

2019 Novel Coronavirus Disease (COVID-19)

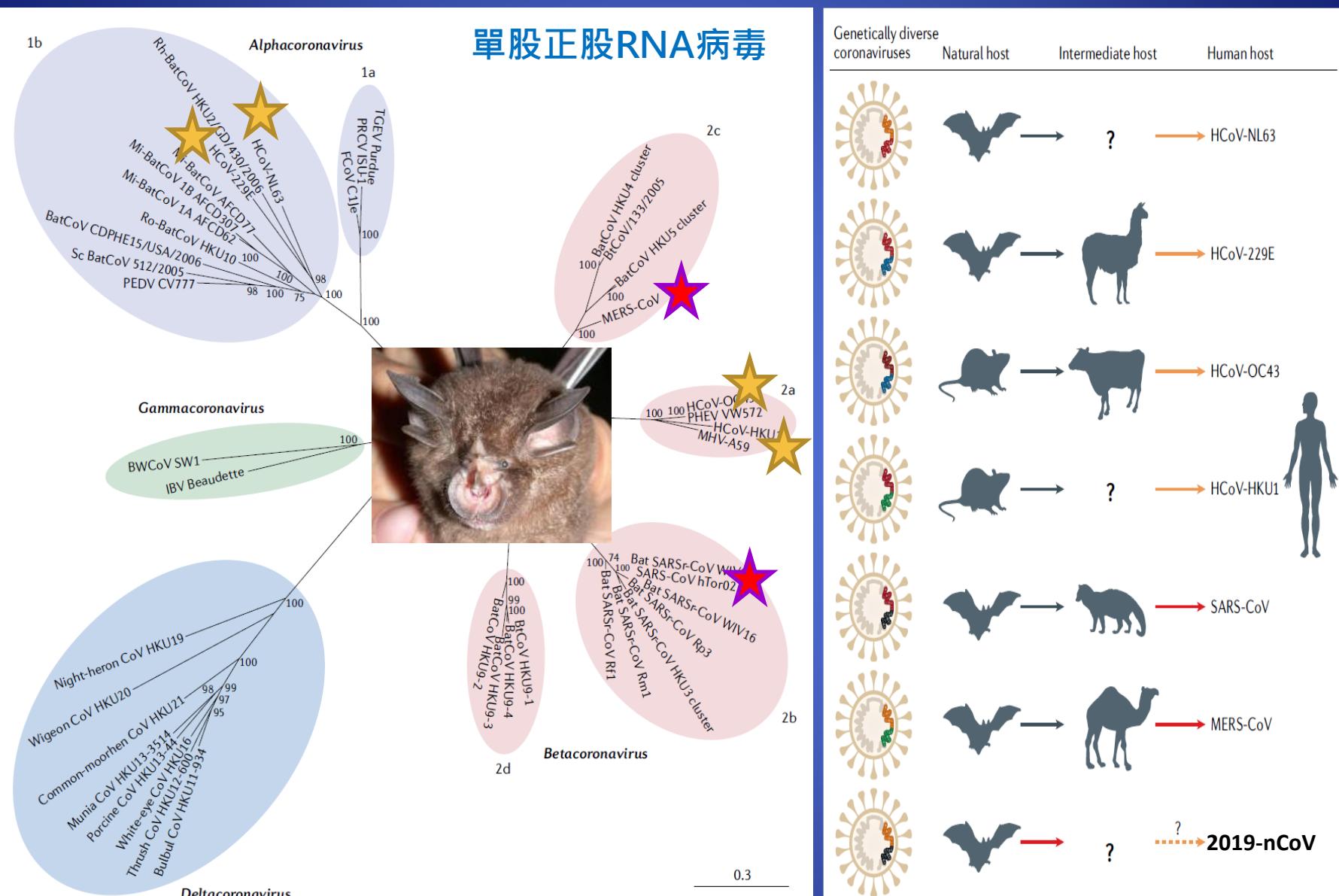
Translating Potential Therapeutics into Clinical Practice

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Feb. 16, 2020



Coronavirus & Their Hosts, Before 2019-nCoV

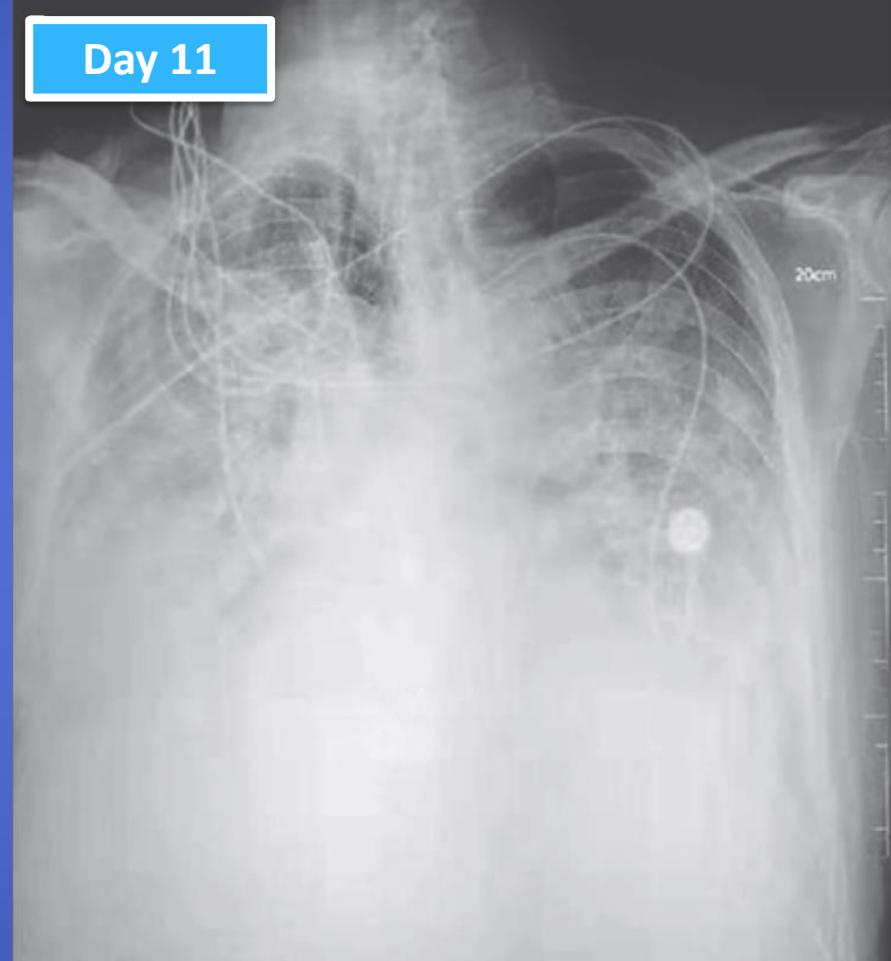


A 61-Year-Old Man with Fever and Cough

Day 8



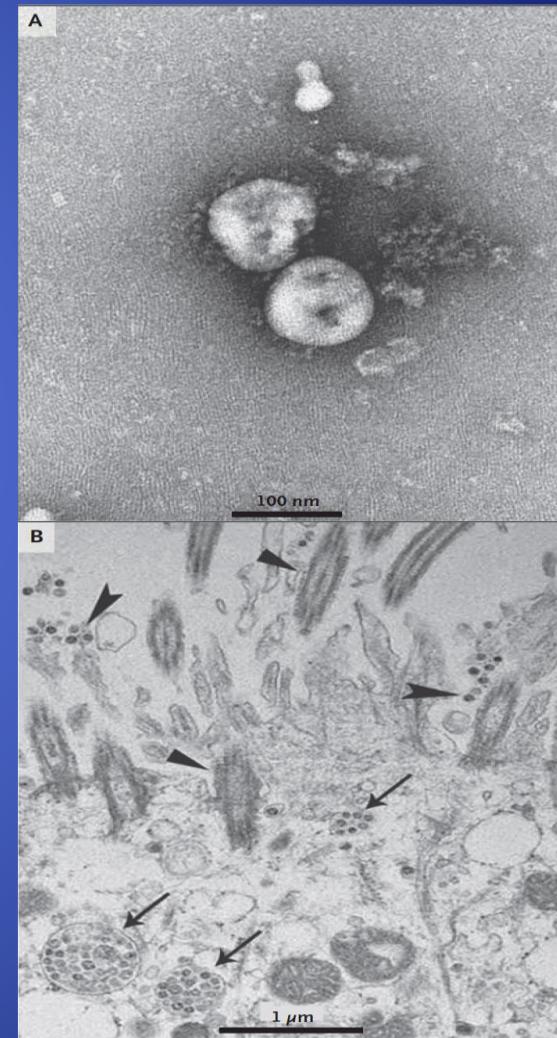
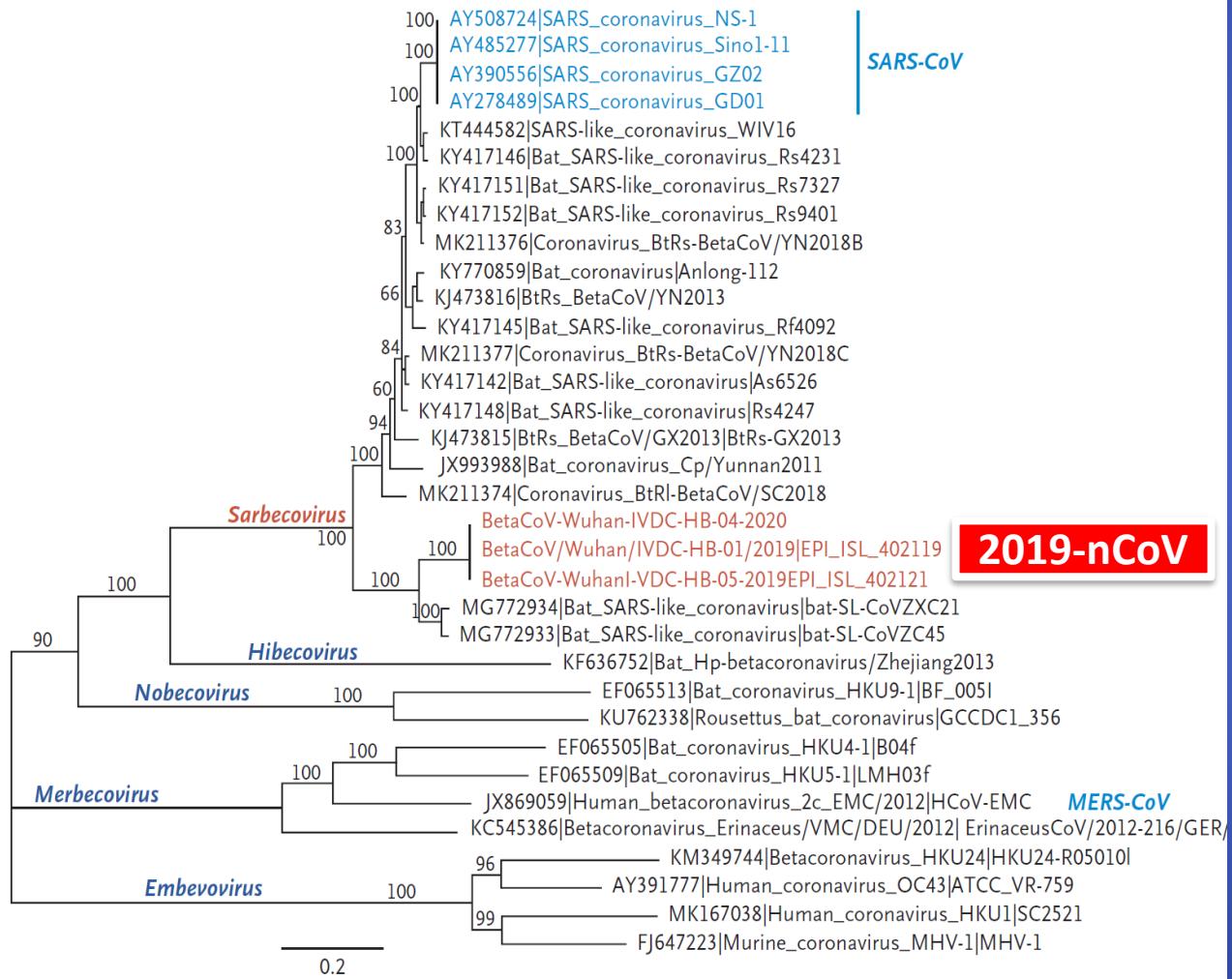
Day 11



