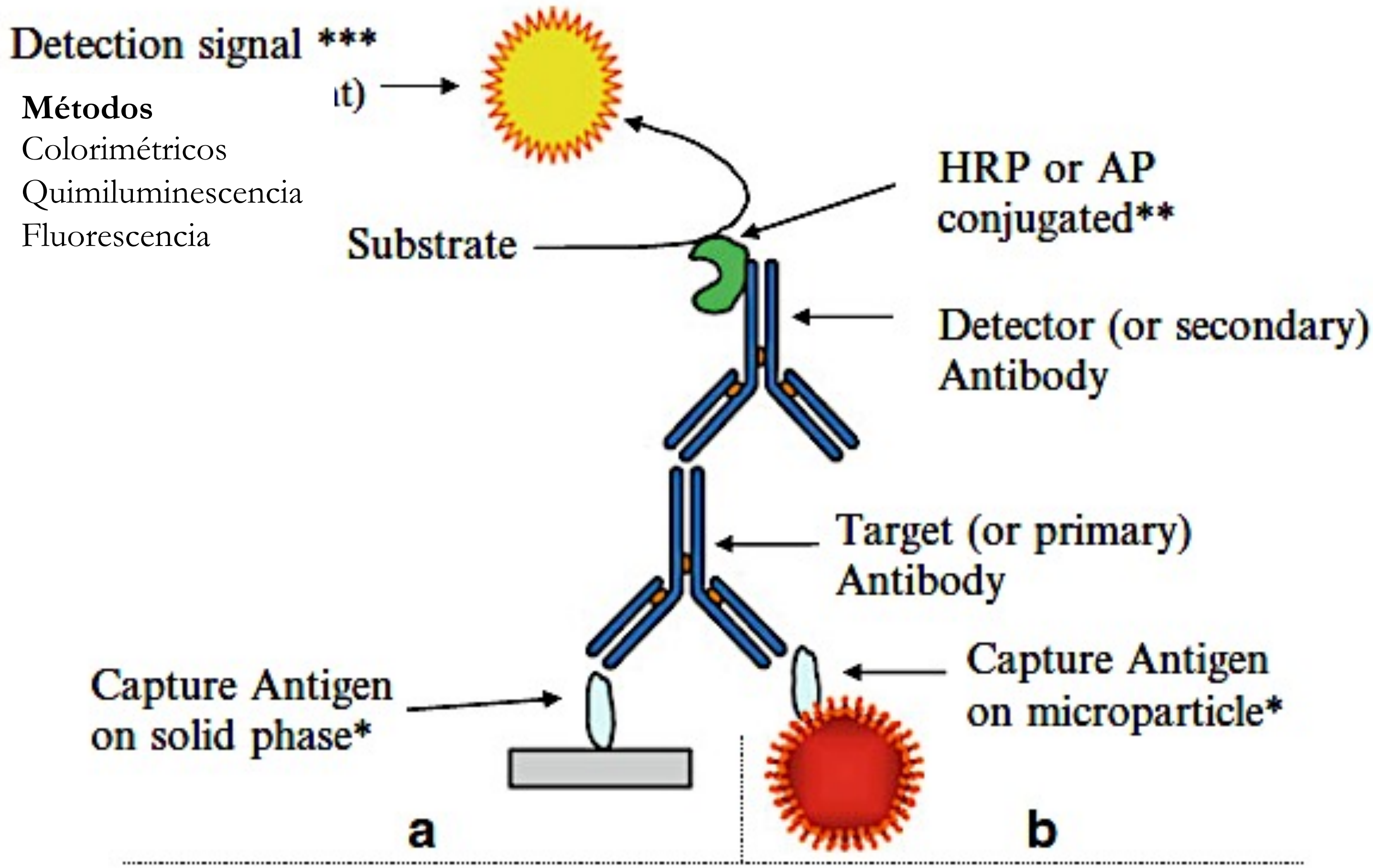


Traditional rapid diagnostics, such as immunoassays, produce quick results and are simple to perform; but, have sub-optimal sensitivity

Fields Virology 2013, Volumen 1 pag 418

Detección de anticuerpos

Métodos
Colorimétricos
Quimiluminescencia
Fluorescencia



Advanced Techniques in Diagnostic Microbiology. Antibody Detection: Principles and Applications. 2013

Virus respiratorios: diagnóstico molecular

Nom de la trousse	Fabricant
Easyplex Respiratory Pathogen 12	Ausdiagnostics, Sydney, Australia
FilmArray RP	BioMérieux, France
MultiCode®-PLx	EraGen Biosciences, Madison, WI, US
Fast Track Diagnostics Respiratory Pathogen 33	Fast Track Diagnostics, Luxembourg
eSensor RVP XT-8 / ePlex	GenMark Diagnostics, Carlsbad, CA, US
CLART PneumoVir 2	Genomica, Coslada, Spain
AdvanSure™ RV	LG life science, Seoul, Korea
xTAG® Respiratory Viral Panel fast	Luminex Molecular Diagnostics, Toronto, Canada
RespiFinder® SMART 22	Pathofinder, Maastricht, Netherlands
ResPlex II Panel v2.0	Qiagen, Germany
Magicplex™ RV Panel Real-time Test	Seegene Inc., Seoul, Korea
Anyplex II RV16	Seegene, Seoul, Korea

Revue Francophone Des Laboratoires. DÉCEMBRE 2016 - N°487 // 25-34

Covid-19: diagnóstico molecular rt-RT-PCR

Assay/use	Oligonucleotide	Sequence[a]	Concentration[b]
RdRP gene	RdRp_SARSr-F	GTGARATGGTCATGTGTGGCGG	Use 600 nM per reaction
	RdRp_SARSr-P2	FAM-CAGGTGGAACCTCATCAGGAGATGC-BBQ	Specific for 2019-nCoV, will not detect SARS-CoV. Use 100 nM per reaction and mix with P1
	RdRP_SARSr-P1	FAM-CCAGGTGGWACRTCATCMGGTGATGC-BBQ	Pan Sarbeco-Probe will detect 2019-nCoV, SARS-CoV and bat-SARS-related CoVs. Use 100 nM per reaction and mix with P2
	RdRp_SARSr-R	CARATGTTAAASACACTATTAGCATA	Use 800 nM per reaction
E gene	E_Sarbeco_F	ACAGGTACGTTAATAGTTAATAGCGT	Use 400 nm per reaction
	E_Sarbeco_P1	FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ	Use 200 nm per reaction
	E_Sarbeco_R	ATATTGCAGCAGTACGCACACA	Use 400 nm per reaction
N gene	N_Sarbeco_F	CACATTGGCACCCGCAATC	Use 600 nm per reaction
	N_Sarbeco_P	FAM-ACTTCCTCAAGGAACAACATTGCCA-BBQ	Use 200 nm per reaction
	N_Sarbeco_R	GAGGAACGAGAAGAGGCTTG	Use 800 nm per reaction

Falsos negativos

- Espécimen no representativo
- Manipulación.
- Transporte.
- Fase inicial infección

Euro Surveill. 2020;25(3):pii=2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045

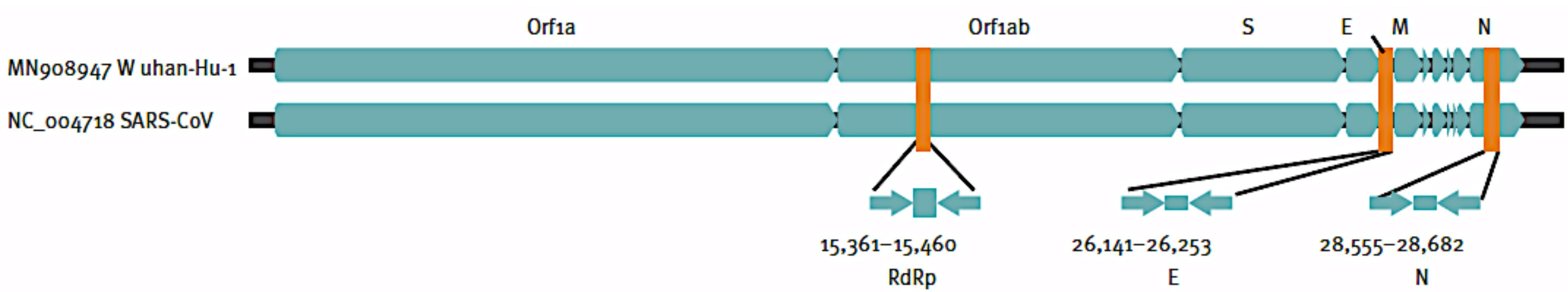
Covid-19: posición relativa de amplicones rt-RT-PCR

Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR

Victor M Corman[1], Olfert Landt[2], Marco Kaiser[2], Richard Molenkamp[3], Adam Meijer[4], Daniel KW Chu[5], Tobias Bleicker[1], Sebastian Brünink[1], Julia Schneider[1], Marie Luisa Schmidt[1], Daphne GJC Mulders[3], Bart L Haagmans[3], Bas van der Veer[4], Sharon van den Brink[4], Lisa Wijsman[4], Gabriel Goderski[4], Jean-Louis Romette[6], Joanna Ellis[7], Maria Zambon[7], Malik Peiris[5], Herman Goossens[8], Chantal Reusken[4], Marion PG Koopmans[3], Christian Drosten[1]

