

The Daily COVID-19 Literature Surveillance Summary

November 11, 2020



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COVID-19 Daily Literature Surveillance

COVID19LST



Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard"**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)*	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

EXECUTIVE SUMMARY

Epidemiology

- An observation-based modeling study conducted at Columbia University analyzed reproductive numbers of COVID-19 in the United States and found a [significant and rapid drop following social distancing and other control measures](#). Based on changes expected from such control measures in counterfactual models, a substantial number of cases and deaths could have been avoided if control measures were implemented 1 to 2 weeks earlier.
- An optimization model by mathematicians and data scientists using daily travel surveys, census data, and USPS building locations across various states estimated that [>94% of Americans would travel to a nearby USPS facility \(<7miles for 90% of travelers\) for COVID-19 testing](#), suggesting that while high cost and additional precautions to protect USPS employees need to be considered, the USPS network has potential to provide greater ease of access to COVID-19 testing for a majority of Americans.

R&D: Diagnosis & Treatments

- A [systematic review of 22 reports of rapid COVID-19 tests](#) (n=3,198 total samples with 1,755 RT-PCR confirmed positive SARS-CoV-2 samples) published before May 25, 2020 revealed that antigen tests have variable sensitivity (average = 56.2%), while specificity was 99.5%; rapid molecular assays had a sensitivity of 95.2% and a specificity 98.9%; and calculated pooled results for individual tests revealed that Xpert Xpress assay had a summary sensitivity of 99.4% and specificity of 96.8%, while ID NOW assay had a summary sensitivity of 76.8% and a specificity of 99.6%.

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EPIDEMIOLOGY

MODELING

DIFFERENTIAL EFFECTS OF INTERVENTION TIMING ON COVID-19 SPREAD IN THE UNITED STATES

Pei S, Kandula S, Shaman J.. Sci Adv. 2020 Nov 6:eabd6370. doi: 10.1126/sciadv.abd6370. Online ahead of print.

Level of Evidence: Other - Modeling

BLUF

An observation-based modeling study, conducted at Columbia University, analyzed reproductive numbers of COVID-19 in the United States from March 15 to May 3, 2020 and found a significant and rapid drop following social distancing and other control measures (Figures 1, 2). Based on changes expected from such control measures, the authors proposed counterfactual models in which control measures were implemented 1 to 2 weeks earlier and found that a substantial number of cases and deaths could have been avoided (Figure 3). This study demonstrates that early intervention and aggressive control are important to combat highly contagious diseases such as COVID-19.

ABSTRACT

Assessing the effects of early non-pharmaceutical interventions on COVID-19 spread is crucial for understanding and planning future control measures to combat the pandemic. We use observations of reported infections and deaths, human mobility data, and a metapopulation transmission model to quantify changes in disease transmission rates in US counties from March 15 to May 3, 2020. We find that marked, asynchronous reductions of the basic reproductive number occurred throughout the US in association with social distancing and other control measures. Counterfactual simulations indicate that, had these same measures been implemented 1-2 weeks earlier, substantial cases and deaths could have been averted, and that delayed responses to future increased incidence will facilitate a stronger rebound of infections and death. Our findings underscore the importance of early intervention and aggressive control in combatting the COVID-19 pandemic.

FIGURES

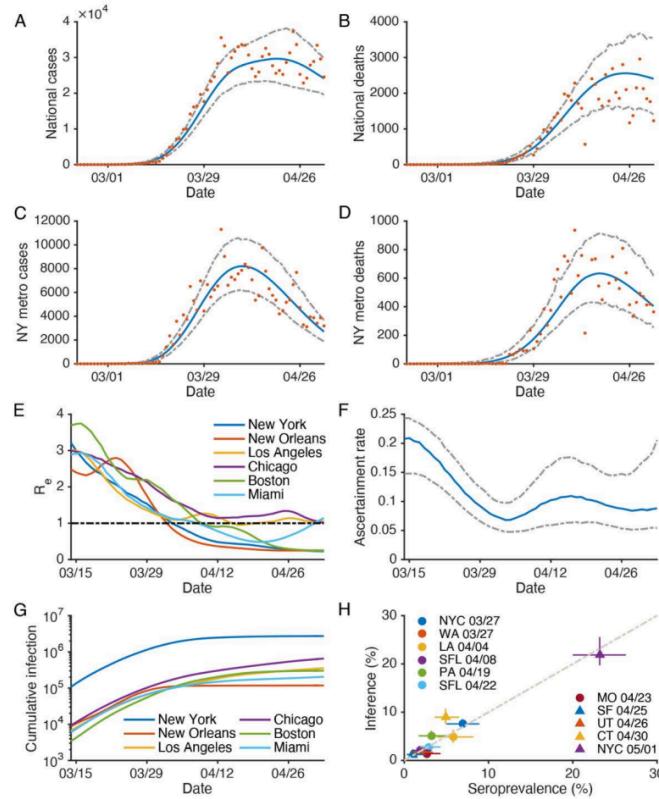


Fig. 1. Model fit and parameter inference. Posterior fitting to daily cases and deaths in the US (A-B) and the New York metropolitan area (C-D). Red dots represent observations. Blue and grey lines are the median estimate and 95% CIs. The estimated effective reproductive number, R_e , in six metropolitan areas are shown in (E). The black dotted line indicates $1 R_e = 1$. Panel (F) shows the estimated ascertainment rate over time. The blue line and grey lines are the median estimates and 95% CIs. Panel (G) shows the estimated cumulative infections (both reported and unreported) in six metropolitan areas. We compare the reported seroprevalence (%) in nine locations on different dates with the inferred percentage cumulative infections on those dates in (H). Whiskers show 95% CIs. Details on the serological survey are provided in Materials and Methods.

