SARS-CoV-2 an Ending or Never-Ending Pandemic?

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Today’s Seminar

• The origins of SARS-CoV-2

• The (possible) future evolution of SARS-CoV-2

• Lessons learned from the COVID-19 pandemic
Respiratory Disease in Wuhan

- Meta-transcriptomic analysis (total RNA sequencing) of bronchoalveolar lavage fluid (BALF) samples from 408 patients presenting with pneumonia and acute respiratory infections at Wuhan Central Hospital of Wuhan between 2016 and (Dec) 2017.

- Complex mix of potential viral, bacterial and fungal pathogens
- One sporadic zoonotic pathogen – *Chlamydia psittaci*
- No SARS-CoV-2, but many common cold CoVs
SARS-CoV-2: The Early Days

2019-nCoV = SARS-CoV-2

- SARS-CoV-2 contains a furin cleavage site insertion of 4 amino acids at the junction of S1 and S2 subunits of the Spike (S) protein.
- Furin cleavage sites commonly evolve in coronaviruses and other RNA viruses (e.g. identical amino acid sequence in feline coronavirus).
- No strong evidence of COVID-19 in any location before Wuhan.
- Epidemic events before mid-October are unlikely.

Most likely time of origin: mid-November 2019

Was SARS-CoV-2 in Europe in 2019?

From Wuhan to Paris to Milan, the search for ‘patient zero’

Pekar et al. Science 372, 412-417; 2021

The Washington Post
What is the Animal Reservoir?

- Closest relatives are found in various species of horseshoe bat (*Rhinolophus* sp.)
- Guangdong pangolin coronavirus - close to SARS-CoV-2 in the receptor binding domain
- The reservoir/intermediate host for SARS-CoV-2 is not established: the closest viruses are still >10 years evolutionary divergent. Major sampling bias toward bats.

**Horseshoe bat**

(*Rhinolophus affinis*)

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**Malayan pangolin**

(*Manis javanica*)

- RaTG13 from the Wuhan Institute of Virology (WIV) is not the closest relative of SARS-CoV-2
- Two viruses - RpYN06 and RnYN02 – were sampled from the same 1100 hectare botanical garden in Yunnan province

Lytras *et al.* *Science* **373**, 968-970; 2021
Ecology of Bat Viruses

- 26 novel bat coronaviruses from a 1100 hectare tropical botanic garden
- *Rhinolophus* bat species are common in Asia and co-exist in multiple localities

Xishuangbanna Tropical Botanical Garden, Mengla County, Yunnan Province, China

**Alphacoronaviruses (inc. relatives of PEDV)**
Rhinolophus Bat Viruses from Laos

Coronaviruses with a SARS-CoV-2-like receptor-binding domain allowing ACE2-mediated entry into human cells isolated from bats of Indochinese peninsula

https://www.researchsquare.com/article/rs-871965/v1

- Multiple SARS-CoV-2-like viruses found in bats from Laos
- Virus Banal-20-52 is the closest relative of SARS-CoV-2 (96.8%)
- Very close to SARS-CoV-2 in the receptor binding domain

By Jonathan Corum | Sources: Spyros Lytras et al., Science; Sarah Temman et al., Research Square

 Courtesy of the New York Times
Did SARS-CoV-2 Escape from a Lab?

- Furin cleavage site is suboptimal (canonical = R-X-R/R-R) and is commonly lost in cell culture (e.g. unmodified VeroE6 cells)
- Absence of genomic markers associated with mouse adaptation
- SARS-CoV-2 was not optimally adapted to humans on first emergence – a ‘generalist’ virus that is continually adapting (e.g. white-tailed deer, USA)
- Bat virus RaTG13 is not the direct ancestor of SARS-CoV-2 (~1100 mutations different)
- SARS-CoV-2 is not necessarily directly from bats and not necessarily from Yunnan province
- Cases/excess deaths near WIV only appeared later in the outbreak; early clustering around the Huanan market
- No evidence that the WIV isolated or cultured a virus closely related to SARS-CoV-2 (all cultured viruses are close to SARS-CoV)
- No evidence of SARS-CoV-2 infection in Shi lab at WIV – staff were PCR/antibody negative
- Would require a monumental cover-up/conspiracy
- No evidence of a closer SARS-CoV-2-like virus kept at the WIV (and no reason to keep it secret before the pandemic)

Online paper: https://doi.org/10.1016/j.cell.2021.08.017
SARS-CoV-2 at the WIV

Evidence of SARS-CoV-2 at WIV prior to the pandemic:
- Sequencing databases = 0
- Publications = 0
- Old theses = 0
- Freedom of Information Act information on grants, annual reports and emails = 0
- US Intelligence Community = 0

Reported from the WIV:
- No COVID-19 cases at the lab (ELISA + PCR)
- Denied working with SARS-CoV-2 prior to the pandemic
Huanan Sea Food Market, Wuhan

- Large-scale virus transmission in the Huanan market, Wuhan

October 29th 2014

Raccoon dog (*Nyctereutes procyonoides*)
- susceptible to SARS-CoV-2
- implicated in the emergence of SARS-CoV


The Market – Ground Zero

http://babarlelephant.free-hoster.net/visiting-the-wuhan-seafood-market/

... and kernel density of positive samples
SARS-CoV infected civets in Hubei province in 2004

SARS-CoV-2 in Hubei is not a surprise...