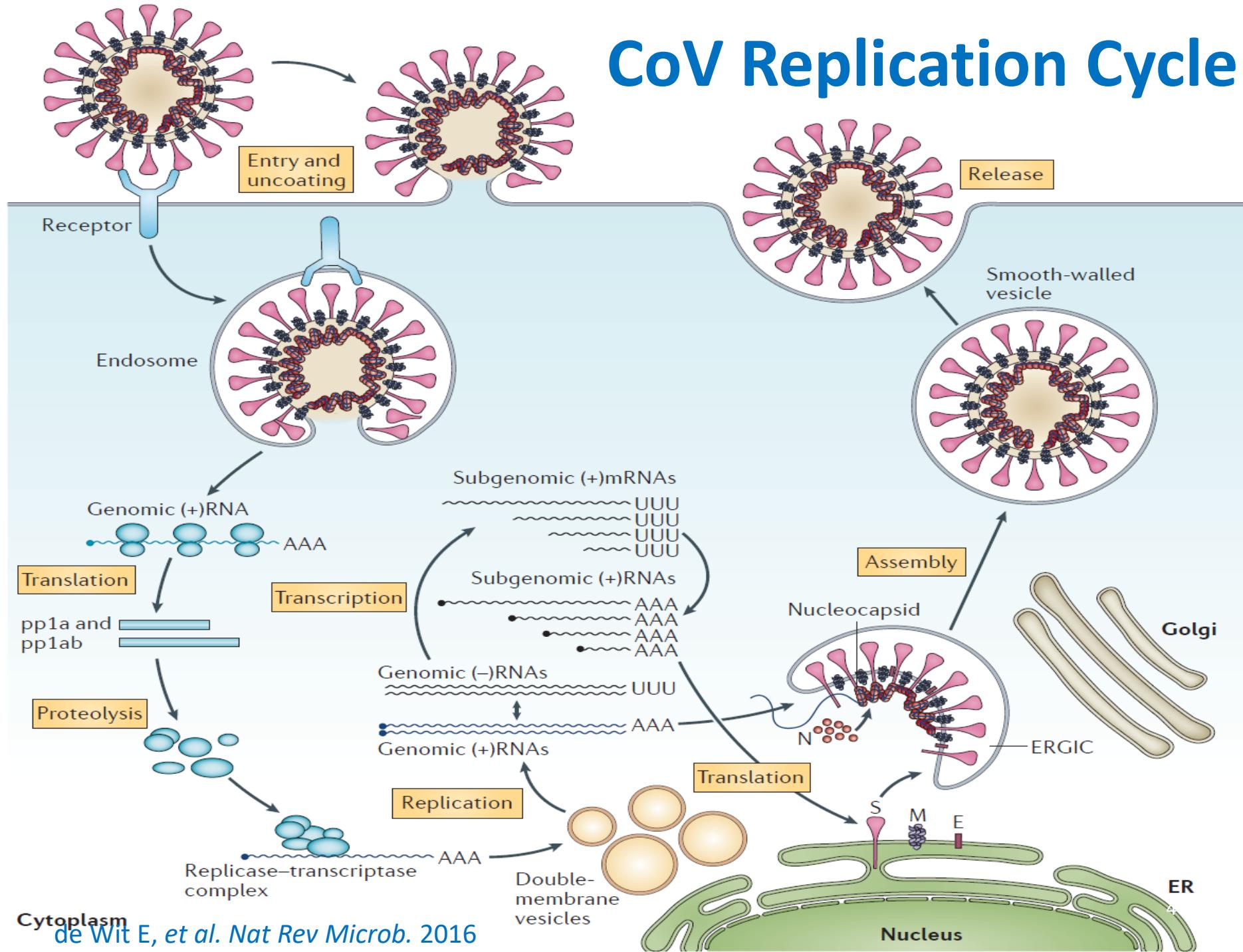
- Subsequent ARDS and mortality on Day 20.
- Which pathogens?

2019新型冠狀病毒

2019 Novel Coronavirus (2019-nCoV)

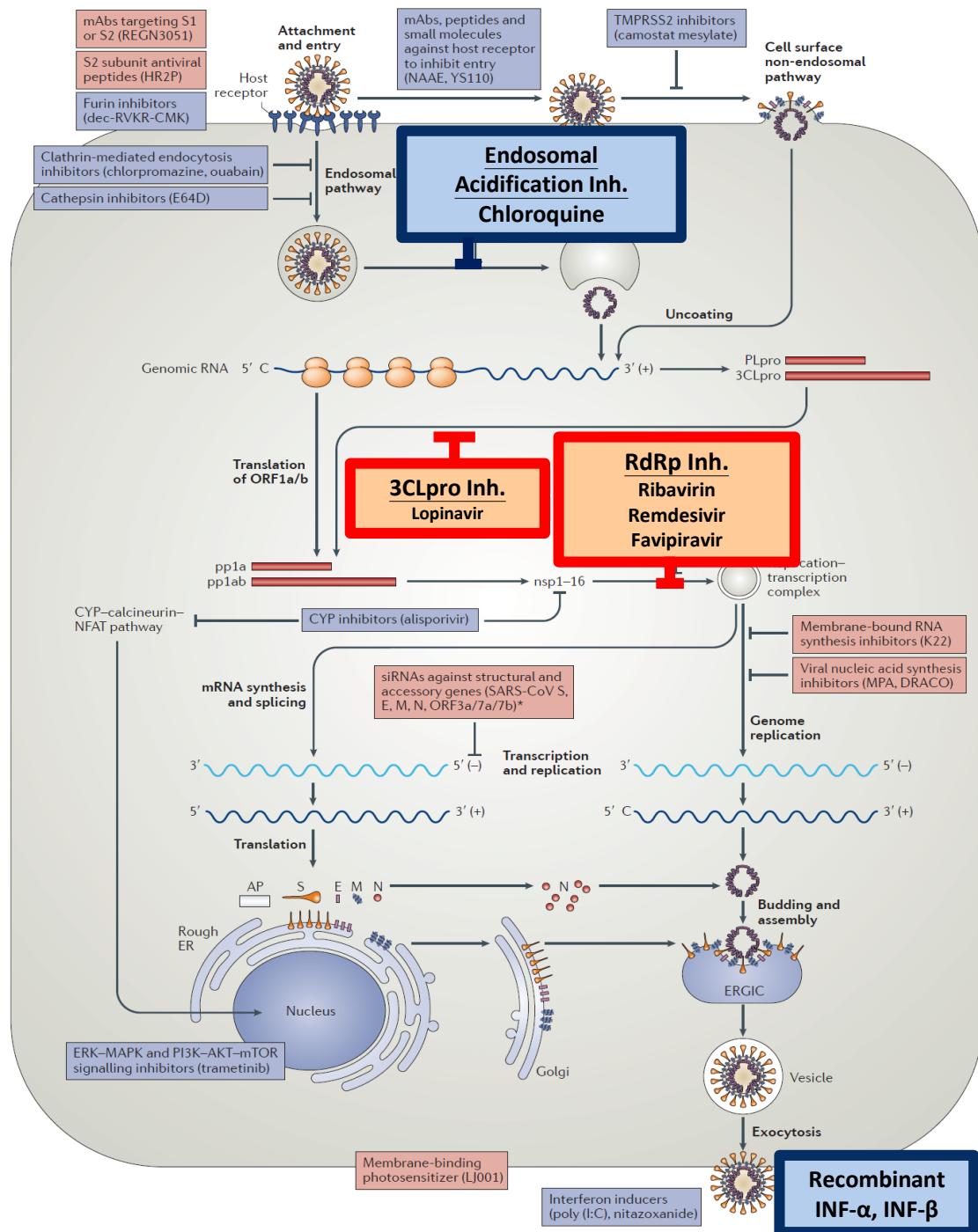


CoV Replication Cycle



Potential Drug Targets

Zumla A, et al. *Nat Rev Drug Discov.* 2016



Genomic Organizations of CoV

Non-structure proteins

ORF1a ORF1b

PLpro 3CLpro
1 2 3 4 5 6 7 8 9 10 11

2019-nCoV (human)

