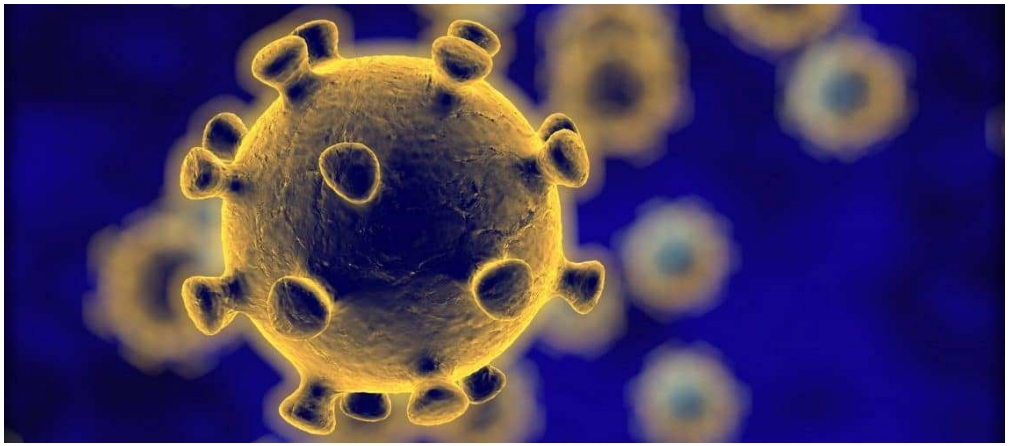
Aspects cliniques et Thérapeutiques du CoViD-19



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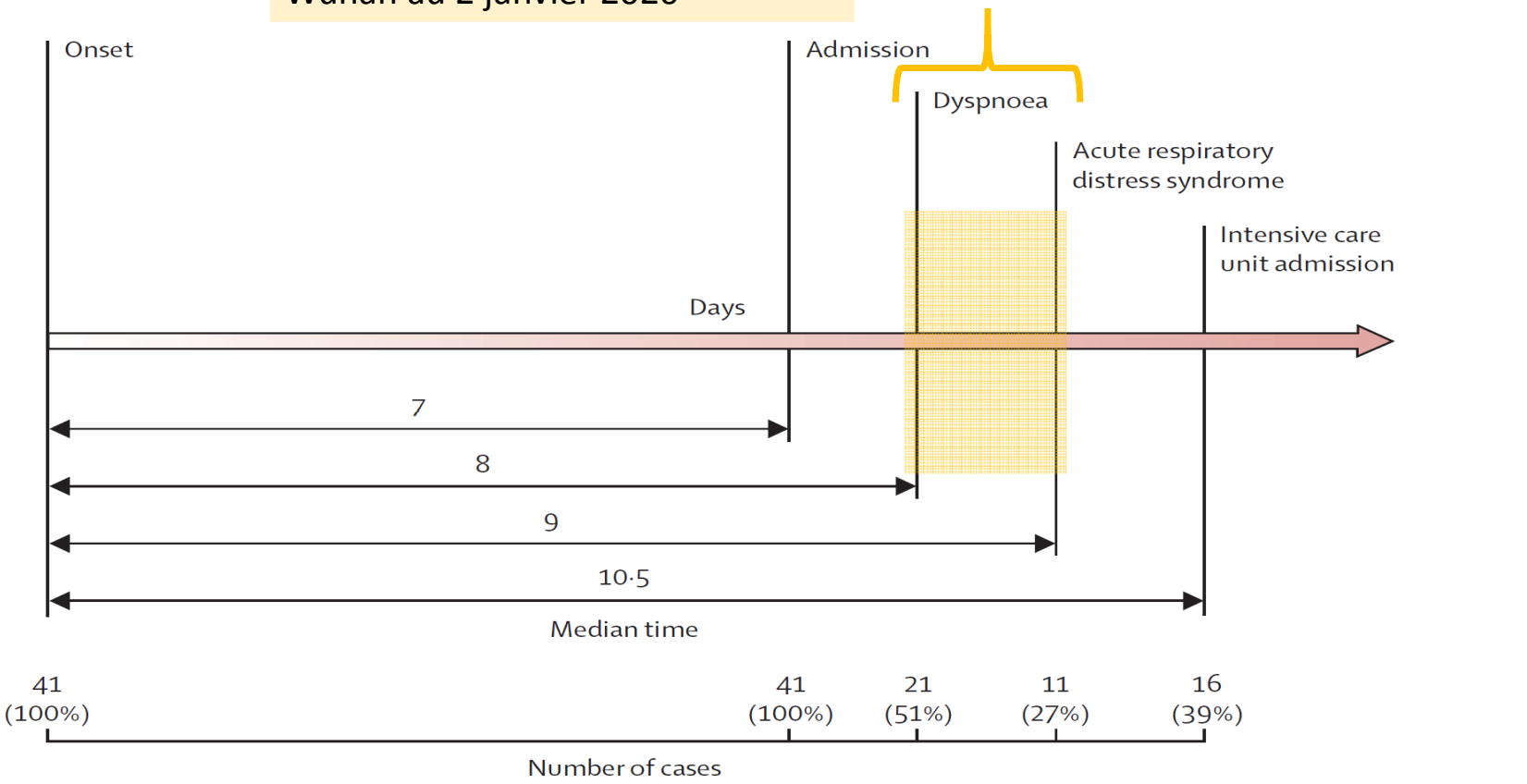
Mercredi 4 mars 2020