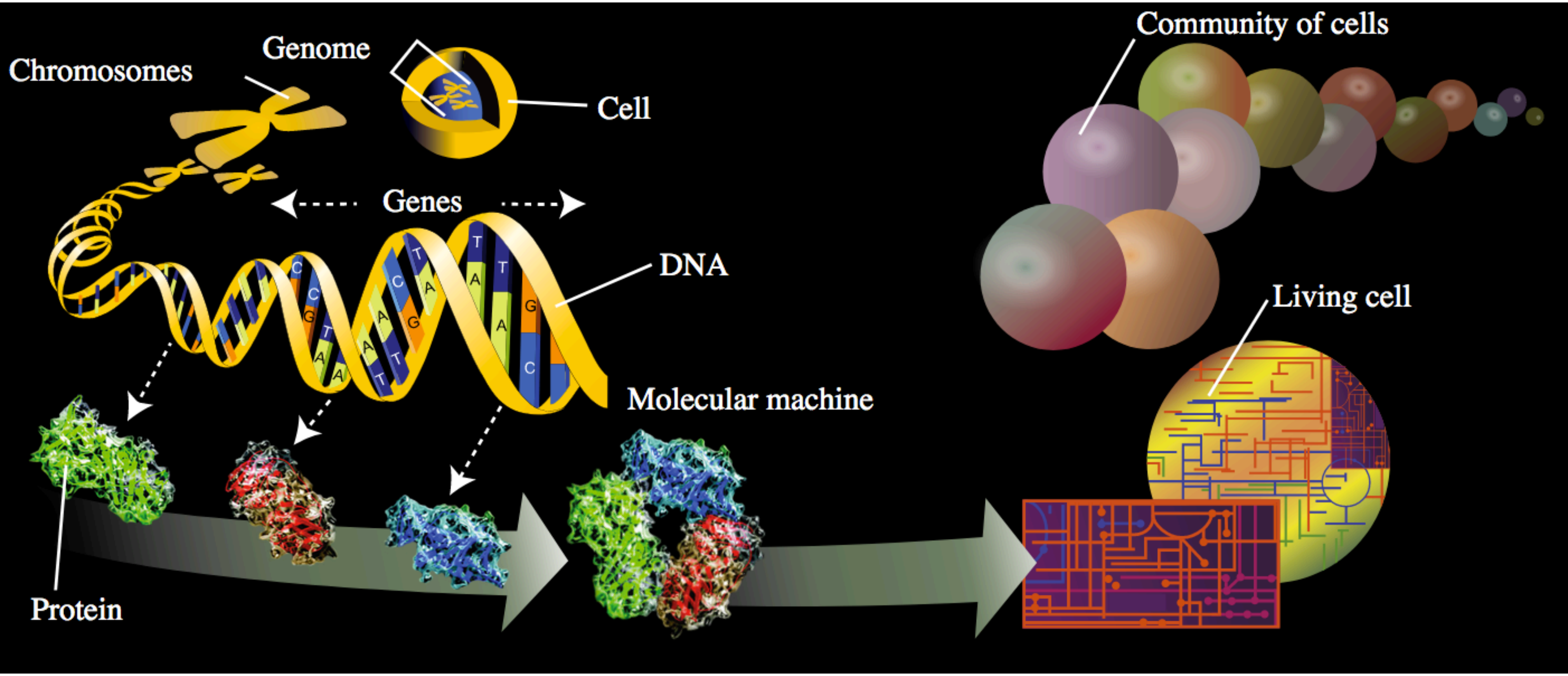
1. Charité – Universitätsmedizin Berlin Institute of Virology, Berlin, Germany and German Centre for Infection Research (DZIF), Berlin, Germany
2. Tib-Molbiol, Berlin, Germany
3. Department of Viroscience, Erasmus MC, Rotterdam, the Netherlands
4. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
5. University of Hong Kong, Hong Kong, China
6. Universite d Aix-Marseille, Marseille, France
7. Public Health England, London, United Kingdom
8. Department of Medical Microbiology, Vaccine and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium

Correspondence: Christian Drosten (christian.drosten@charite.de)



Euro Surveill. 2020;25(3):pii=2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045

Genómica



By This SVG image was created by Medium69.Cette image SVG a été créée par Medium69.Please credit this : William Crochot - http://www.ornl.gov/sci/techresources/Human_Genome/primer_pic.shtml, Public Domain, https://commons.wikimedia.org/w/index.phpcurid=36425663

Utilidad de las pruebas moleculares

Table 1 Examples of Molecular Testing Modalities and Clinical Applications

Clinical questions	Examples of testing modalities	Test requirements	Clinical utility examples
Is the patient infected?	Qualitative PCR/RT-PCR, multiplexed PCR, other amplification-based technologies, oligonucleotide array microchip	Very high sensitivity and specificity for all the virus strains tested	Blood component testing, diagnosis of viral meningitis/encephalitis, diagnosis of respiratory viral disease, HCV infection status in patients with anti-HCV core Ab
What is the viral load?	Quantitative PCR/RT-PCR based tests	Sensitivity requirement dictated by clinical decision-making cutoffs. Requires good precision and accuracy; equal amplification efficiency for all virus strains tested; absence of unwanted cross-reactivity.	Decision support for initiation and monitoring of antiviral therapy. Monitoring of disease activity and treatment efficacy
What is the genotype?	Line probe, genotype-specific multiplex PCR, restriction fragment length polymorphism, PCR followed by informative region DNA sequencing	Adequate genome sampling for confident genotypes assignment. Sensitivity to mixed genotypes/recombinants	Prognosis of disease progression and response to therapy. Epidemiologic surveillance
Is this virus resistant to a drug or are there clinically significant mutations?	Amplification followed by DNA sequencing of the region of interest. Line probe assays. Mutation-specific PCR probes[KJI] Oligonucleotide ligation-based assays	Coverage of all known primary and compensatory resistance mutations for a given target or drugs of interest. Sensitivity to resistant/mutated subpopulations	Determination of drug resistance profiles, determination of core/precore mutation status in HBV

Lennette's laboratory diagnosis of viral infections. 4th Edition pag 61

Diagnóstico 2019-nCoV

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 7
Interval between sample collection and symptom onset (days)	7	6	9	10	NA	7
Conventional RT-PCR	..	..	..	..	..	..
Nasopharyngeal swab	..	..	..	..	..	..
RdRp	+	+	ND	+	ND	+
Spike	+	+	ND	+	+	+
Throat swab	..	..	..	..	..	..
RdRp	NA	NA	ND	ND	ND	+
Spike	NA	NA	ND	+	+	+
Serum	..	..	..	..	..	..
RdRp	ND	ND	NA	NA	NA	NA
Spike	ND	+	NA	NA	NA	NA
Plasma	..	..	..	..	..	..
RdRp	NA	NA	ND	ND	ND	NA
Spike	NA	NA	ND	ND	ND	NA
Urine	..	..	..	..	..	..
RdRp	ND	ND	ND	ND	ND	NA
Spike	ND	ND	ND	ND	ND	NA
Stool	..	..	..	..	..	..
RdRp	NA	NA	ND	ND	ND	NA
Spike	NA	NA	ND	ND	ND	NA

DOI: 10.1056/NEJMoa2001017

Diagnóstico 2019-nCoV

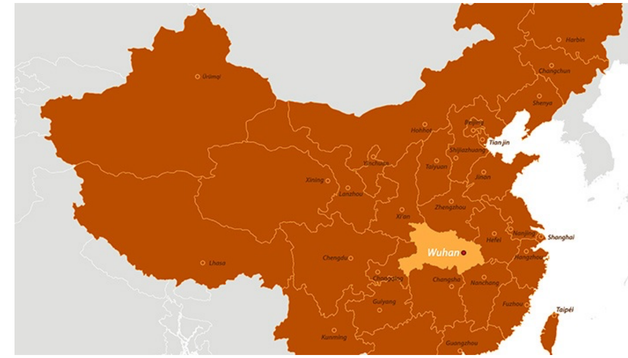
Real-time RT-PCR (spike gene)	..	..	..	..	..	..
Nasopharyngeal swab	+ (Ct 31)	+ (Ct 27)	ND	+ (Ct 31)	ND	+ (Ct 27)
Throat swab	NA	NA	ND	ND	+ (Ct 40)	+ (Ct 33)
Sputum	NA	NA	NA	NA	+ (Ct 27)	+ (Ct 25)
Serum	ND	+ (Ct 40)	NA	NA	ND	NA
Plasma	NA	NA	ND	ND	ND	ND
Urine	ND	ND	ND	ND	ND	NA
Stool	NA	NA	ND	ND	ND	ND
FilmArray RP2 plus (nasopharyngeal swab only)	ND	ND	ND	ND	ND	ND
Xpert Xpress Flu/RSV (nasopharyngeal swab only)	ND	ND	ND	ND	ND	ND
FilmArray GI panel (faecal sample only)	NA	NA	ND	ND	NA	NA

Ct values for real-time RT-PCR presented in parentheses. Ct=cycle threshold. NA=not available. +=positive. ND=not detected. RdRp=RNA-dependent RNA polymerase. RP2=respiratory panel 2. Flu=influenza. RSV=respiratory syncytial virus. GI=gastrointestinal.

DOI: 10.1056/NEJMoa2001017

nCoV humano en China

17-01-2020



- Los **signos y síntomas clínicos** informados son principalmente fiebre, con algunos casos con dificultad para respirar y radiografías de tórax que muestran infiltrados neumónicos invasivos en ambos pulmones.
- Las autoridades nacionales informan que los pacientes han sido aislados y están recibiendo tratamiento en las instituciones médicas de Wuhan.
- Según la investigación epidemiológica preliminar, la mayoría de los casos trabajaban en o eran manejadores y visitantes frecuentes al mercado mayorista de mariscos de Huanan.
- El gobierno informa que no hay evidencia clara de que el virus se transmita fácilmente de persona a persona.

