# COVID-long
# Actualités

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# Liens d’interêt

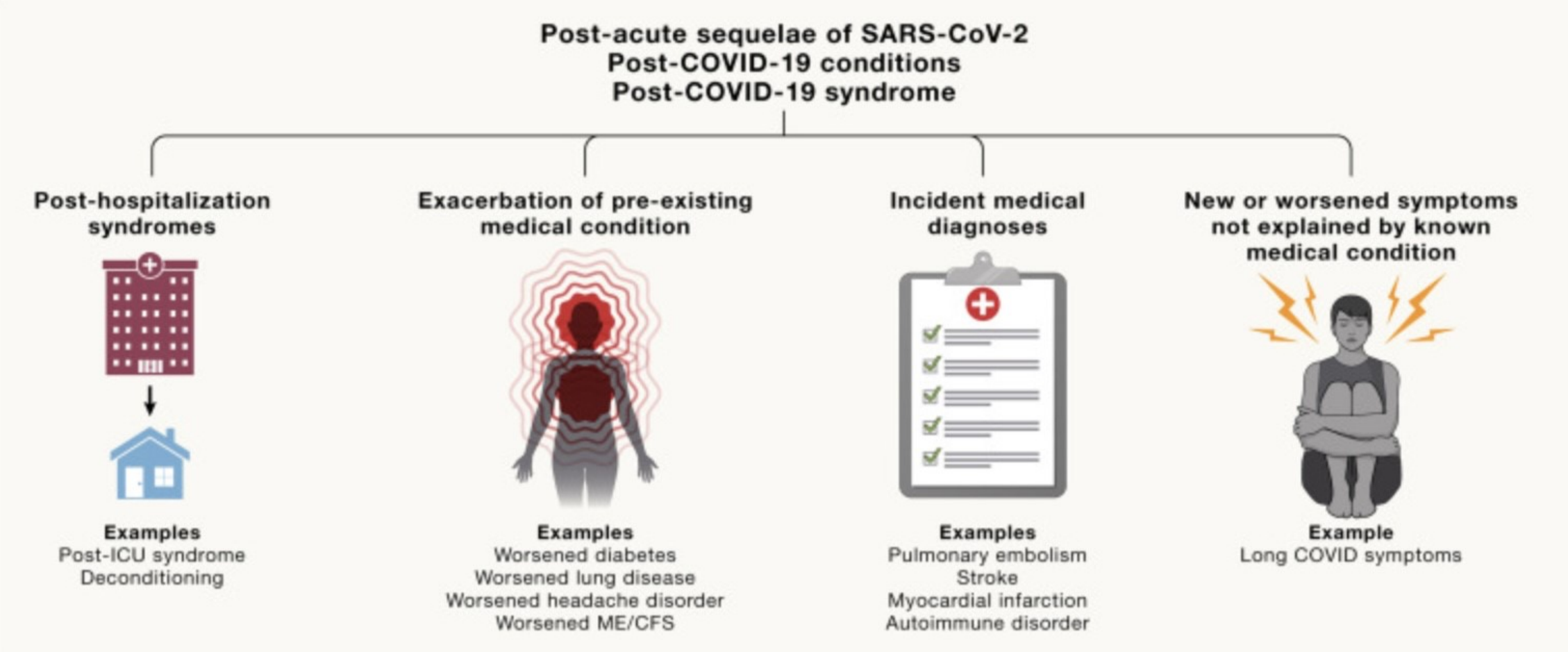
- Orateur et participation à des boards pour:
  - Gilead
  - MSD
  - ViiV
  - Pfizer
  - Moderna

# Définition OMS: affection post-COVID (Post-COVID condition)

- **Antécédents d'infection probable ou confirmée par le SARS-CoV-2**
- associé à des **Symptômes**:
  - **qui persistent au moins 2 mois**
  - **qui ne peuvent être expliqués par un autre diagnostic**
  - **qui apparaissent en général dans les 3 mois**
- Ces symptômes :
  - peuvent être **d'apparition nouvelle** après un rétablissement initial, ou **persister** depuis la maladie initiale.
  - peuvent également **fluctuer** ou **récidiver** au fil du temps.
  - ont généralement un **impact** sur le fonctionnement quotidien

OMS Oct 2021

# Les différents  »états » du post-covid




Peluso et al Cell 2024

# Définition des cas de COVID-long

**Table 1. Components of Long Covid Definitions.***

| Elements of Disease Definition | U.S. CDC, 2020[11] | U.K. NICE, 2020[12] | U.S. OASH, 2022[13] | WHO Adults, 2022[14] | WHO Children, 2022[15] | U.S. RECOVER, 2023[16] | NASEM, 2024[5] |
|---|---|---|---|---|---|---|---|
| **Classification** | | | | | | | |
| Uses the term "long Covid" | Yes | No | Yes | No | No | No | Yes |
| Describes long Covid as a disease state | No | No | No | No | No | No | Yes |
| Places long Covid among infection-associated chronic conditions | No | No | No | No | No | No | Yes |
| **Attribution to infection** | | | | | | | |
| Allows inclusion of asymptomatic, mild, or severe acute SARS-CoV-2 | Yes | No | No | No | No | Yes | Yes |
| Requires proof of confirmed or probable infection or requirement of SARS-CoV-2 test | No | No | No | Yes | Yes | No | No |
| **Timing** | | | | | | | |
| States symptoms or conditions present for at least 3 mo | No | Yes | No | No | No | Yes | Yes |
| Indicates continuous or delayed onset of symptoms or conditions | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Clinical features** | | | | | | | |
| Indicates long Covid is a single or multiple organ disease state | No | Yes | Yes | No | No | Yes | Yes |
| Includes new clinical features or exacerbation of preexisting features | No | No | No | Yes | Yes | No | Yes |
| Mentions severity of symptoms | No | No | Yes | No | No | Yes | Yes |
| Describes continuous, relapsing–remitting, or progressive nature of symptoms | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Includes language on recovery timeline (can resolve or persist for months to years) | No | No | No | No | No | Yes | Yes |
| **Patient-oriented features** | | | | | | | |
| Includes equity language | No | Yes | No | No | No | No | Yes |
| Highlights effect on daily functioning | No | No | No | Yes | Yes | Yes | Yes |
| Incorporates alternative diagnoses | No | No | No | No | Yes | No | Yes |
| Indicates that diagnosis is a clinical judgment due to absence of proven biomarkers | No | No | Yes | No | No | No | Yes |
| Includes risk factors | No | No | Yes | No | No | No | No† |

Ely E et col, N Engl J Med, 2024

# Définition des cas de COVID-long

**BOX 1. 2024 NASEM LONG COVID DEFINITION***

**Long Covid is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.**

**Long Covid manifests in multiple ways.** A complete enumeration of possible signs, symptoms, and diagnosable conditions of long Covid would have hundreds of entries. Any organ system can be involved, and patients can present with the following:

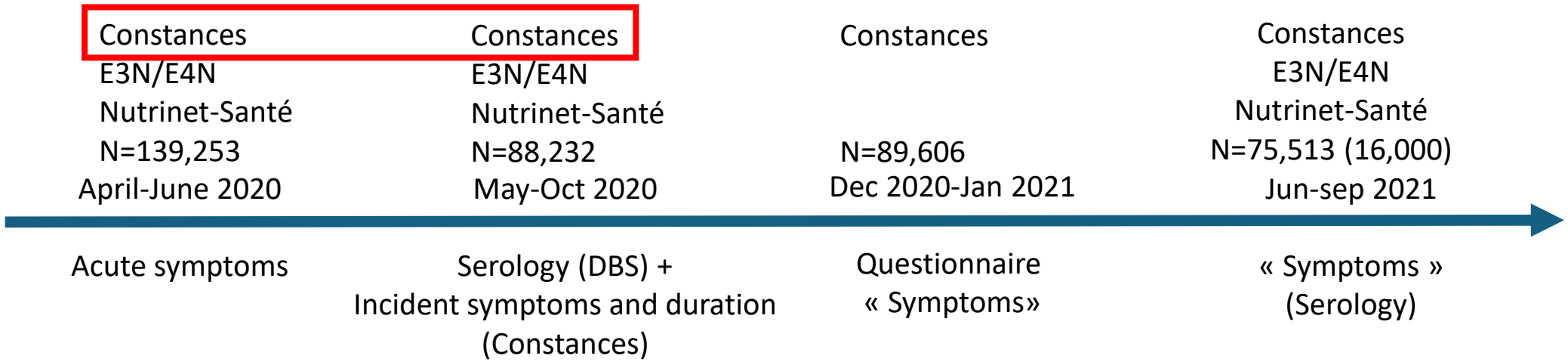
- **Single or multiple symptoms, such as** shortness of breath, cough, persistent fatigue, postexertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.

- **Single or multiple diagnosable conditions, such as** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome and other forms of dysautonomia, myalgic encephalomyelitis–chronic fatigue syndrome, mast-cell activation syndrome, fibromyalgia, connective-tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjögren's syndrome.

Ely E et col, N Engl J Med, 2024

# Etape 1: confirmer son existence

# SAPRIS/COPER Survey (existing cohort)




**Aims**

**Epidemiological studies**

Symptoms duration, resolution of the symptoms

Quality of life

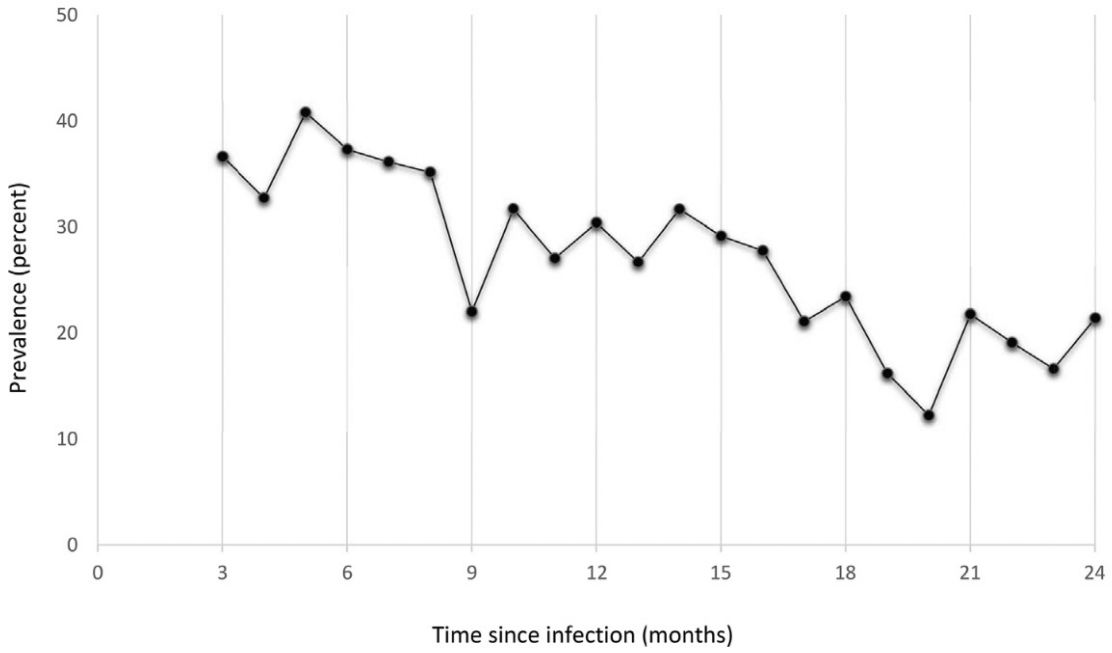
# Prevalence des symtpoems et attribution aux SARS-CoV-2

| | ECDC+/Sero- N=3534 | ECDC+/Sero+ N=494 | OR [95% CI] | p | aOR* [95% CI] | p |
|---|---|---|---|---|---|---|
| **At least one persistent symptom** | 1364 (38.6%) | 213 (43.1%) | 1.21 [1-1.46] | 0.05 | 1.14 [0.91-1.42] | 0.25 |
| **Dysgeusia/anosmia** | 65 (1.8%) | 64 (13.0%) | 7.94 [5.54-11.39] | <0.0001 | 6.83 [4.47-10.42] | <0.0001 |
| **Cardiothoracic complaints** | | | | | | |
| Cough | 118 (3.3%) | 13 (2.63%) | 0.78 [0.42-1.35] | 0.41 | 0.70 [0.33-1.31] | 0.29 |
| Dyspnea | 134 (3.8%) | 35 (7.1%) | 1.93 [1.32-2.81] | 0.0008 | 1.69 [1.07-2.60] | 0.02 |
| Thoracic pain | 85 (2.4%) | 19 (3.9%) | 1.62 [0.95-2.63] | 0.06 | 1.15 [0.61-2.06] | 0.65 |
| Palpitations | 74 (2.1%) | 16 (3.2%) | 1.57 [0.87-2.64] | 0.11 | 1.23 [0.63-2.26] | 0.53 |
| **Pains** | | | | | | |
| Backpain | 356 (10.1%) | 38 (7.7%) | 0.74 [0.52-1.04] | 0.10 | 0.78 [0.52-1.15] | 0.22 |
| Arthralgia | 364 (10.3%) | 48 (9.7%) | 0.94 [0.68-1.27] | 0.69 | 1.02 [0.69-1.46] | 0.92 |
| Myalgia | 206 (5.8%) | 28 (5.7%) | 0.97 [0.63-1.43] | 0.89 | 0.82 [0.49-1.31] | 0.42 |
| Headache | 119 (3.37%) | 23 (4.66%) | 1.40 [0.87-2.17] | 0.15 | 1.11 [0.64-1.85] | 0.69 |
| **Digestive complaints** | | | | | | |
| Nausea | 17 (0.5%) | 0 (0.0%) | - | - | - | - |
| Diarrhoea | 51 (1.4%) | 6 (1.2%) | 0.84 [0.32-1.82] | 0.68 | 0.61 [0.21-1.48] | 0.31 |
| Constipation | 75 (2.1%) | 7 (1.4%) | 0.66 [0.28-1.35] | 0.30 | 0.38 [0.11-0.99] | 0.08 |
| Abdominal pain | 126 (3.6%) | 11 (2.2%) | 0.62 [0.31-1.10] | 0.13 | 0.51 [0.24-0.96] | 0.05 |
| **Other complaints** | | | | | | |
| Asthenia | 260 (7.4%) | 70 (14.2%) | 2.08 [1.56-2.74] | <0.0001 | 1.48 [1.05-2.07] | 0.02 |
| Cognitive complaints | 190 (5.4%) | 45 (9.1%) | 1.76 [1.24-2.45] | 0.0011 | 1.47 [0.98-2.16] | 0.06 |
| Fever | 17 (0.5%) | 2 (0.4%) | 0.84 [0.13-2.94] | 0.82 | 0.68 [0.10-2.84] | 0.64 |
| Cranial nerves abnormalities | 9 (0.3%) | 0 (0.0%) | - | - | - | - |
| Sensory disorders | 126 (3.6%) | 7 (1.4%) | 0.39 [0.16-0.78] | 0.02 | 0.40 [0.16-0.85] | 0.03 |
| Talk abnormalities | 22 (0.6%) | 4 (0.8%) | 1.30 [0.38-3.42] | 0.63 | 1.00 [0.21-3.41] | >0.99 |
| Auditive disorders | 107 (3.0%) | 9 (1.8%) | 0.59 [0.28-1.12] | 0.14 | 0.62 [0.25-1.32] | 0.26 |
| Dizziness | 45 (1.3%) | 10 (2.0%) | 1.60 [0.76-3.07] | 0.18 | 1.54 [0.65-3.35] | 0.30 |
| Vertigo | 7 (0.2%) | 0 (0.0%) | - | - | - | - |
| Sleep disorders | 556 (15.7%) | 56 (11.3%) | 0.68 [0.51-0.91] | 0.01 | 0.69 [0.49-0.95] | 0.02 |
| Skin disorders | 136 (3.9%) | 13 (2.6%) | 0.68 [0.36-1.16] | 0.18 | 0.61 [0.29-1.15] | 0.15 |

Robineau et col, Lancet reg Health Europe, 2022

# Step 2: Estimer la prévalence et les facteurs de risque

# Santé Publique France(22/03/22-8/04/22)
# 4.0% (3.7–4.2) de la population adulte




Attribution?