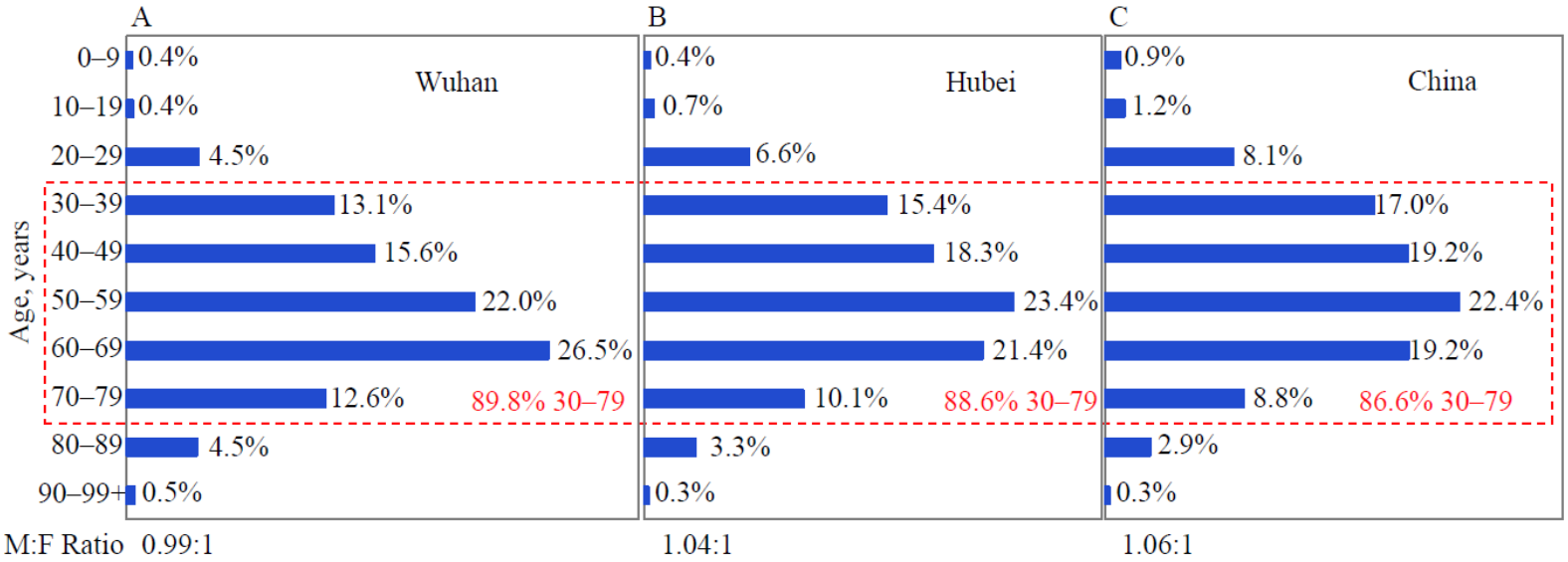
Tableau clinique, évolution

41 premiers patients hospitalisés à Wuhan au 2 janvier 2020



Ref. 8

Tableau clinique pyramide des âges



Age des cas confirmés de CoViD-19 en Chine au 11 fev 2020 (N=44672)

Ref. 6

Tableau clinique, biologique et imagerie

trois séries *Ref. 3*, n = 99; *Ref. 5*, n = 138; *Ref. 6*,n = 44672

Démographie

- Age médian (ans) : 56
- Femme : 48,6%
- Comorbidités(n=20985): 26%
  - HTA: 12,8%
  - Cardiovasculaire : 4,2%
  - Diabète : 5%
  - Cancer : 0,5%