454 casos para el 17-02-2020
EUA evacua 300 ciudadanos de ellos 14 casos positivos

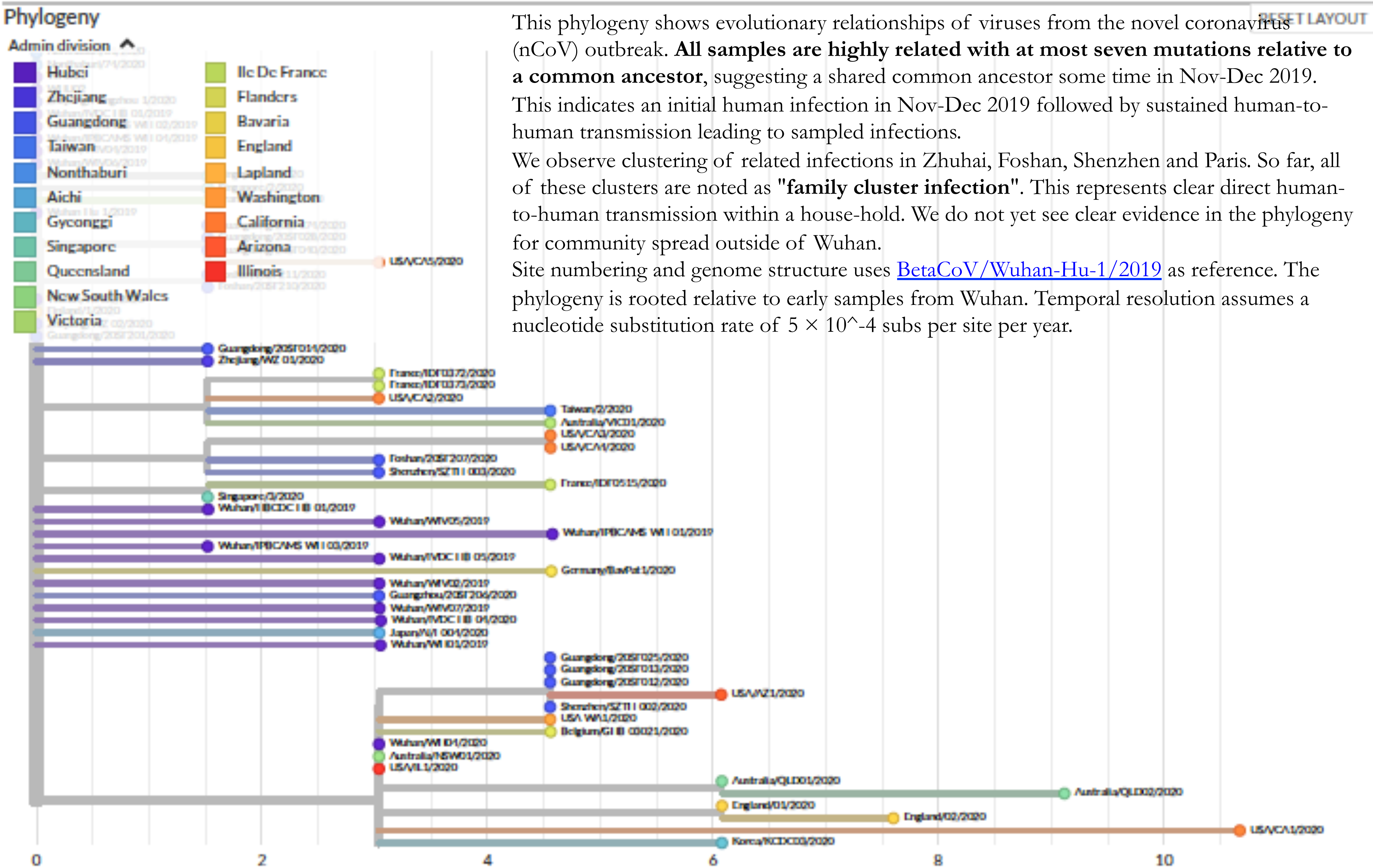
https://www.businessinsider.com/wuhan-coronavirus-japan-cruise-ship-diamond-princess-quarantined-cases-2020-2

3.711 personas atrapadas en un barco crucero "The Diamond Princess" luego de que fueran detectados 11 casos de infección por 2019-nCoV. La fuente: un pasajero que desembarcó en Hong Kong

nCoV humano en el mundo.

https://nextstrain.org/ncov

nCoV humano en el mundo.



This phylogeny shows evolutionary relationships of viruses from the novel coronavirus (nCoV) outbreak. **All samples are highly related with at most seven mutations relative to a common ancestor**, suggesting a shared common ancestor some time in Nov-Dec 2019. This indicates an initial human infection in Nov-Dec 2019 followed by sustained human-to-human transmission leading to sampled infections.

We observe clustering of related infections in Zhuhai, Foshan, Shenzhen and Paris. So far, all of these clusters are noted as **"family cluster infection"**. This represents clear direct human-to-human transmission within a house-hold. We do not yet see clear evidence in the phylogeny for community spread outside of Wuhan.

Site numbering and genome structure uses BetaCoV/Wuhan-Hu-1/2019 as reference. The phylogeny is rooted relative to early samples from Wuhan. Temporal resolution assumes a nucleotide substitution rate of 5 × 10^-4 subs per site per year.

https://nextstrain.org/ncov

nCoV humano en el mundo.

This phylogeny shows evolutionary relationships of viruses from the novel coronavirus (nCoV) outbreak. All samples are highly related with at most seven mutations relative to a common ancestor, suggesting a shared common ancestor some time in Nov-Dec 2019. This indicates an initial human infection in Nov-Dec 2019 followed by sustained human-to-human transmission leading to sampled infections.

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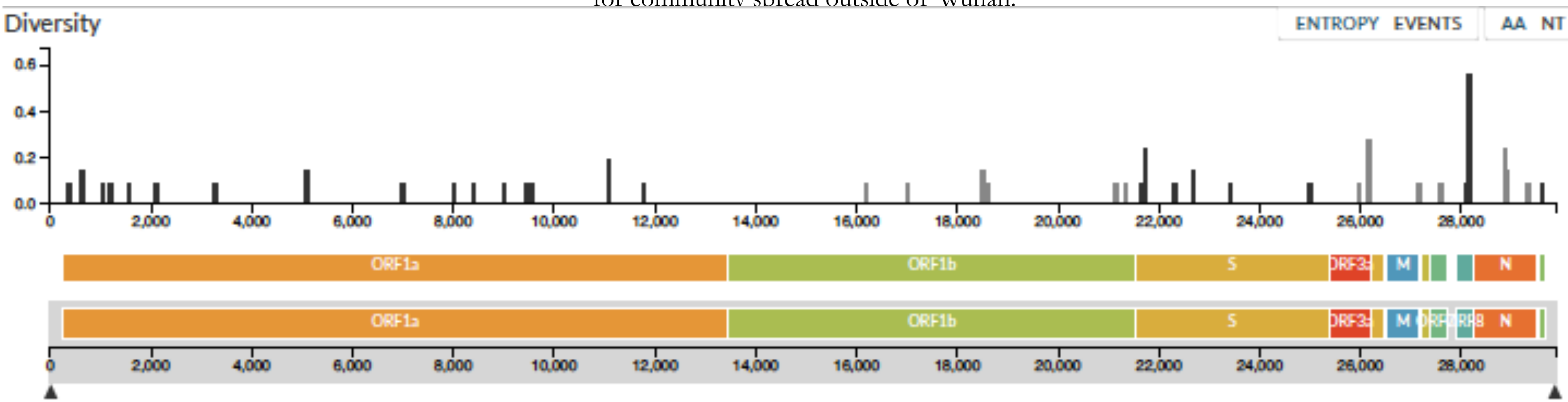
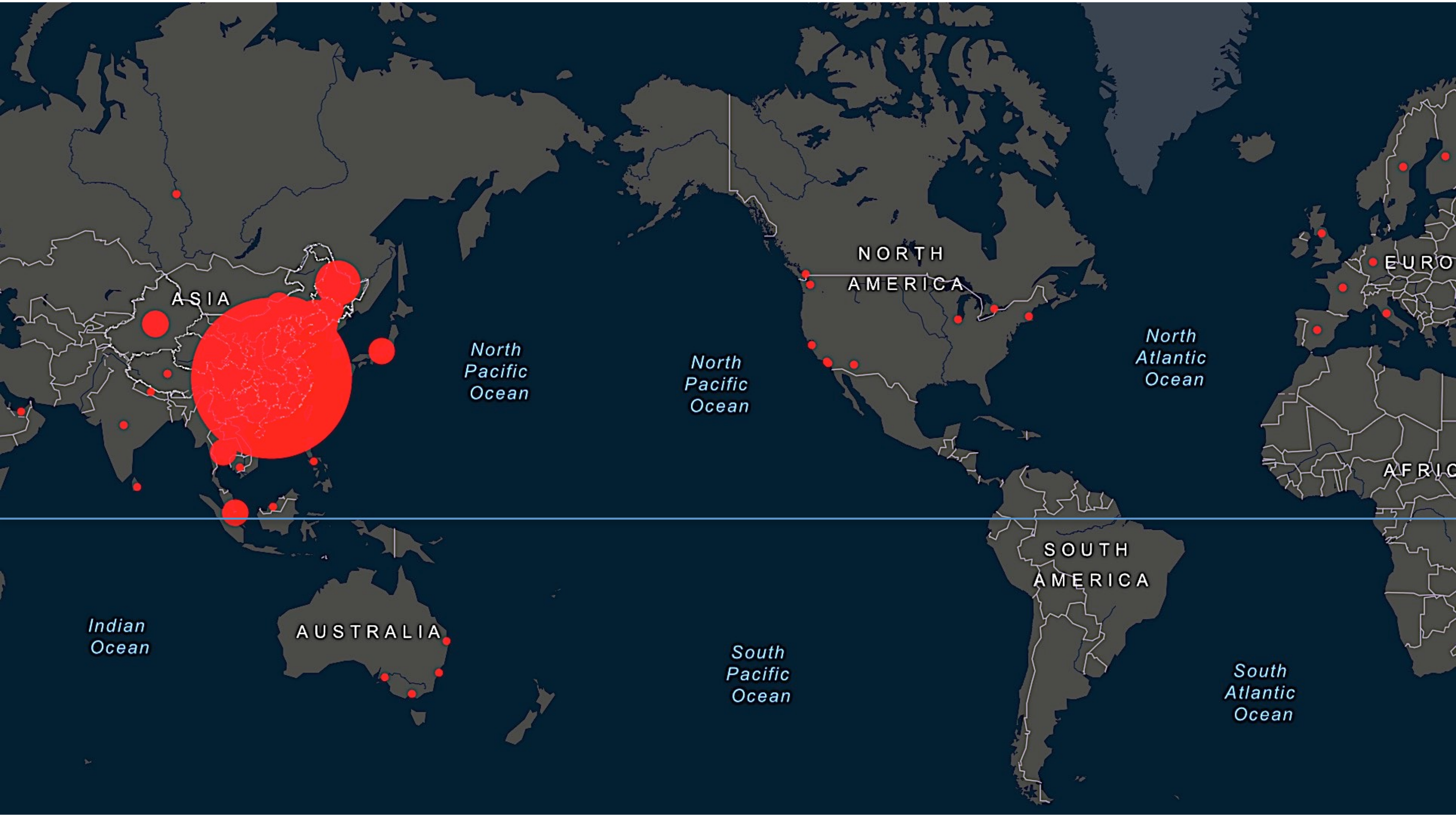