Table S3. Profiles of WHO defined PCC and self-reported long COVID (confirmed SARS-COV-2 of more than 3 months, N= 1,095 and 573)

| | | WHO defined PCC | Self-reported long COVID |
|---|---|---|---|
| Sex | Women | 664 (61) | 363 (63) |
| Age | 18-24 years | 107 (10) | 53 (9) |
| | 25-34 years | 304 (28) | 158 (28) |
| | 35-44 years | 213 (19) | 107 (19) |
| | 45-54 years | 194 (18) | 112 (20) |
| | 55-64 years | 153 (14) | 81 (14) |
| | ≥ 65 years | 124 (11) | 62 (11) |
| Education | Less than secondary | 217 (20) | 142 (25) |
| | Secondary | 242 (22) | 122 (21) |
| | Tertiary (1-3 years) | 392 (36) | 195 (34) |
| | Tertiary (>3 years) | 244 (22) | 114 (20) |
| Living alone | | 200 (18) | 98 (17) |
| Employment status | Paid employment | 788 (72) | 409 (71) |
| | Unemployed | 39 (4) | 24 (4) |
| | Retired | 243 (22) | 126 (22) |
| | Other inactive | 25 (2) | 14 (3) |
| Occupation | Company manager, entrepreneur | 33 (3) | 21 (4) |
| | Senior manager, professional | 232 (21) | 119 (21) |
| | Middle manager, teacher | 162 (15) | 85 (15) |
| | Office employee | 370 (34) | 190 (33) |
| | Manual worker | 31 (3) | 18 (3) |
| | No occupation, retired or studying (inactive) | 268 (24) | 140 (24) |
| Workplace SARS-CoV-2 exposure | Yes | 325 (30) | 205 (36) |
| | No | 607 (55) | 299 (52) |
| | Don't know | 164 (15) | 70 (12) |
| Symptoms | Fatigue | 779 (71) | 366 (64) |
| | Shortness of breath | 412 (38) | 247 (43) |
| | Cognitive dysfunction/impaired memc | 418 (38) | 247 (43) |
| | Tinnitus | 215 (20) | 147 (26) |
| | New onset allergies | 81 (7) | 49 (9) |

Coste et col, Infect Dis Now., 2023

Caracaillon et col, J Infect, 2023

# Deuxième étude (Aout Novembre 2022): 4% (95% CI: 3.6-4.5)de covid long(WHO)

Proportion of individuals presenting limitations of activities (Global Activity Limitation Indicator) in WHO post-COVID-19 condition (PCC), infected non PCC and never infected groups. N (%) and age and sex-adjusted prevalence ratios

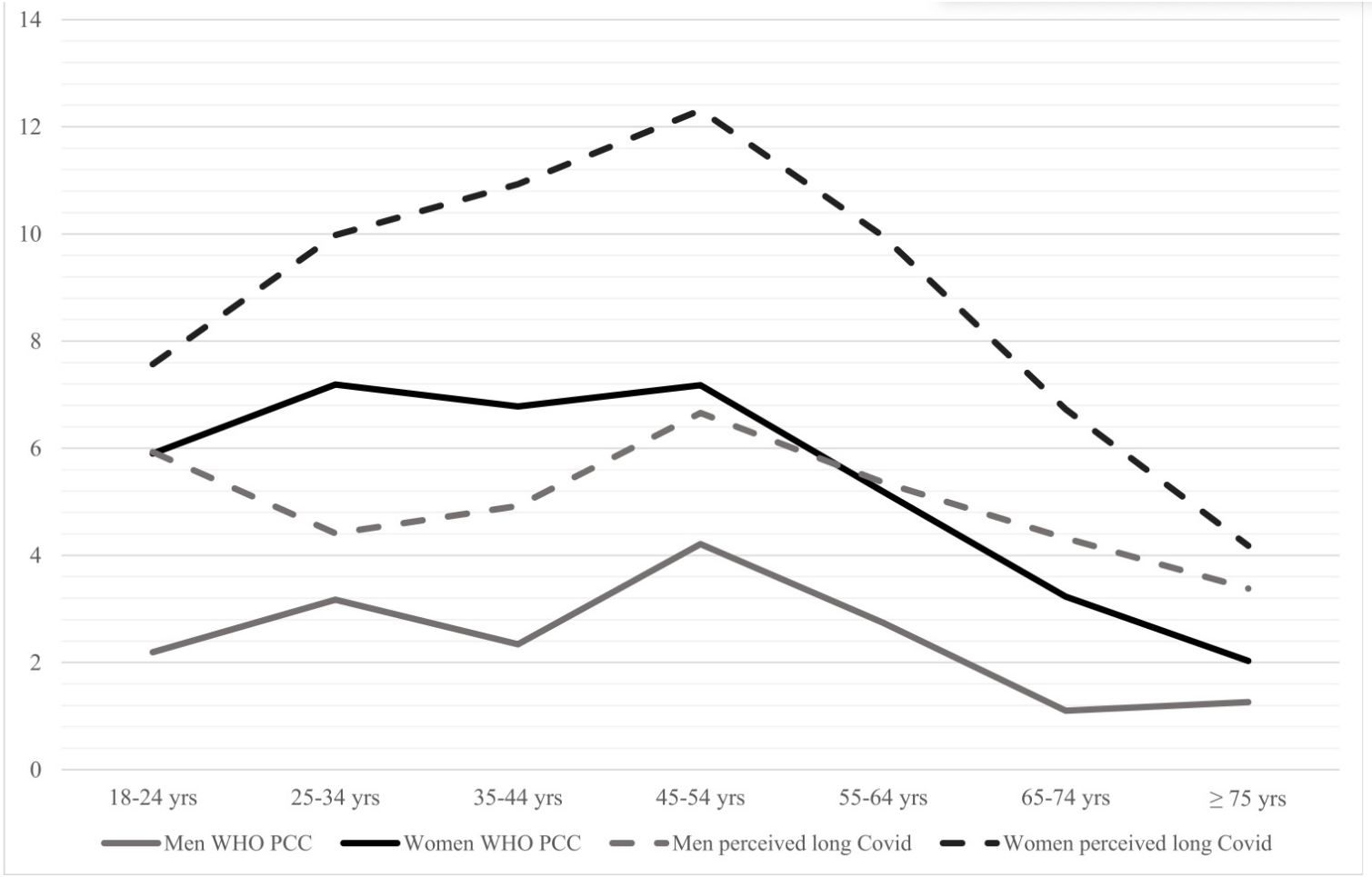
| | PCC | infected non PCC | | never infected | |
|---|---|---|---|---|---|
| | N (%) | N (%) | PR* (95% CI) | N (%) | PR* (95% CI) |
| GALI | | | | | |
| Not Limited | 222 (60.0) | 4178 (78.2) | 1 | 3548 (73.6) | 1 |
| Limited | 207 (40.0) | 1168 (21.8) | 2.30 (1.82-2.90) | 1276 (26.4) | 2.31 (1.83-2.93) |

Distribution of World Health Organisation post-COVID-19 condition (WHO PCC) and infections according to epidemic waves, strains and variants

| | | All infections reported with dates (N=7,157) | | WHO PCC (N=430) | |
|---|---|---|---|---|---|
| Epidemic wave | Predominant strain or variant | N | % | N | % |
| 1 | Wuhan | 789 | 11.0 | 44 | 10.2 |
| 2 | Wuhan | 472 | 6.6 | 27 | 6.3 |
| 3 | Alpha, Beta, Gamma | 794 | 11.1 | 39 | 9.0 |
| 4 | Delta | 937 | 13.1 | 92 | 21.3 |
| 5 | Omicron BA1 | 1,541 | 21.6 | 86 | 19.9 |
| 6 | Omicron BA2 | 1,296 | 18.1 | 79 | 18.5 |
| 7 | Omicron BA4-5 | 1,328 | 18.5 | 63 | 14.8 |

Coste et col CMI 2023

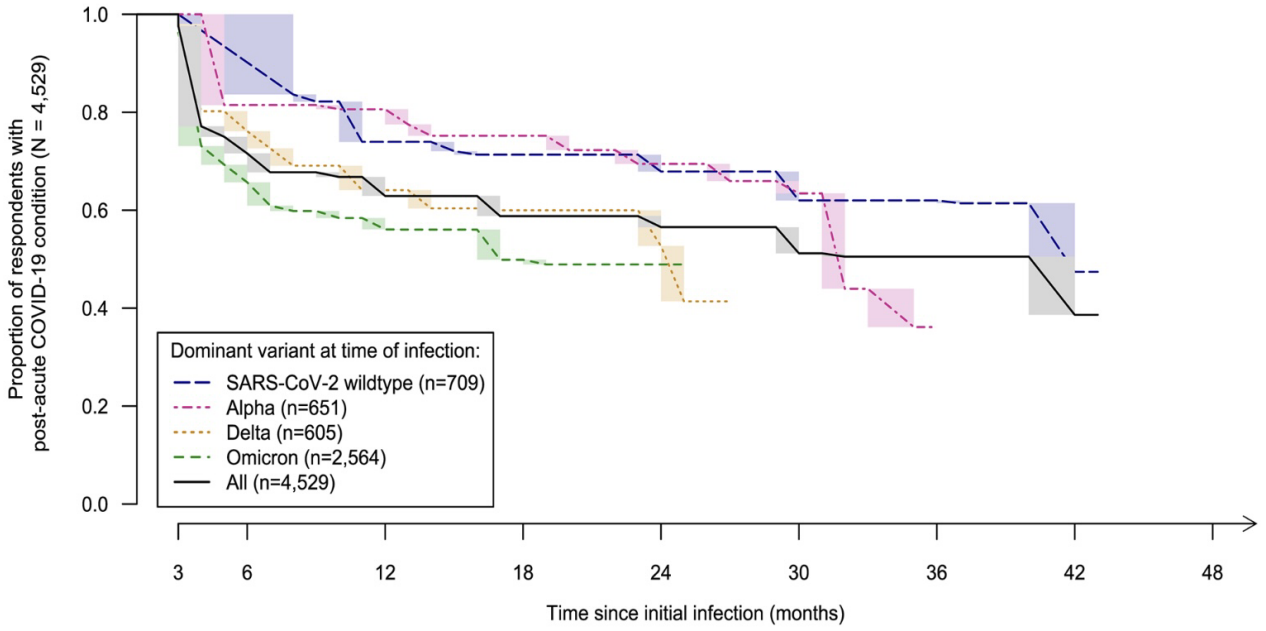
# Different definition, different estimates ranging from 2.5% to 12%




