
Legoland Two tickets for £20 Worth up to £116

THE TIMES

VIRUS

Health minister with virus had been in No10

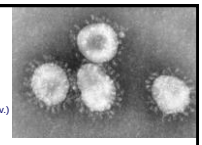
Nadine Dorries in isolation after diagnosis Sixth patient dies as British cases rise to 373

Let them cry! Cold comfort teaches babies self-control

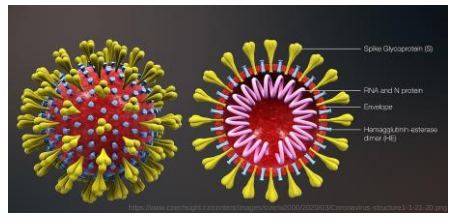
Petr Hubáček

Ústav lékařské mikrobiologie a Klinika dětské hematologie a onkologie
2. LF UK a FN Motol

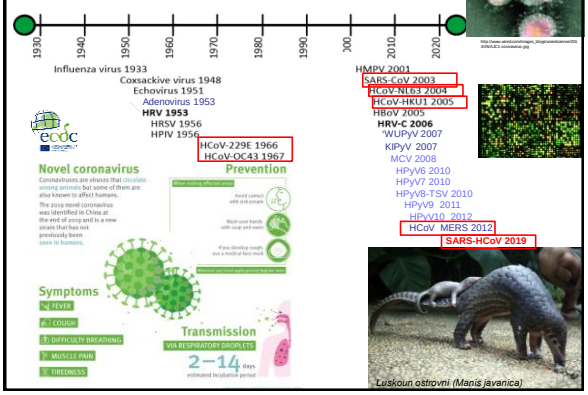
# Coronaviruses



- Coronaviridae
- ss (+) RNA, genome lenth 26-32 kb (one of the biggest RNA v.)
- First identified in mid 60th
  - α – HCoV 229E and NL63
  - β - HCoV OC43, HKU1, SARS-CoV (severe acute respiratory syndrome), MERS-CoV (Middle East Respiratory Syndrome), SARS-CoV-2




# Coronaviruses are here for long time





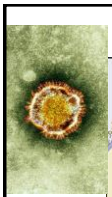
Luskoun ostrovní (Manis javanica)

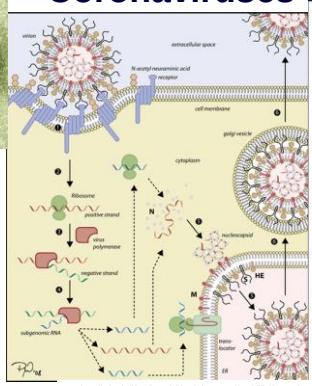
# Coronaviruses

| Čeleď a podčeleď | Rod | Podrod | Druh | Rok popsání | Klinické příznaky |
|---|---|---|---|---|---|
| Coronaviridae – Orthocoronavirinae | Alphacoronavirus | Duvinacoronavirus | Lidský coronavirus 229E (HCoV-229E) | 1966 | Lehčí respirační onemocnění typu „common cold" s výrazným edémem sliznic. ID 2–5 dní |
| | | Setracoronavirus | Lidský coronavirus NL63 (HCoV-NL63) | 2004 | Lehčí respirační onemocnění typu „common cold" s výrazným edémem sliznic. ID 2–4 dny |
| | Betacoronavirus | Embecovirus (skupina A) | Lidský coronavirus HKU-1 (HCoV-HKU-1) | 2005 | Lehčí respirační onemocnění typu „common cold" s výrazným edémem sliznic. ID 2–4 dny |
| | | | Lidský coronavirus OC43 (HCoV-OC43) | 1967 | Lehčí respirační onemocnění typu „common cold" s výrazným edémem sliznic. ID 2–5 dní |
| | | Sarbecovirus (skupina B) | Severe acute respiratory syndrome-related virus (SARS-CoV) | 2003 | Respirační onemocnění s těžším, život ohrožujícím průběhem. Popsaná mortalita u těžších případů je přibližně 9,6 %. ID 2–11 dní |
| | | | Severe acute respiratory syndrome-related virus 2 (SARS-CoV-2) | 2019 | Respirační onemocnění v celém rozsahu od asymptomatických a mírných případů (zatím popsaná přibližně polovina případů až po život ohrožující případy. Dosud popsaná mortalita u těžších případů je přibližně 6,7 %; celková pak přibližně 0,5–1 %. ID 2–14 dní |
| | | Merbecovirus (skupina C) | Middle-East respiratory syndrom virus (MERS virus) | 2012 | Respirační onemocnění s těžším, život ohrožujícím průběhem. Popsaná mortalita u těžších případů je přibližně 35,5 % ID 2–13 dní |