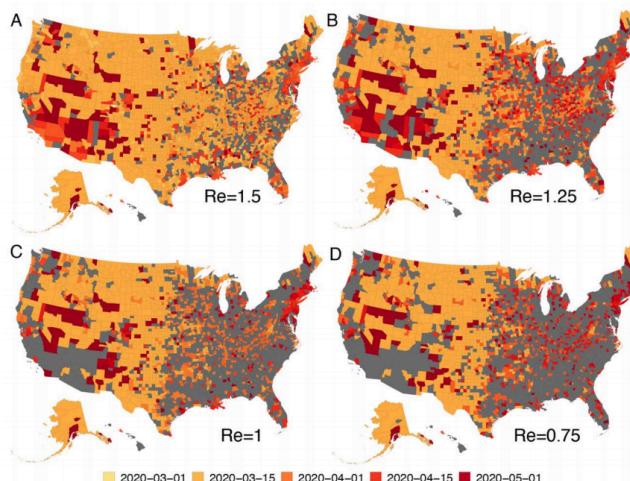


Fig. 2. Asynchronous reduction of effective reproductive numbers. For each county, we show the date when the local effective reproductive number dropped below 1.5 (A), 1.25 (B), 1 (C) and 0.75 (D), and maintained below that threshold until May 3. Counties in grey are those that either never reached the threshold or failed to remain below the threshold.

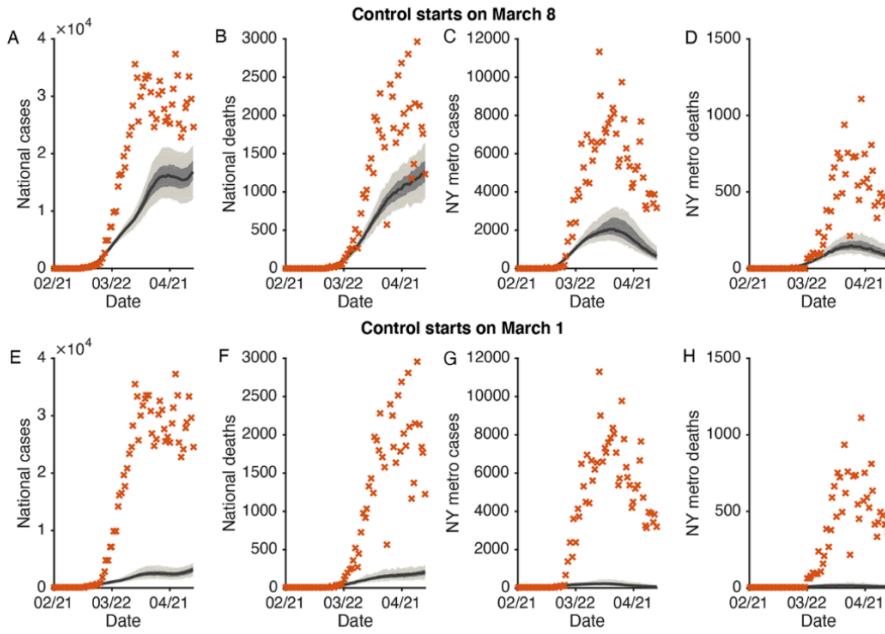


Fig. 3. Counterfactual simulations with control interventions beginning in early March – 1 and 2 weeks earlier than implemented. Daily cases and deaths in the US (A, B, E, F) and the New York metropolitan area (C, D, G, H) under early interventions are compared with the observations (red crosses). The upper and lower rows present counterfactuals with interventions implemented on March 8 and March 1, respectively. The black lines and surrounding bands show the median estimate, interquartile and 95% CIs.

EXPANDING ACCESS TO COVID-19 TESTS THROUGH US POSTAL SERVICE FACILITIES

Singh B, Risanger S, Morton D, Pignone M, Meyers LA.. Med Decis Making. 2020 Oct 30:272989X20969690. doi: 10.1177/0272989X20969690. Online ahead of print.

Level of Evidence: Other - Modeling

BLUF

An optimization model by mathematicians and data scientists using daily travel surveys, census data, and USPS building locations across various states estimated that >94% of Americans would travel to a nearby USPS facility (<7miles for 90% of travelers) for COVID-19 Testing (Tables 1,2,3). The authors acknowledge limitations to this model including high cost and additional precautions to protect USPS employees, but encourage more research on the USPS network as it has potential to provide greater ease of access to COVID-19 testing for a majority of Americans.

ABSTRACT

Widespread, convenient access to COVID-19 testing has been challenging in the United States. We make a case for provisioning COVID-19 tests through the United States Postal Service (USPS) facilities and demonstrate a simple method for selecting locations to improve access. We provide quantitative evidence that even a subset of USPS facilities could provide broad access, particularly in remote and at-risk communities with limited access to health care. Based on daily travel surveys, census data, locations of USPS facilities, and an established care-seeking model, we estimate that more than 94% of the US population would be willing to travel to an existing USPS facility if warranted. For half of the US population, this would require traveling less than 2.5 miles from home; for 90%, the distance would be less than 7 miles. In Georgia, Illinois, and Minnesota, we estimate that testing at USPS facilities would provide access to an additional 4.1, 3.1, and 1.3 million people and reduce the median travel distance by 3.0, 0.8, and 1.2 miles, respectively, compared with existing testing sites per 28 July 2020. We also discuss the option of distributing test-at-home kits via USPS instead of private carriers. Finally, our proposal provides USPS an opportunity to increase revenues and expand its mission, thus improving its future prospects and relevance.