Coste et col CMI 2023

# Step 3:  évolution du covid long: 3 voies pour l’évaluer

# Results from population-based cohort study for digital health research in Germany (DigiHero)

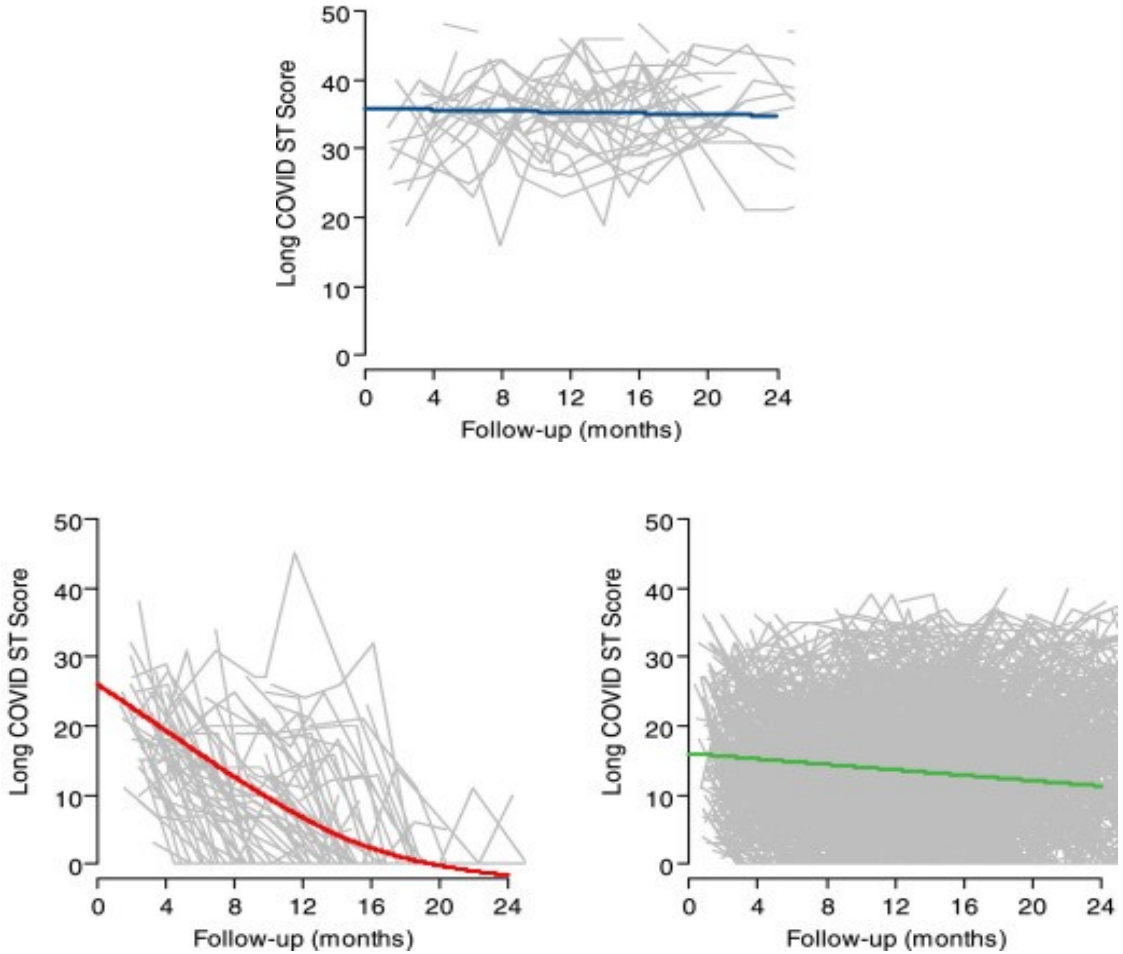



| **A. Considering vaccination status, not variant (*N*=4,529)** | **crude HR** | **95%CI** | | **adjusted HR[a]** | **95%CI** | |
|---|---|---|---|---|---|---|
| Vaccination status prior to infection (ref: not vaccinated, *n*=1,593) | | | | | | |
| Received one dose (*n*=136) | 1.09 | 0.77 | 1.55 | 1.10 | 0.78 | 1.56 |
| Received two doses (*n*=692) | 1.51 | 1.31 | 1.73 | 1.50 | 1.31 | 1.72 |
| Received booster dose (*n*=2,108) | 1.94 | 1.73 | 2.17 | 1.89 | 1.69 | 2.12 |
| **B. Analyses stratified for virus variant** | **crude HR** | **95%CI** | | **adjusted HR[a]** | **95%CI** | |
| **B.1 Omicron variant only (*N*=2, 564)** | | | | | | |
| Vaccination status prior to infection (ref: not vaccinated, *n*=114) | | | | | | |
| Received one dose (*n*=48) | 0.59 | 0.31 | 1.09 | 0.56 | 0.30 | 1.04 |
| Received two doses (*n*=322) | 0.87 | 0.63 | 1.22 | 0.82 | 0.58 | 1.14 |
| Received booster dose (*n*=2,080) | 0.99 | 0.74 | 1.32 | 0.94 | 0.70 | 1.27 |
| **B.2 Delta variant only (*N*=605)** | | | | | | |
| Vaccination status prior to infection (ref: not vaccinated, *n*=175) | | | | | | |
| Received one dose (*n*=43) | 0.98 | 0.56 | 1.74 | 0.92 | 0.51 | 1.66 |
| Received two doses (*n*=359) | 0.93 | 0.68 | 1.28 | 0.92 | 0.66 | 1.29 |
| Received booster dose (*n*=28) | 0.66 | 0.27 | 1.61 | 0.61 | 0.25 | 1.48 |
| **B.3 Alpha variant only (*N*=651)** | | | | | | |
| Vaccination status prior to infection (ref: not vaccinated, *n*=595) | | | | | | |
| Received at least one dose (*n*=56) | 0.80 | 0.43 | 1.47 | 0.85 | 0.46 | 1.58 |
| **B.4 SARS-CoV-2 wildtype or Alpha variant (*N*=1, 360)** | | | | | | |
| Vaccination status prior to infection (ref: not vaccinated, *n*=1,304) | | | | | | |
| Received at least one dose (*n*=56) | 0.77 | 0.41 | 1.43 | 0.84 | 0.44 | 1.57 |
| **C. Considering variant, not vaccination status (*N*=4,529)** | **crude HR** | **95%CI** | | **adjusted HR** | **95%CI** | |
| **Dominant virus variant at time of infection** (ref: SARS-Cov-2 wildtype or Alpha, *n*=1,360) | | | | | | |
| Delta (*n*=605) | 1.63 | 1.37 | 1.94 | 1.69 | 1.43 | 2.01 |
| Omicron (*n*=2,564) | 2.24 | 1.99 | 2.52 | 2.20 | 1.96 | 2.48 |
| **Sex** (ref: male; *n*=1,239) | | | | | | |
| Female (*n*=3,290) | | | | 0.81 | 0.73 | 0.90 |
| **Age** (ref: <30; *n*=499) | | | | | | |
| 30–39 (*n*=737) | | | | 0.79 | 0.66 | 0.94 |
| 40–49 (*n*=956) | | | | 0.59 | 0.48 | 0.72 |
| 50–59 (*n*=1,328) | | | | 0.60 | 0.50 | 0.72 |
| 60–69 (*n*=763) | | | | 0.64 | 0.52 | 0.78 |
| ≥70 (*n*=246) | | | | 0.62 | 0.46 | 0.82 |
| **Education level** (ref: high; *n*=2,555) [b] | | | | | | |
| Low (*n*=155) | | | | 0.99 | 0.74 | 1.34 |
| Medium (*n*=1,738) | | | | 0.91 | 0.82 | 1.01 |
| Not available (*n*=81) | | | | 0.72 | 0.46 | 1.13 |
| **Net household income in €** (ref: <2.250; *n*=918) | | | | | | |
| 2.250 to <4.000 (*n*=1,680) | | | | 1.06 | 0.93 | 1.21 |
| ≥4.000 (*n*=1,519) | | | | 1.24 | 1.08 | 1.42 |
| Not available (*n*=412) | | | | 1.05 | 0.87 | 1.26 |

Pfrommer et col, Infection 2024

# Longitudinal analysis from long covid cohort: COmPare

- Tools made for chronic condition
- Self-definition of long covid
- Online follow-up

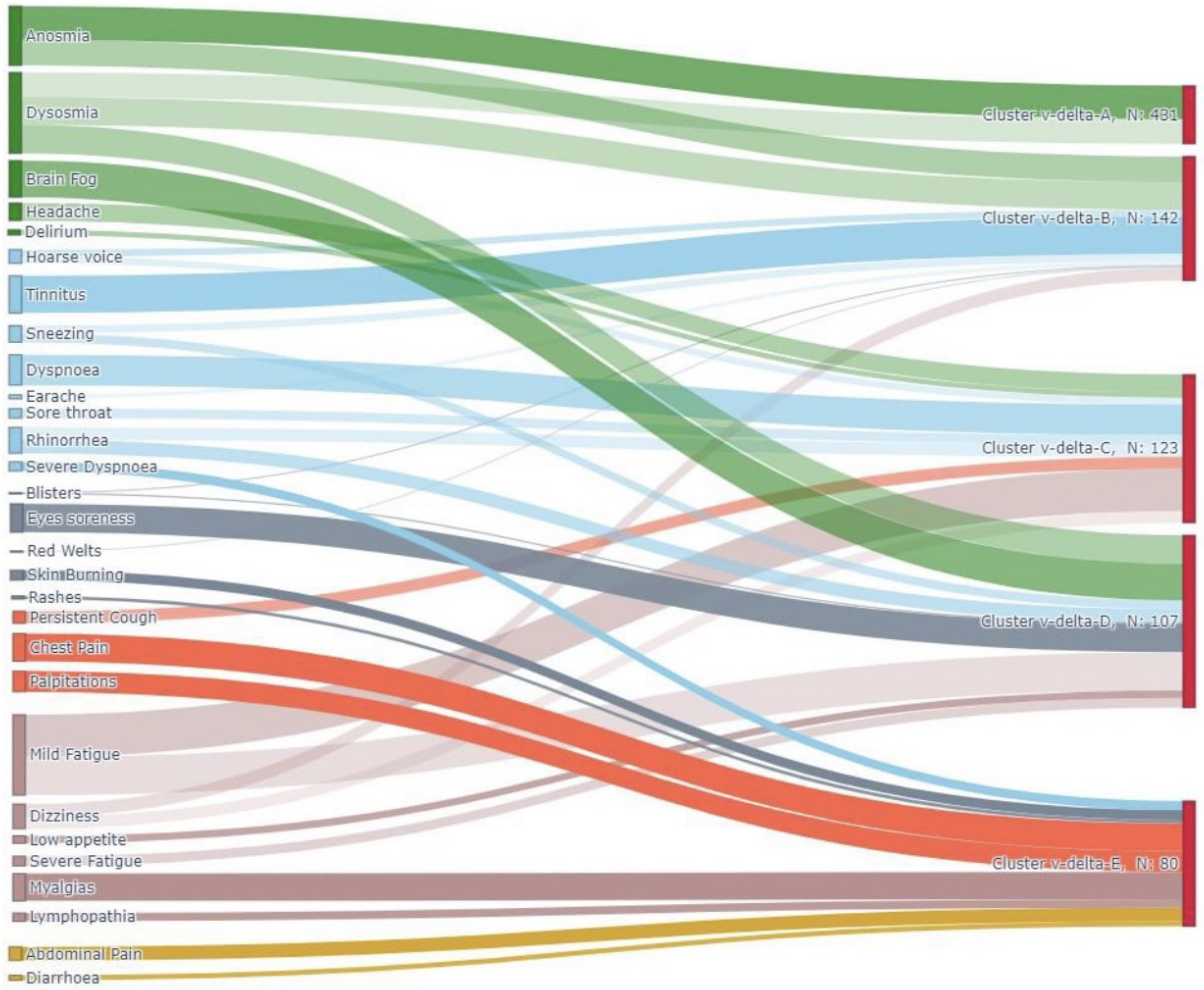



Servier et col Int J Infect Dis. 2023

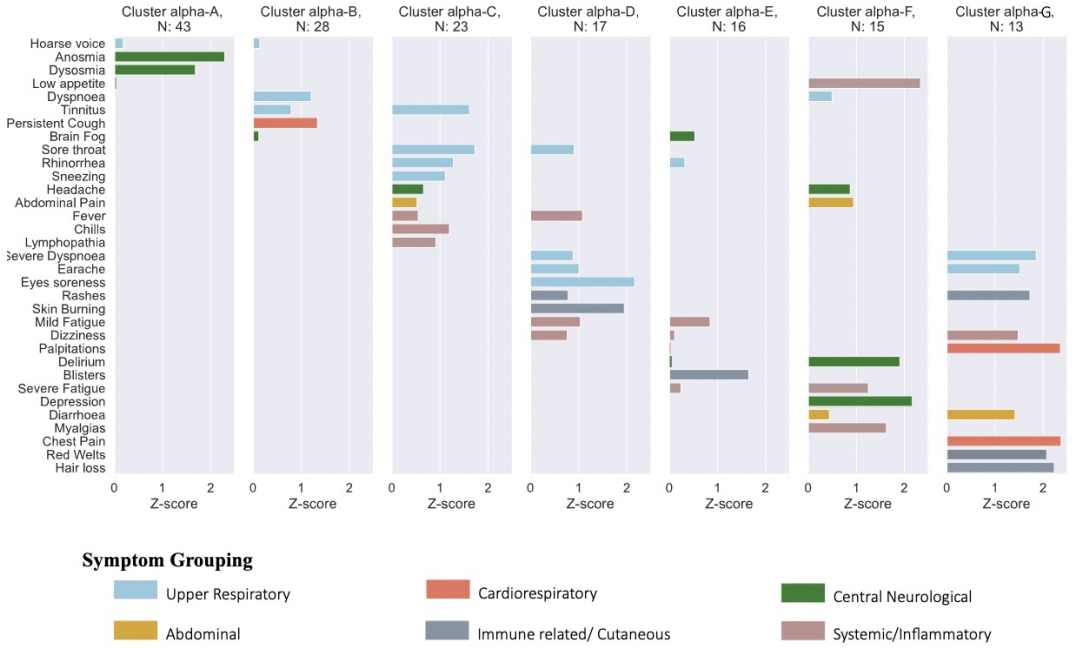
# Step 4: définir le covid long en utilisant des données épidémiologiques?