Biologie

- Leucocytes (/mm^3) : 4500
- Lymphocytes (/mm^3) : 800
- LDH (U/L) : 261
- Procalcitonine (ng/mL) : 49

Imagerie

- Pneumopathie unilatérale : 25 (25%)
- Pneumopathie bilatérale : 74 (75%)
- Opacités en verre dépoli : 14 (14%)

Clinique

- Fièvre : 136 (99%)
- Toux : 82 (59%)
- Dyspnée : 43 (31%)
- Myalgies : 48 (35%)
- Odynophagie : 24 (11%)
- Diarrhée : 14 (10%)

Evolution

- Critique: 2087 (4,7%)
- Admis USI : 36 (26%)
- SDRA : 27 (20%)
- Insuffisance rénale aigue : 5 (4%)
- Choc septique : 12 (9%)
- Guérison : 47 (34%)
- Décès : 14 (14%) ; 6 (4%); 1023 (2,3%)

Ref. 3-6

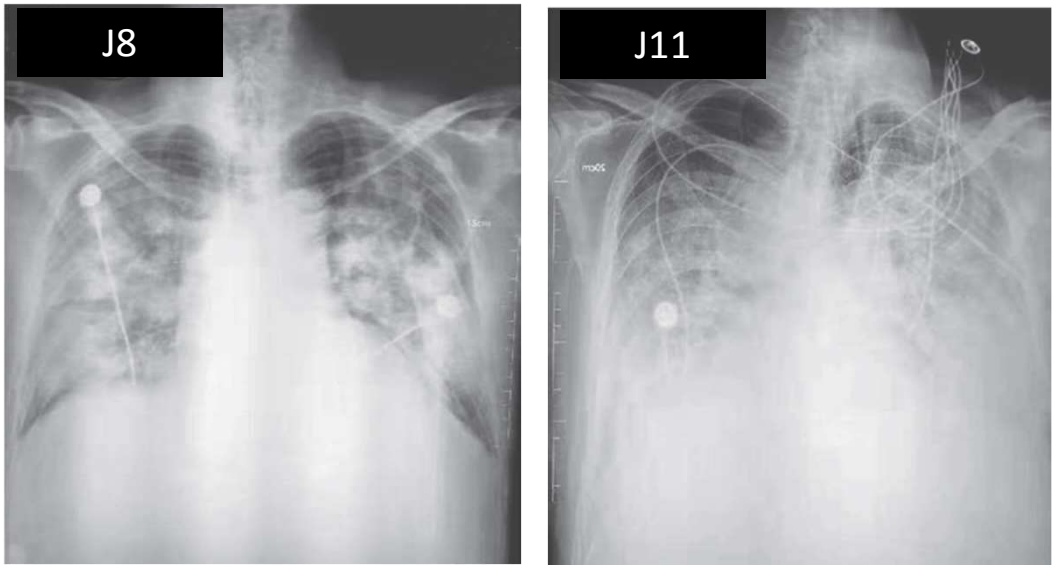
Mortalité selon le terrain

Baseline characteristics	Confirmed cases, N (%)	Deaths, N (%)	Case fatality rate, %
Overall	44,672	1,023	2.3
Age, years			
0–9	416 (0.9)	–	–
10–19	549 (1.2)	1 (0.1)	0.2
20–29	3,619 (8.1)	7 (0.7)	0.2
30–39	7,600 (17.0)	18 (1.8)	0.2
40–49	8,571 (19.2)	38 (3.7)	0.4
50–59	10,008 (22.4)	130 (12.7)	1.3
60–69	8,583 (19.2)	309 (30.2)	3.6
70–79	3,918 (8.8)	312 (30.5)	8.0
≥80	1,408 (3.2)	208 (20.3)	14.8
Sex			
Male	22,981 (51.4)	653 (63.8)	2.8
Female	21,691 (48.6)	370 (36.2)	1.7

Baseline characteristics	Confirmed cases, N (%)	Deaths, N (%)	Case fatality rate, %
Comorbid condition†			
Hypertension	2,683 (12.8)	161 (39.7)	6.0
Diabetes	1,102 (5.3)	80 (19.7)	7.3
Cardiovascular disease	873 (4.2)	92 (22.7)	10.5
Chronic respiratory disease	511 (2.4)	32 (7.9)	6.3
Cancer (any)	107 (0.5)	6 (1.5)	5.6
None	15,536 (74.0)	133 (32.8)	0.9
Missing	23,690 (53.0)	617 (60.3)	2.6
Case severity§			
Mild	36,160 (80.9)	–	–
Severe	6,168 (13.8)	–	–
Critical	2,087 (4.7)	1,023 (100)	49.0
Missing	257 (0.6)	–	–