NSP 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
5' -

PL^{pro} 3CL^{pro}
DMV formation primase

Structure & accessory proteins

SARS-CoV 27.9 kb

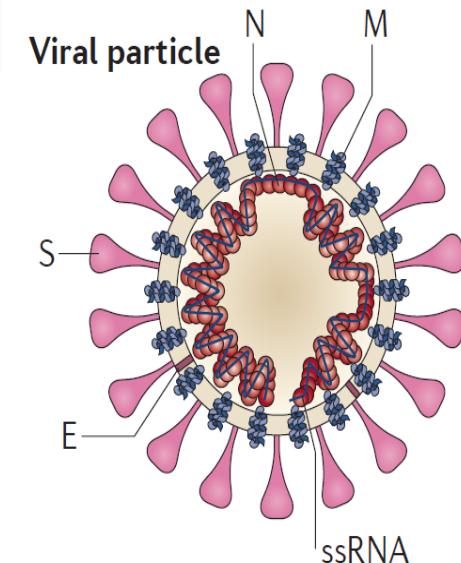
MERS-CoV 30.1 kb

RdRp

Hel ExoN

RdRP

Hel ExoN EndoU 2'-O-MT

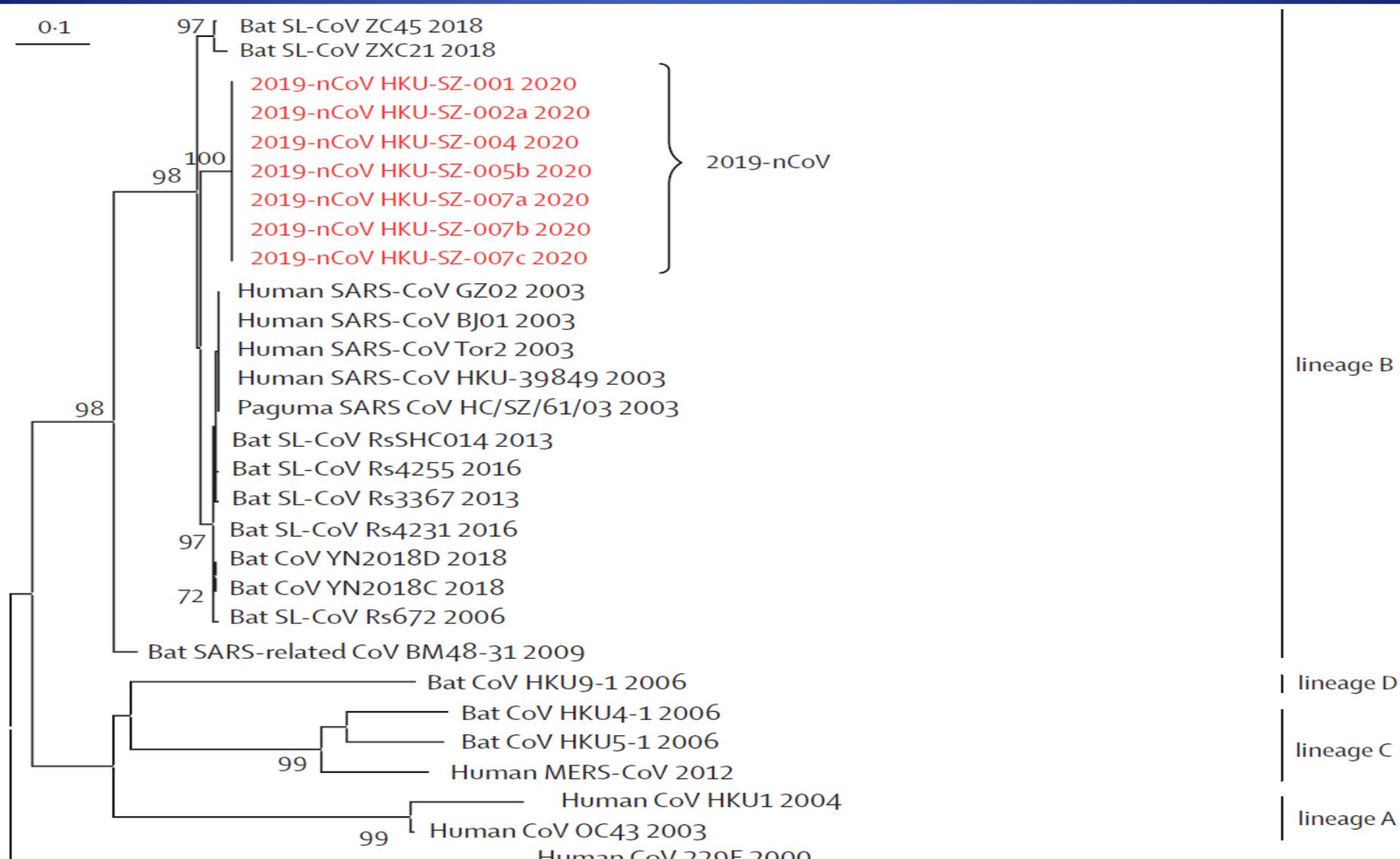


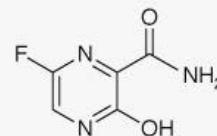
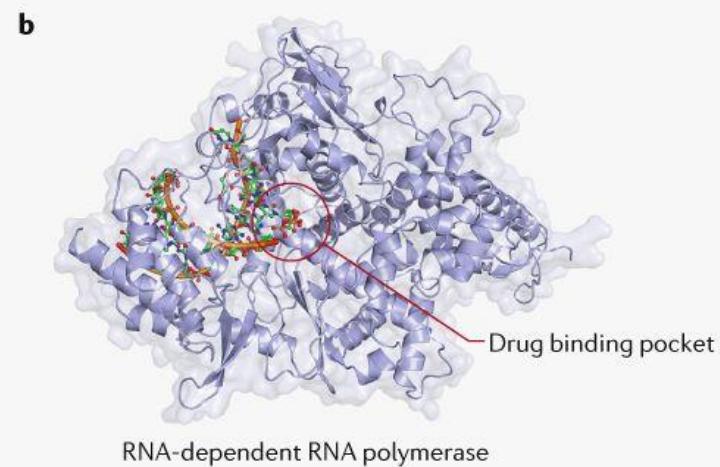
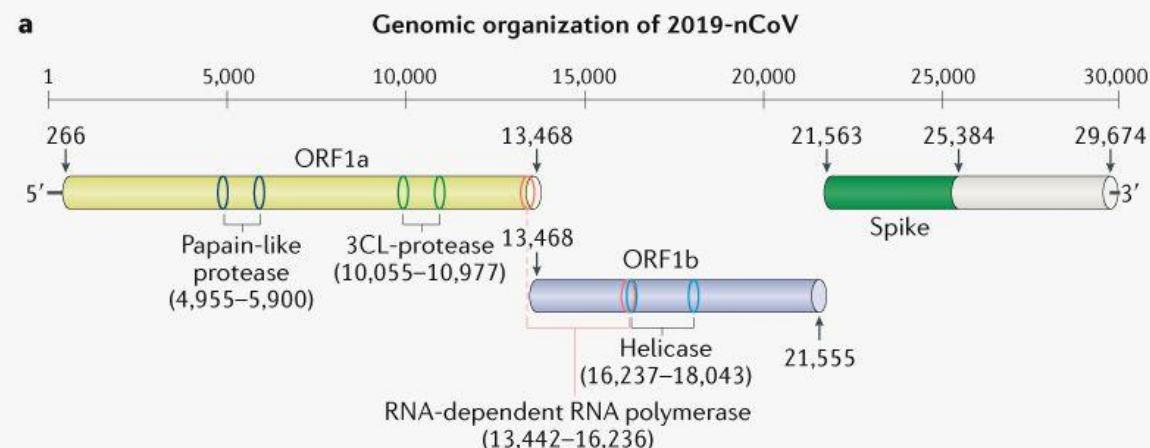
3CLpro: 3C-like protease

RdRp: RNA-dependent RNA polymerase

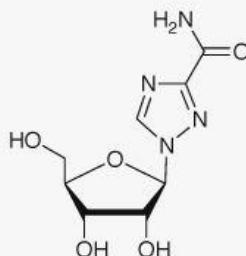
3a E 6 7a 9b
3b M 7b 8 N
-3'

Genetic Sequences of RNA-dependent RNA Polymerase (*RdRp*) are Conserved.