# associations of symptoms/clustering

**A: Relative contribution of the highest ranked symptoms to each cluster**

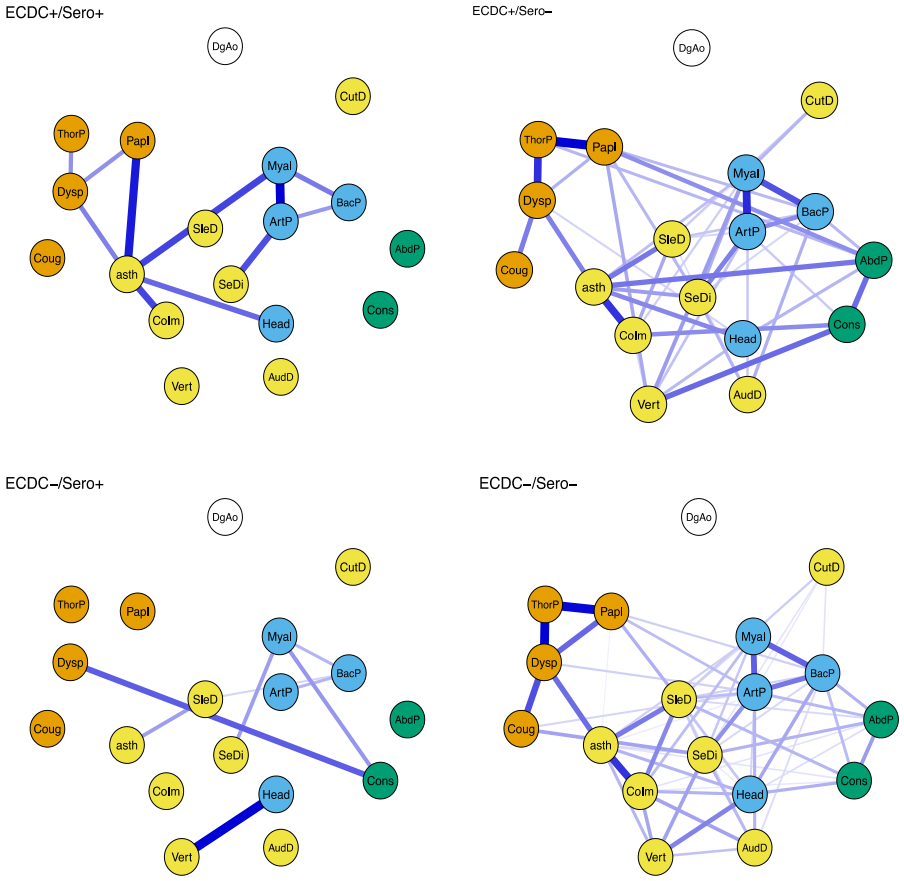


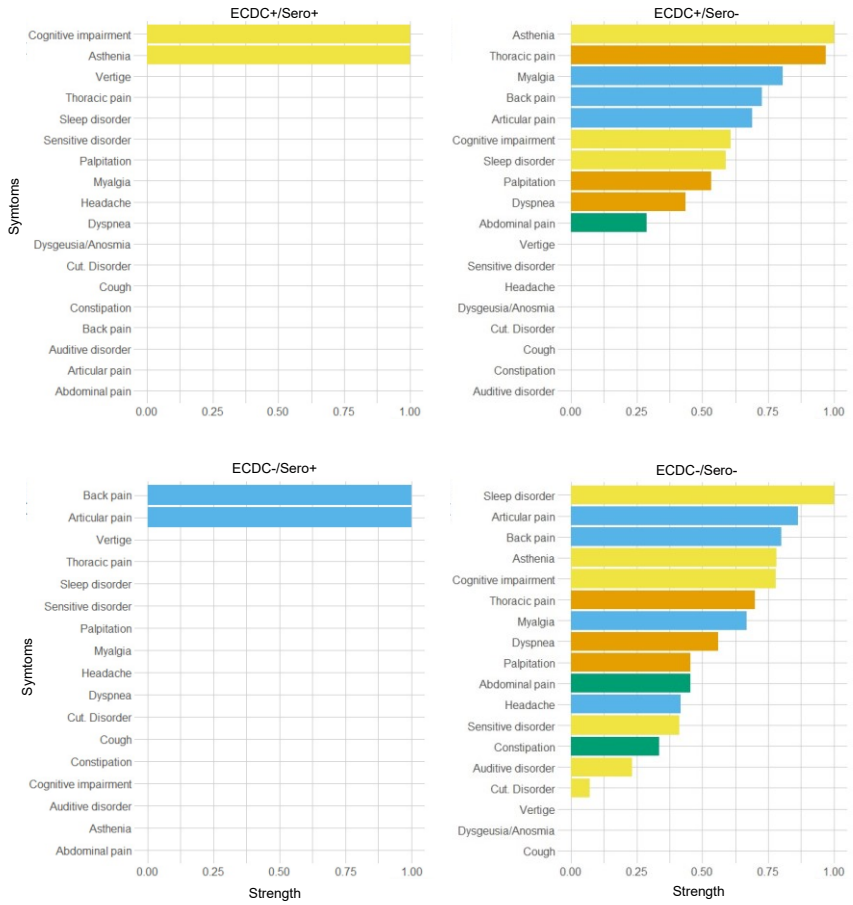

**B: Ranking of symptoms per cluster based on z-score**




Canas et col, Lancet digital Health, 2023

# Network d'associations de symptomes (SAPRIS survey)




Robineau et col, not publish

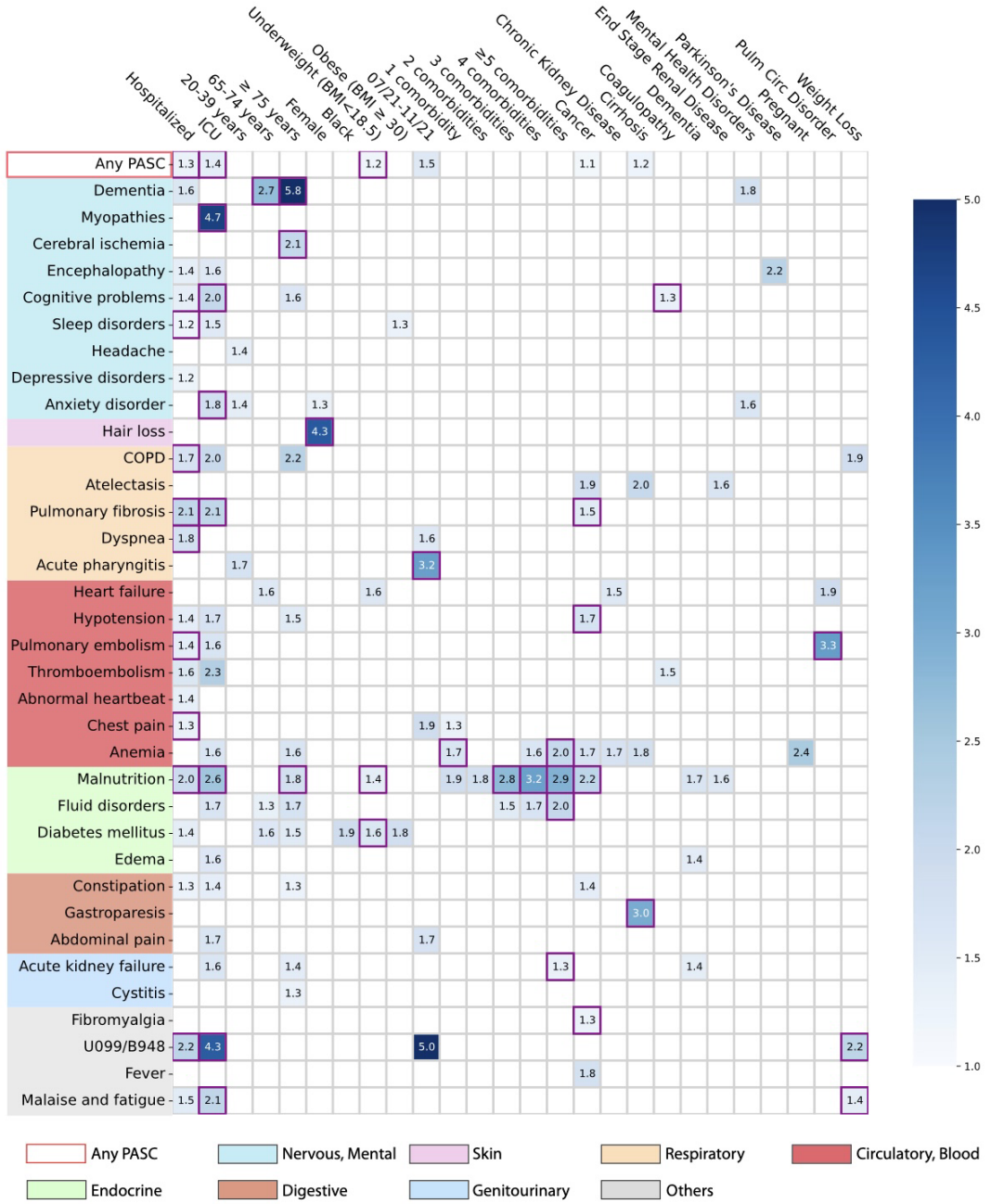
# Définir par les symptômes

- Les plus prévalents  »toutes causes »: Asthénie, céphalées, anosmie, dyspnées, myalgies/douleurs thoraciques et toux
- Les plus associées au SARS-CoV-2: Anosmie, dyspnée, asthénie, plaintes cognitives, douleurs, Malaises post effort, insomnie?, T de l'humeur?, symptômes cardiologiques?
- Présentation « syndromiques » des symptômes:
  - Syndrome d'hyperventilation
- Evolution des associations de symptômes au cours du temps?

Al-Aly, Nature Med, 2022
Wanga et col, MMWR, 2021
Nehme et col Ann Internal Medicine 2021
Robineau et col JAMA open 2022
Taquet Plos medicine 2021
Servier et col, IJID, 2023

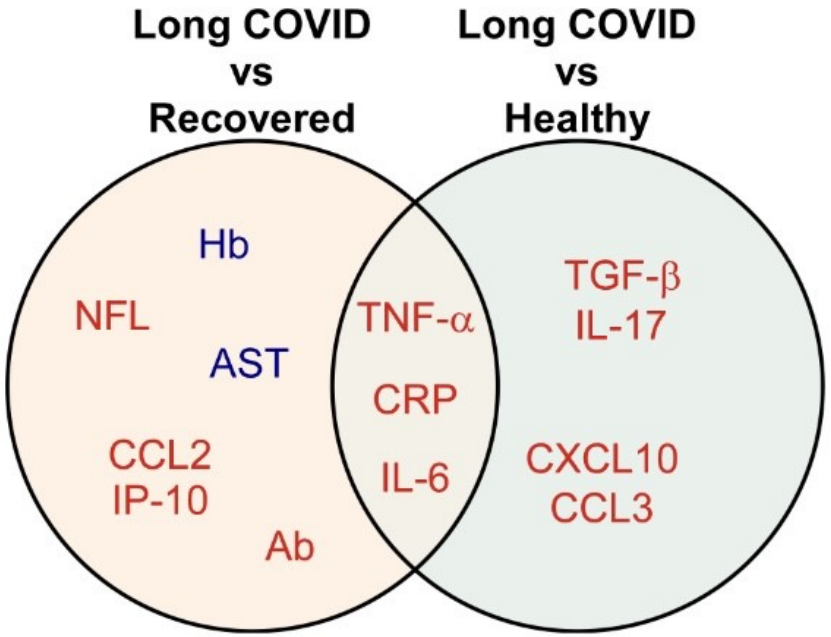
# Facteurs de risque

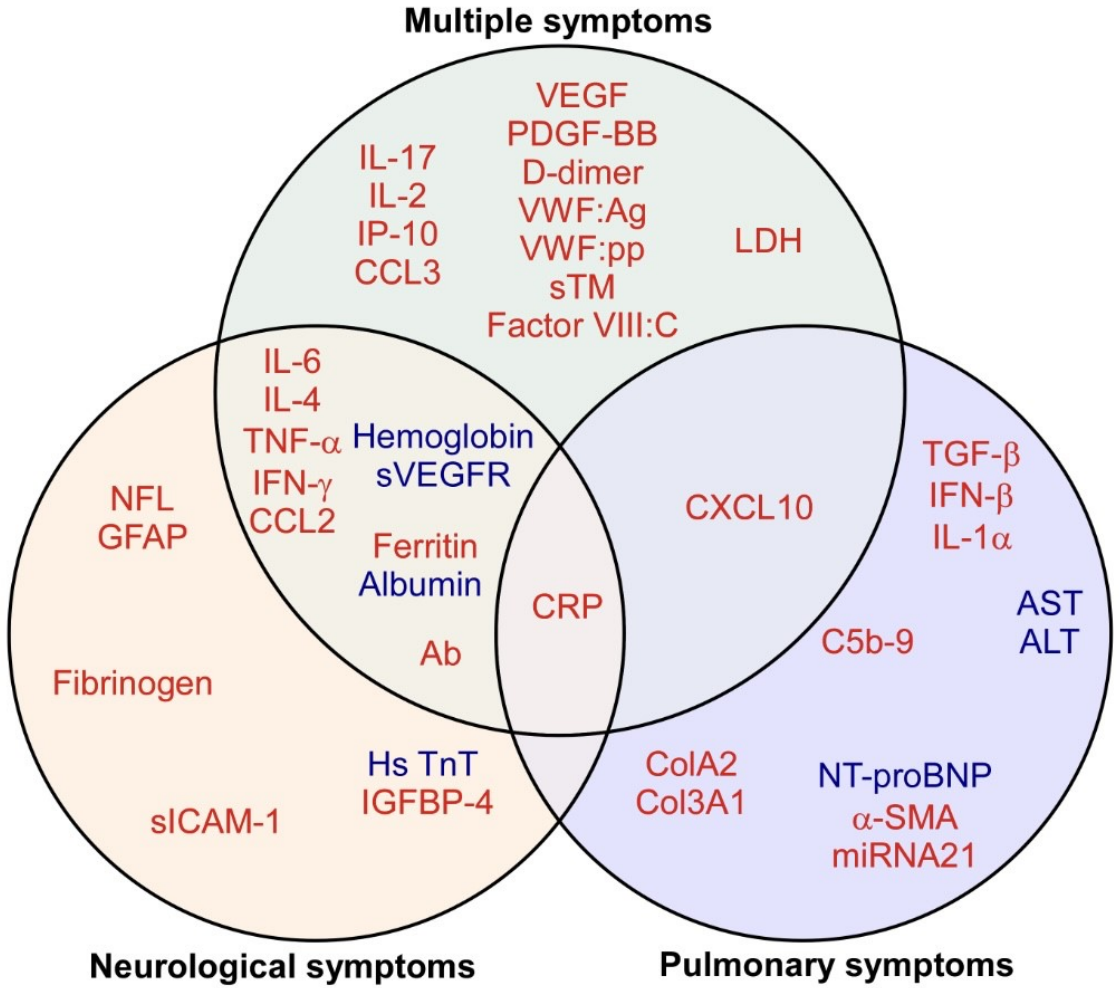
| Moins à risque de développer un COVID-long (plus de chance de se rétablir rapidement) | Plus à risque de Développer un COVID-long (moins de chance de se rétablir rapidement) | Niveau de preuve |
|---|---|---|
| Pas de comorbidités antérieures | Comorbidités antérieures | +++ |
| Hommes | Femme | +++ |
| Conditions socio-économiques favorables | Difficultés sociales/précarité | ++ |
| COVID-19 pauscisymptomatique/asymtomatique | Hospitalisation et/ou symptômes intenses et/ou nombreux | ++ |
| Vaccination complète et rappels faits | Non vacciné ou sous-vacciné | ++ |
| Possibilité de repos en phase aigue | Repos non possible | + |
| Antiviraux données à la phase aigue | Pas d'antiviraux à la phase aigue | + |
| Pas de réinfection | Réinfections multiples | + |
| Personne jeune | Personne âgée | +/- |




Zang et al. Com Medicine 2024

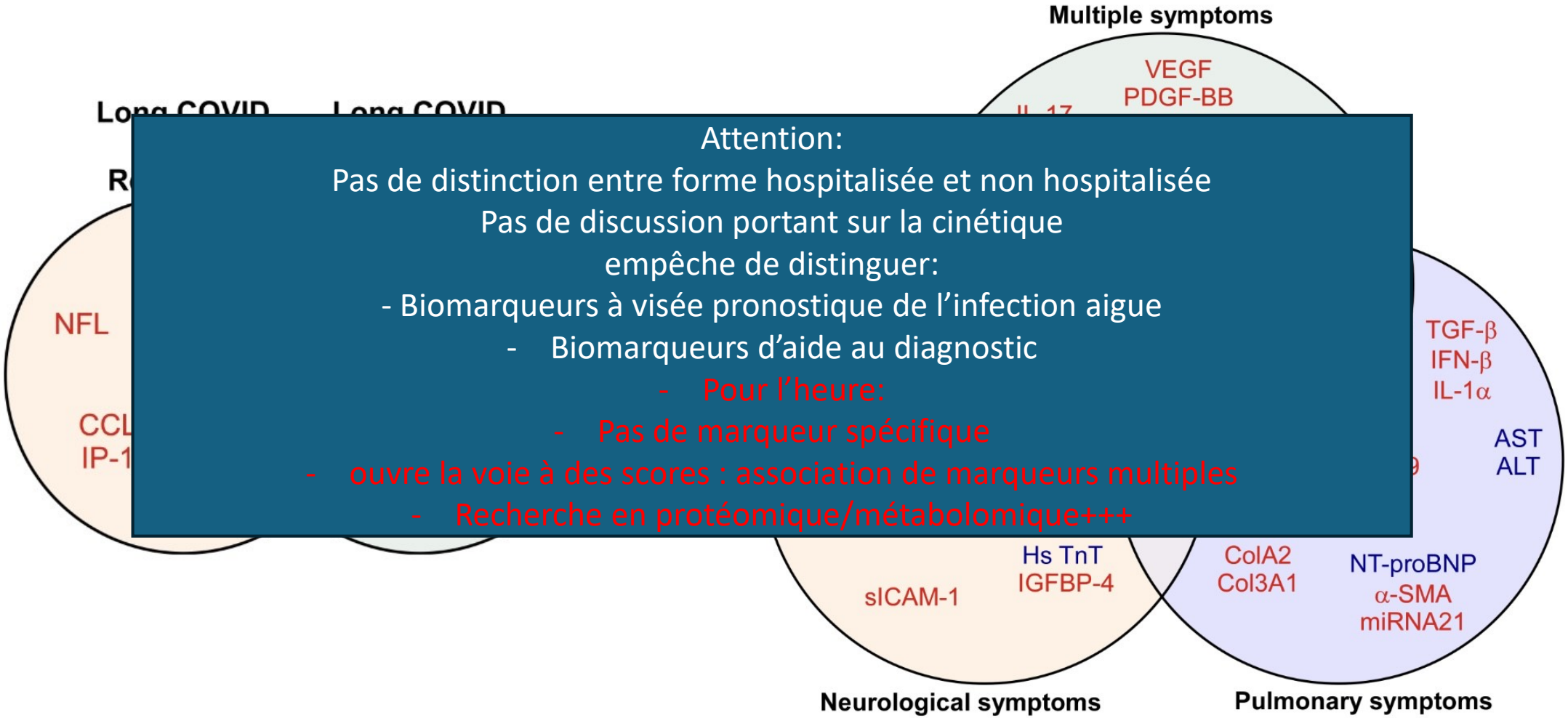
# Biomarqueurs du COVID-long




Lai et col Front. Med 2023

# Biomarqueurs du COVID-long




Attention:

Pas de distinction entre forme hospitalisée et non hospitalisée

Pas de discussion portant sur la cinétique

empêche de distinguer:

- Biomarqueurs à visée pronostique de l'infection aigue
- Biomarqueurs d'aide au diagnostic

- Pour l'heure:
- Pas de marqueur spécifique
- ouvre la voie à des scores : association de marqueurs multiples
- Recherche en protéomique/métabolomique+++

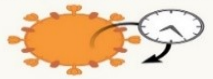
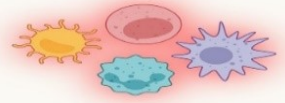
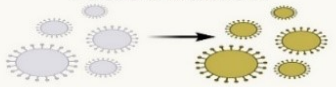
Lai et col Front. Med 2023

