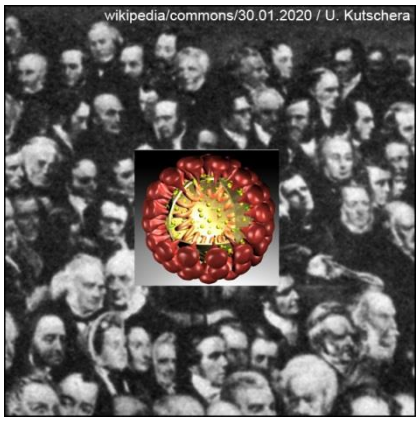
Kutschera, U. (2020) Science 368/808: E-Letter June 2, 1–3.

The Coronavirus: Seasonality and host-specific action of a "sexy" killer

In his *Article* "Case clustering emerges as key pandemic puzzle" (Science 368, p. 808–809; 2020), K. Kupferschmidt argues that SARS-CoV-2, which causes the novel coronavirus disease 2019 (COVID-19), is spreading in clusters: "… COVID-19, like two of its cousins, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), seems especially prone to attacking groups of tightly connected people while sparing others … (and this) … super-spreading usually happens indoors." In addition, Kupferschmidt refers to a study showing that "the risk of infection indoors is almost 19 times higher than outdoors" and argues that "… Meatpacking plants are likely vulnerable because many people work closely together in spaces where low temperature helps the virus survive."



These observations may be interpreted with reference to a recent article published in the "Annual Review of Virology" entitled "Seasonality of Respiratory Viral Infections" (1). In this contribution, M. Moriyama, W. J. Hugentobler and A. Iwasaki summarize evidence showing that, in temperate regions (Europe, North America), winter epidemics of respiratory infectious diseases, caused by the influenza- or human coronavirus, display peak incidences during the cold season (Nov./December through the end of April). Hence, the viral "species" SARS-CoV-2, which shows a gender-specific infection pattern (2, 3), is classified by microbiologists as a "winter virus".

In the modern (industrialized) world, the majority of people work, commute, interact and sleep indoors. Accordingly, they spend up to 90 % of their lifetime in enclosed spaces, where environmental conditions differ significantly from those outdoors, in which humans evolved (i.e., exposure to direct sunlight, wind, rain, moist/fresh air etc.). This "evolutionary mismatch" is particularly severe during the winter, when, under outdoor conditions, cold/dry air and a lack of sunlight/vitamin D have negative impacts on health. Importantly, indoor relative humidity (RH) – caused by central heating and air-tight buildings (closed windows) – can reach values of < 25 %. In this "thermal comfort zone" (ca. 22 °C; dry, standing air; enhanced CO_2-level), where tight people-to-people-contacts occur, the epithelium of the lung

is physiologically stressed or damaged, so that host susceptibility to virus infections is high (1).

These facts explain why in German meatpacking plants, where employees are working close together in a cold and dry indoor-environment, the novel coronavirus SARS-CoV-2 can easily spread from an infected person to a susceptible host. In this context it should be noted that the popular phrase of a "survival" of virus particles on cool surfaces etc. is misleading. These RNA/protein-complexes are not alive. They need a metabolically active host cell (containing DNA/RNA, plus an ATP-cycle) to "reproduce their kind" and spread (2, 3).

The SARS-CoV-2-virus is a relatively large RNA-protein-complex (containing an oily outer layer); diameter ca. 125 nanometer. With ca. 30.000 ribonucleid acid letters (a, g, c, u), these sub-cellular particles have the largest genomes of all RNA-viruses analyzed so far. Moreover, molecular data revealed that the mutation rate of SARS-CoV-2 is only about 1/3 of that of influenza viruses. However, this relatively low rate of "evolvability via mutations" is compensated for by a feature usually restricted to sexually reproducing eukaryotic cells: the exchange of pieces of RNA, i.e., recombination. In the body cells of Asian bats, which can harbor up to 61 different virus-"species" capable of infecting the accidential host *Homo sapiens*, recombination between distantly related coronaviruses, that reproduce in the same cytoplasmic unit, can yield "deadly" new versions of these "sexy killers" (4). As a result, novel coronavirus-recombinants represent evolved versions of their ancestral forms that can infect not only new cell types of their host organisms *H. sapiens*, but may also develop the potential to jump to other mammalian species. After super-spreading in "un-natural" indoor environments, SARS-CoV-2 acts in a host-specific pattern (2, 3).

What are the clinical and biological risk factors for death from COVID-19? Based on the largest data set compiled so far (5), the Open SAFELY collaborative (population of 17.425.445 adults, representing a large proportion of all patients in England) analyzed 5.683 deaths in hospitals attributed to COVID-19 (0.03 %; time period 1st Febr. to 25th April 2020). The results confirmed earlier studies showing that COVID-19 death rates are almost two-fold higher in men vs. women (2, 3). In other words, death from COVID-19 was strongly associated to (a) being male (x 2). Other risk factors are (b) increasing age (older than 60 years: x 3 to x 26, compared to the age group 50 to 59 years); (c) biological race (Non-White ethnic groups i.e., Black/Asian or Mixed Ethnicities: x 2, compared to Whites); (d) suffering from deprivation (x 2 with respect to average people). Finally, other prior medical conditions or co-morbidities (severe asthma, diabetes, cancer, obesity, chronic respiratory [or liver]

disease, reduced kidney function, organ transplant, stroke or dementia etc. are important risk factors: x 2 to x 5, compared to healthy adults).

An unexpected result of this study (5) was the finding that people with evolutionary roots in Africa and Asia, who live in England, where at higher risk of death from COVID-19 compared to Caucasians. This difference persisted after adjustment for all other risk factors. The reason for this race-specific effect of the "sexy killer-virus" SARS-CoV-2 is unknown.

Finally, J. P. A. Ioannidis et al. (6) have estimated the "population-level COVID-19 mortality risks". Their analysis revealed that, despite the fact that COVID-19 is a formidable threat to old men with co-morbidities; the risk of death for healthy people younger than 65 years is very low. A conversion of the absolute risk of COVID-19-deaths into the equivalent death risk from motor vehicle-travelled miles per day (as of May 1, 2020) is 13 in Canada, 20 in Germany, 58 in Italy, 92 in Sweden, 95 in Spain, 185 in the UK, and 668 in New York (USA). Surprisingly, in Sweden, where no lockdown of the economy (but social distancing) was ordered by the Government, the death risk (expressed as "miles travelled per day equivalent") was only about 50 % of that in the UK, where severe restrictions for business and travelling were enforced (6). The reason for this difference (Sweden vs. England) is unknown. Hence, more studies are necessary before we fully understand the "super-spread" and deadly action of the SARS-CoV-2-virus. This "unconscious molecular machine without metabolism" creates its variable, infectious offspring via genetic recombination, an evolved feature that represents the true danger of this "sexy Bat-virus" from Wuhan/China.

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Original Article: https://science.sciencemag.org/content/368/6493/808/tab-e-letters