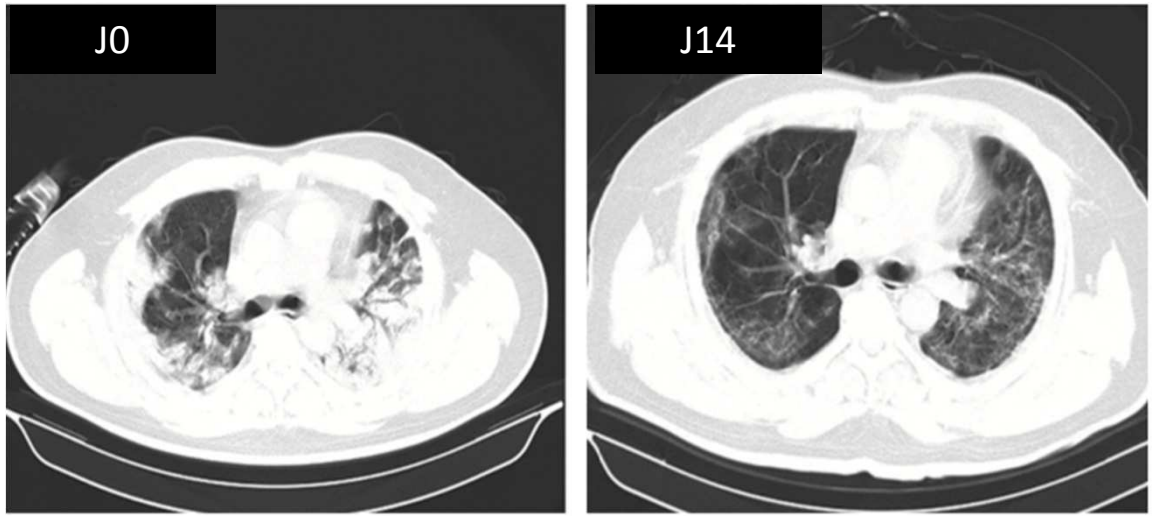
Ref. 6

Tableau clinique, imagerie



Aggravation clinique et radiologique avec décès du patient

Amélioration clinique et radiologique à J14



Ref. 1,5

Tableau clinique, traitement

Deux séries *Ref. 7*, n = 99; *Ref. 9*, n = 138

Traitements antiviraux

- Patients traités:
  - Oseltamivir: 124 (90%)
- Patients traités: 75 (76%)
  - Oseltamivir
  - Ganciclovir
  - Lopinavir/ritonavir

Traitements antibiotiques

- Patients traités:
  - Moxifloxacine: 89 (64%)
  - Ceftriaxone: 34 (25%)
- Patients traités: 70 (71%)

Traitements de support

- Oxygénothérapie: 106 (77%)
- Ventilation mécanique
  - Non invasive: 15 (11%)
  - Invasive: 17 (12%)
- Dialyse: 2 (1%)
- ECMO: 4 (3%)

Ref. 3,5

Tableau clinique, évolution

CDC Chinois, n = 72672

- **<u>Confirmés par PCR</u>** : 44 672 (62%)
- Asymptomatique: 889 (1%)

- Age : (n = 44 672)
  - ≥80 ans: 1408 (3%)
  - 30-79 ans: 38 680 (87%)
  - 20-29 ans: 3619 (8%)
  - 10-19 ans: 549 (1%)
  - <10 ans: 416 (1%)
- Homme : 22 981 (51%)

Démographie

- Comorbidités: connues pour 20 812 pts
  - HTA : 2 683 (13%)
  - Diabète : 1 102 (5%)
  - Cardiovasculaire : 873 (4%)
  - Insuffisance respiratoire chronique: 511 (2,4%)
  - Cancer : 107 (0.5%)

- Forme clinique: (n = 44 415)
  - Modérée: 36160 (81%)
  - Grave: 6168 (14%)
  - Critique: 2087 (5%)

Clinique

- Décès
  - Total: 2.3% (1023/44 672)
  - Age ≥80: 14.8% (208/1408)
  - Age 70-79: 8.0% (312/3918)
  - Forme clinique critique : 49.0% (1023/2087)

Evolution

- Professionnels de santé
  N=1716 (3,8%)
  - Wuhan: 63% (n=1080)
  - Formes graves ou critiques: 14% (n=247)
  - Décès: 0,3% (n=5)

Ref. 2

Tableau clinique critique

Etude monocentrique, rétrospective, **unité de soins intensifs**, n = 52

Démographie

- Age moyen (ans) : 59,7 (+/-13,3)
- Homme : 35 (67%)