FIGURES

Share of Facilities Offering Tests	Population Access	Travel Distance (Miles)		
		10th Percentile	Median	90th Percentile
100%	94.1%	1.0	2.6	7.0
90%	94.1%	1.0	2.6	7.0
80%	93.8%	1.0	2.6	7.0
70%	93.4%	1.0	2.6	7.1
60%	92.5%	1.0	2.6	7.2
50%	91.2%	1.1	2.6	7.6
40%	88.9%	1.1	2.7	8.1
30%	85.0%	1.2	2.8	9.1
20%	78.3%	1.3	3.1	11.1
10%	65.3%	1.5	3.8	18.1

^aFor each budget, the facilities are selected via an optimization model that maximizes national access. For details, see Appendix A.

Table 1: Expected Proportion of Population Willing to Travel to a USPS-Based COVID-19 Testing Site and Corresponding Travel Distances, Depending on the Budget (Percentage of USPS Facilities Offering Tests, Allowing at Most 1 per ZCTA)

State	Population Access	Travel Distance (Miles)		
		10th Percentile	Median	90th Percentile
New Jersey	99.2%	0.7	1.4	3.3
Rhode Island	99.3%	0.8	1.4	2.7
Massachusetts	99.2%	0.7	1.7	2.8
Connecticut	97.6%	1.1	2.1	3.1
Maryland	97.9%	1.1	1.9	3.9
Alaska	96.6%	1.3	7.2	29.6
Wyoming	96.8%	3.8	14.1	21.5
Montana	95.5%	2.9	9.8	16.3
North Dakota	97.0%	2.2	5.8	12.0
South Dakota	98.6%	2.3	6.2	10.9

Table 2: Expected Proportion of Population Willing to Travel to a USPS-Based COVID-19 Testing Site and Corresponding Travel Distances, for the Most Densely Populated (New Jersey, Rhode Island, Massachusetts, Connecticut, and Maryland) and Least Densely Populated States (Alaska, Wyoming, Montana, North Dakota, and South Dakota)

State	Distribution	Population Access	Travel Distance (Miles)		
			10th Percentile	Median	90th Percentile
Georgia	USPS	95.5%	1.7	3.5	6.9
	Existing sites	53.5%	2.8	6.5	13.3
Illinois	USPS	98.0%	0.9	1.8	4.8
	Existing sites	73.5%	1.0	2.6	10.7
Minnesota	USPS	97.5%	1.2	3.2	6.8
	Existing sites	73.7%	1.3	4.4	12.3

Table 3: Estimated Proportion of State Population Willing to Travel to the Nearest USPS Facility or Existing Testing Location to Obtain a COVID-19 Test and Median, 10th Percentile, and 90th Percentile Travel Distances

UNDERSTANDING THE PATHOLOGY

EVIDENCE OF STRUCTURAL PROTEIN DAMAGE AND MEMBRANE LIPID REMODELING IN RED BLOOD CELLS FROM COVID-19 PATIENTS

Thomas T, Stefanoni D, Dzieciatkowska M, Issaian A, Nemkov T, Hill RC, Francis RO, Hudson KE, Buehler PW, Zimring JC, Hod EA, Hansen KC, Spitalnik SL, D'Alessandro A. J Proteome Res. 2020 Oct 26. doi: 10.1021/acs.jproteome.0c00606. Online ahead of print.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Researchers mainly from Columbia University and University of Colorado Denver evaluated the effect of SARS-CoV-2 on red blood cells (RBCs) of 29 COVID-19-positive patients confirmed by molecular testing of nasopharyngeal swabs (compared to 23 healthy patients) at the Columbia University Irving Medical Center. They found that RBCs in the COVID-19 patients had higher levels of glycolytic intermediates and altered RBC structural integrity, but unchanged hemoglobin and hematocrit levels (Figure 1-3). These results suggest that COVID-19 may influence RBCs via changing RBC structural membrane and oxygen transport capacities.

ABSTRACT

The SARS-CoV-2 beta coronavirus is the etiological driver of COVID-19 disease, which is primarily characterized by shortness of breath, persistent dry cough, and fever. Because they transport oxygen, red blood cells (RBCs) may play a role in the severity of hypoxemia in COVID-19 patients. The present study combines state-of-the-art metabolomics, proteomics, and lipidomics approaches to investigate the impact of COVID-19 on RBCs from 23 healthy subjects and 29 molecularly diagnosed COVID-19 patients. RBCs from COVID-19 patients had increased levels of glycolytic intermediates, accompanied by oxidation and fragmentation of ankyrin, spectrin beta, and the N-terminal cytosolic domain of band 3 (AE1). Significantly altered lipid metabolism was also observed, in particular, short- and medium-chain saturated fatty acids, acyl-carnitines, and sphingolipids. Nonetheless, there were no alterations of clinical hematological parameters, such as RBC count, hematocrit, or mean corpuscular hemoglobin concentration, with only minor increases in mean corpuscular volume. Taken together, these results suggest a significant impact of SARS-CoV-2 infection on RBC structural membrane homeostasis at the protein and lipid levels. Increases in RBC glycolytic metabolites are consistent with a theoretically improved capacity of hemoglobin to off-load oxygen as a function of allosteric modulation by high-energy phosphate compounds, perhaps to counteract COVID-19-induced hypoxia. Conversely, because the N-terminus of AE1 stabilizes deoxyhemoglobin and finely tunes oxygen off-loading and metabolic rewiring toward the hexose monophosphate shunt, RBCs from COVID-19 patients may be less capable of responding to environmental variations in hemoglobin oxygen saturation/oxidant stress when traveling from the lungs to peripheral capillaries and vice versa.