# Biomarqueurs probablement dépendant des symptômes et du temps depuis l'infection


Robineau et col, sous presse

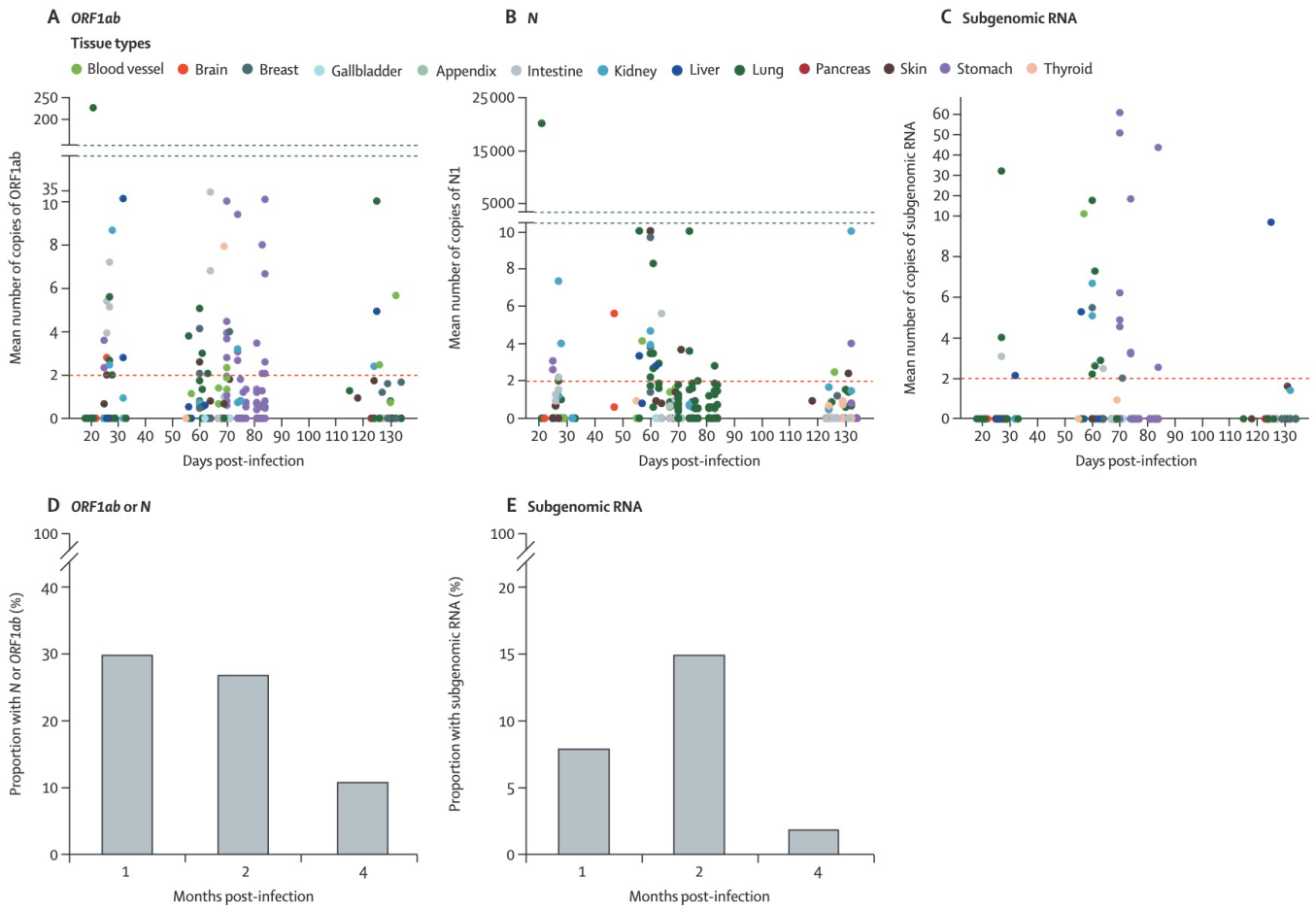
# Physiopathologie

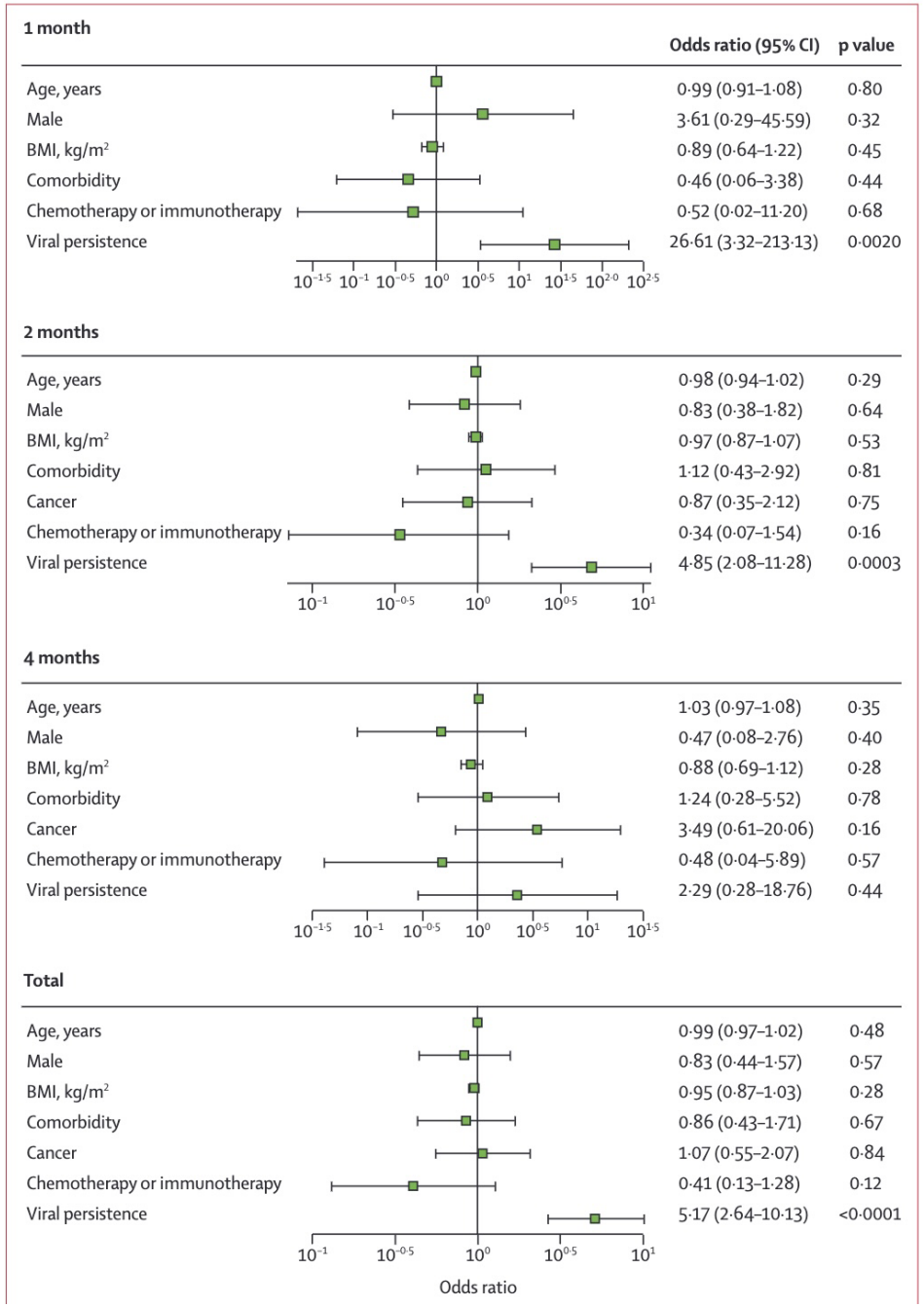
**Biological mechanisms of Long COVID**

| | Research testing | Therapeutics for evaluation |
|---|---|---|
| **Acute infection (prevention)**  | COVID-19 testing<br>Viral dynamics | Vaccination<br>COVID-19 antivirals<br>Monoclonals<br>Metformin<br>Anti-inflammatories<br>Anti-platelet drugs<br>Anticoagulants |
| **Virus persistence**  | Blood antigen<br>Blood PCR<br>Tissue biopsy | Vaccination (therapeutic)<br>COVID-19 antivirals<br>Monoclonals |
| **Post-acute inflammation**  | Blood markers (e.g., CRP)<br>Cellular immunology<br>Proteomics<br>Radiographic imaging<br>PET imaging<br>Tissue biopsy | JAK/STAT inhibitors<br>Interleukin inhibitors<br>Inflammasome inhibitors<br>Checkpoint inhibitors<br>Rapamycin |
| **Autoimmunity**  | Blood markers (e.g., ANA)<br>Autoantibody testing<br>B cell testing | IVIG<br>Plasmapheresis<br>B cell depletion |
| **Thrombosis**  | Blood markers (e.g., fibrinogen, D-dimer)<br>"Microclot" assays | Anti-platelet drugs<br>Anticoagulants<br>Thrombolytics<br>Plasmapheresis |
| **Latent virus reactivation**  | EBV PCR<br>EBV serology<br>EBV cellular assays<br>VZV assays<br>HHV-6 assays | Antivirals (e.g., ganciclovir)<br>EBV cellular therapies |
| **Dysbiosis and gut translocation**  | Microbial markers (e.g., B-glucan, LPS, zonulin)<br>Fecal microbiota | Probiotics<br>Larazotide<br>Fecal transplant |
| **Mitochondrial dysfunction**  | Mitochondrial proteins<br>Reactive oxygen species<br>Muscle biopsy | Amino acids<br>N-acetylcysteine<br>Metformin |

Peluso et al Nat com 2023

# Persistance virale



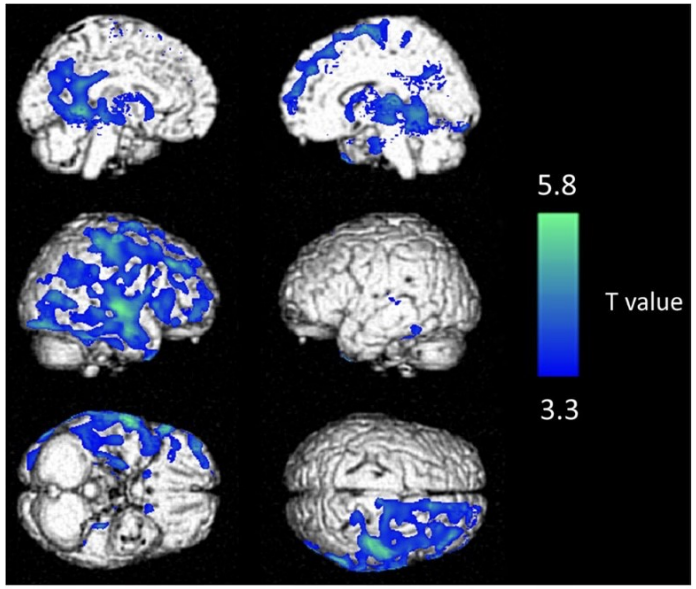

Zuo et al Lancet Infectious disease 2024

# Maladie poly-symptomatique ou multisystémique? L'hypothèse neurologique

- Une hypothèse pour unir les symptômes
- Anomalie TEP
- élévation des marqueurs de souffrance neuronale?

**Conséquences**:

- Trouble de « l'adaptation »
- Dysautonomie à minima
- Déconditionnement

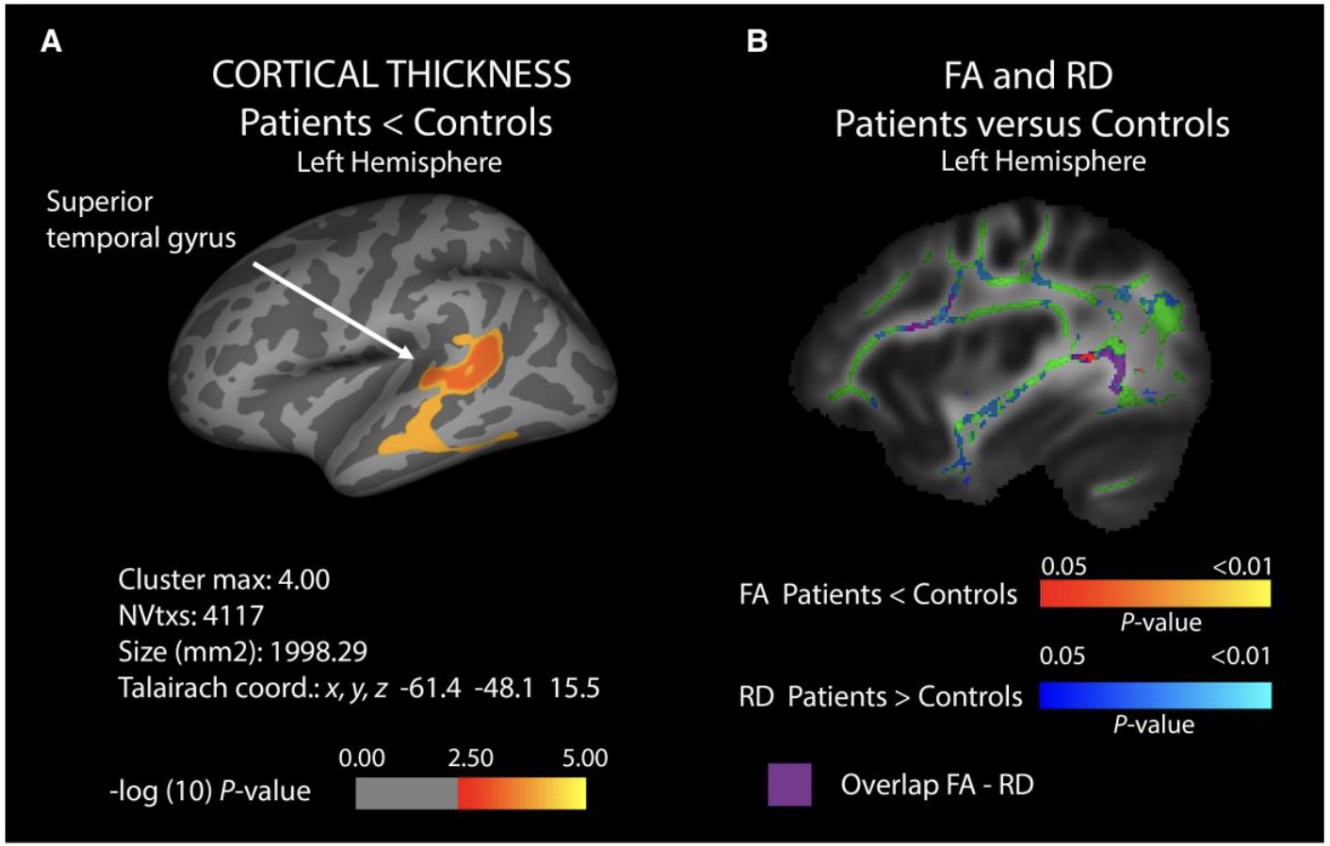



N'élimine aucune hypothèse sur le mécanisme lésionnel (vasculaire, inflammation, fonctionnel, virus persistant…)