V tabulce vynechán Realm (Riboviria), Říše (Orthornavirae), Kmen (Pisuviricota), Třída (Pisoniviricetes), Řád (Nidovirales) a Podřád (Cornidovirineae)

# Coronaviruses






**Replication of Coronavirus**

1 With their S-protein, coronaviruses bind on cell surface molecules such as the metallopretease -amino-peptidase N-. Viruses, which accessorily have the HE-protein, can also bind on N-acetyl neuraminic acid that serves as a co-receptor.

2 So far, it is not clear whether the virus get into the host cell by fusion of viral and cell membrane or by receptor mediated endocytosis in that the virus is in-corporated via an endosome, which is subsequently acidified by proton pumps. In that case, the virus have to escape destruction and transport to the lysosome.

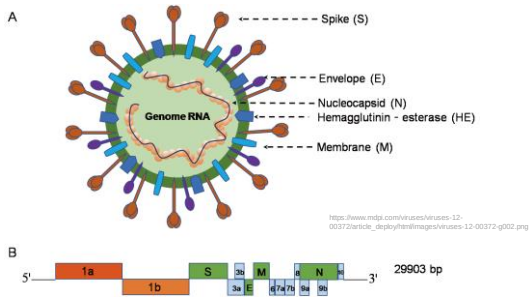
3 Since coronaviruses have a single positive stranded RNA genome, they can directly produce their proteins and new genomes in the cytoplasm. At first, the virus synthesize its RNA polymerase that only recognizes and produces viral RNAs. This enzyme synthesize the minus strand using the positive strand as template.

4 Subsequently, this negative strand serves as template to transcribe smaller subgenomic positive RNAs which are used to synthesize all other proteins. Furthermore, this negative strand serves for replication of new positive stranded RNA genomes.

5 The protein N binds genomic RNA and the protein M is integrated into the membrane of the endoplasmatic reticulum (ER) like the envelope proteins S and HE. After binding, assembled nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its membrane.

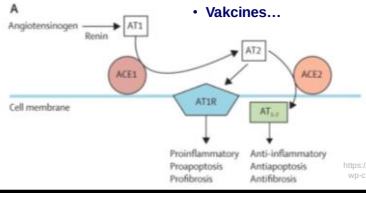
6 These viral progeny are finally transported by golgi vesicles to the cell-membrane and are exocytosed into the extracellular space.

# SARS-CoV-2



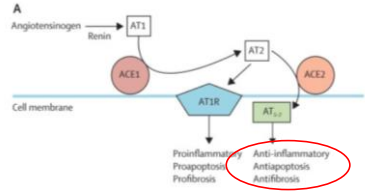
- **SARS-CoV (SARS)**
  - Cell receptor – ACE2
  - 8 098 infected worldwide
  - Mortality – approx. 9.5%
- Incubation period – 2-4 days
- Increased temperature – fever (>38.0°C); headache, pain of muscles, joints and orevall discomfort. In part of the patients mild, in about 10-20% diarrhoe, after 2 to 7 days possible dry cought and in most pneumonia.
- **Virostatics** (ribavirine + lopinavir/ritonavir) **Symptomatic treatment**