FIGURES

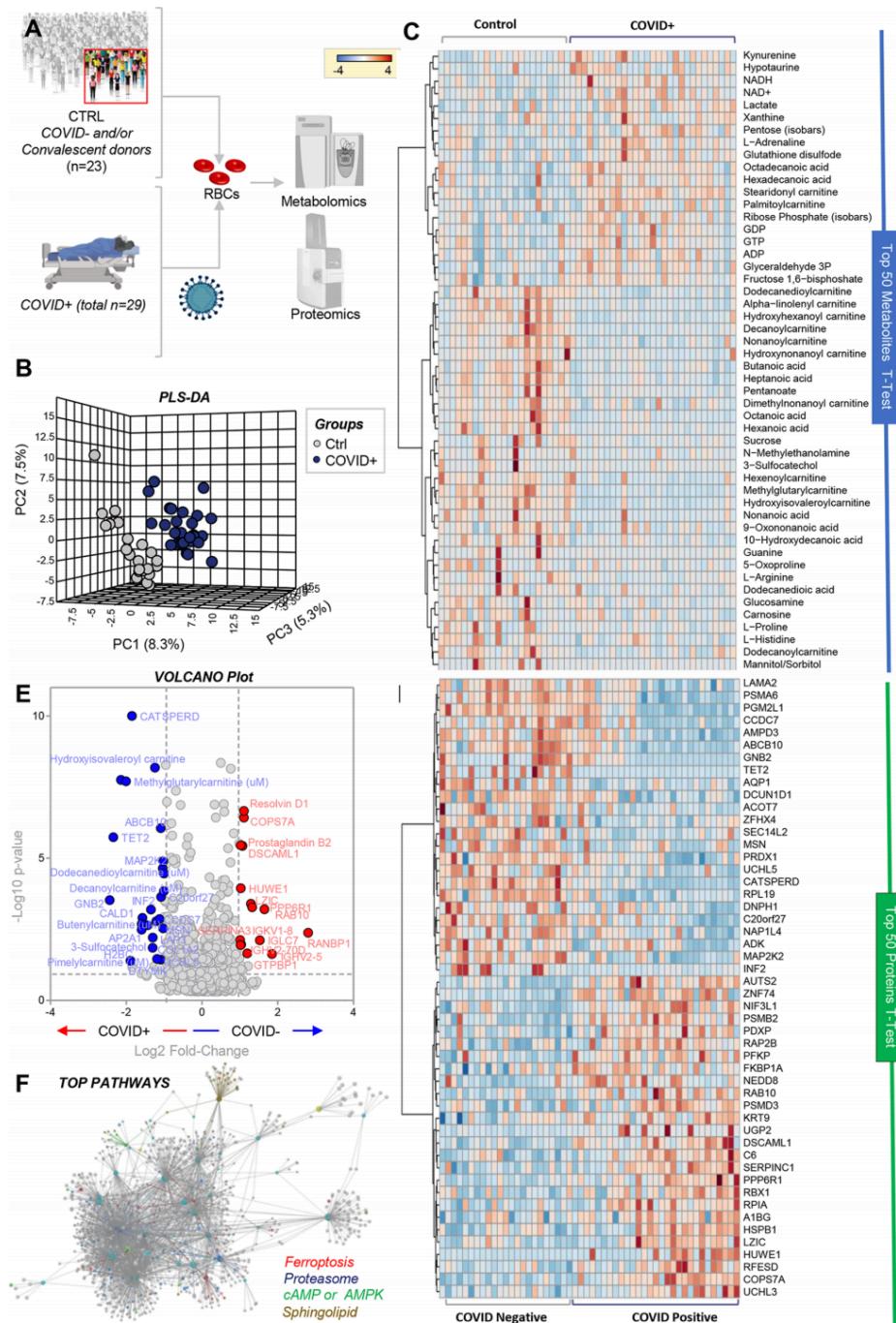


Figure 1. RBC metabolism and proteome are influenced by COVID-19. Metabolomics and proteomics analyses were performed on RBCs from COVID-19-negative (n = 23) and -positive (n = 29) subjects, as determined by the molecular testing of nasopharyngeal swabs (A). The effects of COVID-19 on RBCs, as gleaned by PLS-DA (B) and hierarchical clustering analysis of the top 50 metabolites (C) and proteins (D) by t test. (E) Volcano plot highlights the significant metabolites and proteins increasing (red) or decreasing (blue) in RBCs from COVID-19 patients as compared with noninfected controls. (F) Pathway analyses were performed on the significant features from the analyses in panels B–E.