- Comorbidités: 21 (40%)
  - cardiaque : 5 (10%)
  - respiratoire : 4 (8%)
  - cérébro-vasculaire: 7 (13,5%)
  - diabète : 9 (17%)
  - cancer : 2 (4%)

Clinique

- Fièvre : 51 (98%)
- Toux : 40 (77%)
- Dyspnée : 33 (64%)
- Malaise: 18 (35%)
- Myalgies : 6 (12%)
- Rhinorrhée : 3 (6%)

Imagerie

- Pneumopathie bilatérale : 52 (100%)

- Délais médians entre début des signes cliniques et:
  - diagnostic de pneumopathie: 5 (IQR 3-7)
  - admission en USI: 9,5 (IQR 7-12,5)

Gravité

- Score APACHE II: 17 (IQR14-19)
- SDRA: 35 (67%)
- Insuffisance rénale aiguë : 15 (29%)
- Insuffisance cardiaque: 12 (23%)
- Insuffisance hépatique: 15 (29%)
- Choc septique : 12 (9%)

Traitement

- VNI: 29 (56%)
- Intubation: 22 (42%)
- Décubitus ventral: 6 (12%)
- ECMO: 6 (12%)
- Antiviraux (anti-COVID -19) : 23 (44%)
- Antibiotiques: 49 (94%)
- Corticoïdes: 30 (58%)
- Immunoglobulines: 28 (54%)

Evolution

- Décès: 32 (62%)
- Guérison: 8 (15%)

Ref. 7

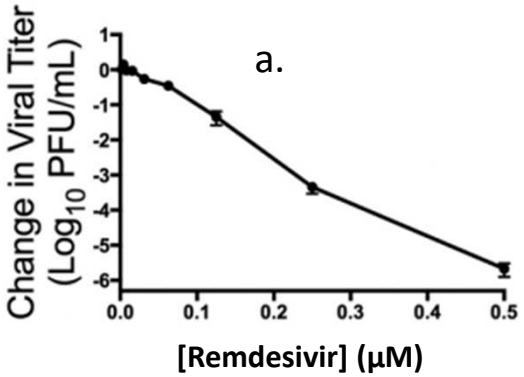
Tableau clinique, synthèse

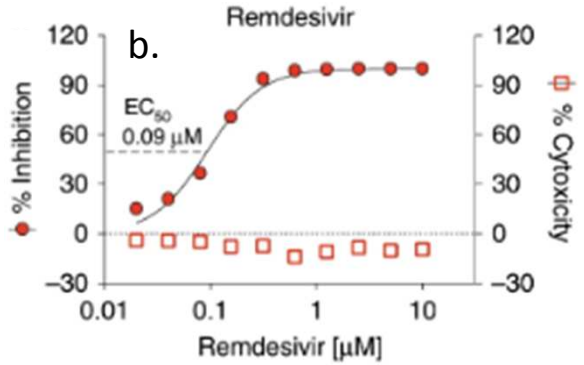
- Patients atteints de COVID-19
- Signes cliniques les plus fréquents: fièvre, toux, dyspnée
- Signes radiologiques: foyers de condensation et infiltrats extensifs
- Formes bénignes les plus fréquentes ; graves/critiques: 15/5%
- Possible aggravation secondaire, vers J8-J9 (dyspnée – SDRA)
- Issue fatale: décès 2% à 14% *(selon type de série)*