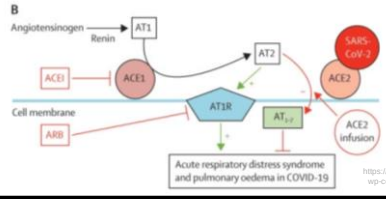
- **SARS-CoV-2 (COVID-19)**
  - Cell receptor – ACE2
  - So far 40 210 950 infected worldwide
  - Mortality – approx. 6.7%
- Incubation period – 2-14 days
- Increased temperature – fever (>38.0°C); headache, pain of muscles, joints and orevall discomfort. In part of the patients mild. After 7 days often worsening and development of interstitial pneumonia.
- **Virostatics** (remdesivir, favipiravir,…) **Symptomatic treatment**
- **Vakcines…**




https://www.physicianseweekly.com/wp-content/uploads/2020/04/AT1-receptor.png

1

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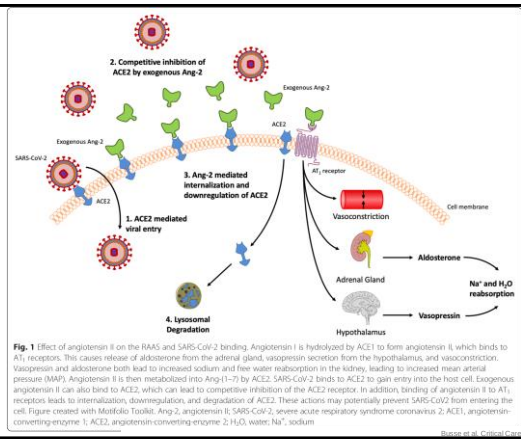


**Fig. 1** Effect of angiotensin II on the RAAS and SARS-CoV-2 binding. Angiotensin I is hydrolyzed by ACE1 to form angiotensin II, which binds to $AT_1$ receptors. This causes release of aldosterone from the adrenal gland, vasopressin secretion from the hypothalamus, and vasoconstriction. Vasopressin and aldosterone both lead to increased sodium and free water reabsorption in the kidney, leading to increased mean arterial pressure (MAP). Angiotensin II is then metabolized into Ang-(1–7) by ACE2. SARS-CoV-2 binds to ACE2 to gain entry into the host cell. Exogenous angiotensin II can also bind to ACE2, which can lead to competitive inhibition of the ACE2 receptor. In addition, binding of angiotensin II to $AT_1$ receptors leads to internalization, downregulation, and degradation of ACE2. These actions may potentially prevent SARS-CoV2 from entering the cell. Figure created with Motifolio Toolkit. Ang-2, angiotensin II; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE1, angiotensin-converting-enzyme 1; ACE2, angiotensin-converting-enzyme 2; $H_2O$, water; $Na^+$, sodium

Busse et al. Critical Care 2020

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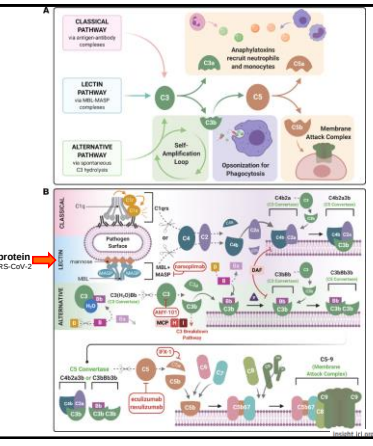


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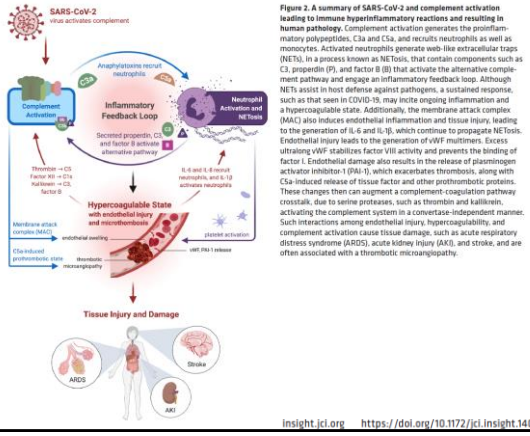