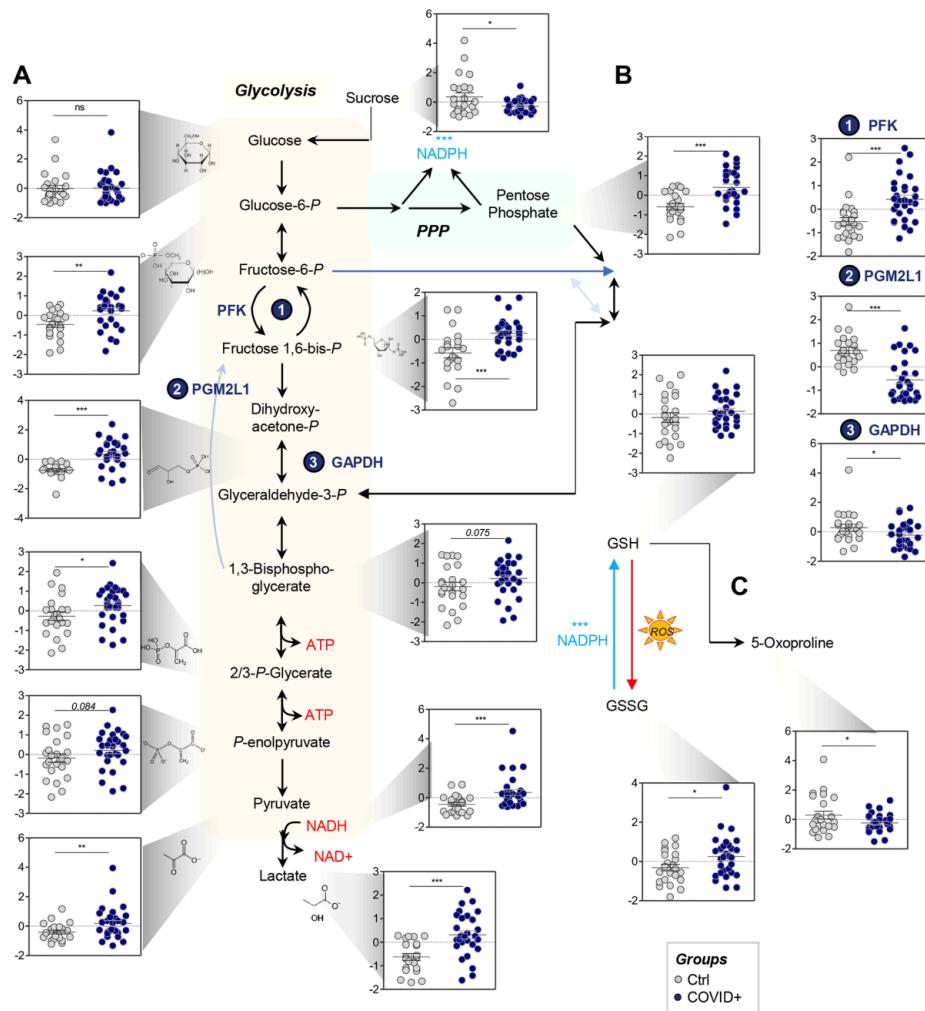


Figure 2. COVID-19 significantly affects the RBC glycolysis (A) and the pentose phosphate pathway (PPP) (B), with no significant effect on glutathione homeostasis (C). Metabolomics of RBCs from COVID-19 subjects identified a significant increase in several glycolytic intermediates as compared with controls, including glucose 6-phosphate, fructose bisphosphate, glyceraldehyde 3-phosphate, 2,3-diphosphoglycerate, lactate, and

NADH. This phenomenon was at least in part explained by the higher protein levels of PFK, the rate-limiting enzyme of glycolysis, in RBCs from COVID-19 subjects as compared with controls. These subjects also had a significant decreases in the levels of PGM2L1, which catalyzes the synthesis of hexose bisphosphate and thus slows down glycolysis, and GAPDH, a redox-sensitive enzyme. On the contrary, ribose phosphate (isobars), the end product of the PPP, significantly accumulated in RBCs from COVID-19 patients, suggesting a higher degree of oxidant stress in these RBCs; this was confirmed, in part, by the significantly higher levels of GSSG and the lower levels of 5-oxoproline (C). Asterisks indicate significance by t test (* p < 0.05; ** p < 0.01; *** p < 0.001). Groups are color-coded according to the legend in the bottom right corner of the figure.

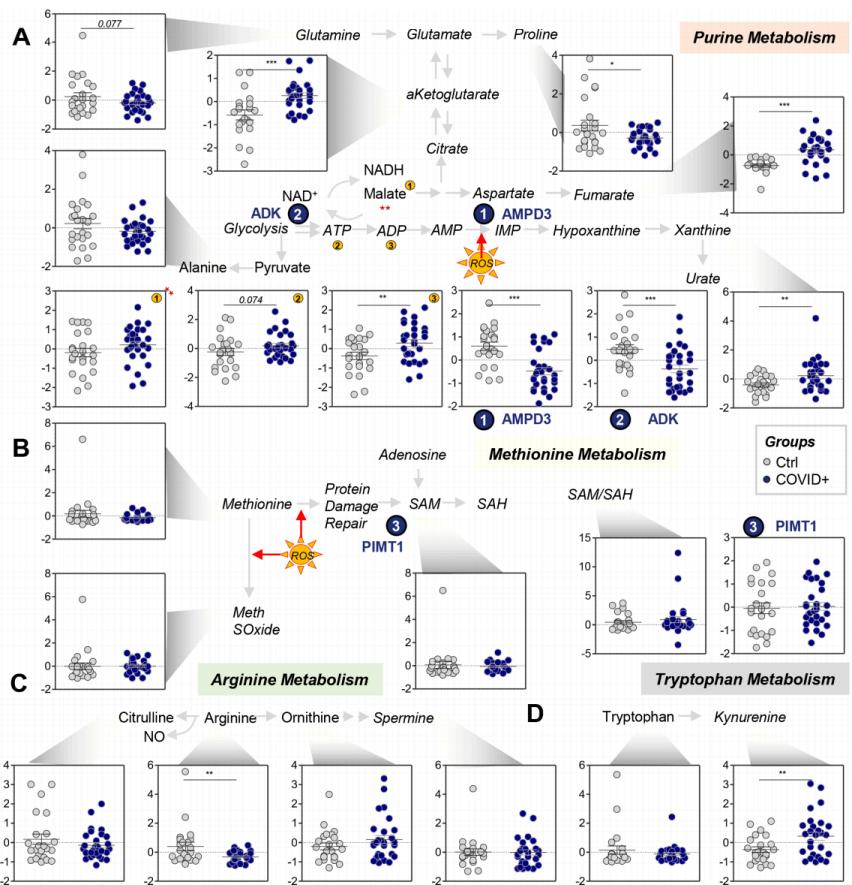


Figure 3. COVID-19 significantly affects the transamination and carboxylic acid metabolism in RBCs (A), but not the purine deamination (B), with only limited effects on arginine (C) and tryptophan (D) metabolism. Asterisks indicate significance by t test (* p < 0.05; ** p < 0.01; *** p < 0.001). Groups are color-coded according to the legend in the center of the figure.

SARS-COV-2 WILL CONTINUE TO CIRCULATE IN THE HUMAN POPULATION: NO WORRIES WITH STATE-OF-THE-ART RESEARCH AND DEPENDABLY USEFUL RESULTS

Oberemok VV, Laikova KV, Yurchenko KA, Fomochkina II, Kubyshkin AV.. Inflamm Res. 2020 Oct 30:1-2. doi: 10.1007/s00011-020-01417-y. Online ahead of print.