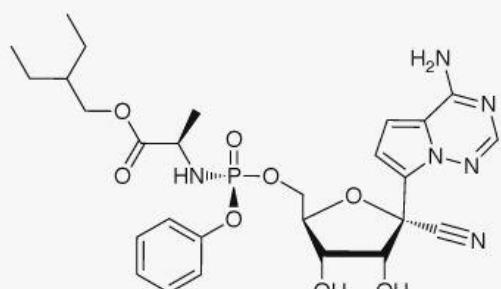




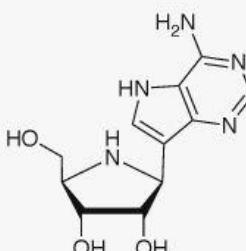
Favipiravir
(approved for influenza)



Ribavirin
(approved for HCV, RSV)



Remdesivir (GS-5734)



Galidesivir (BCX4430)

Rationale to Choose Potential Therapeutics at the Current Stage

- Currently available
- Antiviral activities against CoV
- PK/PD
- Clinical studies
- Tolerable safety profile
- Convenient administration

Repurposing & Developing Therapeutics for CoV

- 1. Mycophenolic acid
- 2. Kinase inhibitors
- 3. Cyclosporin
- 4. Estrogen modulating drugs

1. Chloroquine

1. RNA-dependent RNA polymerase (RdRp) inhibitors

Ribavirin, favipiravir, remdesivir*, galidesivir*

2. Protease inhibitors

Lopinavir/ritonavir

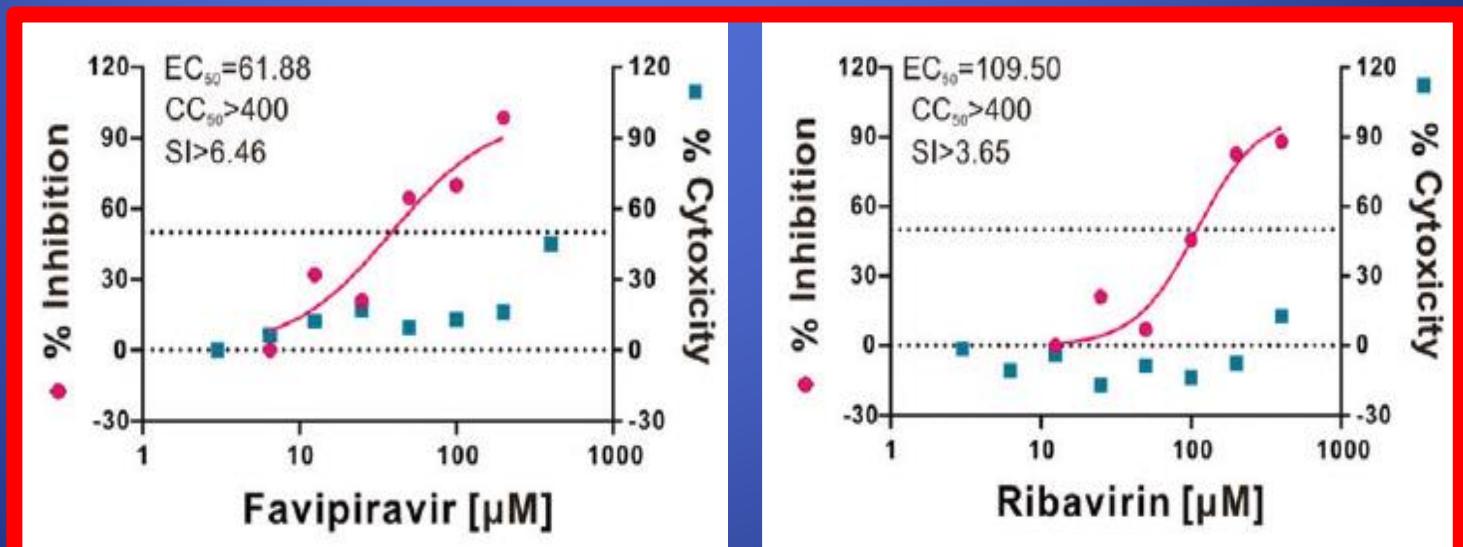
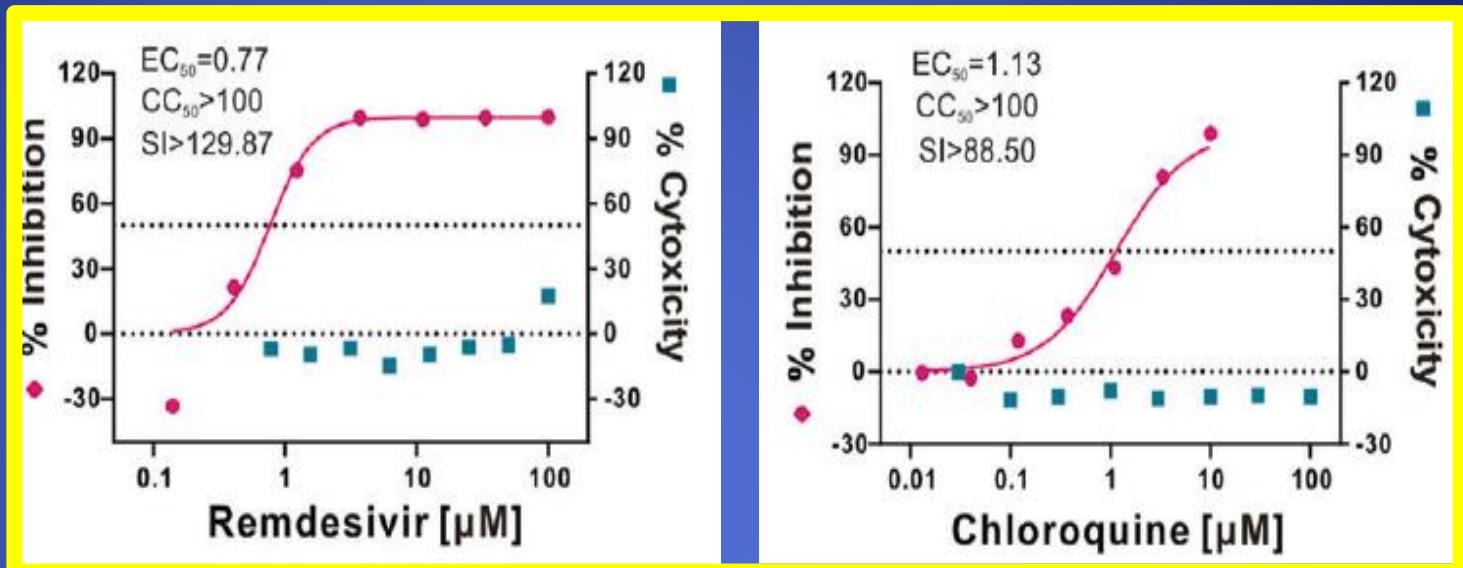
3. Interferons



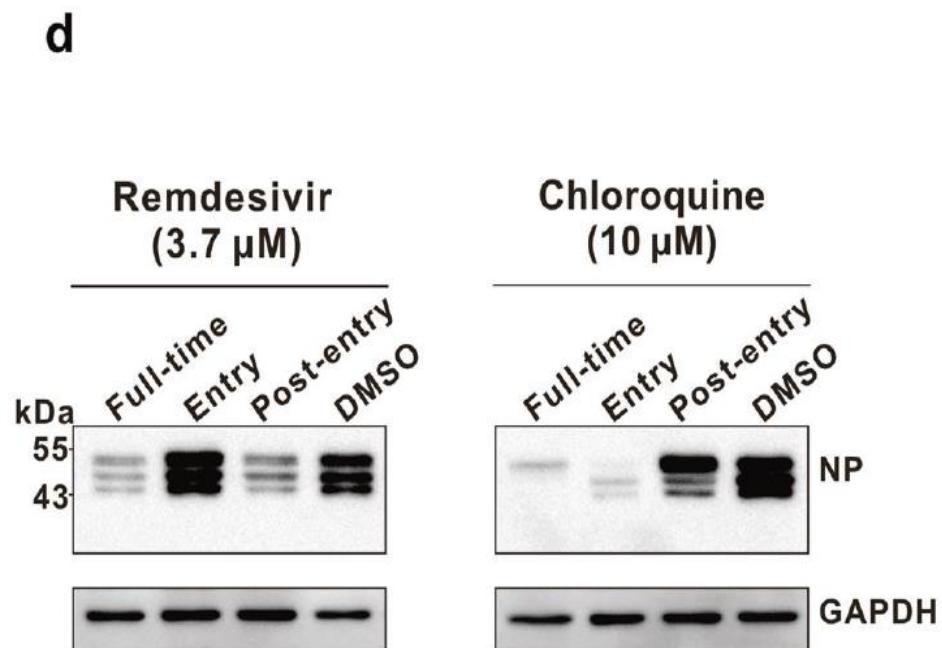
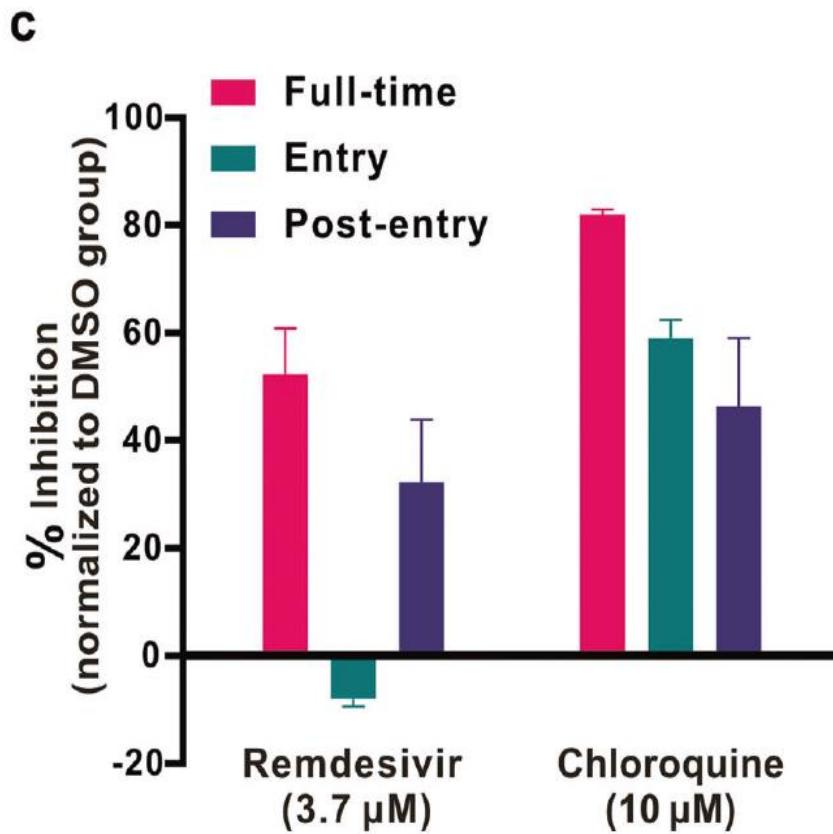
Summary of Potential Therapeutics

Medication	Mechanism of Action	Status	In Vitro studies		Animal experiments		Human studies	
			No data.	SARS-CoV	MERS-CoV	2019-nCoV	No data.	SARS-CoV
Interferon	Exogenous interferon	Marketed	😊	😊		😊	😊	😊
Lopinavir	Inhibitors of 3CLpro activity	Phase III	😊	😊		😊		😊
Ribavirin	Guanosine analogue that inhibits viral RNA synthesis and mRNA capping	Marketed	😊	😊	😊	😊		😊
Remdesivir	Nucleotide prodrug, transforming to adenosine triphosphate analog, inhibiting viral polymerase	Phase III	😊	😊	😊	😊		😊
Favipiravir	Purine nucleoside analog, inhibiting viral polymerase	Marketed						
Chloroquine	Sequestering protons in lysosomes to increase the intracellular pH	Marketed	😊	😊	😊	😊		