**Figure 2. A summary of SARS-CoV-2 and complement activation leading to immune hyperinflammatory reactions and resulting in human pathology.** Complement activation generates the proinflammatory polypeptides, C3a and C5a, and recruits neutrophils as well as monocytes. Activated neutrophils generate web-like extracellular traps (NETs). In a process known as NETosis, that contain components such as C3, properdin (P), and factor B (B) that activate the alternative complement pathway and engage an inflammatory feedback loop. Although NETs assist in host defense against pathogens, a sustained response, such as that seen in COVID-19, may incite ongoing inflammation and a hypercoagulable state. Additionally, the membrane attack complex (MAC) also induces endothelial inflammation and tissue injury, leading to the generation of IL-6 and IL-1β, which continue to propagate NETosis. Endothelial injury leads to the generation of vWF multimers. Excess ultralong vWF stabilizes factor VIII activity and prevents the binding of factor I. Endothelial damage also results in the release of plasminogen activator inhibitor-1 (PAI-1), which exacerbates thrombosis, along with C5a-induced release of tissue factor and other prothrombotic proteins. These changes then can augment a complement-coagulation pathway crosstalk, due to serine proteases, such as thrombin and kallikrein, activating the complement system in a convertase-independent manner. Such interactions among endothelial injury, hypercoagulability, and complement activation cause tissue damage, such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and stroke, and are often associated with a thrombotic microangiopathy.

insight.jci.org https://doi.org/10.1172/jci.insight.140711

2

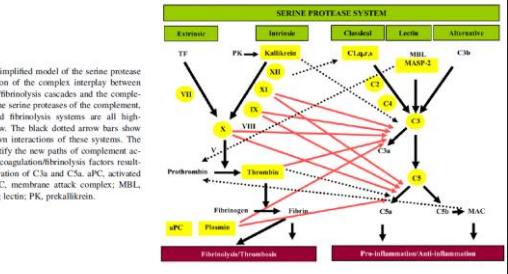
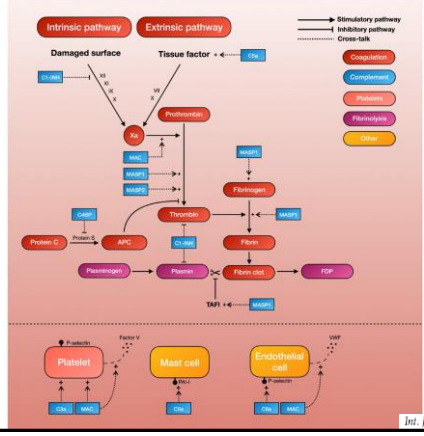
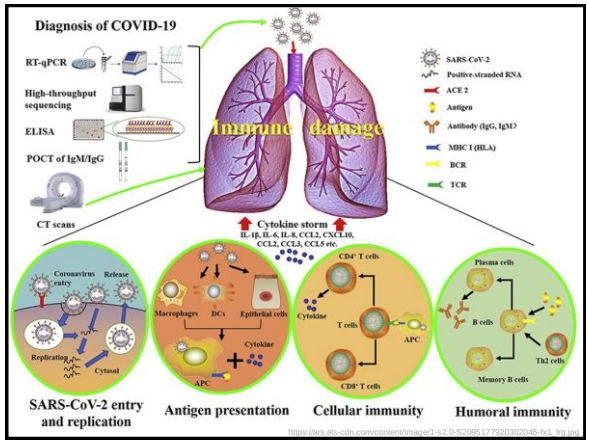



**FIGURE 7.** Simplified model of the serine protease system. Depiction of the complex interplay between the coagulation/fibrinolysis cascades and the complement system. The serine proteases of the complement, coagulation, and fibrinolysis systems are all highlighted in yellow. The black dotted arrow bars show previously known interactions of these systems. The red arrows identify the new paths of complement activation by the coagulation/fibrinolysis factors resulting in the generation of C3a and C5a. aPC, activated protein C; MAC, membrane attack complex; MBL, mannan-binding lectin; PK, prekallikrein.

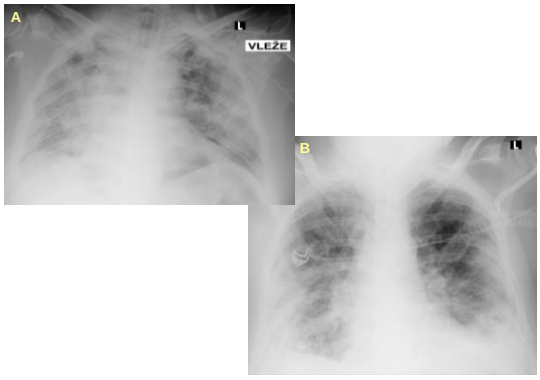
*J Immunol* 2010; 185:5628-5636; Prepublished online 24 September 2010; doi: 10.4049/jimmunol.0903678 http://www.jimmunol.org/content/185/9/5628