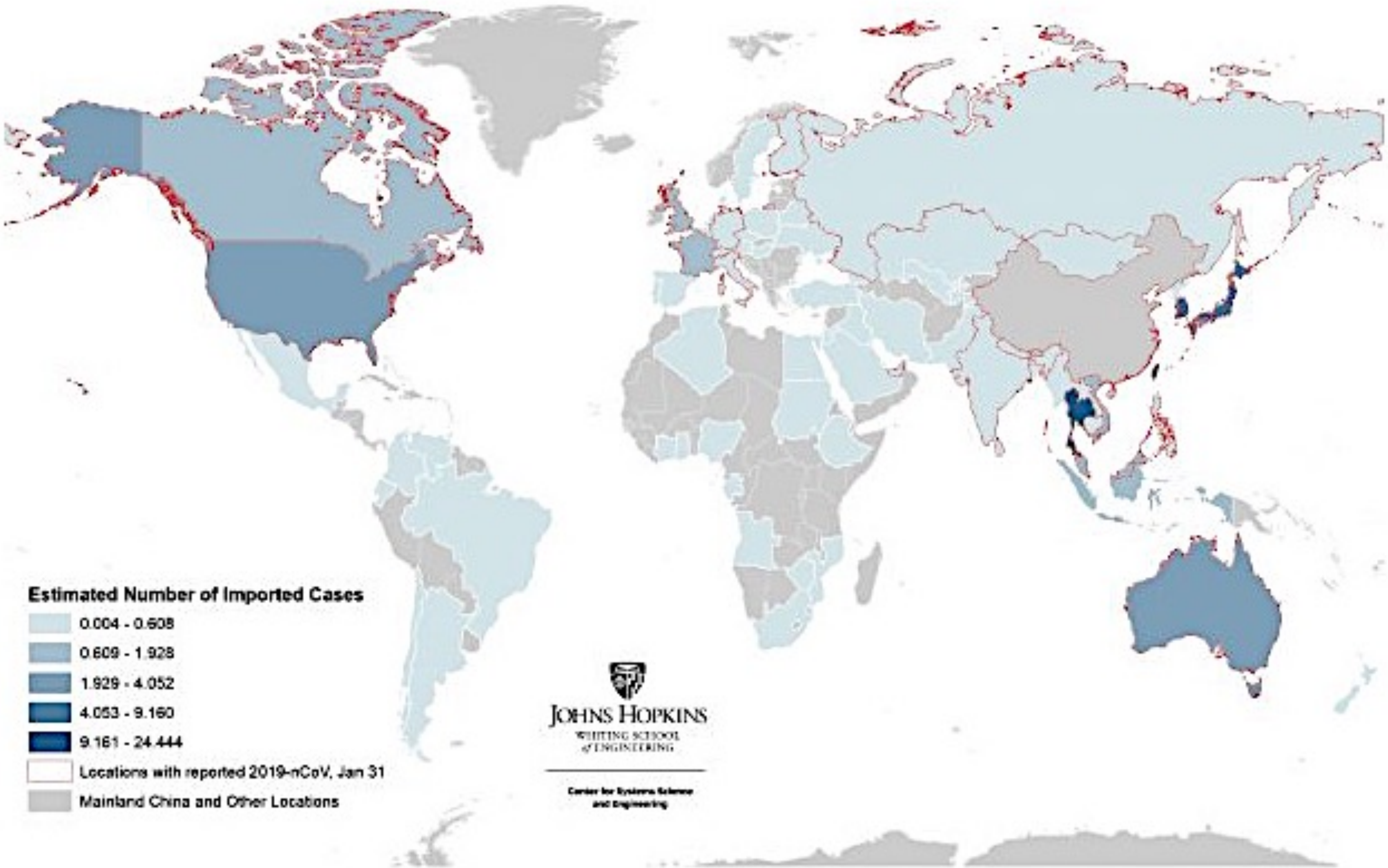
https://nextstrain.org/ncov

Covid-19: casos



http://www.microbe.tv/twiv/wp-content/uploads/sites/2/Screenshot-2020-02-01-15.21.13.png

Covid-19: riesgo de importar el virus.



https://systems.jhu.edu/research/public-health/ncov-model-2/

Covid-19: aeropuertos con mayor número de viajeros provenientes de China

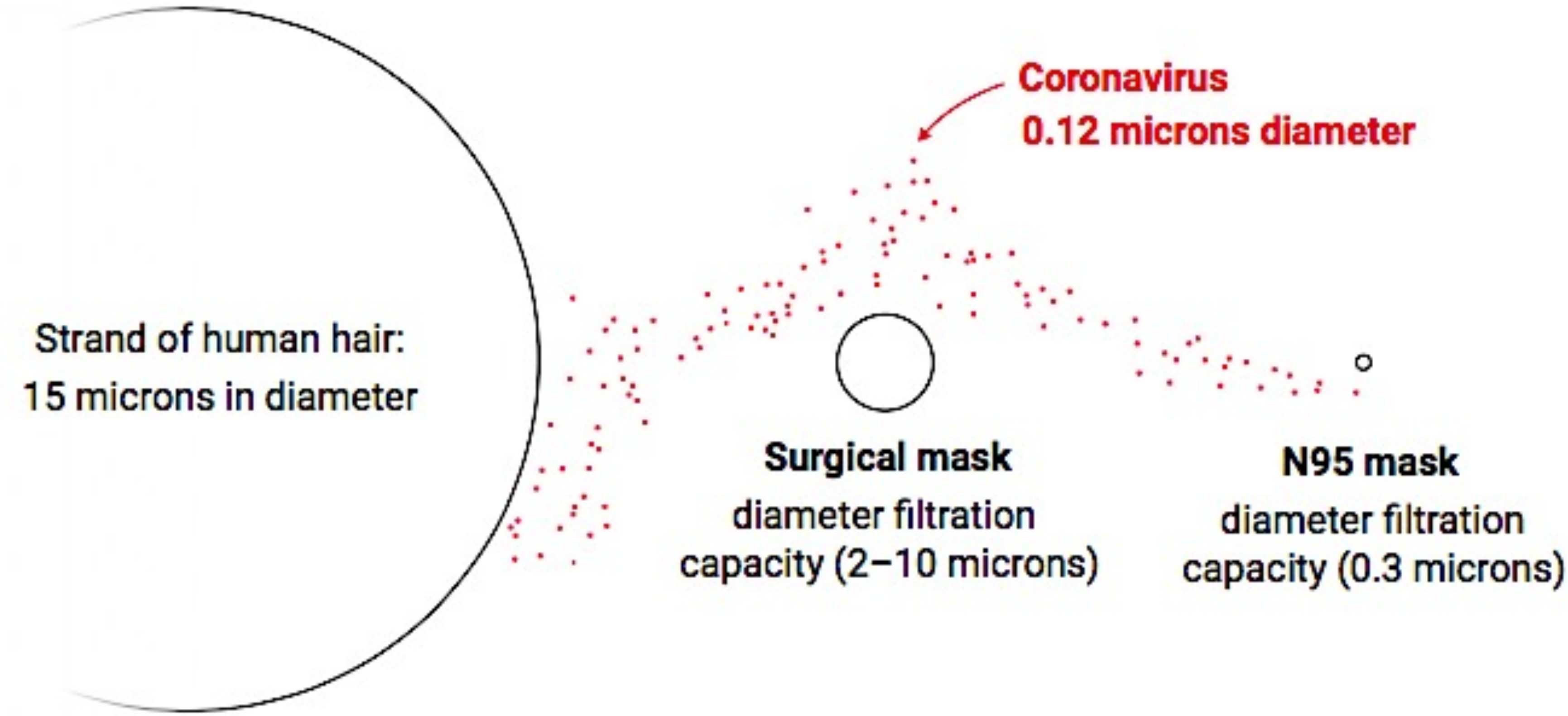
https://systems.jhu.edu/research/public-health/ncov-model-2/