Level of Evidence: Other - Opinion

BLUF

Virologists from V.I. Vernadsky Crimean Federal University in Russia criticize the article "Don't Worry! The Next Generation Would be More Resistant to SARS-CoV-2" by J. Bevelacqua and S. Mortazavi's, which was in itself a response to "SARS-CoV-2 will continue to circulate in the human population: an opinion from the point of view of the virus-host relationship" by Oberemok V. et al. They suggest Bevelacqua and Mortazavi failed to recognize Oberemok's point that as the population changes SARS-CoV-2 will also evolve, making SARS-CoV-2 continually dangerous and life threatening. Authors further criticize the notion that low dose radiation therapy (LDRT) can be used to treat SARS-CoV-2 without selection pressure given the insufficient evidence to support the claim.

ABSTRACT

This short article provides additional justification for our understanding of the virus-host relationship in the population. Some new data are presented concerning viral structure/behavior and a critical assessment on the possibilities of using new approaches for the treatment of patients with COVID-19.

ADJUSTING PRACTICE DURING COVID-19

MEDICAL SUBSPECIALTIES

CARDIOLOGY

EFFECT OF STATIN THERAPY ON SARS-COV-2 INFECTION-RELATED

Masana L, Correig E, Rodríguez-Borjabad C, Anoro E, Arroyo JA, Jericó C, Pedragosa A, Miret M, Näf S, Pardo A, Perea V, Pérez-Bernalte R, Plana N, Ramírez-Montesinos R, Royuela M, Soler C, Urquiza-Padilla M, Zamora A, Pedro-Botet J, Group OBOTSR.. Eur Heart J Cardiovasc Pharmacother. 2020 Nov 2:pvaa128. doi: 10.1093/ehjcvp/pvaa128. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Physician members of the Lipids and Arteriosclerosis Units Net (XULA) of Catalonia conducted a retrospective observational study assessing correlation between statin therapy and outcomes of RT-PCR confirmed COVID-19 patients ($n=2157$) admitted to 19 hospitals in Spain over an unclear time period. Mortality was significantly lower among those who continued statin therapy during hospital admission ($n=581$) compared to the genetically matched non-statin group (19.8% vs. 25.4%, $p=0.027$; Figures 1,2). Authors acknowledge numerous confounding variables precluding causal inference but encourage continued statin administration in hospitalized COVID-19 patients given possible mortality benefit.

ABSTRACT

AIM: Assessing the effect of statin therapy at hospital admission for COVID-19 on in-hospital mortality. **METHODS AND RESULTS:** Retrospective observational study. Patients taking statins were 11 years older and had significantly more comorbidities than patients who were not taking statins. A genetic matching (GM) procedure was performed prior to analysis of the mortality risk. A Cox proportional hazards model was used for the cause-specific hazard (CSH) function, and a competing-risks Fine and Gray (FG) model was also used to study the direct effects of statins on risk. Data from reverse transcription-polymerase chain reaction-confirmed 2157 SARS-CoV-2-infected patients (1234 men, 923 women; age: 67 y/o (IQR 54-78)) admitted to the hospital were retrieved from the clinical records in anonymized manner. 353 deaths occurred. 581 patients were taking statins. Univariate test after GM showed a significantly lower mortality rate in patients on statin therapy than the matched non-statin group (19.8% vs. 25.4%, chi² with Yates continuity correction: $p = 0.027$). The mortality rate was even lower in patients ($n = 336$) who maintained their statin treatments during hospitalization compared to the GM non-statin group (17.4%; $p = 0.045$). The Cox model applied to the CSH function ($HR = 0.58$ (CI: 0.39-0.89); $p = 0.01$) and the competing risks FG model ($HR = 0.60$ (CI: 0.39-0.92); $p = 0.02$) suggest that statins are associated with reduced COVID-19-related mortality. **CONCLUSIONS:** A lower SARS-CoV-2 infection-related mortality was observed in patients treated with statin therapy prior to hospitalization. Statin therapy should not be discontinued due to the global concern of the pandemic or in patients hospitalized for COVID-19.

FIGURES

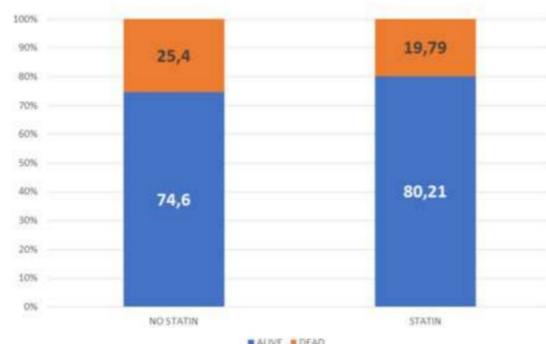


Figure 1A. Statin use before admission. $P=0.027$ between non-statin and statins at admission groups.

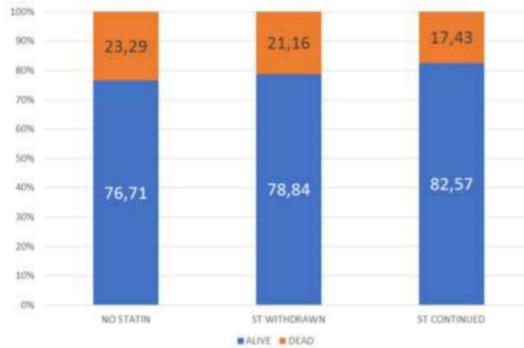


Figure 1B. No statin, statin withdrawn, and statin continued groups. P=0.045 between non-statin and statins maintained during admission.