2

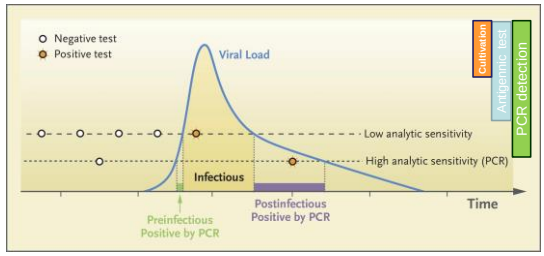



COVID-19 penumonia (A) and subsequent HSV pneumonia (B)



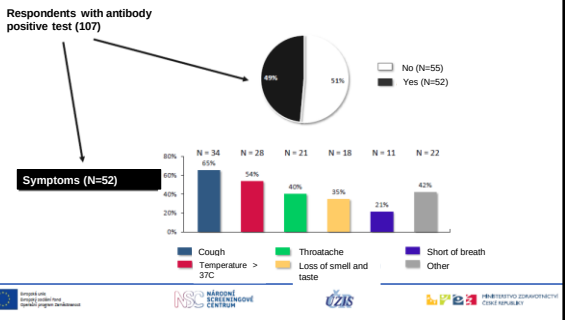

## Diagnostic „window“ for different types of detection.




Mina et al. September 30, 2020 DOI: 10.1056/NEJMp2025631

# SARS-CoV-2

### Presence of respiratory symptoms after 1.1.2020




# SARS-CoV-2

### Major endpoint of the study?

**Status of immunization of czech population is low (April 2020) and even in the highly exposed localities is about bellow 4-5%**

- Emergency rules started in time and helped to stop further continue of the infection in the population.
- For next waves of the pandemia is necessary to take actions to improve immunity of naive population.
- Preparation of programms for possible protection of risk group of the citizens is reasonable.

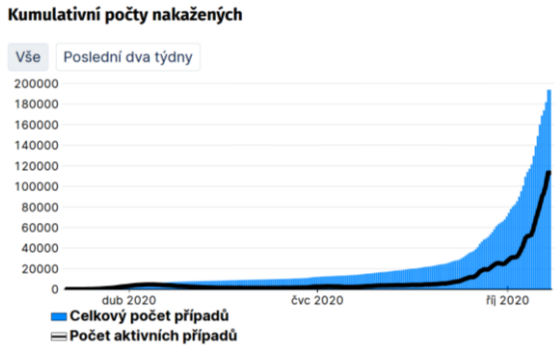
# Mortality

Confirmed cases **40 251 950**
Confirmed deaths **1 116 131**
Countries, areas or territories with 235

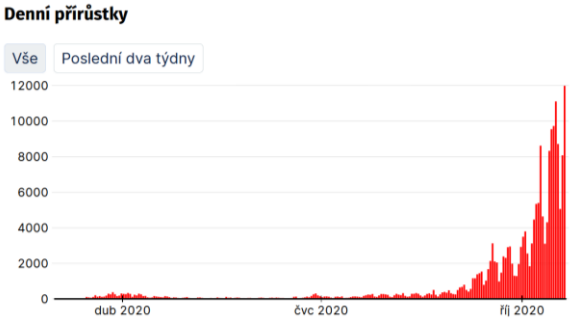
Last update: 20 October 2020, 02:00 CEST