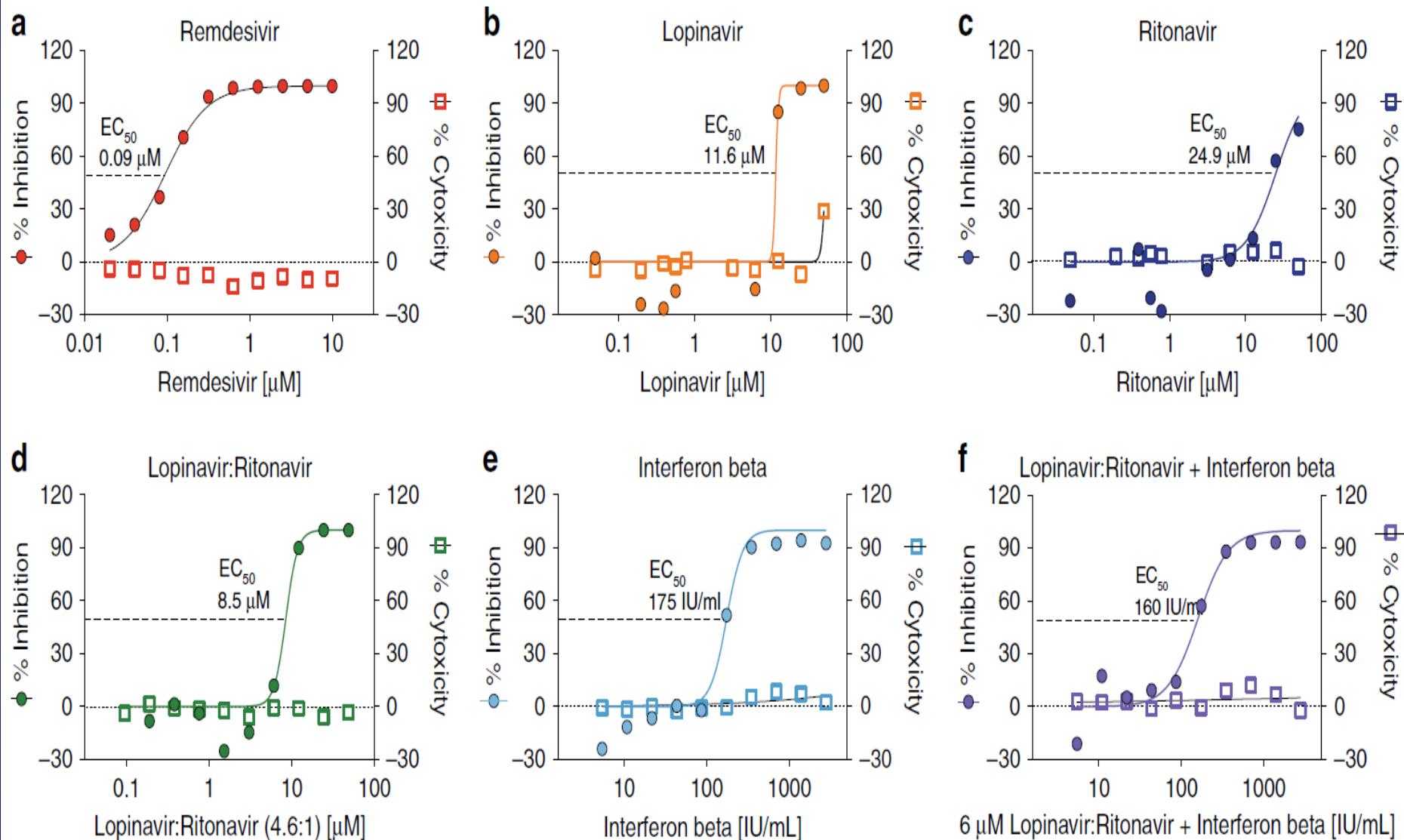
Antiviral Activities Against 2019-nCoV



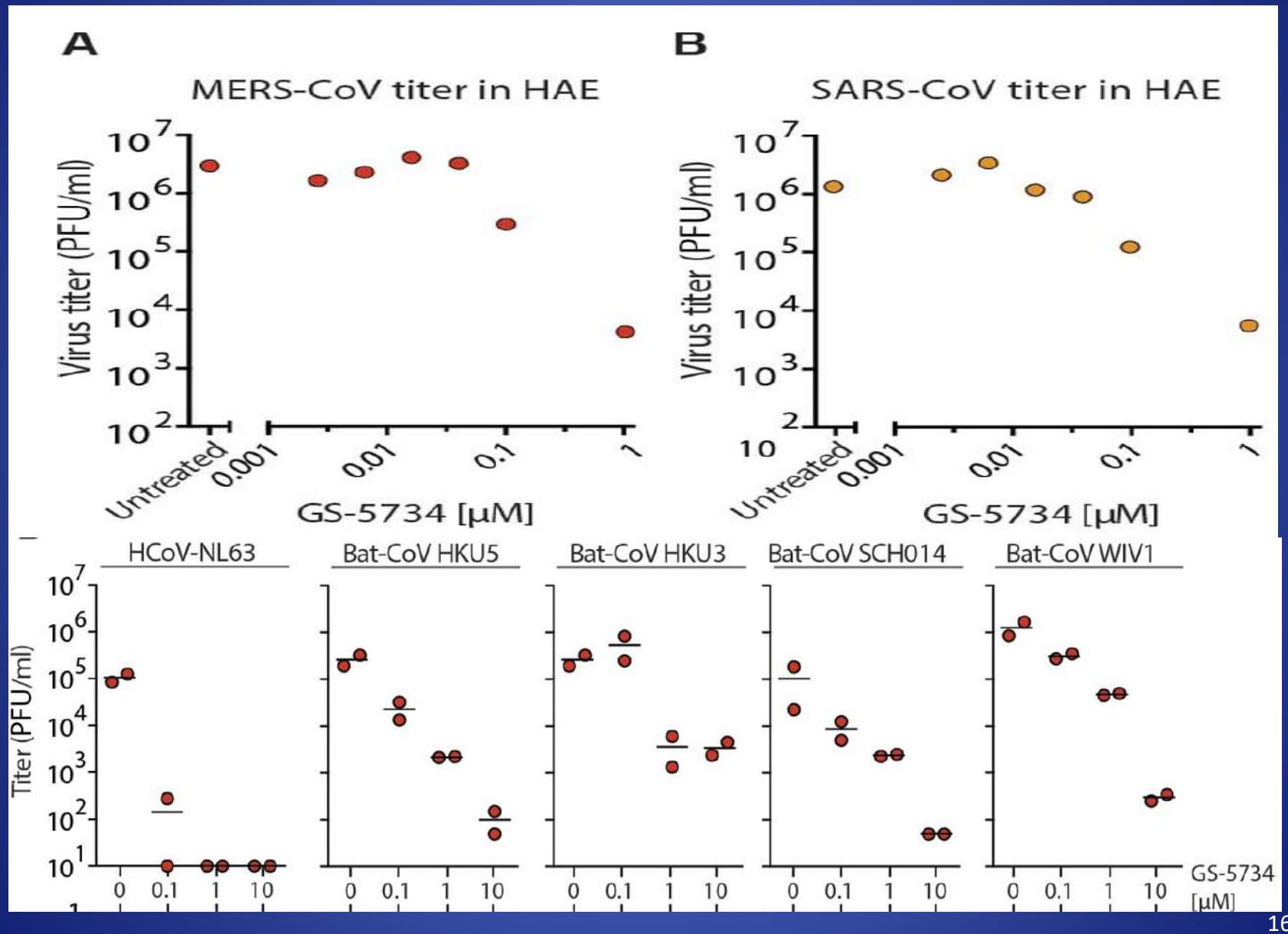
Time-of-addition Experiments Reflect Drug Mechanisms: 2019-nCoV