Coronavirus y enfermedad

- The World Health Organisation (WHO) says that while wearing a medical mask **can help to limit the spread of some respiratory diseases**, it is not enough to stop all infections.
- The best precautions are the usual everyday ways of avoiding germs. **Wash your hands frequently**, try **not to touch your face, avoid crowded places** and **try to maintain a metre distance** from other people.
- **The WHO also only advises using masks if you have respiratory symptoms such as coughing or sneezing, mild coronavirus-like symptoms or are caring for someone suspected of having a coronavirus infection**

DOI: 10.1056/NEJMc2001468

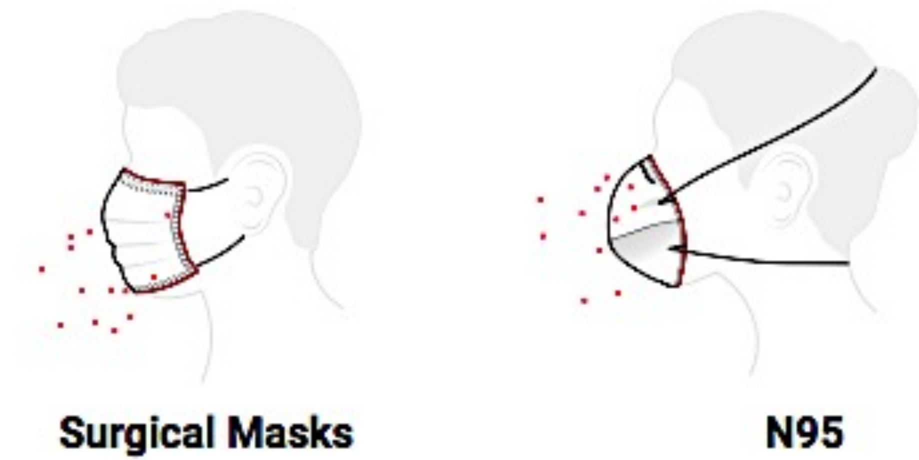
Covid-19: máscaras



Usually the virus travels through droplets during sneezing or coughing. The vast majority of the droplets are **less than 100 microns** (0.1mm) across.

https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

Covid-19: máscaras



Surgical masks are designed to prevent **large particle droplets** passing from one person's mouth to other people and nearby surfaces, impeding mouth-borne germs from spreading meanwhile **the respirator N95**: protects the wearer from breathing particles measuring over **0.3 microns** in diameter. When fitted correctly they filter 95 per cent of airborne particles

https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

2019-nCoV: máscaras

Key Points

- **Question** Is the use of N95 respirators or medical masks more effective in preventing influenza infection among outpatient health care personnel in close contact with patients with suspected respiratory illness
- **Findings** In this pragmatic, cluster randomized clinical trial involving 2862 health care personnel, there was no significant difference in **the incidence of laboratory-confirmed influenza** among health care personnel with the use of N95 respirators (**8.2%**) vs medical masks (**7.2%**).
- **Meaning** As worn by health care personnel in this trial, use of N95 respirators, compared with medical masks, in the outpatient setting **resulted in no significant difference in the rates of laboratory-confirmed influenza**.

JAMA. 2019;322(9):824-833. doi:10.1001/jama.2019.11645

Covid-19: máscaras

Don't pull down your mask. It needs to stay put to avoid contamination

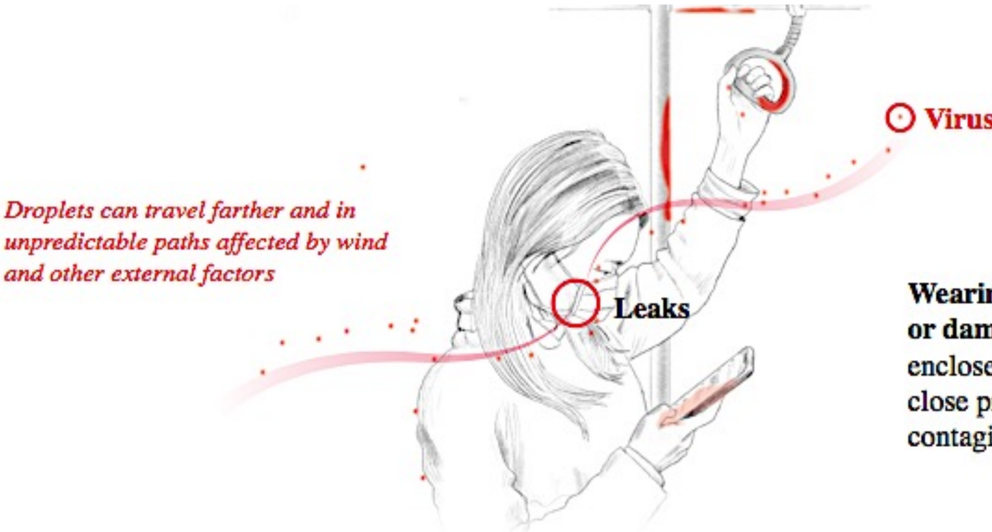
Coronavirus may survive a few hours

Do not touch the front of your mask when you take it off

On average, people touch their face 23 times per hour

https://multimedia.scmp.com/infographics/news/china/article/3047038/wuhan-virus/index.html

Covid-19: máscaras



Wearing poorly fitted or damaged masks in enclosed spaces in close proximity to contagious

Using the same mask longer than a day is worse than not wearing a mask at all: secretions from your mouth and nose coat the inside of the mask and turn it into a breeding ground for bacteria

DOI: 10.1056/NEJMc2001468

Manejo

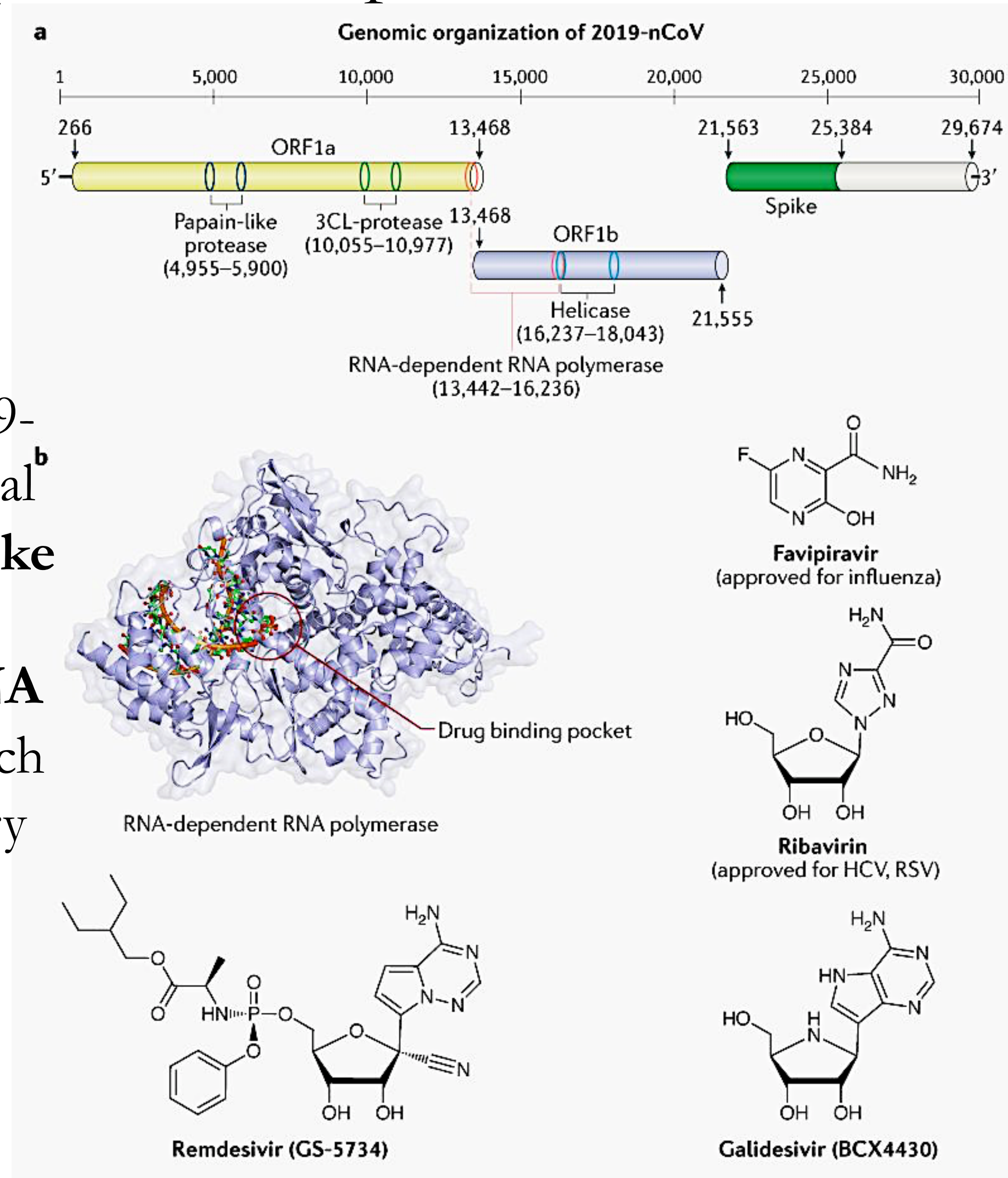
- No specific antiviral agent is available for treatment of this infection, and there is no vaccine.
- Treatment is supportive and includes supplemental oxygen and conservative fluid management, as indicated by clinical condition.
- WHO provides detailed guidance on such supportive measures and cautions that severely ill patients should be treated empirically for other possible causes while diagnostic test results are pending.

https://www.elsevier.com/connect/coronavirus-information-center

Covid-19: Opciones terapéuticas

Covid-19 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus.