| | State | No. of infected | Deceased | Mortality |
|---|---|---|---|---|
| 152. | Yemen | 2 057 | 597 | 29,02% |
| 10. | Mexiko | 860 714 | 86 893 | 10,10% |
| 16. | Itálie | 434 449 | 36 705 | 8,45% |
| 33. | Ecuador | 154 115 | 12 404 | 8,05% |
| 34. | Bolivia | 140 037 | 8 526 | 6,09% |
| 11. | UK | 765 487 | 44 057 | 5,76% |
| 43. | Švédsko | 106 380 | 5 922 | 5,57% |
| 28. | Kanada | 206 349 | 9 849 | 4,77% |
| 27. | Belgie | 240 159 | 10 489 | 4,37% |
| 6. | Španělsko | 988 322 | 34 210 | 3,46% |
| 31. | Rumunsko | 186 254 | 5 996 | 3,22% |
| 81. | Bulharsko | 31 863 | 1 019 | 3,20% |
| 3. | Brazílie | 5 273 954 | 154 837 | 2,94% |
| 1. | USA | 8 274 797 | 221 076 | 2,67% |
| 18. | Německo | 385 591 | 9 882 | 2,56% |
| 54. | Švýcarsko | 86 167 | 2 145 | 2,49% |
| 68. | Maďarsko | 48 757 | 1 211 | 2,48% |
| 85. | Řecko | 26 469 | 528 | 1,99% |
| 30. | Polsko | 192 539 | 3 721 | 1,93% |
| 77. | Dánsko | 36 877 | 688 | 1,87% |
| 48. | Japonsko | 94 102 | 1 679 | 1,78% |
| 4. | Rusko | 1 422 775 | 24 473 | 1,72% |
| 135. | Estonsko | 4 127 | 71 | 1,72% |
| 2. | Indie | 7 651 107 | 115 914 | 1,51% |
| 58. | Rakousko | 67 451 | 914 | 1,36% |
| 99. | Slovinsko | 14 473 | 192 | 1,33% |
| **29.** | **Česká republika** | **193 946** | **1 619** | **0,83%** |
| **82.** | **Slovensko** | **31 400** | **98** | **0,31%** |

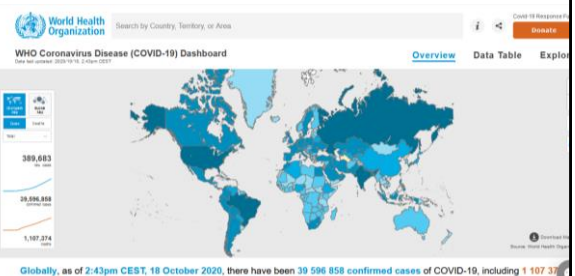
# Cumulative data CR




# Daily increase CR




# Epidemiological data

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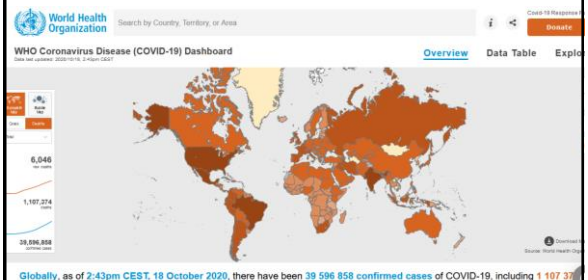
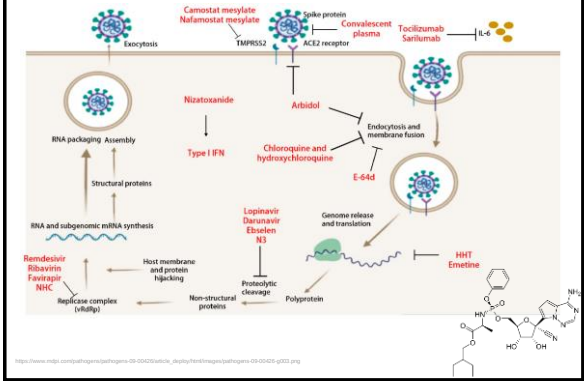



# Possible treatment options



# The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients

Ali Daneshkhah[1], Vasundhara Agrawal[1], Adam Eshein[1], Hariharan Subramanian[1], Hemant K. Roy [2], and Vadim Backman[1*]

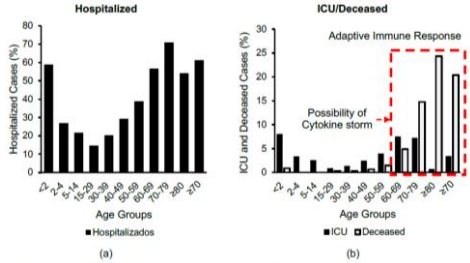



**Figure 7** Age distribution of the a) hospitalized, b) admitted to ICU or deceased in Spain based on data from 145,429 cases[26].