Ghoeringer et col, Eur J Nucl Med Mol Imaging, 2023

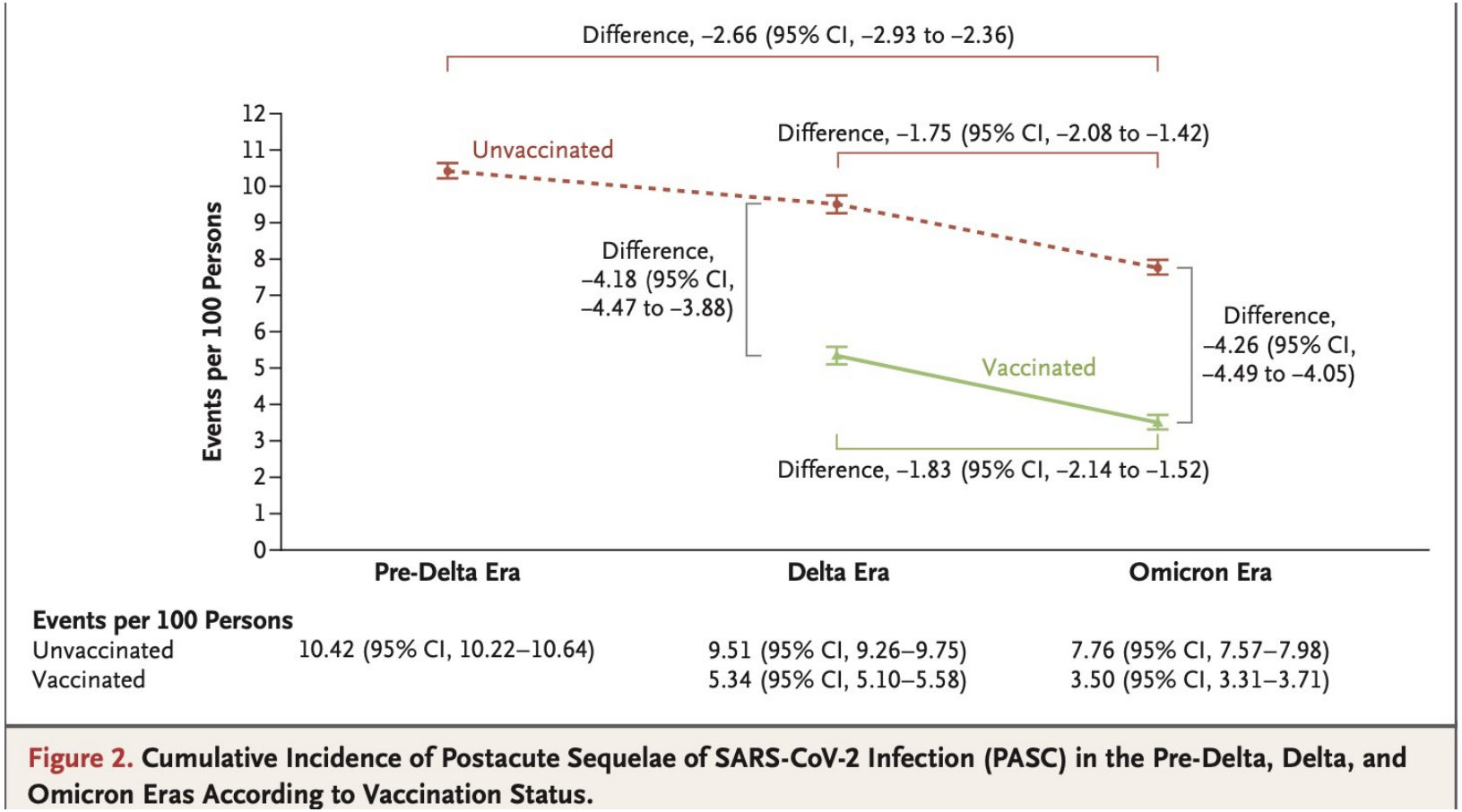
# Atteintes neurologiques: images IRM

| Cognitive assessment | Control $n = 22$ | Patients $n = 83$ | Patients versus controls |
|---|---|---|---|
| **Tests and cognitive dimensions** | **Mean ± SEM** | **Mean ± SEM** | ***P*** |
| Addenbrooke III (ACE-III) | | | |
| Overall cognitive level | 0.32 ± 00.16 | −0.39 ± 0.12 | 0.002* |
| Visuospatial | 0.35 ± 00.15 | −0.15 ± 0.11 | 0.005* |
| Language | 0.42 ± 00.06 | 0.22 ± 0.08 | 0.025* |
| Fluency | 0.33 ± 00.18 | −0.35 ± 0.13 | 0.002* |
| Memory | 0.06 ± 00.23 | −0.54 ± 0.14 | 0.022* |
| Attention | 0.16 ± 00.24 | −0.37 ± 0.17 | 0.040* |
| Premorbid IQ (WAIS III Vocabulary) | 2.30 ± 0.19 | 1.60 ± 0.10 | 0.004* |
| Boston Naming test | 1.30 ± 0.21 | 0.49 ± 0.14 | 0.004* |
| **Long-term memory** | | | |
| REY figure copy speed | −0.03 ± 0.15 | 0.07 ± 0.10 | 0.308 |
| REY figure copy precision | 1.22 ± 0.29 | 1.38 ± 0.13 | 0.299 |
| REY figure delayed free recall | 0.41 ± 0.16 | −0.33 ± 0.12 | <0.001** |
| Retention index (FCSRT,16 words list learning) | 0.97 ± 0.21 | 0.35 ± 0.15 | 0.011* |
| Free recall trial 1 | 0.40 ± 0.26 | −0.13 ± 0.11 | 0.016* |
| Total recall | 0.89 ± 0.30 | 0.02 ± 0.13 | 0.003** |
| Delayed free recall | 0.90 ± 0.24 | −0.04 ± 0.13 | 0.001** |
| Delayed total recall | 1.70 ± 0.31 | 0.62 ± 0.20 | 0.007** |
| Total free recall | 0.68 ± 0.23 | −0.24 ± 0.43 | 0.152 |
| RMBT episodic memory index | 0.69 ± 0.20 | −0.59 ± 0.13 | <0.001** |
| Names and last names | 0.22 ± 0.13 | −0.27 ± 0.12 | 0.003** |
| Belongings | −0.10 ± 0.18 | −0.62 ± 0.12 | 0.022* |
| Appointments delayed recall | 0.30 ± 0.14 | −0.19 ± 0.09 | 0.002** |
| Objects delayed recognition | −0.02 ± 0.19 | −0.89 ± 0.14 | 0.002** |
| Story immediate | 0.24 ± 0.16 | −0.37 ± 0.08 | <0.001** |
| Story delayed | 0.24 ± 0.11 | −0.36 ± 0.09 | <0.001** |
| Faces delayed recognition | 0.14 ± 0.22 | −0.58 ± 0.13 | <0.005* |
| Spatial route immediate | 0.15 ± 0.13 | −0.50 ± 0.13 | <0.001** |
| Spatial route delayed | 0.18 ± 0.12 | −0.56 ± 0.13 | <0.001** |
| Messages immediate memory | 0.35 ± 0.02 | −0.01 ± 0.9 | <0.001** |
| Messages delayed memory | 0.33 ± 00.02 | −0.01 ± 0.9 | <0.001** |
| Orientation and date | 0.09 ± 00.16 | −0.19 ± 0.10 | 0.071 |
| Visuospatial puzzle immediate | 0.48 ± 00.15 | 0.10 ± 0.11 | 0.023* |
| Visuospatial puzzle delayed | 0.39 ± 00.08 | −0.04 ± 0.11 | 0.005** |
| Every day/spatial memory | 0.36 ± 0.25 | −1.21 ± 0.26 | <0.001** |




Serrano del Pueblo et al Brain 2024

# Vaccination et COVID-Long




| Events per 100 Persons | | | |
|---|---|---|---|
| Unvaccinated | 10.42 (95% CI, 10.22–10.64) | 9.51 (95% CI, 9.26–9.75) | 7.76 (95% CI, 7.57–7.98) |
| Vaccinated | | 5.34 (95% CI, 5.10–5.58) | 3.50 (95% CI, 3.31–3.71) |

**Figure 2. Cumulative Incidence of Postacute Sequelae of SARS-CoV-2 Infection (PASC) in the Pre-Delta, Delta, and Omicron Eras According to Vaccination Status.**

Xie et al NEJM 2024

# Essais thérapeutiques

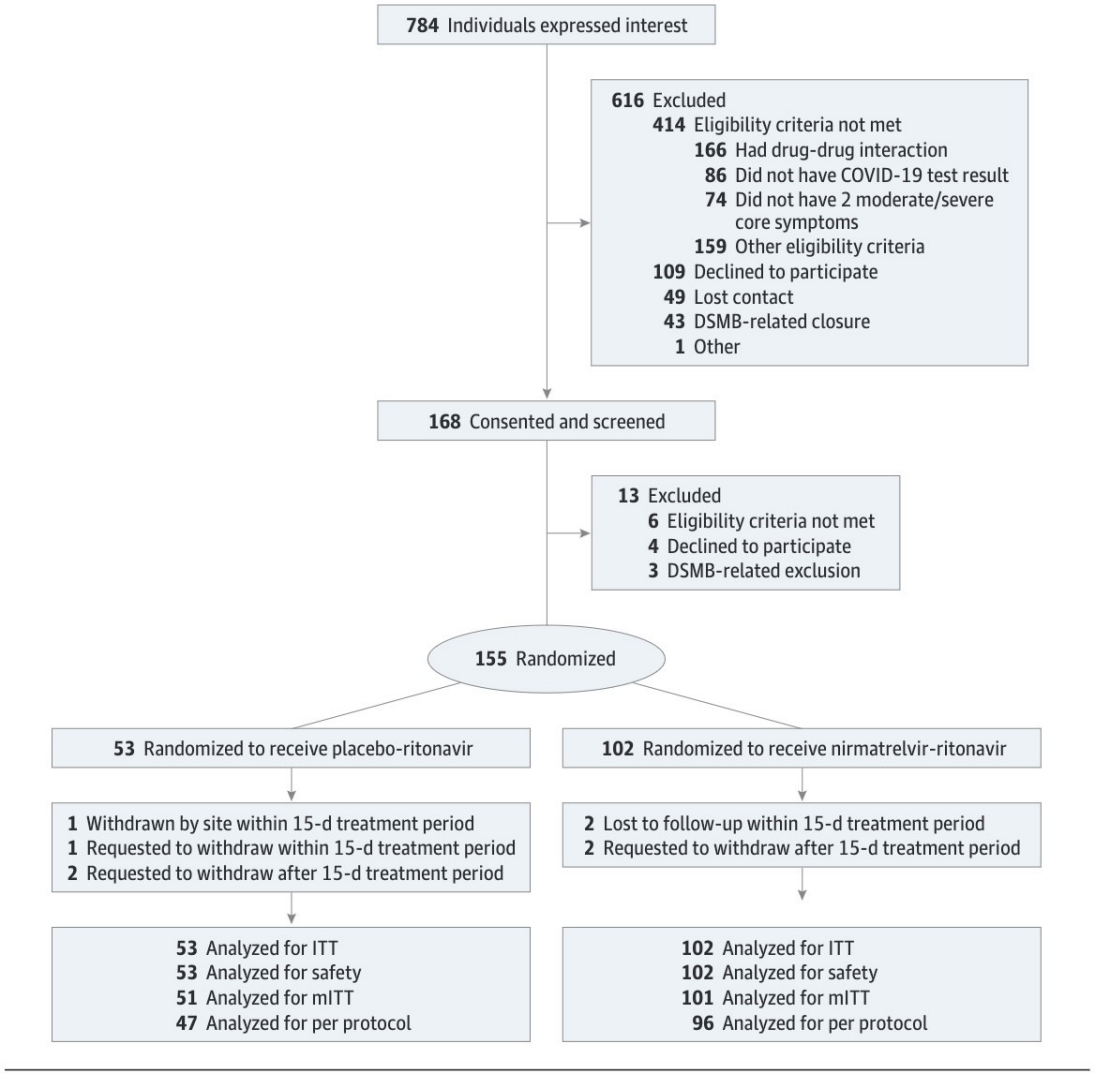
# ClinicalTrials.gov.

Près de 500 essais randomisés

- Rééducation
- Prise en charge neuropsychologique
- Traitement médicamenteux symtpomatiques
- Traitements immunomodulateurs et antiviraux

| molécules | ce qui est évalué | mécanisme/mode d'action |
|---|---|---|
| TNX-102 SL | Douleur | analgésique |
| Montelukast | Effort/dyspnée | Antagoniste des récepteurs des leucotriènes |
| Nirmatrelvir/ Ritonavir | Exacerbation des symptomes à l'effort/fatigue/qualité de vie | Antiviral |
| Ensitrevir | Santé global | Antiviral |
| Remdesevir | Qualité de vie | Antiviral |
| Naltrexone | Fatigue | antagoniste opioide |
| pimozide | Fatigue | neuroleptique |
| plasmaphérèse | Fatigue | |
| homéopathie | Fatigue | - |
| AXA125 | Fatigue | métabolisme mitochondrial |
| colchicine | Fatigue/douleurs | Anti-inflammatoire |
| RSLV-132 | Fatigue/dyspnée/effort | anti ADN-circulant |
| Metoprolol succinate | Fatigue/effort | bbloquant |
| mitoquinone Q | Fatigue/effort | anti-oxydant |
| S-1226 | Fatigue/fonction respiratoire | bronchodilatateur |
| oxygénothèrapie hyperbare | Fatigue | ? |
| Ivabradine | POTS | contrôle cardiaque |
| Bupivacaine | PRO | analgésique |
| Ibudilast | Qualité de vie | anti-inflammatoire |
| Pentoxifylline | Qualité de vie | inhibiteur PDE4 |
| LYT-100 | Qualité de vie | antifibrosant/anti-inflammatoire pulmonaire |
| maraviroc | Symptomes | anti -CCR5/ immunomodulateur |
| Vortioxetine | T cognitifs | anti-transporteur de la serotonine |
| Temelimab | T cognitifs/fatigue | anticorps anti HERV-W ENV |
| famotidine | T digestifs/fatigues | Anti-H1 |

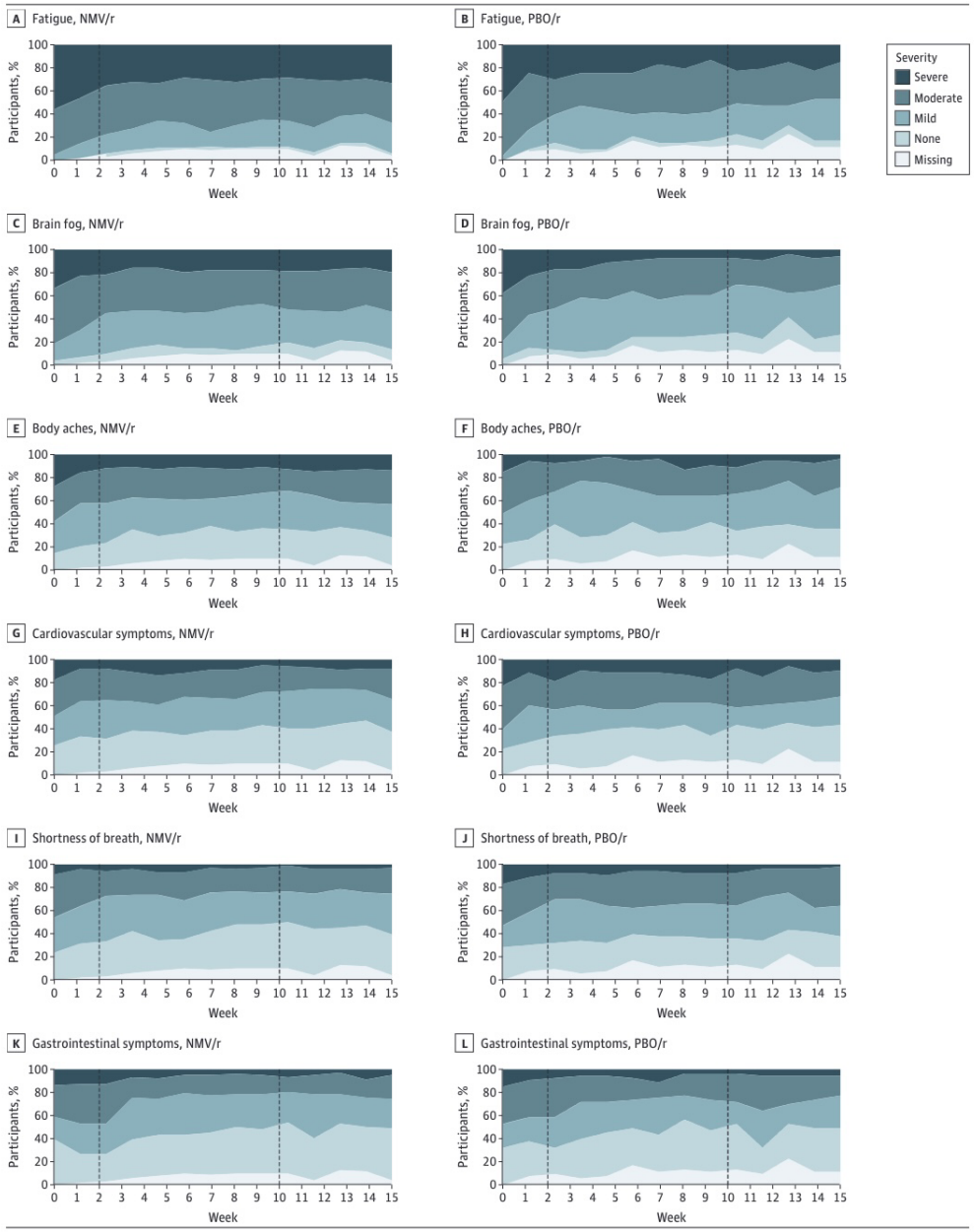
# Association nirmatrelvir-ritonavir VS Placebo