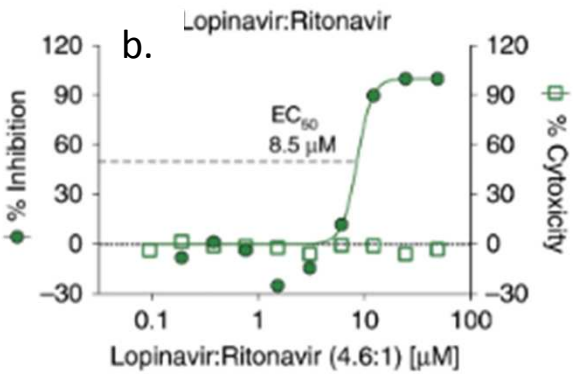
Ref. 3,5

Traitements SRAS-CoV, MERS-CoV

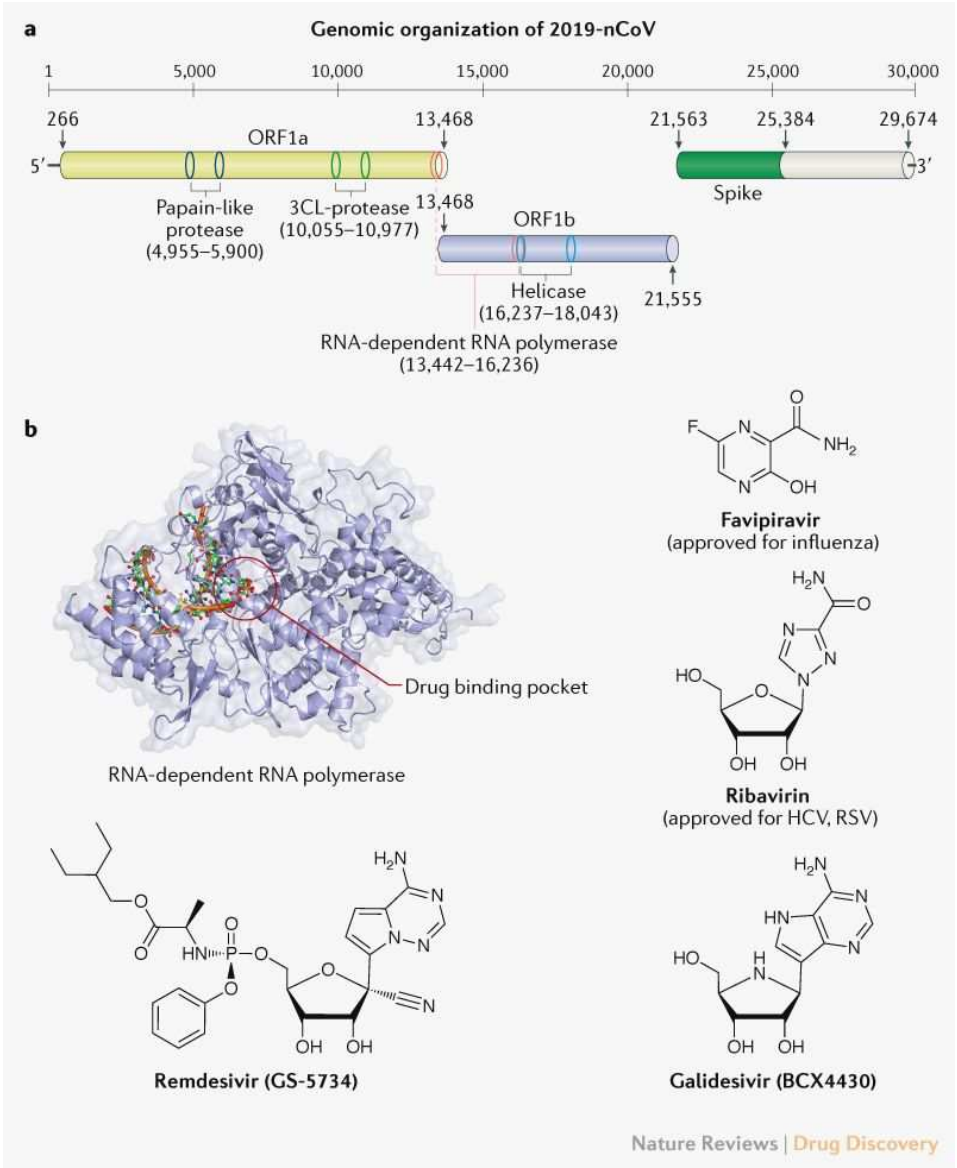
- **Lopinavir-ritonavir+Ribavirine:**
  - SRAS-CoV : 41 patients infectés, traités pendant 21 jours, amélioration clinique des sujets traités
  - MERS-CoV: 76 patients infectés, étude en cours (MIRACLE), Arabie Saoudite
- **Remdesivir (RDV):** Antiviral large spectre
  a. Modèle du virus de l'hépatite murine (β-coronavirus) : inhibition de la réplication virale *in vitro*
  b. MERS-CoV : remdesivir activité supérieure au LPVr *in vitro*