Similar to SARS and MERS, the 2019-nCoV genome encodes non-structural proteins (such as 3-**chymotrypsin-like protease**, **papain-like protease**, **helicase**, and **RNA-dependent RNA polymerase**), structural proteins (such as **spike glycoprotein**) and accessory proteins.

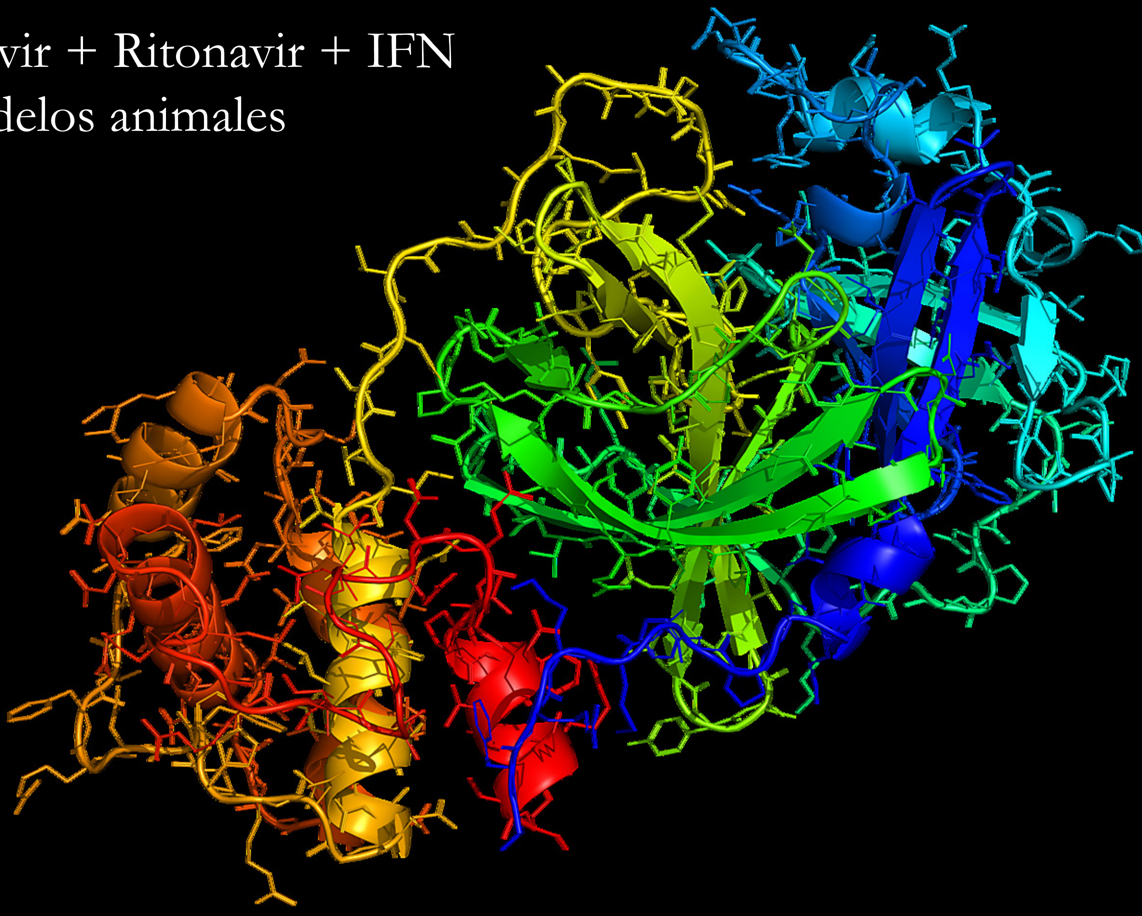


De Clerck. Nature Reviews Drug Discovery. Febraury 2020

Nature Reviews | Drug Discovery

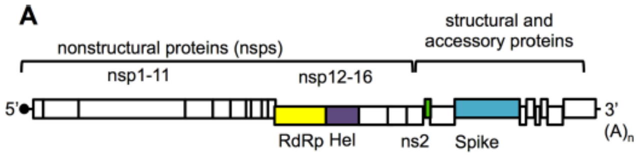
Proteasa 2019-nCoV

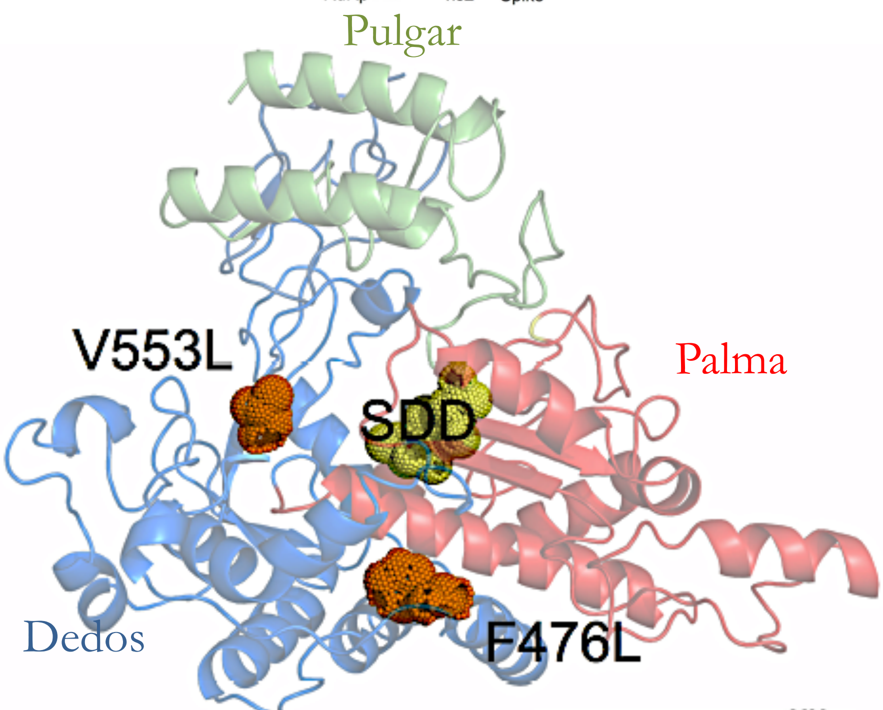
Kaletra: Lopinavir + Ritonavir + IFN
En modelos animales



https://figshare.com/articles/Comparative_model_of_novel_coronavirus_2019-nCoV_protease_Mpro/11752752

RpRd-nsp12 polymerase -HCoV



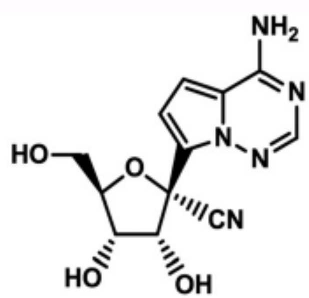


Estudios de replicación in vitro
Estudios de campo en Ébola

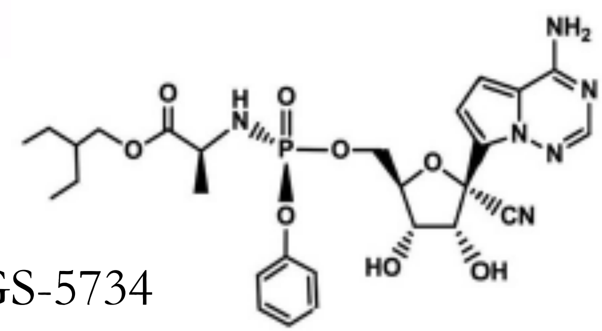
D

β-2a	MHV-A59	473	NKYFEIY	.	550	ARTVAGV
	HCoV-OC43	473	YKYFEIY	.	550	ARTVAGV
	HCoV-HKU1	473	YKYFEIY	.	550	ARTVAGV
β-2b	SARS-CoV	477	DKYFDCY	.	554	ARTVAGV
β-2c	MERS-CoV	478	NKYFEIY	.	555	ARTVAGV
	Bat-HKU5	479	DRYFEIY	.	556	ARTVAGV
α	HCoV-229E	472	ARYFDCY	.	549	ARTVGGV
	HCoV-NL63	472	SRYFDIY	.	549	ARTVGGV
γ	IBV	486	SKYFECY	.	562	ARTVAGV

GS-441524



Remdesivir GS-5734



mBio 9:e00221-18. https://doi.org/10.1128/mBio.00221-18.