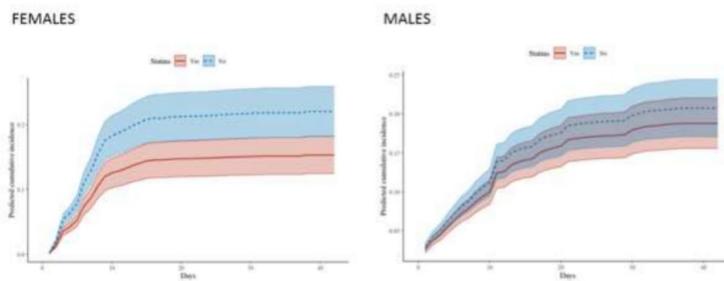


Figure 2. Cumulative mortality risk in patients stratified by sex, females (A) and males (B), as determined using a competing-risks Fine and Gray analysis. (global sub-distribution HR=0.60 with (0.39-0.92) 95% CI; p = 0.02).

RAPID, POINT-OF-CARE ANTIGEN AND MOLECULAR-BASED TESTS FOR DIAGNOSIS OF SARS-COV-2 INFECTION

Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hoot L, Leeftlang MM, Spijker R, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group.. Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705. doi: 10.1002/14651858.CD013705.

Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A systematic review evaluating articles before May 25, 2020 included 22 reports (n=3,198 total samples with 1,755 RT-PCR confirmed positive SARS-CoV-2 samples) revealed that:

- 1) antigen tests have variable sensitivity (average = 56.2%), while specificity was 99.5% (Figure 3)
 - 2) rapid molecular assays had a sensitivity of 95.2% and a specificity 98.9% (Figure 4)
 - 3) calculated pooled results for individual tests revealed that Xpert Xpress assay had a summary sensitivity of 99.4% and specificity of 96.8%, while ID NOW assay had a summary sensitivity of 76.8% and a specificity of 99.6% (Figure 7)
- The authors suggest that "prospective and comparative evaluations of rapid tests for COVID-19 infection" is important for clinical applicability and further studies should continue to evaluate these tests in the clinical setting. Limitations of this systematic review are summarized below.

SUMMARY

The authors of this systematic review note several limitations regarding the findings of this review:

- 3/4 of the studies did not follow the instructions of the test manufacturer
- "studies did not use the most reliable methods or did not report enough information for us to judge their methods"
- 1/4 of the studies included in the review were published early as 'preprints'
- "It is unclear whether the limitations in the primary studies will lead to over- or under-estimates of test accuracy, thus all results we report should be interpreted with a high degree of caution."

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting COVID-19 pandemic present important diagnostic challenges. Several diagnostic strategies are available to identify or rule out current infection, identify people in need of care escalation, or to test for past infection and immune response. Point-of-care antigen and molecular tests to detect current SARS-CoV-2 infection have the potential to allow earlier detection and isolation of confirmed cases compared to laboratory-based diagnostic methods, with the aim of reducing household and community transmission. **OBJECTIVES:** To assess the diagnostic accuracy of point-of-care antigen and molecular-based tests to determine if a person presenting in the community or in primary or secondary care has current SARS-CoV-2 infection. **SEARCH METHODS:** On 25 May 2020 we undertook electronic searches in the Cochrane COVID-19 Study Register and the COVID-19 Living Evidence Database from the University of Bern, which is updated daily with published articles from PubMed and Embase and with preprints from medRxiv and bioRxiv. In addition, we checked repositories of COVID-19 publications. We did not apply any language restrictions.

SELECTION CRITERIA: We included studies of people with suspected current SARS-CoV-2 infection, known to have, or not to have SARS-CoV-2 infection, or where tests were used to screen for infection. We included test accuracy studies of any design that evaluated antigen or molecular tests suitable for a point-of-care setting (minimal equipment, sample preparation, and biosafety requirements, with results available within two hours of sample collection). We included all reference standards to define the presence or absence of SARS-CoV-2 (including reverse transcription polymerase chain reaction (RT-PCR) tests and established clinical diagnostic criteria). **DATA COLLECTION AND ANALYSIS:** Two review authors independently screened studies and resolved any disagreements by discussion with a third review author. One review author independently extracted study characteristics, which were checked by a second review author. Two review authors independently extracted 2x2 contingency table data and assessed risk of bias and applicability of the studies using the QUADAS-2 tool. We present sensitivity and specificity, with 95% confidence intervals (CIs), for each test using paired forest plots. We pooled data using the bivariate hierarchical model separately for antigen and molecular-based tests, with simplifications when few studies were available. We tabulated available data by test manufacturer. **MAIN RESULTS:** We included 22 publications reporting on a total of 18 study cohorts with 3198 unique samples, of which 1775 had confirmed SARS-CoV-2 infection. Ten studies took place in North America, two in South America, four in Europe, one in China and one was conducted internationally. We identified data