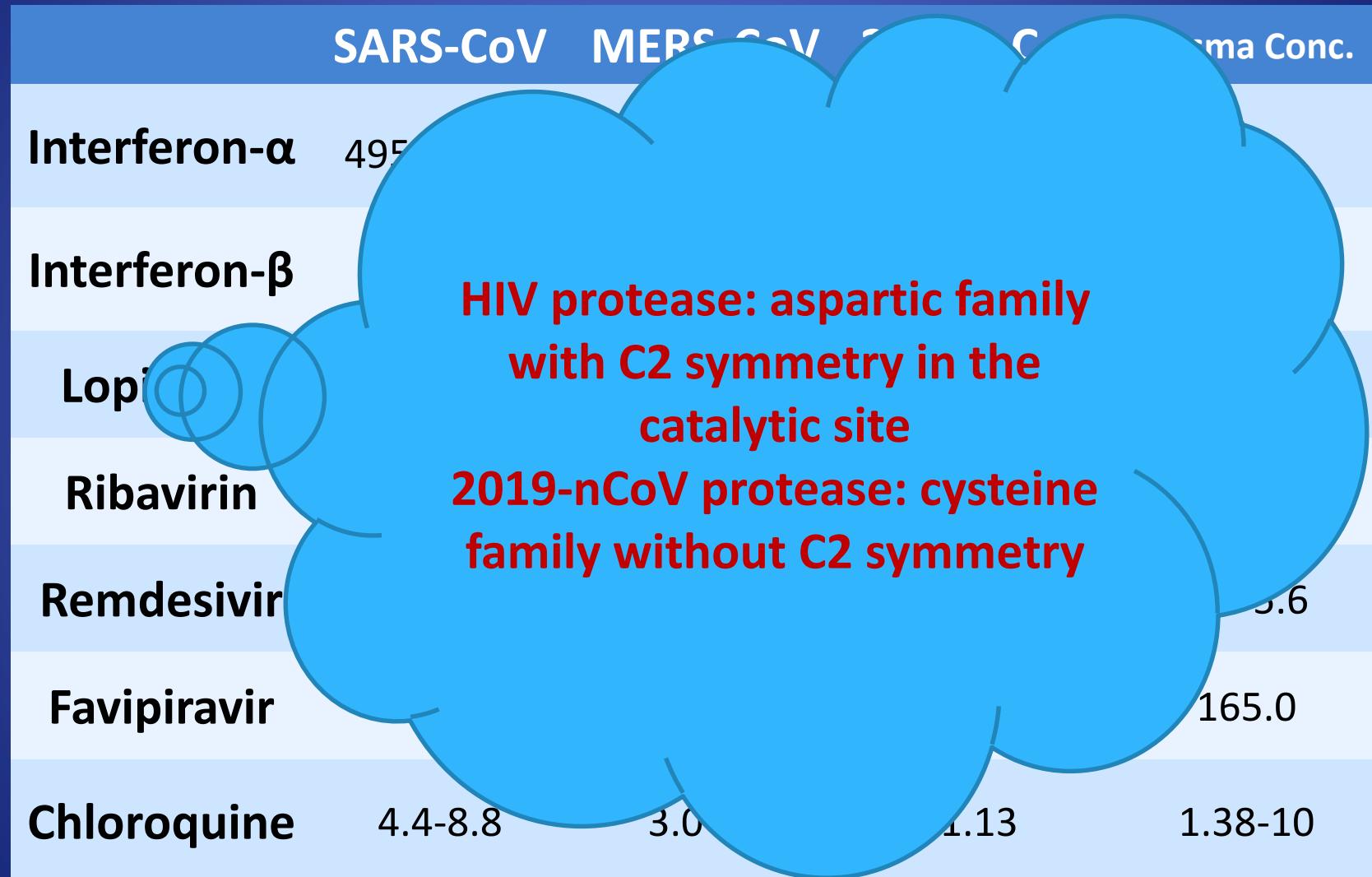
Antiviral Activities Against MERS-CoV



Remdesivir Against Human & Zoonotic CoVs



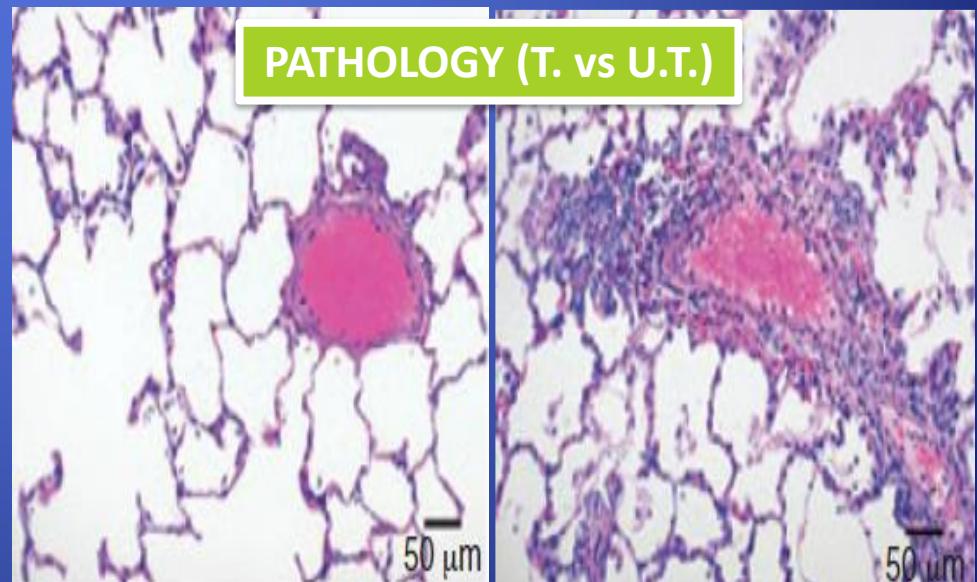
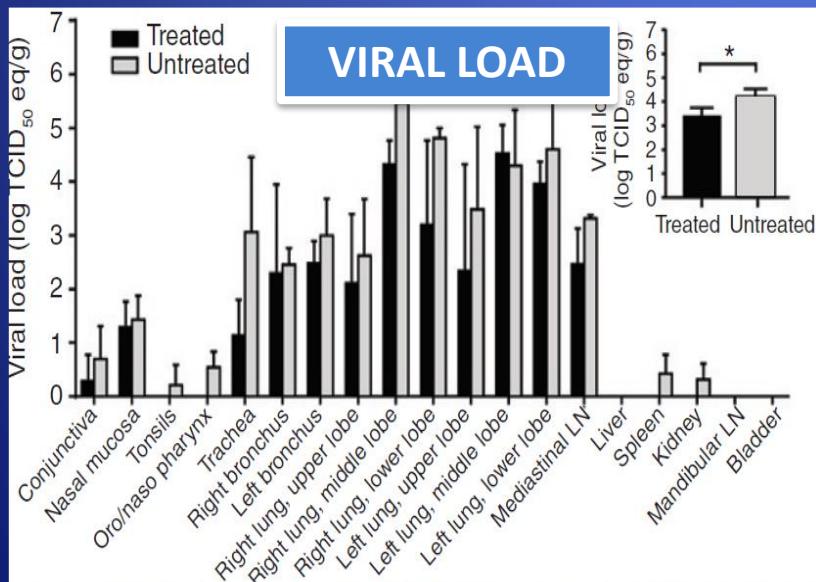
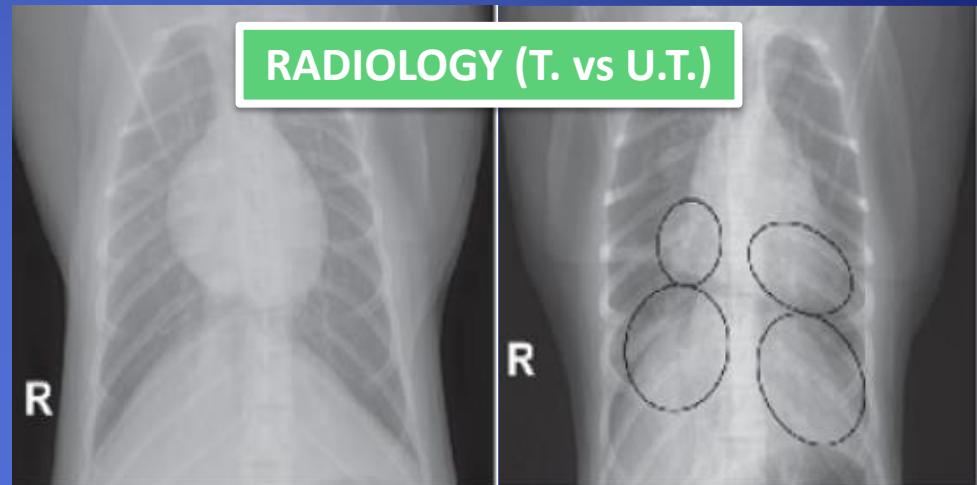
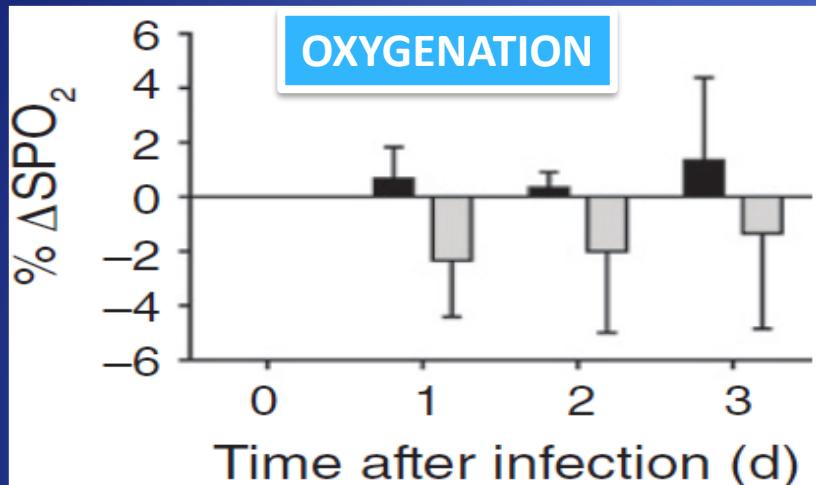
In Vitro Efficacies (EC_{50})