| Characteristic | No. (%) NMV/r | PBO/r | ASD[a] |
|---|---|---|---|
| Group participants, No. | 102 | 53 | NA |
| Age, median (IQR), y | 44.5 (35.25-56) | 41 (31-45) | 0.34 |
| Female | 61 (59.8) | 31 (58.5) | NA |
| Male | 41 (40.2) | 22 (41.5) | NA |
| Race | | | |
| Asian | 11 (10.8) | 9 (17) | 0.37 |
| Black or African American | 1 (1) | 2 (3.8) | |
| Native Hawaiian or other Pacific Islander | 1 (1) | 0 | |
| White | 76 (74.5) | 39 (73.6) | |
| More than 1 race | 5 (4.9) | 1 (1.9) | |
| Unknown | 8 (7.8) | 2 (3.8) | |
| Hispanic ethnicity | 12 (11.8) | 7 (13.2) | 0.04 |
| Index COVID-19 infection date[b] | | | |
| Before May 2021 | 39 (38.2) | 22 (41.5) | 0.17 |
| May to December 2021 | 20 (19.6) | 7 (13.2) | |
| After December 2021 | 43 (42.2) | 24 (45.3) | |
| Hospitalized for index COVID-19 infection | 6 (5.9) | 3 (5.7) | 0.01 |
| Time from index infection to randomization, mean (SD), mo | 17.6 (9.1) | 17.3 (9.1) | 0.03 |
| Total COVID-19 infections, mean (SD)[c] | 1.45 (0.75) | 1.34 (0.55) | 0.17 |
| Prior use of SARS-CoV-2 acute medication | | | |
| Prior use of medication[d] | 27 (26.5) | 14 (26.4) | <0.01 |
| Prior use of Paxlovid | 18 (17.6) | 9 (17) | 0.02 |
| No prior use | 75 (73.5) | 39 (73.6) | NA |
| Vaccination status at randomization | | | |
| Initial series completed | 101 (99) | 52 (98.1) | 0.08 |
| Initial series not completed | 1 (1) | 1 (1.9) | |
| BMI, mean (SD) | 27 (6.19) | 28 (6.66) | 0.18 |

Geng et col JAMA Intern Med 2024

# Association nirmatrelvir-ritonavir VS Placebo

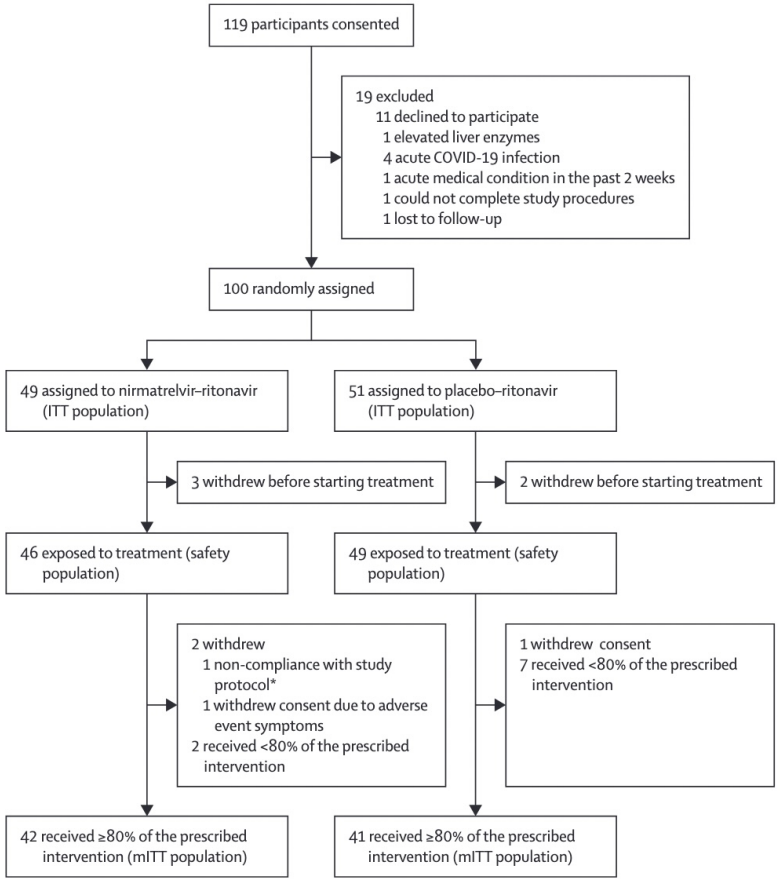



| Outcome or event | NMV/r | PBO/r | | |
|---|---|---|---|---|
| Participants in group | 102 | 53 | | |
| **Moderate to severe symptoms, change from baseline at 10 wk, % of participants** | | | | |
| Fatigue | −23.5 | −43.4 | | |
| Brain fog | −28.4 | −47.2 | | |
| Body aches | −22.5 | −20.8 | | |
| Cardiovascular | −23.5 | −20.8 | | |
| Shortness of breath | −20.6 | −24.5 | | |
| Gastrointestinal | −19.6 | −11.3 | | |
| | **Mean (SD)** | | **β (95% CI)[a]** | ***P* value** |
| PROMIS, change from baseline to 10 wk | | | | |
| Physical function | 2.73 (6.62) | 1.32 (5.75) | 0.57 (−1.96 to 3.10) | .66 |
| Fatigue | −3.92 (7.88) | −4.05 (5.90) | 0.38 (−2.40 to 3.15) | .79 |
| Dyspnea | −1.96 (7.90) | −2.38 (6.13) | 0.60 (−2.55 to 3.75) | .70 |
| Cognitive function | 4.84 (8.18) | 5.05 (7.56) | 0.03 (−3.21 to 3.28) | .98 |
| PGIC score at 10 wk | 3.38 (1.31) | 3.13 (1.03) | 0.10 (−0.48 to 0.67) | .74 |
| PGIS score at 10 wk | 4 (1.03) | 3.79 (1.06) | 0.19 (−0.25 to 0.62) | .40 |
| Summative score at 10 wk | 7.62 (3.75) | 7.69 (4.09) | −0.24 (−1.46 to 0.97) | .69 |
| | | | **HR (95% CI)** | ***P* value** |
| Time to relief of most bothersome symptom[b] | | | 0.74 (0.40 to 1.38) | .33 |
| | **No. (%)** | | **OR (95% CI)** | ***P* value** |
| Experiencing relief at 10 wk[b] | 33 (32.4) | 22 (41.5) | 0.55 (0.27 to 1.09) | .09 |
| Experiencing alleviation at 10 wk[c] | 7 (6.86) | 5 (9.43) | 0.72 (0.21 to 2.44) | .60 |
| | **Median (IQR)** | | **OR (95% CI)[d]** | ***P* value** |
| Proportion of weeks 1-15 with mild or no symptoms | | | | |
| Fatigue | 0.15 (0 to 0.39) | 0.15 (0 to 0.77) | 0.55 (0.33 to 0.92) | .02 |
| Brain fog | 0.31 (0 to 0.75) | 0.56 (0.15 to 0.85) | 0.50 (0.31 to 0.82) | .01 |
| Body aches | 0.54 (0.10 to 0.92) | 0.64 (0.29 to 0.83) | 1.32 (0.74 to 2.33) | .34 |
| Cardiovascular symptoms | 0.67 (0.19 to 0.92) | 0.46 (0 to 0.92) | 1.37 (0.76 to 2.48) | .29 |
| Shortness of breath | 0.769 (0.25 to 1) | 0.62 (0.09 to 0.89) | 1.32 (0.73 to 2.38) | .35 |
| Gastrointestinal symptoms | 0.63 (0.31 to 0.92) | 0.52 (0.28 to 0.90) | 1.40 (0.79 to 2.47) | .25 |
| | **No. (%)** | | | |
| Participants with AEs | 101 (99) | 49 (92) | | |
| No. of AEs | 771 | 313 | | |
| Total SAE[e] | 3 (2.9) | 1 (1.9) | | |
| Participants with grade 3 or 4 AEs[f] | 5 (4.9) | 3 (5.7) | | |
| Fatalities | 0 | 0 | | |

Geng et col JAMA Intern Med 2024

# Nirmatrelvir–ritonavir versus placebo–ritonavir in individuals with long COVID in the USA (PAX LC): a double-blind, randomised, placebo-controlled, phase 2, decentralised trial

*Mitsuaki Sawano*, Bornali Bhattacharjee*, César Caraballo, Rohan Khera, Shu-Xia Li, Jeph Herrin, Dany Christian, Andreas Coppi, Frederick Warner, Julie Holub, Yashira Henriquez, Maria A Johnson, Theresa B Goddard, Erica Rocco, Amy C Hummel, Mohammad AL Mouslmani, William Brenham Hooper, David F Putrino, Kevin D Carr, Lawrence Charnas, Magdia De Jesus, Dale Nepert, Paula Abreu, Frank W Ziegler 3rd, John A Spertus, Akiko Iwasaki†, Harlan M Krumholz†*




| | Nirmatrelvir–ritonavir (n=49) | Placebo–ritonavir (n=51) |
|---|---|---|
| Age, years | 42·0 (12·3) | 43·1 (11·8) |
| Sex at birth | | |
| Male | 17 (35%) | 17 (33%) |
| Female | 32 (65%) | 34 (67%) |
| Child-bearing potential | 24 (49%) | 29 (57%) |
| Race | | |
| White | 46 (94%) | 45 (88%) |
| Black or African American | 0 | 2 (4%) |
| Asian | 2 (4%) | 3 (6%) |
| Native Hawaiian or other Pacific Islander | 0 | 0 |
| American Indian or Alaskan Native | 0 | 0 |
| More than one race | 0 | 1 (2%) |
| Other | 1 (2%) | 0 (0%) |
| Hispanic or Latino | 4 (8%) | 1 (2%) |
| US census region | | |
| Northeast | 27 (55%) | 24 (47%) |
| Midwest | 7 (14%) | 12 (24%) |
| South | 7 (14%) | 4 (8%) |
| West | 8 (16%) | 11 (22%) |
| COVID-19 history | | |
| Days from acute SARS-CoV-2 infection* | 511 (362–777) | 722 (433–1159) |
| Days from long COVID diagnosis or onset* | 442 (282–645) | 561 (362–1058) |
| Received at least 1 dose of COVID-19 vaccine | 48 (98%) | 49 (96%) |
| Received vaccine later than Sept 11, 2023, and before consent | 6 (12%) | 8 (16%) |
| Days from latest COVID-19 vaccination* | 303 (92–588) | 302 (37–483) |

Data are mean (SD), n (%), or median (IQR). *All durations were calculated as the number of days between the date of the event, as documented in electronic health records, and the date of study consent.

***Table 1:*** **Patient characteristics at time of enrolment (intention-to-treat population)**

| | Nirmatrelvir–ritonavir (n=49) | Placebo–ritonavir (n=51) | Difference | p value |
|---|---|---|---|---|
| **Modified GSQ-30 score** | | | | |
| Day 15 | −9·72 (−14·52 to −4·92) | −7·98 (−12·40 to −3·57) | −1·74 (−7·82 to 4·34) | 0·57 |
| Day 28 | −12·62 (−17·31 to −7·93) | −9·19 (−13·59 to −4·79) | −3·43 (−9·37 to 2·50) | 0·26 |
| **COVID Core Outcome Measures for Recovery score** | | | | |
| Day 15 | −0·10 (−0·36 to 0·15) | −0·10 (−0·34 to 0·14) | −0·01 (−0·33 to 0·32) | 0·97 |
| Day 28 | −0·15 (−0·40 to 0·11) | −0·08 (−0·32 to 0·16) | −0·07 (−0·39 to 0·26) | 0·68 |
| **EuroQol EQ-5D-5L** | | | | |
| Day 15 | −0·41 (−1·11 to 0·30) | −0·48 (−1·14 to 0·17) | 0·07 (−0·82 to 0·97) | 0·87 |
| Day 28 | −0·57 (−1·25 to 0·12) | −0·54 (−1·20 to 0·11) | −0·02 (−0·89 to 0·85) | 0·96 |
| **EuroQol Visual Analogue Scale score** | | | | |
| Day 15 | 5·79 (1·28 to 10·30) | 1·23 (−2·97 to 5·43) | 4·57 (−1·00 to 10·14) | 0·11 |
| Day 28 | 7·81 (3·32 to 12·30) | 4·05 (−0·22 to 8·31) | 3·76 (−1·91 to 9·44) | 0·19 |
| **Patient Global Impression of Severity score** | | | | |
| Day 15 | 3·96 (3·62 to 4·30) | 3·88 (3·56 to 4·20) | 0·08 (−0·34 to 0·50) | 0·71 |
| Day 28 | 3·97 (3·63 to 4·31) | 3·97 (3·65 to 4·29) | −0·00 (−0·42 to 0·42) | 1·00 |
| Week 6 | 3·98 (3·65 to 4·32) | 3·86 (3·54 to 4·18) | 0·12 (−0·30 to 0·54) | 0·56 |
| **Patient Global Impression of Change overall health score** | | | | |
| Day 15 | 4·04 (3·69 to 4·38) | 4·03 (3·70 to 4·35) | 0·01 (−0·42 to 0·44) | 0·97 |
| Day 28 | 4·06 (3·71 to 4·40) | 3·96 (3·64 to 4·29) | 0·09 (−0·34 to 0·53) | 0·67 |
| Week 6 | 4·05 (3·71 to 4·39) | 3·90 (3·58 to 4·23) | 0·15 (−0·28 to 0·58) | 0·49 |

Data are mean (95% CI) change from baseline unless otherwise indicated. Mean difference estimates with 95% CIs were obtained from a mixed models for repeated measures analysis fitted to assess the change from baseline in each secondary endpoint, including treatment, time, and treatment-by-time interaction as fixed effects; age, sex, and baseline as covariates; and participant as a random effect. GSQ=General Symptom Questionnaire. ITT=intention to treat.

***Table 3:*** **Secondary endpoints (change from baseline, ITT with imputation)**

# Raisons de l'échec?

- Considérer les COVID-long comme une entité homogène physiopathologique?
- Mauvaises hypothèses?
- Posologie/durée de traitement?
- Pénétration tissulaire?