for eight commercial tests (four antigen and four molecular) and one in-house antigen test. Five of the studies included were only available as preprints. We did not find any studies at low risk of bias for all quality domains and had concerns about applicability of results across all studies. We judged patient selection to be at high risk of bias in 50% of the studies because of deliberate over-sampling of samples with confirmed COVID-19 infection and unclear in seven out of 18 studies because of poor reporting. Sixteen (89%) studies used only a single, negative RT-PCR to confirm the absence of COVID-19 infection, risking missing infection. There was a lack of information on blinding of index test ($n = 11$), and around participant exclusions from analyses ($n = 10$). We did not observe differences in methodological quality between antigen and molecular test evaluations. Antigen tests Sensitivity varied considerably across studies (from 0% to 94%): the average sensitivity was 56.2% (95% CI 29.5 to 79.8%) and average specificity was 99.5% (95% CI 98.1% to 99.9%; based on 8 evaluations in 5 studies on 943 samples). Data for individual antigen tests were limited with no more than two studies for any test. Rapid molecular assays Sensitivity showed less variation compared to antigen tests (from 68% to 100%), average sensitivity was 95.2% (95% CI 86.7% to 98.3%) and specificity 98.9% (95% CI 97.3% to 99.5%) based on 13 evaluations in 11 studies of on 2255 samples. Predicted values based on a hypothetical cohort of 1000 people with suspected COVID-19 infection (with a prevalence of 10%) result in 105 positive test results including 10 false positives (positive predictive value 90%), and 895 negative results including 5 false negatives (negative predictive value 99%). Individual tests We calculated pooled results of individual tests for ID NOW (Abbott Laboratories) (5 evaluations) and Xpert Xpress (Cepheid Inc) (6 evaluations). Summary sensitivity for the Xpert Xpress assay (99.4%, 95% CI 98.0% to 99.8%) was 22.6 (95% CI 18.8 to 26.3) percentage points higher than that of ID NOW (76.8%, 95% CI 72.9% to 80.3%), whilst the specificity of Xpert Xpress (96.8%, 95% CI 90.6% to 99.0%) was marginally lower than ID NOW (99.6%, 95% CI 98.4% to 99.9%; a difference of -2.8% (95% CI -6.4 to 0.8)) AUTHORS' CONCLUSIONS: This review identifies early-stage evaluations of point-of-care tests for detecting SARS-CoV-2 infection, largely based on remnant laboratory samples. The findings currently have limited applicability, as we are uncertain whether tests will perform in the same way in clinical practice, and according to symptoms of COVID-19, duration of symptoms, or in asymptomatic people. Rapid tests have the potential to be used to inform triage of RT-PCR use, allowing earlier detection of those testing positive, but the evidence currently is not strong enough to determine how useful they are in clinical practice. Prospective and comparative evaluations of rapid tests for COVID-19 infection in clinically relevant settings are urgently needed. Studies should recruit consecutive series of eligible participants, including both those presenting for testing due to symptoms and asymptomatic people who may have come into contact with confirmed cases. Studies should clearly describe symptomatic status and document time from symptom onset or time since exposure. Point-of-care tests must be conducted on samples according to manufacturer instructions for use and be conducted at the point of care. Any future research study report should conform to the Standards for Reporting of Diagnostic Accuracy (STARD) guideline.

FIGURES

Figure 3. Forest plot of studies evaluating antigen tests. Studies grouped by test
(FIA: fluorescence immunoassays; CGIA: colloidal gold-based immunoassays; NP: nasopharyngeal; OP: oropharyngeal)

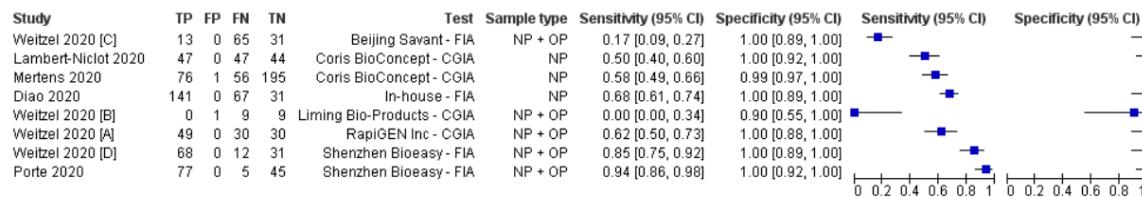


Figure 4. Forest plot of studies evaluating rapid molecular tests. Studies grouped by test and sample type
(NP: nasopharyngeal; OP: oropharyngeal; RUO: research use only)

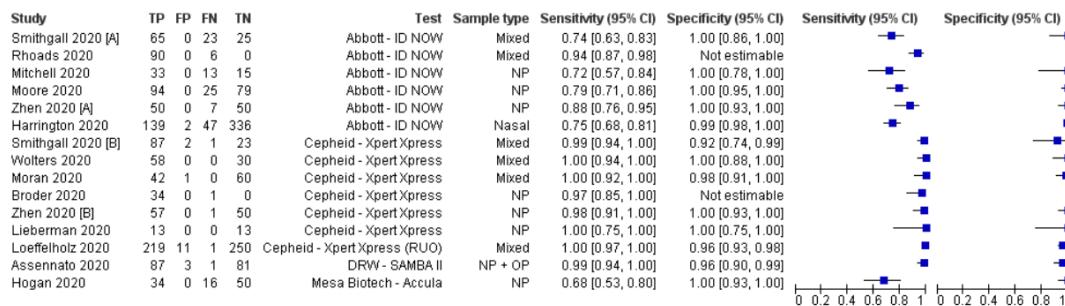
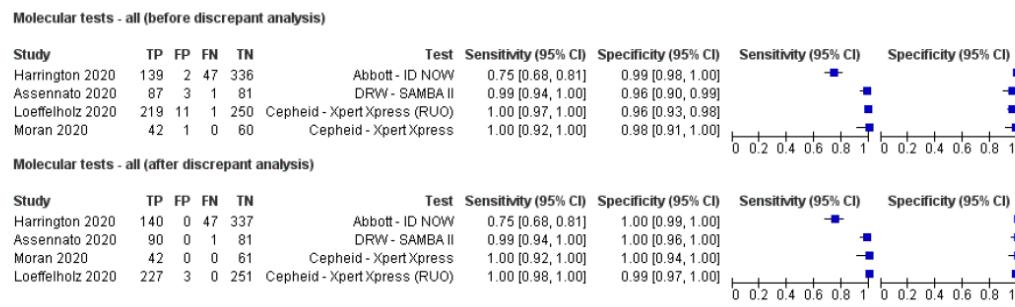


Figure 7. Forest plot of studies of molecular tests before and after discrepant analysis. Studies grouped by test (DRW: Diagnostics for the Real World; RUO: research use only)



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