IFN- α 2b + RBV vs. Placebo

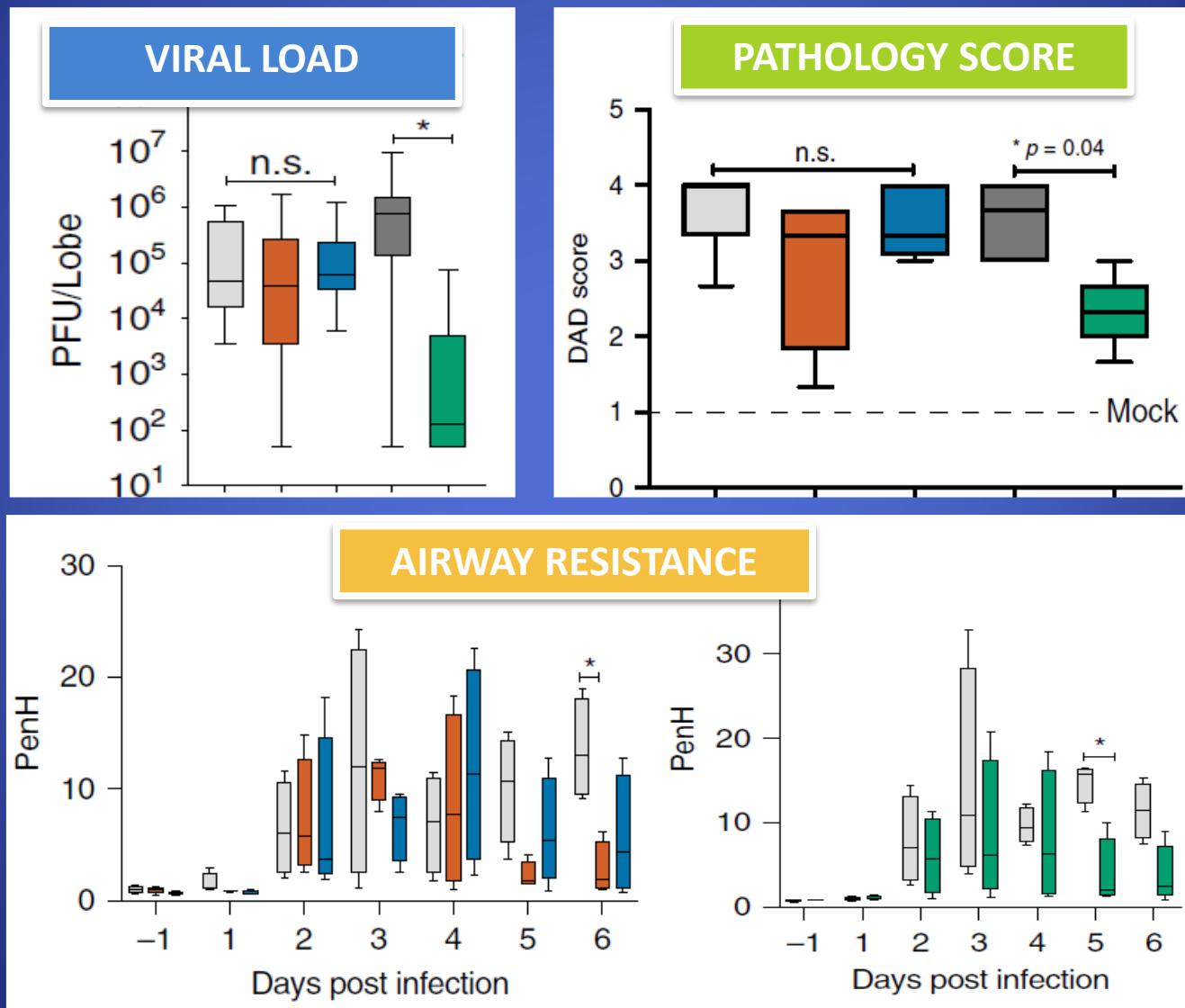
MERS-CoV infected rhesus macaques



IFN- β low/high + LPVr vs. RDV



MERS-CoV infected mice



Summary of Animal Experiments

Medication	SARS-CoV	MERS-CoV
Interferon	INF α reduced viral titres in lungs of SARS-CoV infected mice & cynomolgus macaques.	<ul style="list-style-type: none">Intranasal INFβ administered before or after MERS-CoV challenge reduced viral titres in the lungs of Ad5hDPP4 C57BL/6 and Rag1$-/-$ mice by 10–100 fold.Subcutaneous INFβ1 improved outcomes of MERS-CoV infected common marmosets.
Lopinavir	-	Improved outcome of MERS-CoV infected common marmosets
Ribavirin	RBV monotherapy showed mixed results in mice models for SARS-CoV	Subcutaneous INF α 2b and RBV combination improved outcomes of MERS-CoV infected rhesus macaques
Remdesivir	RDV more effective than placebo in prophylactic and therapeutic SARS infected mice model.	LPV/RTV+low or high INF β less effective than RDV in prophylactic and therapeutic MERS infected mice model.
Chloroquine	Not active against SARS-CoV infected mice.	-

Type of intervention	Therapeutic intervention	Treatment effects	Refs
Treatments used for SARS patients			
Antivirals	Ribavirin	No significant effect on clinical outcome	10,21
	Ribavirin, lopinavir–ritonavir + corticosteroids	Patients who received ribavirin, lopinavir–ritonavir and a corticosteroid had lower 21-day ARDS and death rates than those who received ribavirin and a corticosteroid	76,77
Interferon combination	Interferon alfa-1 + corticosteroid	Associated with improved oxygen saturation and more rapid resolution of radiographic lung opacities than systemic corticosteroid alone (uncontrolled study)	78
Corticosteroids	Pulsed methylprednisolone	Associated with an increased 30-day mortality rate (adjusted OR = 26.0, 95% CI = 4.4–154.8). Disseminated fungal infection and avascular osteonecrosis occurred following prolonged systemic corticosteroid therapy	79–81
		A randomized, placebo-controlled study showed that plasma SARS-CoV RNA levels in weeks 2–3 of the illness were higher in patients given hydrocortisone ($n = 10$) than those given normal saline ($n = 7$) in the early phase of the illness, suggesting that early use of pulsed methylprednisolone might prolong viraemia	82
Treatments used for MERS patients			
Combination of antivirals and interferons	Ribavirin + interferon alfa-2a or interferon alfa-2b	No significant effect on clinical outcome; case–control study showed significantly improved survival (14 out of 20 and 7 out of 24 in the treated and control groups, respectively; $P = 0.004$) at 14 days, but not at 28 days	86–89
	Ribavirin + interferon beta-1a	Retrospective analyses showed no significant effect on clinical outcome	89
	Ribavirin, lopinavir–ritonavir + interferon alfa-2a	Viraemia resolved 2 days after commencement of treatment in a patient with severe MERS	90

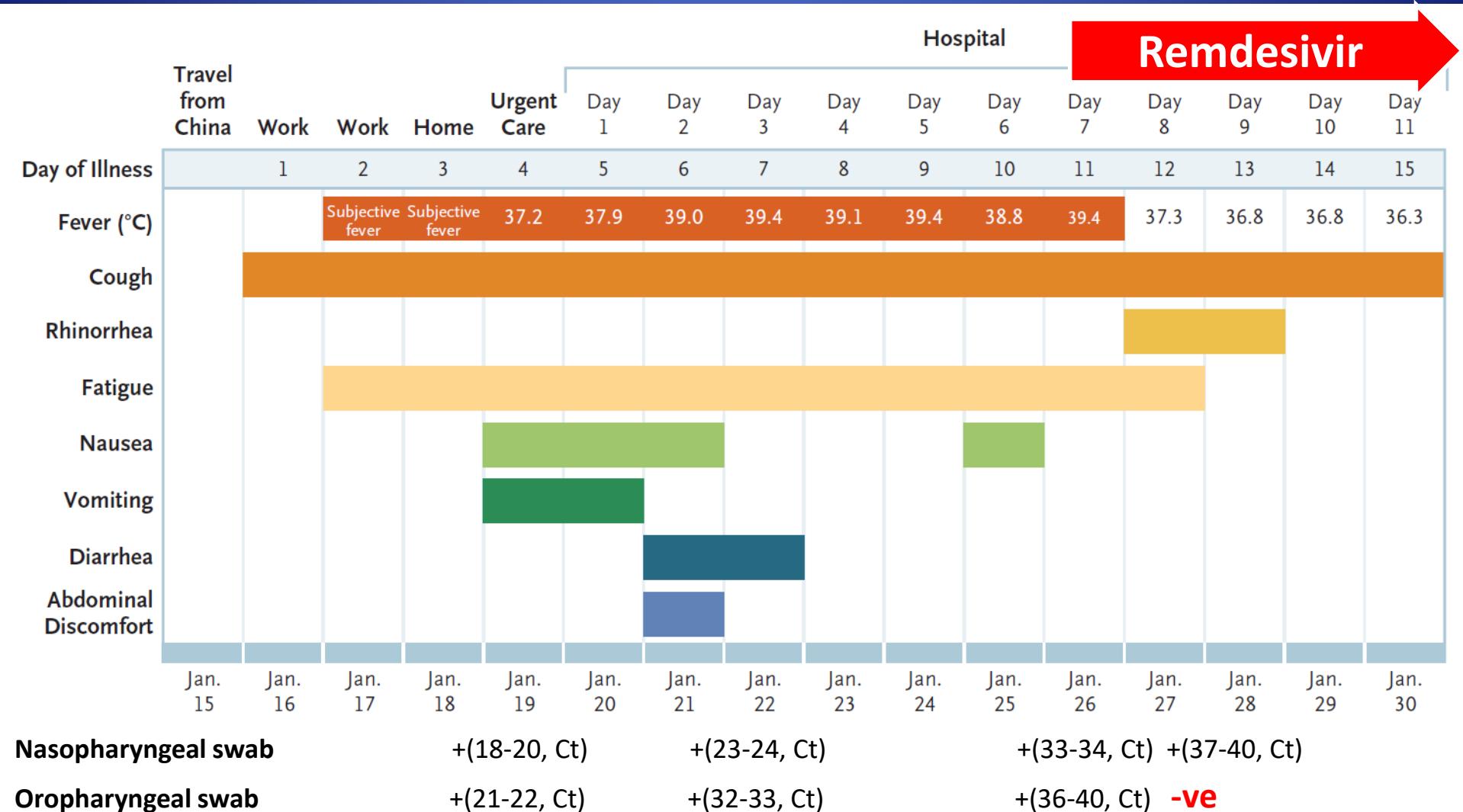


No Steroid



Combinations

Remdesivir as Potential Therapeutics for 2019-nCoV



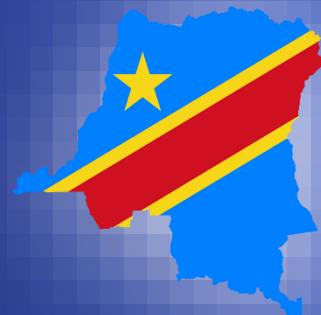
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 12, 2019

VOL. 381 NO. 24

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics



Patients of
any age

Remdesivir
LOADING: 200 mg (10mg/kg) on
Day 1
MAINTENANCE: 100 mg (5mg/kg)
on Day 2-14

ZMapp

N = 169

Remdesivir

N = 175

MAb114

N = 155

REGN-EB3

N = 154

SAE

7 (4.1%)