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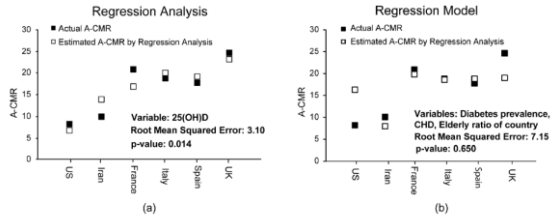


**Figure 6** Regression analysis based on (a) 25(OH)D, (b) Diabetes prevelance among men and women (age standardized), elderly ratio (≥70 yo) in the country, CHD death rate per 100, 000 (age standardized)

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# The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients

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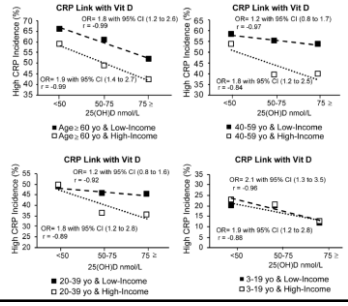
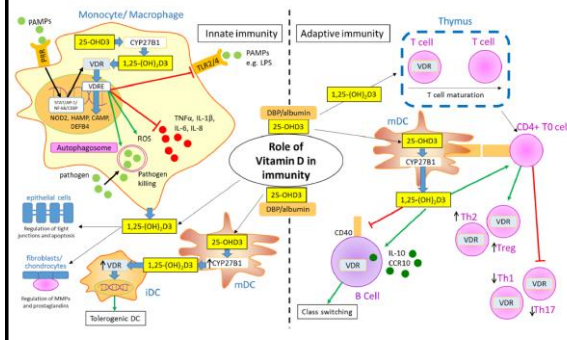


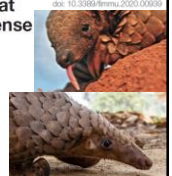

S.R. Harrison et al. Calcified Tissue International (2020) 106:58–75

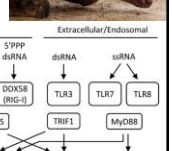
frontiers in Immunology

# Pangolins Lack IFIH1/MDA5, a Cytoplasmic RNA Sensor That Initiates Innate Immune Defense Upon Coronavirus Infection

ORIGINAL RESEARCH
published: 08 May 2020
doi: 10.3389/fimmu.2020.00998

Heinz Fischer[1], Erwin Tschachler[2] and Leopold Eckhart[2]*








Article

# Proteomics of SARS-CoV-2-infected host cells reveals therapy targets

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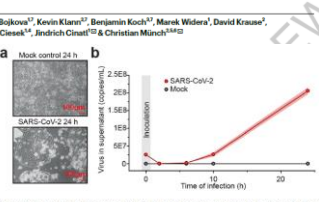


**Fig. 1 | SARS-CoV-2 replication model in in human cells. a**, Caco-2 cells were either mock or SARS-CoV-2 infected and cultured for 24 h. Microscopy pictures were taken to demonstrate cytopathic effect. Scale bars indicate 100 µm. Representative pictures from three independent biological replicates are shown. **b**, Quantitative PCR analysis of viral genome copies per mL cell culture after indicated infection time points ($n = 3$ independent biological samples). Points indicate mean of replicate measurements and shades represent s.d.

Article

# Proteomics of SARS-CoV-2-infected host cells reveals therapy targets

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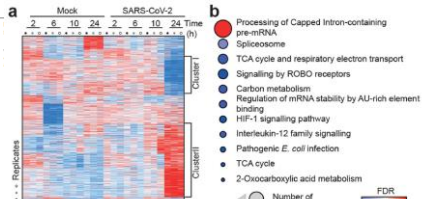


**These analyses revealed that SARS-CoV-2 reshapes central cellular pathways, such as translation, splicing, carbon metabolism and nucleic acid metabolism. Small molecule inhibitors targeting these pathways prevented viral replication in cells. Our results reveal the cellular infection profile of SARS-CoV-2 and led to the identification of drugs inhibiting viral replication. We anticipate our results to guide efforts to understand the molecular mechanisms underlying host cell modulation upon SARS-CoV-2 infection. Furthermore, our findings provide insight for the development of the therapy options for COVID-19.**