Manejo

Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected

Interim guidance

12 January 2020

WHO/nCoV/Clinical/2020.1

World Health Organization

https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdfsfvrsn=bc7da517_2&download=true

Inmunización pasiva

- Administración de plasma de pacientes convalecientes recuperados.
- Uso en cuatro casos aislados de pacientes con infección severa.
- Mejora en la oxigenación y pO_2
- Utilizado en Ébola sin mayor éxito.
- ¿Cuál es el mejor momento para tomar el plasma de pacientes convalecientes para obtener los mejores títulos protectores y neutralizantes?

https://www.france24.com/fr/20200218-coronavirus-pr%C3%A8s-de-1-900-morts-l-oms-contre-toute-mesure-disproportionn%C3%A9e

Uso de corticoides y SARS

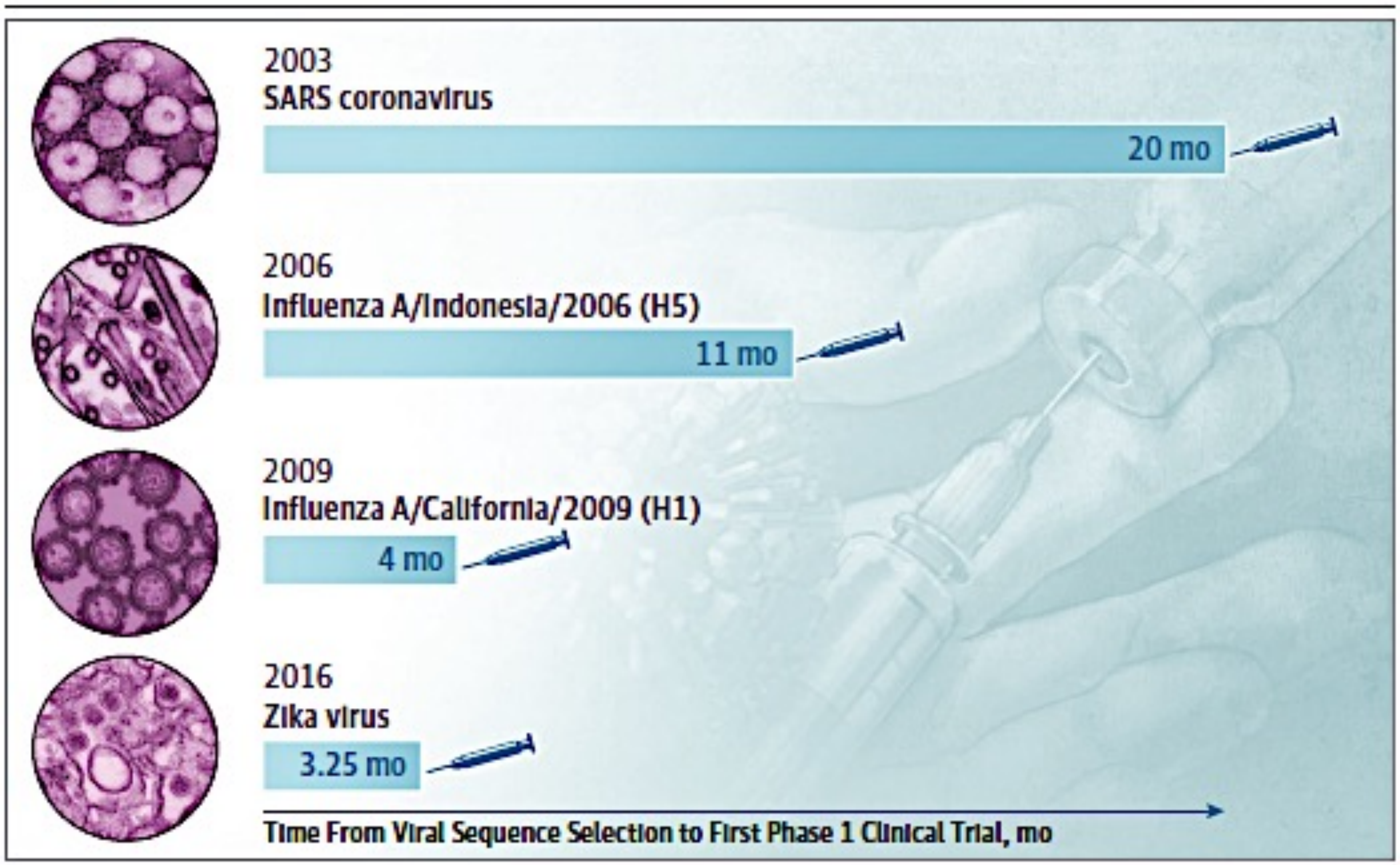
- Los pacientes que recibieron corticoides fueron más propensos a requerir ventilación mecánica, vasopresores y terapia de reemplazo renal.
- No hay diferencia en la mortalidad en tratados y no tratados con corticoides a 90 día de seguimiento.
- Quienes recibieron corticoides demoraron más en eliminar el virus de las secreciones respiratorias.
- Quienes recibieron corticoides presentaron mayores viremias, mayores tasas de infección bacteriana o fúngica secundaria.
- En saco de infecciones por VRS se observa una respuesta inmune humoral alterada

https://www.france24.com/fr/20200218-coronavirus-pr%C3%A8s-de-1-900-morts-l-oms-contre-toute-mesure-disproportionn%C3%A9e

Medidas de control de infecciones

- Provide the patient with a face mask and place the patient in a closed room (preferably with structural safeguards against airborne transmission).
- Persons entering the room should follow standard, contact, and airborne precautions.
- Patients managed at home are encouraged to self-isolate to a single area of the house (preferably with a separate bathroom) and to wear a face mask during any contact with household members.
- The patient and all household members should follow diligent hand and cough hygiene.

Prevención: tiempos de respuesta para una vacuna por plásmidos



JAMA April 10, 2018 Volume 319, Number 14 1431-2

Estrategias vacunales: proteína S

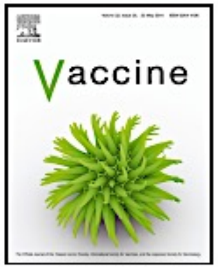
Vaccine 32 (2014) 3169–3174

ELSEVIER

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice

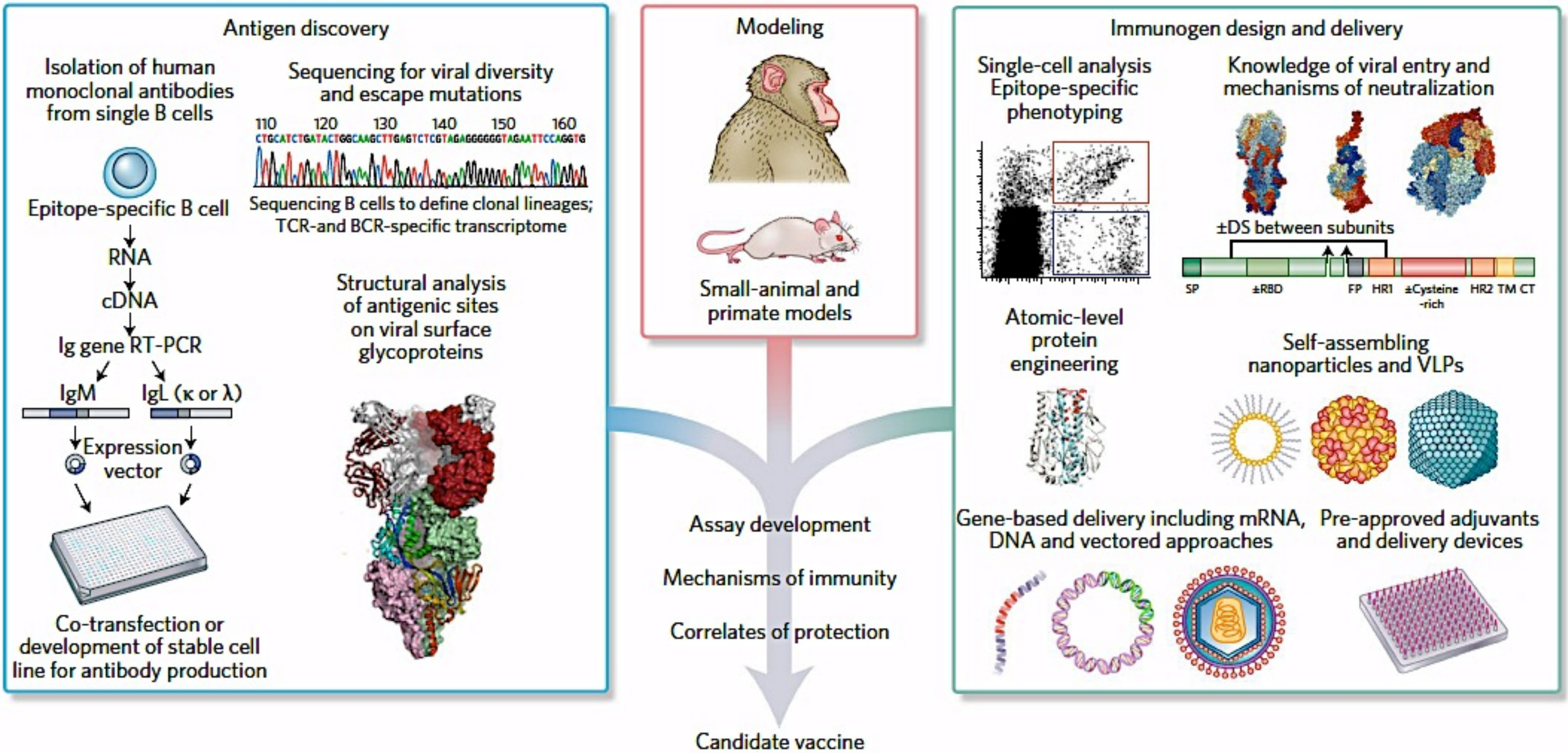
CrossMark

Christopher M. Coleman[a,1], Ye V. Liu[b,1], Haiyan Mu[b], Justin K. Taylor[a], Michael Massare[b], David C. Flyer[b], Gregory M. Glenn[b], Gale E. Smith[b,1], Matthew B. Frieman[a,*,1]

[a] University of Maryland, School of Medicine, 685 West Baltimore St, Baltimore, MD 21201, USA
[b] Novavax, Inc. 22 Firstfield Rd, Gaithersburg, MD 20852, USA