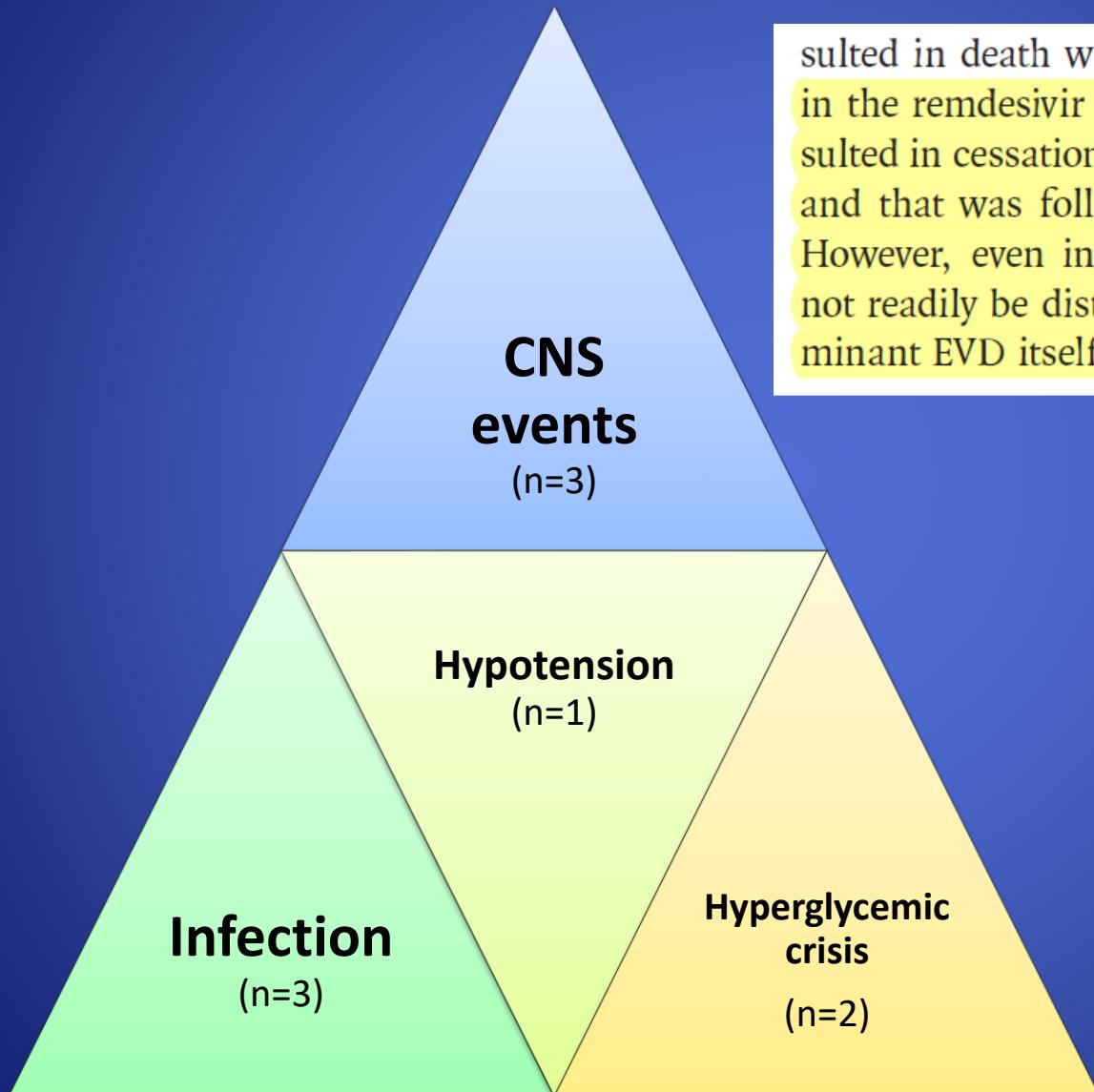
9 (5.1%)

10 (6.5%)

3 (1.9%)

23

SAE of Patients with EVD in RDV Group



sulted in death within 24 hours; and one patient in the remdesivir group had hypotension that resulted in cessation of a loading dose of remdesivir and that was followed rapidly by cardiac arrest. However, even in these cases, the deaths could not readily be distinguished from underlying fulminant EVD itself.

Elevated Amylase and Lactate After Prolonged Use of RDV in an EVD Patient

Jacobs M, et al. Lancet. 2016

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	40	
	Day of illness																									
Haemoglobin (110-150 g/L)	119	105	116	115	122	121	127	117	120	124	122	114	106	106	101	101	98	106	103	98	97	104	
Total white cell count (3.5-11.0 × 10 ⁹ /L)	13.1	16.1	16.8	13.4	9.6	8.5	10.4	14.9	12.8	12.5	12	14.5	16.6	12.8	12.6	13.1	10.4	12.5	9.8	8.9	8.3	7.9	
Neutrophil count (2.0-7.5 × 10 ⁹ /L)	11.4	14.4	15.1	11.6	7.7	5.9	7.1	12.8	11.1	10.1	9.8	12.9	13.8	11.3	8.3	7.4	6	11.2	4.7	5.1	4.7	4.9	
Lymphocyte count (1.3-3.5 × 10 ⁹ /L)	0.8	0.5	0.4	0.7	1.2	1.9	2.3	1	0.6	0.8	1	0.8	0.8	0.5	2.4	0.8	3.1	0.8	4.1	3	2.8	2	
Platelet count (150-400 × 10 ⁹ /L)	359	313	348	375	423	465	584	569	603	671	619	646	646	637	648	651	575	603	570	496	464	425	
Sodium	140	128	127	127	133	135	133	132	135	131	132	134	133	135	134	136	137	138	136	137	138	137	137
Potassium (3.5-5.0 mmol/L)	4.1	2.6	3.1	3.1	3.4	3.6	4.1	3.8	3.8	3.6	3.6	3.8	4	3.7	3.1	3.3	3.3	3.8	3.2	3.2	3.5	4.2	
Urea (3.0-6.5 mmol/L)	5.3	<1.0	<1.0	<1.0	1.2	2	3.3	2.8	4.3	4.6	6.3	6.3	6.6	6.7	7.5	8.4	5.4	5	3.8	3.1	2.4	2	
Creatinine (44-97 µmol/L)	57	39	39	37	41	38	45	37	36	34	42	36	41	40	42	48	31	38	45	49	44	55	
Aspartate aminotransferase (5-40 IU/L)	17	27	44	32	31	35	54	40	41	32	30	33	30	32	30	30	22	24	30	23	21	12	
Creatine kinase (0-220 IU/L)	132	754	430	203	102	110	82	99	112	125	113	86	84	76	78	75	81	65	70	59	..	
Amylase (70-220 IU/L)	63	53	60	59	76	95	104	170	220	253	323	429	395	398	313	229	233	193	175	156	..	
Lactate (0.5-2.0 mmol/L)	2.8	1.3	2.8	2.7	2.4	2.8	3.1	2.2	2.5	3	3.1	3.1	2	1.9	2.1	3.4	3	2.6	1.8	
C-reactive protein (<5 mg/L)	18	56	128	163	130	50	24	17	9	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<1	

Remdesivir (150mg x2, 225mg x 12)

Ongoing Trials, At least 90*

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	Severe 2019-nCoV Remdesivir RCT NEW	<ul style="list-style-type: none"> • 2019-nCov • Remdesivir 	<ul style="list-style-type: none"> • Drug: Remdesivir • Drug: Remdesivir 	<ul style="list-style-type: none"> • Bin Cao Beijing, Beijing, China
2	<input type="checkbox"/>	Not yet recruiting	Mild/Moderate 2019-nCoV Remdesivir RCT NEW	<ul style="list-style-type: none"> • 2019-nCoV 	<ul style="list-style-type: none"> • Drug: Remdesivir • Drug: Remdesivir 	<ul style="list-style-type: none"> placebo

RDV 200 mg loading dose on day 1 is given, followed by 100 mg iv once-daily maintenance doses for 9 days.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Drug Adverse Events

Medication	Common	Occasional	Rare
Interferon	Flu-like syndrome, GI intolerance, Neuropsychiatric toxicity, Hepatitis, Rash	Marrow suppression	Suicidal ideation or behavior, thyroiditis, ITP/TTP, retinopathy
Lopinavir	Diarrhea	Hepatitis, N/V	Rash, prolonged OTc
Ribavirin	Hemolytic anemia	Fatigue, Dyspepsia, Anorexia	Lactic acidosis, Decreased vision
Remdesivir	Elevated transaminases	?	?
Favipiravir	Elevated transaminases, leukopenia, hyperuricemia	N/V, Diarrhea	Elevated CPK
Chloroquine	-	Visual disturbance, Hemolysis with G6PD deficiency	Retinopathy, peripheral neuropathy, Rash

Other Potential Therapeutics for CoV

- Convalescent plasma and immunoglobulins
- Monoclonal/Polyclonal antibodies
- Vaccines



Zumla A, et al. *Nat Rev Drug Discov.* 2016
Mo Y, et al. *J Antimicrob Chemother.* 2016
Dyall J et al. *Drugs.* 2017
Russell CD, et al. *Lancet.* 2020

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury

Outcomes of corticosteroid therapy*	Comment
MERS-CoV Delayed clearance of viral RNA from respiratory tract ²	Adjusted hazard ratio 0·4 (95% CI 0·2-0·7)
SARS-CoV Delayed clearance of viral RNA from blood ⁵	Significant difference but effect size not quantified
SARS-CoV Complication: psychosis ⁶	Associated with higher cumulative dose, 10 975 mg vs 6780 mg hydrocortisone equivalent
SARS-CoV Complication: diabetes ⁷	33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes
SARS-CoV Complication: avascular necrosis in survivors ⁸	Among 40 patients who survived after corticosteroid treatment, 12 (30%) had avascular necrosis and 30 (75%) had osteoporosis
Influenza Increased mortality ⁹	Risk ratio for mortality 1·75 (95% CI 1·3-2·4) in a meta-analysis of 6548 patients from ten studies
RSV No clinical benefit in children ^{10,11}	No effect in largest randomised controlled trial of 600 children, of whom 305 (51%) had been treated with corticosteroids

At the Bottom Line

- No therapeutics for CoVs are approved at present.
- Remdesivir is a reasonable choice for compassionate use.
- Combination of interferon and lopinavir/ritonavir with or without ribavirin is an alternative.
- Steroid is strongly recommended against use in COVID-19 patients.

Thanks! Any Comments?

勿恃敵之不來，恃吾有以待之

Biei, Japan, 2017