- 2 autres essais en cours (USA) au design similaire…mais avec plus de patients
  - Etudes physiopathologiques associées

# Traitement symptomatique: Amantadine

Baseline

| Basic information | Total (n = 62) | Amantadine (n = 30) | Control (n = 32) | *P*-value |
|---|---|---|---|---|
| Sex (Percentage (number)) | | | | |
| Female | 62.90% (39) | 63.33% (19) | 62.50% (20) | 0.945 |
| Male | 37.10% (23) | 36.67% (11) | 37.50% (12) | |
| Age (mean ± SD) | 37.31 ± 8.98 | 36.16 ± 1.52 | 38.42 ± 1.68 | < 0.0001 |
| BMI (mean ± SD) | 26.52 ± 4.43 | 25.78 ± 0.75 | 27.31 ± 0.82 | < 0.0001 |
| Hospitalization (Percentage (number)) | | | | |
| Yes | 43.55% (27) | 40.00% (12) | 46.87% (15) | 0.585 |
| No | 56.45% (35) | 60.00% (18) | 53.13% (17) | |

résultats

| Fatigue scoring scales | Before treatment (Mean ± SD) | After treatment (Mean ± SD) | Difference between before and after treatment (Mean ± SD) |
|---|---|---|---|
| VAFS | | | |
| Amantadine group | 7.90 ± 0.60 | 3.37 ± 0.44 | 4.53 ± 0.44 |
| Control group | 7.34 ± 0.58 | 5.97 ± 0.29 | 1.37 ± 0.13 |
| *P*-value | 0.087 | < 0.001 | < 0.001 |
| FSS | | | |
| Amantadine group | 53.10 ± 5.96 | 28.40 ± 2.42 | 24.70 ± 7.20 |
| Control group | 50.38 ± 4.88 | 42.59 ± 1.50 | 7.79 ± 0.86 |
| *P*-value | 0.053 | < 0.001 | < 0.001 |

Effets secondaires

| Side effects | Percentage (number) |
|---|---|
| Headache | 13.33% (4) |
| Dizziness | 16.67% (5) |
| Dry mouth | 26.67% (8) |
| Seizure | 0.00% (0) |
| Peripheral edema | 0.03% (1) |
| Total | 33.33% (10) |

Harandi et al Sci rep 2024

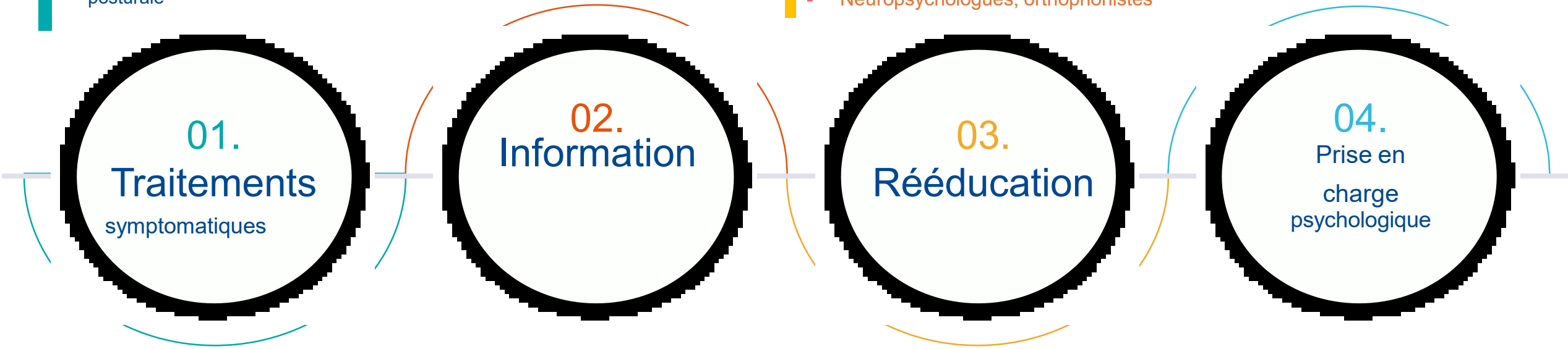
# La stratégie thérapeutique repose sur 4 piliers et se veut holistique

**Traitements symptomatiques**

- douleurs (AINS non contre-indiqués)
- reflux, hyperréactivité bronchique, tachycardie posturale

**Rééducation : place centrale**

- Respiratoire si SHV, olfactive, orthophonique
- Par le sport
- Progressive, adaptée aux possibilités de chaque patient
- Neuropsychologues, orthophonistes




**Délivrer toute l'information au patient, lui apprendre à s'autogérer**

- Connaitre situations déclenchant symptômes et limites
- Poursuite activités physiques même modérée

**Troubles anxieux & dépressifs, voire fonctionnels**

- Dépistage systématique
- IRSN et benzodiazépine non contre-indiqués

D'après la réponse rapide HAS 2021

# COVID-Long: Une opportunité pour étudier les syndromes post-infectieux

| | fièvre Q | ebola | Sars-CoV-1 | Chikungunya | West-Nile | Polio | Lambliase | Sars-CoV-2 |
|---|---|---|---|---|---|---|---|---|
| asthénie | + | + | + | + | + | + | + | + |
| dyspnée | + | | + | + | + | + | | + |
| céphalées | + | + | + | + | + | | | +/- |
| arthralgies myalgies | + | + | + | + | + | | + | + |
| T du sommeil | + | + | + | + | + | + | | +/- |
| T cardiaques | + | **+/-** | + | ? | ? | | | + |
| T occulaires | ? | + | ? | | + | | | +/- |
| Paires craniennes | ? | + | + | ? | + | | | +/- |
| T sensitifs | + | ? | ? | + | + | | | + |
| T neurocognitifs | + | + | + | ? | ? | | | + |
| Anxiété/depression | + | + | + | + | + | + | + | + |
| T du gout et odorat | - | - | - | - | - | | | + |
| Faiblesse musculaire | + | + | + | + | + | | | ? |
| post-effort | + | + | + | + | + | | | +/- |
| T moteurs | | | | | | + | | |
| fièvre | + | + | | | | | | + |
| T digestifs | | | | | | | + | |

D'après Choutka et col Nat Comm, 2022

# Conclusions

- Recherche en plein développement
- Difficultés méthodologiques+++
- Importance stratégique de la recherche:
  - Autres syndromes post-infectieux
  - Epidémies futures
- Vaccination: protège de manière directe et indirecte
- Médicaments: léger effet si antiviraux ou metformine à la phase aigue. Essais à reproduire (objectifs secondaires..)
- Nécéssiité de parcours de soins à intégrer à l'existant…sans jugement

# Syndrome post infectieux et maladies respiratoires

## THE EXHAUSTION OF INFLUENZA.

ONE is never astonished or surprised nowadays to hear a very large number of people complain of the exhaustive effects of the influenza.

It is just possible that many ailments are attributed to this disease wrongfully. Yet, as we yearly become more familiar with its results, there is little room for doubt that they are very widespread and productive of grave distress. Patients tell us that they cannot sleep, that they become depressed and despondent, that they are rarely free from pain, and that they fail in energy, and get done up in a manner quite unaccountable, and, in fact, quite unknown to them before.

The brain worker will remark that his memory has become defective, and that he fails in concentration of his powers of ideation.

The neurotic will make all sorts of vague complaints, far too numerous to mention, painful neuralgias being very frequent.

Sometimes we find positive mental derangements leading to suicide.

The most general trouble is failure of the heart's action, and an unaccountable sense of weariness and fatigue, and a feeling of incompetency and inadequacy to the fulfilment of the ordinary duties of life. I shall attempt to analyze these conditions, in order that we may the better comprehend their true meaning and significance and cure.

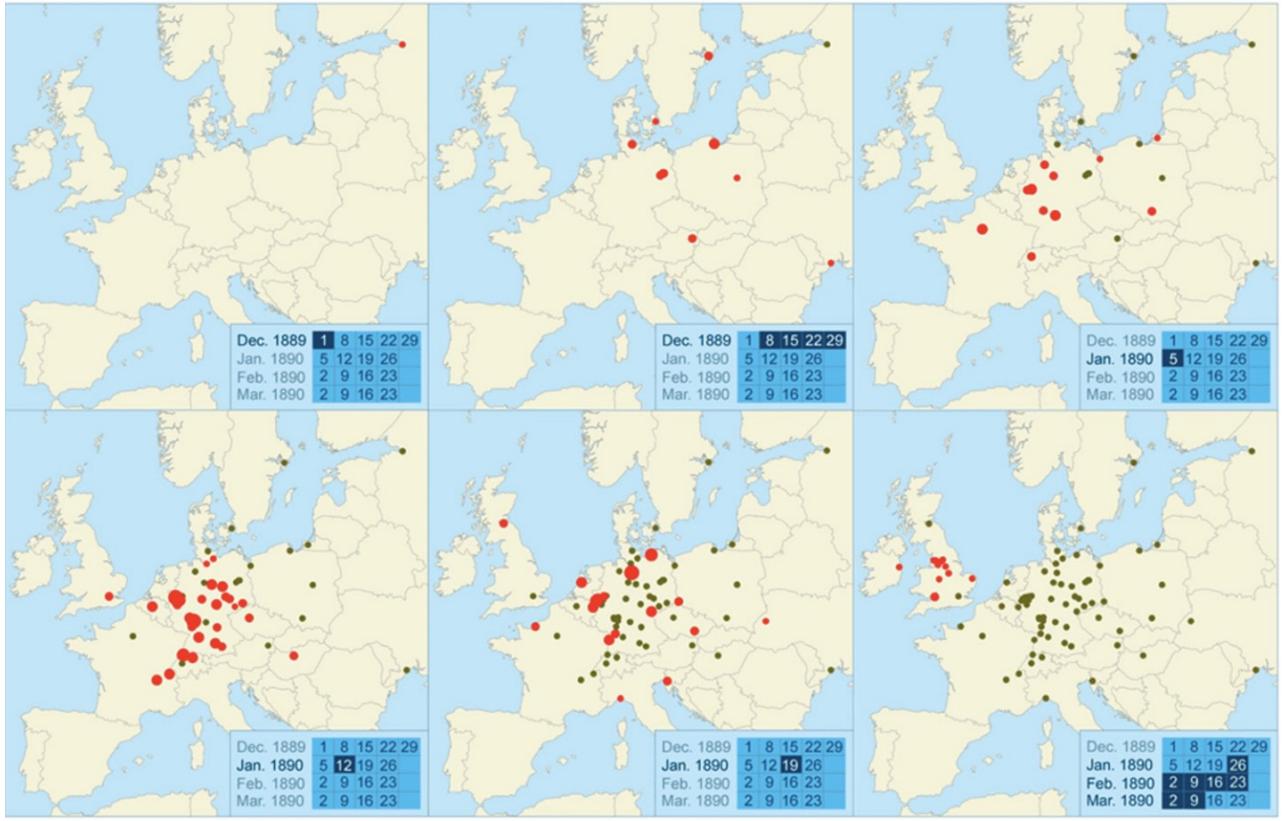
We are inclined to admit that this influenza is essentially a nervous form of fever, sometimes attacking the centres of all the levels of the nervous system, at other times confining its interest to one level only. Thus we may have the encephalic form, the catarrhal or respiratory

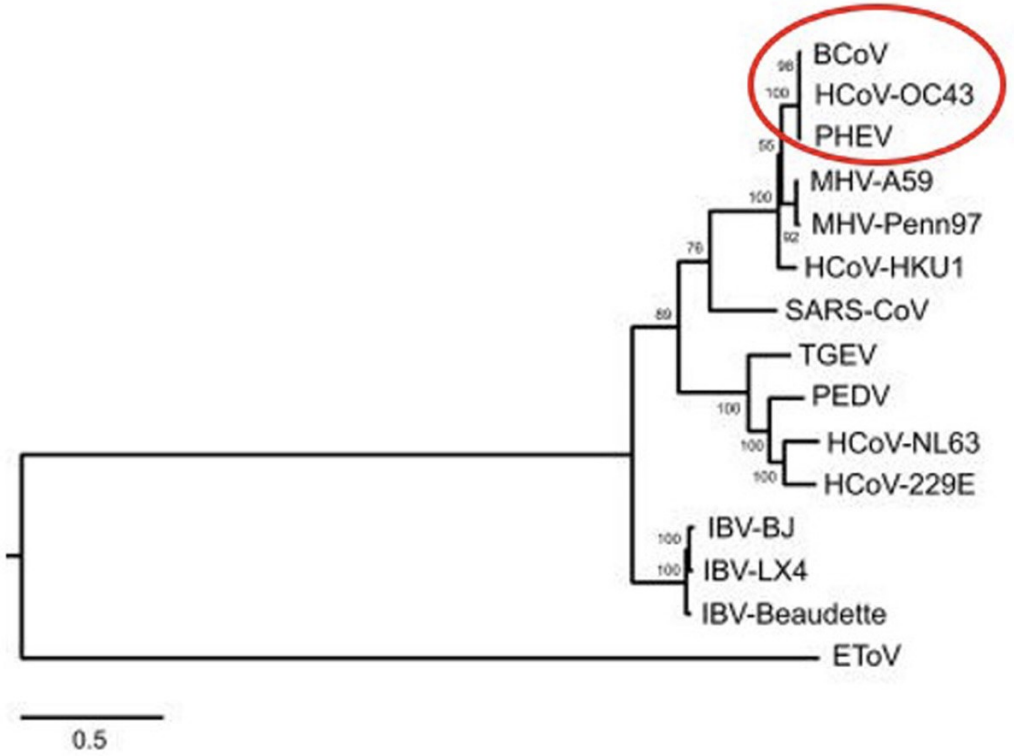


form, and the gastro-intestinal or abdominal form, just according to the level of the nervous system specially invaded by the toxine, and not unfrequently each level may be attacked in succession at varying intervals in the same individual. By this I mean that the primary symptoms may be essentially encephalic, lasting sometimes for three days; secondly, laryngo-tracheal, affecting also the respiration, as well as the heart and circulation; and, thirdly, abdominal symptoms may follow, and be alone present.

Dowse, Baillière, Tindall and Cox, 1894

# Grippe russe et coronavirus?




Valleron et col PNAS 2010

Vigen et col Virology 2005

# Epidémies de fatigue… données un peu plus récentes

*Postgraduate Medical Journal* (1988) **64,** 559–567

## Post-infectious disease syndrome

B.A. Bannister

*The Royal Free Hospital Department of Infectious Diseases at Coppetts Wood Hospital, Coppetts Road, Muswell Hill, London N10 1JN, UK.*

**Table II** Some major outbreaks of fatigue syndrome

| *Outbreak* | *Population affected* | *Approx. no. of cases* |
|---|---|---|
| Los Angeles, 1934[11] | Hospital staff | 200 |
| Switzerland, 1937 and 1939[12,13] | Soldiers in a garrison | 130 and 75 |
| Iceland, 1948–9[14] | Akureyri district residents | Hundreds |
| Adelaide, Aus., 1949–51[15] | Town residents | 700 |
| New York State, 1950[16] | Local residents | 20 |
| London, 1952[17] | Hospital staff | 14 |
| Coventry, 1953[18] | Hospital staff | Tens |
| London, 1955[19] | Hospital staff | 300 |
| London, 1955–58[20] | Suburban residents | 53 |
| Cumbria, 1955[21] | Rural adults and children | 230 |
| Durban, SA, 1955[22] | Hospital staff | 100 |
| London, 1964–6[23] | Suburban residents | 370 |
| London, 1970–71[24] | Hospital staff | 150 |
| Lake Tahoe, USA, 1984–5[25–26] | District residents | 90 |

# Grippe VS SARS-COV-2?

- Evènements post hospitalisation restent plus fréquents après SARS-COV-2 VS grippe
- Sur-risque d'événement après une grippe démontrée sur épidémies antérieurs
- Evènements plus rare mais potentiellement aussi long
- Risque diminué par la vaccination

Xie et Al, Lancet inf dis 2024
Choutka et al Nat med 2022
Magnus et al Vaccine 2020