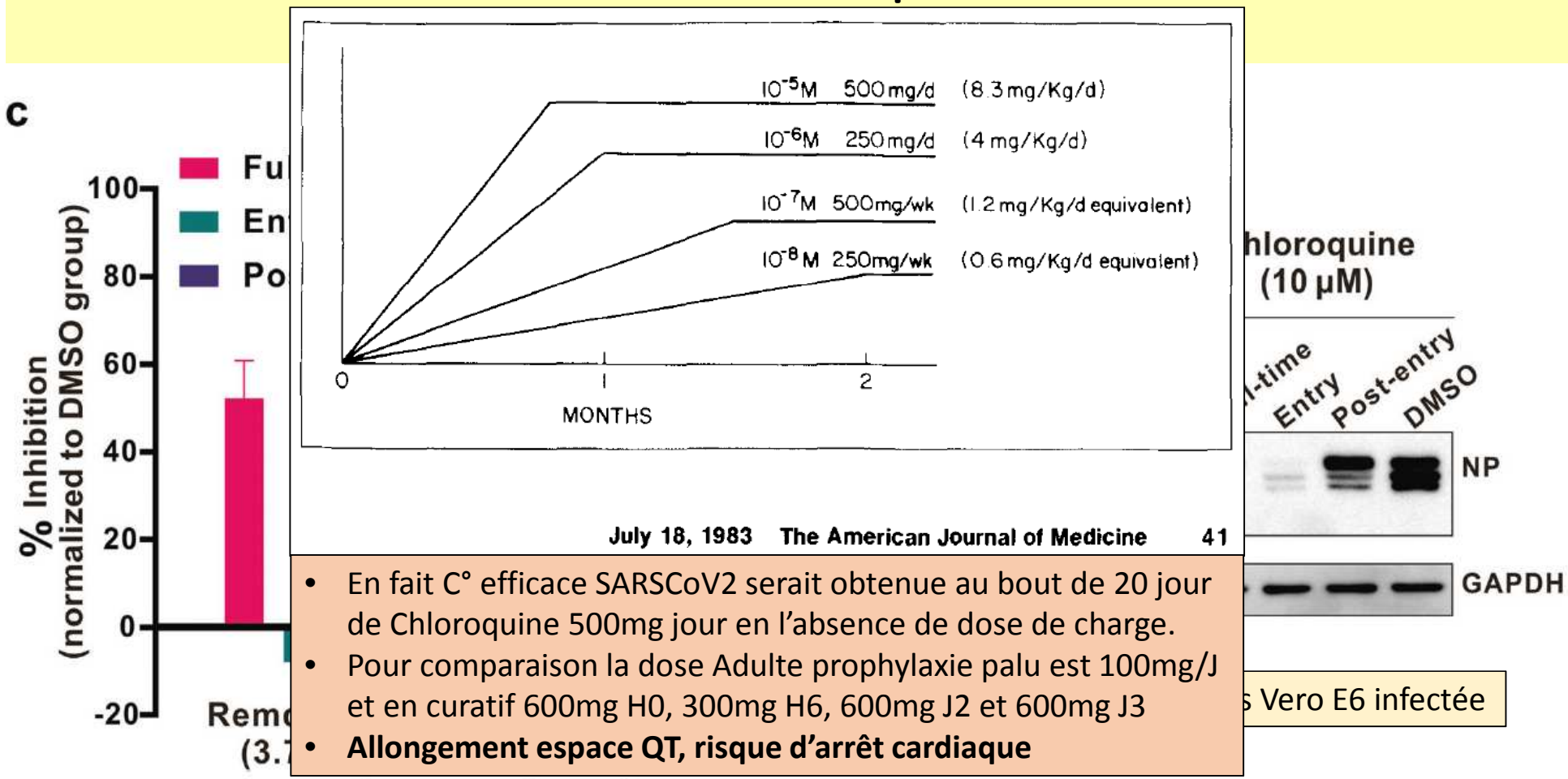
Ref. 9-12



Infectious diseases	Drug targets	Antiviral agents	Reported mechanism of action	Status	Ref.
Virus-based treatment strategies					
2019-nCoV; Influenza	RdRp	Favipiravir	Inhibits RdRp	• Approved for influenza in Japan • Randomized trial for 2019-nCoV (ChiCTR2000029544, ChiCTR2000029600)	[1,2]
2019-nCoV, MERS-CoV, SARS-CoV, RSV, HCV	RdRp	Ribavirin	Inhibits viral RNA synthesis and mRNA capping	• Approved for HCV and RSV • Randomized trial for 2019-nCoV in combination a pegylated interferon (ChiCTR2000029387). • Randomized trial for SARS (NCT00578825)	[2-8]
2019-nCoV	RdRp	Penciclovir	Inhibits RdRp	Approved for HSV	[2]
2019-nCoV, MERS-CoV, SARS-CoV	RdRp	Remdesivir (GS-5734)	Terminates the non-obligate chain	• Phase 3 for 2019-nCoV (NCT04252664, NCT04257656) • Phase 1 for Ebola (NCT03719586)	[1,2, 9-11]
Broad-spectrum (e.g. SARS-CoV, MERS-CoV, IAV)	RdRp	Galidesivir (BCX4430)	Inhibits viral RNA polymerase function by terminating non-obligate RNA chain	• Phase 1 for yellow fever (NCT03891420) • Phase 1 for Marburg virus (NCT03800173)	[12]
Broad-spectrum (e.g. CoV, ZIKV, CHIKV)	RdRp	6′-Fluorinated-aristeromycin analogues (Compound 2c)	Inhibits the activity of RdRp and host cell *S*-adenosyl-L-homocysteine hydrolase	Preclinical	[13]
HCoV-NL63, MERS-CoV	RdRp	Acyclovir fleximer analogues (Compound 2)	Doubly flexible nucleoside analogues inhibit RdRp	Preclinical	[14]
MERS-CoV, SARS-CoV	PLpro	Disulfiram	Inhibits PLpro	Approved for chronic alcohol dependence	[15]
MERS-CoV, SARS-CoV	PLpro	Thiopurine analogues (6-mercaptopurine and 6-thioguanine)	Inhibits PLpro	Preclinical	[16]
MERS-CoV	PLpro	Compound 6	Inhibits PLpro	Preclinical	[17]
2019-nCoV; MERS-CoV, SARS-CoV; HCoV-229E; HIV, HPV	3CLpro	Lopinavir	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04252274, NCT04251871, NCT04255017, ChiCTR2000029539) • Phase 2/3 for MERS (NCT02845843)	[11, 18-21]
2019-nCoV, MERS-CoV	3CLpro	Ritonavir	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04251871, NCT04255017, NCT04261270) • Phase 2/3 for MERS (NCT02845843)	[11,18, 20,21]
2019-nCoV	3CLpro	Darunavir and cobicistat	Inhibits 3CLpro	• Approved for HIV • Phase 3 for 2019-nCoV (NCT04252274)	-
2019-nCoV	3CLpro	ASC09F (HIV protease inhibitor)	Inhibits 3CLpro	Phase 3 for 2019-nCoV in combination with oseltamivir (NCT04261270)	-
MERS-CoV, SARS-CoV	3CLpro	GC376	Inhibits 3CLpro	Preclinical	[22]
MERS-CoV	3CLpro	GC813	Inhibits 3CLpro	Preclinical	[23]
SARS-CoV	3CLpro	Phenylisoserine derivatives (SK80)	Inhibits 3CLpro	Preclinical	[24]
MERS-CoV, SARS-CoV	3CLpro	Peptidomimetic inhibitors (Compound 6)	Inhibits 3CLpro	Preclinical	[25]
HCoV-229E	3CLpro	1,2,3-triazoles (Compound 14d)	Inhibits 3CLpro	Preclinical	[26]
SARS-CoV, MERS-CoV	3CLpro	Neuraminidase inhibitor analogues (compound 3k)	Inhibits 3CLpro	Preclinical	[27]
SARS-CoV	3CLpro	Unsymmetrical aromatic disulfides	-	Preclinical	[28]

Ref. 13

Et la chloroquine?



- En fait C° efficace SARSCoV2 serait obtenue au bout de 20 jour de Chloroquine 500mg jour en l'absence de dose de charge.
- Pour comparaison la dose Adulte prophylaxie palu est 100mg/J et en curatif 600mg H0, 300mg H6, 600mg J2 et 600mg J3
- **Allongement espace QT, risque d'arrêt cardiaque**

Ref. 14

Références

1. Na Zhu *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. NEJM – 24 jan 2020 https://www.nejm.org/doi/10.1056/NEJMoa2001017
2. Wu Z *et al.* Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA – 24 Feb 2020
3. Nanshan Chen *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet – 29 jan 2020 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7/fulltext
4. Jasper Fuk-Woo Chan et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet – 24 jan 2020 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30154-9/fulltext
5. Wang D *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb https://jamanetwork.com/journals/jama/fullarticle/2761044
6. CCDC weekly/Vol. 2/No.8 http://www.ourphn.org.au/wp-content/uploads/20200225-Article-COVID-19.pdf
7. Xiaobo *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study Lancet Respir Med 2020 – 21 fev 2020 https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/fulltext
8. Chaolin Huang et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet – 24 jan 2020 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext
9. Chu CM et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax Mar 2004 https://thorax.bmj.com/content/59/3/252
10. Arabi YM et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials Jan 2018 https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2427-0
11. Maria L. Agostini et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio – Mar 2018 https://mbio.asm.org/content/9/2/e00221-18.long
12. Sheahan TP et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun – 10 Jan 2020 https://www.nature.com/articles/s41467-019-13940-6
13. Li G. et al. Therapeutic options for the 2019 novel coronavirus (2019-nCoV) https://www.nature.com/articles/d41573-020-00016-0
14. Wang M. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro https://www.nature.com/articles/s41422-020-0282-0