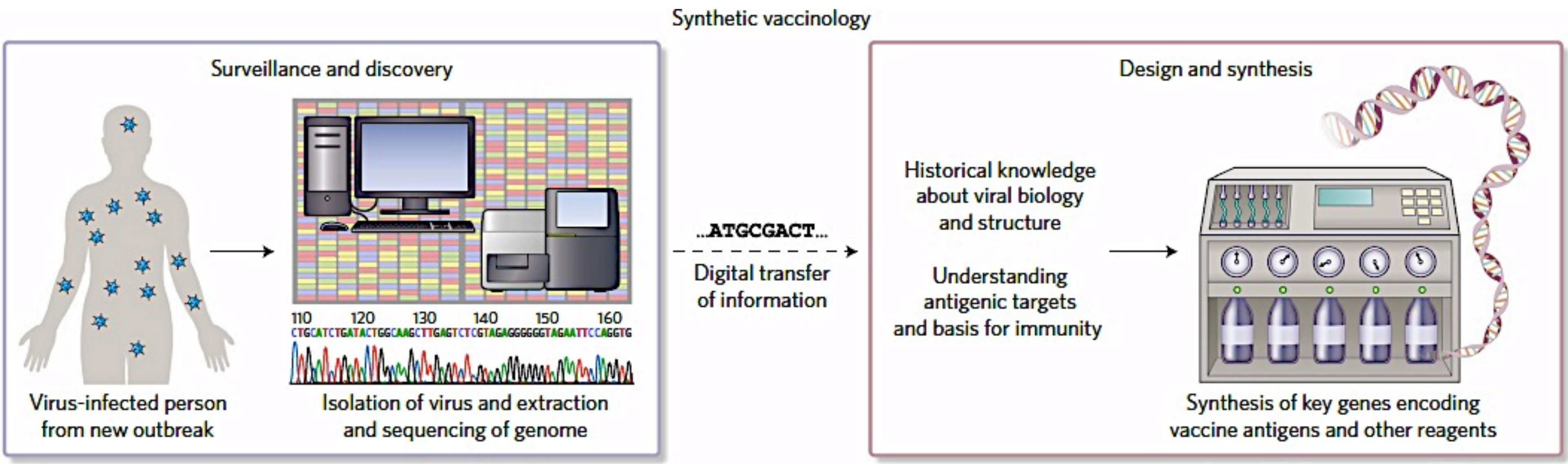
Nature Immunology | VOL 20 19 | JANUARY 2018 | 20–28 | www.nature.com/natureimmunology

Nuevas tecnologías vacunales



Nature Immunology | VOL 20 19 | JANUARY 2018 | 20–28 | www.nature.com/natureimmunology

Vaccinología sintética



Nature Immunology | VOL 20 19 | JANUARY 2018 | 20–28 | www.nature.com/natureimmunology

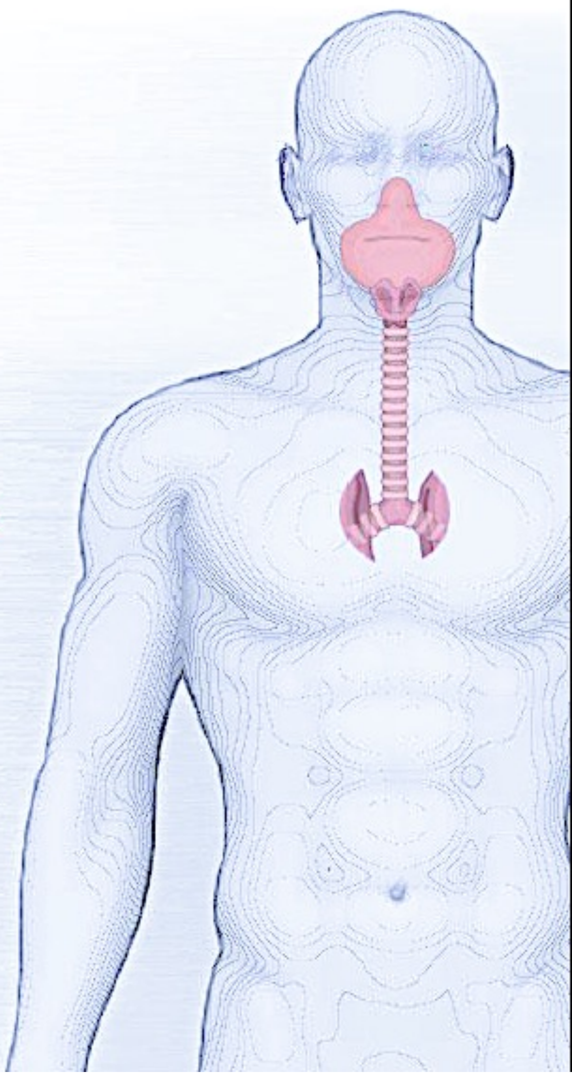
Kit de diagnóstico múltiple IRA

Viruses

Adenovirus
Coronavirus HKU1
Coronavirus NL63
Coronavirus 229E
Coronavirus OC43
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza A/H1
Influenza A/H3
Influenza A/H1-2009
Influenza B
Parainfluenza 1
Parainfluenza 2
Parainfluenza 3
Parainfluenza 4
Respiratory Syncytial Virus

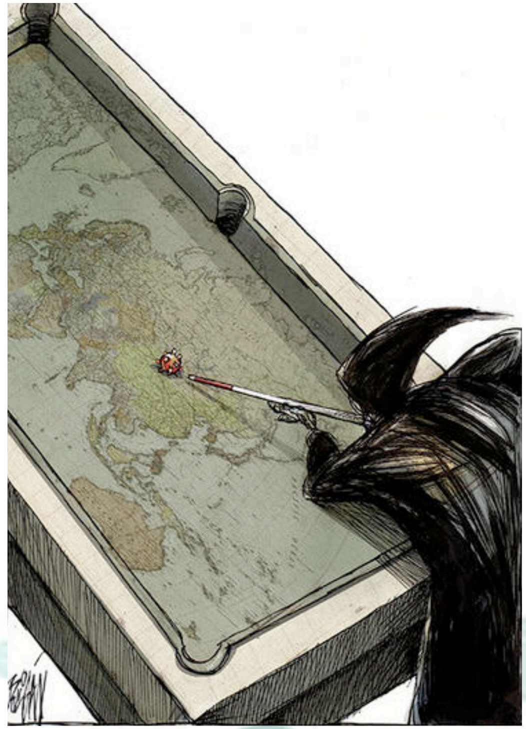
Bacteria

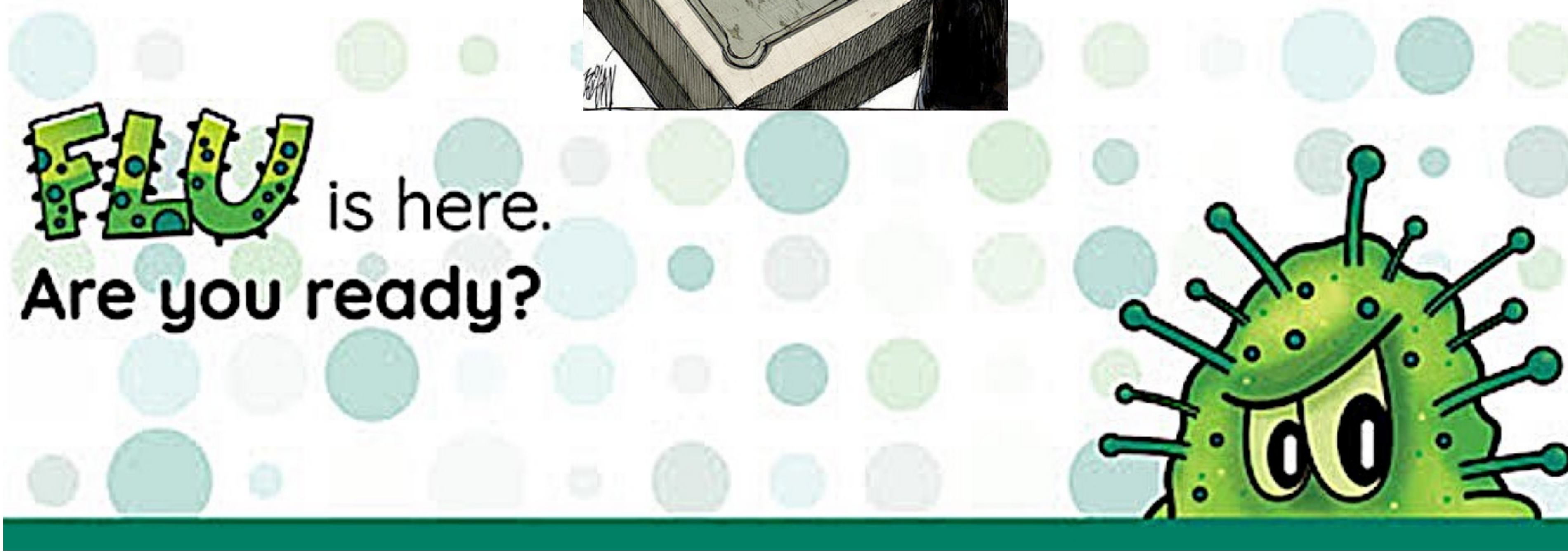
Bordetella pertussis
Chlamydophila pneumoniae
Mycoplasma pneumoniae



FDA-cleared for the first time.

http://www.biofiredx.com/media/InfoSheet-FilmArray-Respiratory-




FLU is here.
Are you ready?