Follow The Animals
Cave diving for the origin of COVID-19, six hours west of Wuhan

- Ensi prefecture closed its live animal markets on Dec 23rd 2019
- Supply animals to Wuhan markets
Viromes of Game Animals in China

- Sampled 1725 game animals from 5 mammalian orders
- 71 mammalian viruses discovered: 18 of potential human risk
- Bat HKU8 coronavirus in a civet
- Avian H9N2 influenza virus in a civet and an Asian badger
Ongoing Evolution of SARS-CoV-2

- Approximately 5,000,000 SARS-CoV-2 genome sequences generated to date

### B.1.1.7
- **WHO:** Alpha
- **PHE:** VOC:20DEC-01
- **Nextstrain:** 20H/501Y/V1, 20H/501Y/V1
- **GISAID:** GY, GR/501Y/V1
- **Related:** B.1.1.1 + E484K

### B.1.351
- **WHO:** Beta
- **PHE:** VOC:20DEC-02, VOC:202012/02
- **Nextstrain:** 20H/501Y/V2
- **GISAID:** GR/501Y/V2

### B.1.617.2
- **WHO:** Delta
- **PHE:** VOC:21APR-02
- **Nextstrain:** 21A/E:478K
- **GISAID:** G4/21R/V3
- **Related:** B.1.617.1 + B.1.617.3 + AY.1 + AY.2

### P.1
- **WHO:** Gamma
- **PHE:** VOC:21JAN-02, VOC:202101/02
- **Nextstrain:** 20I/501Y/V3
- **GISAID:** GR/501Y/V3
- **Related:** P.1.1 + P.1.2 + P.2 + P.3

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**Scripps Research**
https://outbreak.info/situation-reports

**Why convergent evolution and emergence of Variants of Concern?**

- **Increased transmissibility**
- **Impact of population lockdowns**
- **Immune evasion (e.g. mounting interferon resistance)**
- **Inter-host chronic infections (i.e. prolonged shedding and evolution)**
One future scenario

- Virus is endemic
- Serious disease/mortality will decline with increasing immunity.
- SARS-CoV-2 will evolve to evade immunity, necessitating booster vaccine shots.
- Immune escape will be strongest in the first years of the pandemic; strongest adaptive evolution at intermediate protection.
- As time passes the virus will find it harder to find an escape mutation.
- Virulence evolution depends on whether there is selection to infect cells of the lower or upper respiratory tract (or both)

Expect More Coronaviruses

- SARS-CoV-2 is the 9\textsuperscript{th} documented human coronavirus
- Seven have emerged the last 20 years (SARS-CoV, MERS-CoV, HKU1, NL63, SARS-CoV-2 and two new viruses from pigs)
- Bats are involved in the emergence of five (SARS-CoV, MERS-CoV, NL63, 229E, SARS-CoV-2)

Fair Warning - CoV-HKU1:
- Emerged in Shenzhen/Hong Kong in 2005
- Unknown animal origin (closest to MHV)
- Contains a furin cleavage site (common in Embecoviruses)
- Can cause pneumonia
COVID-19: Lessons Learned

• Need a broader set of pandemic plans, not just those based on influenza

• Continual research funding for cross-protective vaccines and antivirals (for coronaviruses, influenza viruses and paramyxoviruses)

• We need a new global pandemic ‘radar’ to rapidly identify emerging diseases

• Climate change will increase the frequency of disease emergence events

• Scientists and public health officials need to share their data as openly and rapidly as possible

• Open global collaboration between scientists should be encouraged and enriched

• Governments need to listen to and trust in scientists

• Science must be depoliticised
A Global “Pandemic Radar”

- Active surveillance of people living/working at the human-animal interface: wildlife trade and fur farming, in animal production and slaughter, live animal markets, animal hunting/bushmeat, people living around bat roosts, animal carers and animal rescue centres etc.
- Active surveillance of animal mortality events
- Regular immunological surveillance (e.g. VirScan/GIO) and occasional metagenomic surveillance (may need new computational tools)
- Rapid and open data sharing

VirScan, or systematic viral epitope scanning, works by displaying bits of protein from more than 1,000 strains of virus. Antibodies in a blood sample latch onto the bits they recognize. Now, scientists have updated VirScan to include the novel coronavirus. Credit: G. Xu et al./Science 2015
The Wuhan Outbreak of SARS-CoV-2
- Fan Wu, Yan-Mei Chen, Jun-Hua Tian, Bin Yu, Wen Wang, Wen-Ping Guo, Xian-Dan Lin, Yan-Mei Chen, Su Zhao, Yong-Zhen Zhang (Fudan University, Shanghai, Wuhan CDC)
- Weifeng Shi, Shiman Ruan, Peiqiang Hou, Xiangkun Jiang, Dianmin Kang, Hong Zhou (Shandong First Medical University & Shandong Academy of Medical Sciences)
- Mang Shi (Sun-Yat Sen University)

Bat Viruses from Yunnan Province, China
- Weifeng Shi, Hong Zhou (Shandong First Medical University)
- Alice Hughes (Xishuangbanna Tropical Botanical Garden, Yunnan)

Gamey Tastes
- Mang Shi, Xin Hou (Sun-Yat Sen University)
- Shuo Su, Wan-Ting He (Nanjing Agricultural University)

SARS-CoV-2 Origins and Evolution
- Andrew Rambaut (University of Edinburgh)
- Kristian Andersen (Scripps Research)
- Bob Garry (Tulane University, New Orleans)
- Angie Rasmussen (University of Saskatchewan)
- Stephen Goldstein (University of Utah)
- Alex Crits-Christoph (UC Berkeley)
- Joel Wertheim (UC San Diego)
- David Robertson (University of Glasgow)

Thanks To: