從數字認識SARS-CoV-2 (COVID-19)

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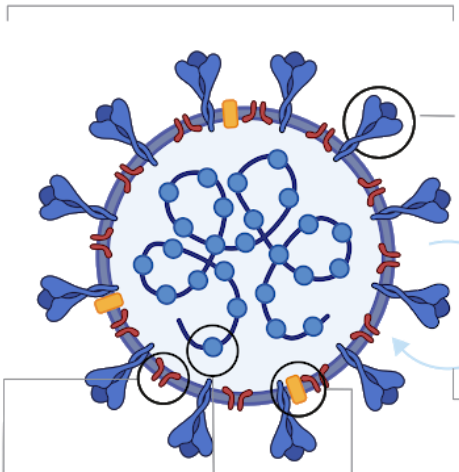
大小及組成

直徑: ≈100 奈米
體積: ~10^6 立方奈米= 10^{-3} 毫微微升
質量: ~10^3 百萬道爾頓 ≈ 1毫微微克



棘蛋白三聚體:
長度: ≈10 奈米
單位病毒顆粒所含數目: ≈100
(即300 個蛋白單體,
此為測量SARS-CoV-1冠狀病毒的數據)
與ACE2受體結合的親和力
K_d: ≈1-30 奈米莫耳濃度
由宿主的跨膜絲胺酸蛋白酶2 (TMPRSS2)所活化

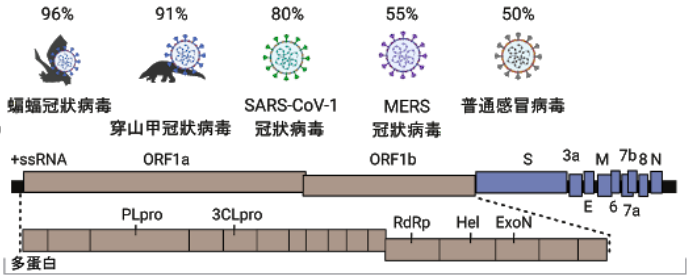
膜蛋白:
≈2000 個
(此為測量SARS-CoV-1冠狀病毒的數據)

核蛋白:
≈1000 個
(此為測量SARS-CoV-1冠狀病毒的數據)

外套膜蛋白:
≈20 個
(100 個蛋白單體, 此為測量TGEV冠狀病毒的數據)

基因組

其他冠狀病毒的核酸序列與SARS-CoV-2一樣的程度:



基因組長度: ≈30千鹼基對

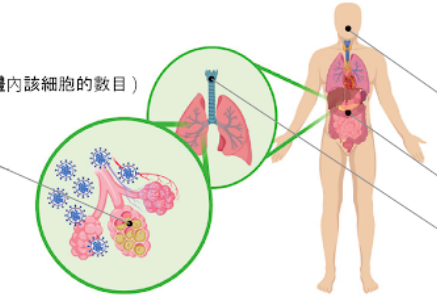
演化速率: ~10^{-3} /鹼基/年 (此為測量SARS-CoV-1冠狀病毒的數據)
突變率: ~10^{-6} /鹼基/複製週期 (此為測量MHV冠狀病毒的數據)

複製時程及複製量

i在組織培養的環境下
病毒進入細胞所需的時間: ~10分鐘 (此為測量SARS-CoV-1冠狀病毒的數據)
隱蝕期: ~10 小時
病毒釋出數量: ~1000 病毒顆粒 (此為測量MHV冠狀病毒的數據)

宿主細胞

(下列清單僅依據截至目前的研究所擬定，顯示每個人體體內該細胞的數目)
第一型及第二型肺泡壁細胞: ~10^{11} 個
肺泡巨噬細胞: ~10^{10} 個
鼻腔黏膜細胞: ~10^9個
宿主細胞體積: ~10^3 立方微米= 10^3 毫微微升



病毒顆粒的相對大小並非實際情況

病毒濃度

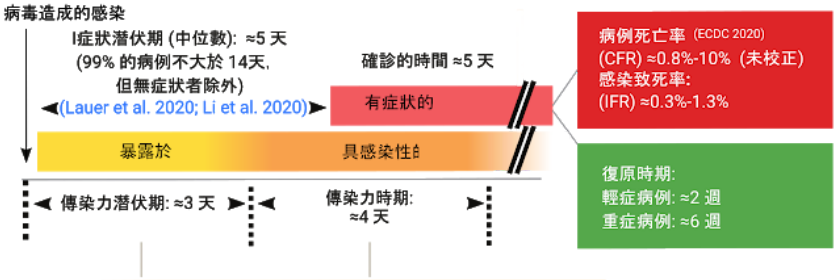
下列為病患確診後所檢測到的最大值
(Woelfel et al. 2020; Kim et al. 2020; Pan et al. 2020)
鼻咽: 10^6-10^9 RNAs/採檢拭子
咽喉: 10^4-10^8 RNAs/採檢拭子
糞便: 10^4-10^8 RNAs/克
痰: 10^6-10^{11} RNAs/毫升
RNA數量很可能高估具感染力的病毒顆粒數目

抗體免疫反應 - 血清轉換

抗體在血液中開始的出現時間: ≈10-20天
抗體存在於人體內的時間: ≈2-3 年
(此為測量SARS-CoV-1冠狀病毒的數據)

感染病例的進程"特徵"

基本再生數, R_0: 普遍介於 2-4,
但此範圍並非固定，會隨著時間及地點改變 (Li et al. 2020; Park et al. 2020)
(此數字代表每個病例可直接造成的傳染人數)



各項數值在病例之間有極大的差異，而目前仍無法適當地描述該差異。
這些數值是藉由中國大陸所收集的病例資料的中位數，經過模型推算所得，
並無法得知病例間的差異 (Li et al. 2020; He et al. 2020).

病毒在環境中的穩定性

病毒存在於下列環境時對實際人體的感染力仍然未知

	半衰期	濃度減少至千分之一的時間
氣溶膠:	≈1 小時	≈4-24 小時
物體表面: 物體如, 塑膠、硬紙板、及金屬等	≈1-7小時	≈4-96 小時

(van Doremalen et al. 2020)

以上數據是在攝氏21-23度及相對溼度40-65%的環境下，
計算具感染力的病毒顆粒數目而推得。在不同環境條件及不同物體種類下，
病毒數目會出現差異 (Otter et al. 2016).
病毒RNA甚至在某些物體表面可持續存在數週 (Moriarty et al. 2020).

請注意，符號≈ 及符號~ 代表不同程度的近似。符號≈ 為偏差在2倍之內; 而符號~ 為偏差在10倍之內。.

Translated by Shu-Ting You, Weizmann Institute of Science

Size & Content

Diameter: ≈100 nm
Volume: ~10^6 nm^3 = 10^{-3} fL
Mass: ~10^3 MDa ≈ 1fg
Membrane: ≈2000 copies (measured for SARS-CoV-1)
Envelope: ≈20 copies (100 monomers, measured for TGEV coronavirus)
Nucleoprotein: ≈1000 copies (measured for SARS-CoV-1)
Spike trimer:
- Length: ≈10 nm
- Copies per virion: ≈100 (measured for SARS-CoV-1) (300 monomers)
- Affinity to ACE2 receptor K_d: ≈1-30 nM
- primed by TMPRSS2

大小及組成

直徑: ≈100 奈米
體積: ~10^6 立方奈米= 10^{-3} 毫微微升
質量: ~10^3 百萬道爾頓 ≈ 1毫微微克
膜蛋白: ≈2000 個 (此為測量SARS-CoV-1冠狀病毒的數據)
外套膜蛋白: ≈20 個 (100 個蛋白單體, 此為測量TGEV冠狀病毒的數據)
核蛋白: ≈1000 個 (此為測量SARS-CoV-1冠狀病毒的數據)
棘蛋白三聚體:
- 長度: ≈10 奈米
- 單位病毒顆粒所含數目: ≈100 (此為測量SARS-CoV-1冠狀病毒的數據) (即300 個蛋白單體)
- 與ACE2受體結合的親和力 K_d: ≈1-30 奈米莫耳濃度
- 由宿主的跨膜絲胺酸蛋白酶2 (TMPRSS2)所活化

Genome

Genome length: ≈30kb
Number of genes: 10-14
Number of proteins: 24-27
Evolution rate: ~10^{-3} nt^{-1} yr^{-1} (measured for SARS-CoV-1)
Mutation rate: ~10^{-6} nt^{-1} $cycle^{-1}$ (measured for MHV coronavirus)
Nucleotide identity to SARS-CoV-2: bat CoV - 96%; pangolin CoV 91%; SARS-CoV-1 80%; MERS 55%; common cold CoV 50%

基因組

基因組長度: ≈30千鹼基對
基因數目: 10-14
蛋白數目: 24-27
演化速率: ~10^{-3} /鹼基/年 (此為測量SARS-CoV-1冠狀病毒的數據)
突變率: ~10^{-6} /鹼基/複製週期 (此為測量MHV冠狀病毒的數據)
其他冠狀病毒的核酸序列與SARS-CoV-2一樣的程度: 蝙蝠冠狀病毒- 96%; 穿山甲冠狀病毒- 91%; SARS-CoV-1冠狀病毒- 80%; MERS冠狀病毒- 55%; 普通感冒病毒- 50%

Replication Timescales

In tissue-culture
Virion entry into cell: ~10 min (measured for SARS-CoV-1)
Eclipse period: ~10 hours
Burst size: ~1000 virions (measured for MHV coronavirus)

複製時程及複製量

在組織培養的環境下
病毒進入細胞所需的時間: ~10分鐘 (此為測量SARS-CoV-1冠狀病毒的數據)
隱蝕期: ~10 小時
病毒釋出數量: ~1000 病毒顆粒 (此為測量MHV冠狀病毒的數據)

Host Cells

(tentative list; number of cells per person)
Type I and Type II pneumocyte: ~10^{11} cells
Alveolar macrophage: ~10^{10} cells
Mucous cells in nasal cavity: ~10^9 cells
Host cell volume: ~10^3 μm^3 = 10^3 fL

宿主細胞

(下列清單僅依據截至目前的研究所擬定，顯示每個人體體內該細胞的數目)
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宿主細胞體積: ~10^3 立方微米= 10^3 毫微微升

Concentration

maximal observed values following diagnosis
Nasopharynx: 10^6-10^9 RNAs/swab
Throat: 10^4-10^8 RNAs/swab
Stool: 10^4-10^8 RNAs/g
Sputum: 10^6-10^{11} RNAs/mL
RNA counts can markedly overestimate infectious virions

病毒濃度

下列為病患確診後所檢測到的最大值
鼻咽: 10^{6}-10^{9} RNAs/採檢拭子
咽喉: 10^{4}-10^{8} RNAs/採檢拭子
糞便: 10^{4}-10^{8} RNAs/克
痰: 10^{6}-10^{11} RNAs/毫升
RNA數量很可能高估具感染力的病毒顆粒數目

Antibody Response - Seroconversion

Antibodies appear in blood after: ≈10-20 days
Maintenance of antibody response: ≈2-3 years (measured for SARS-CoV-1)

抗體免疫反應 - 血清轉換

抗體在血液中開始的出現時間: ≈10-20天
抗體存在於人體內的時間: ≈2-3 年(此為測量SARS-CoV-1冠狀病毒的數據)

Virus Environmental Stability

Relevance to personal safety unclear

	half-life	time to decay 1000-fold
Aerosols:	≈1 hr	≈4-24 hr
Surfaces: E.g. plastic, cardboard And metals	≈1-7 hr	≈4-96 hr

Based on quantifying infectious virions. Tested at 21-23°C and 40-65% relative humidity. Numbers will vary between conditions and surface types (ref).
Viral RNA observed on surfaces even after a few weeks (ref)

病毒在環境中的穩定性

病毒存在於下列環境時對實際人體的感染力仍然未知

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以上數據是在攝氏21-23度及相對溼度40-65%的環境下，計算具感染力的病毒顆粒數目而推得。在不同環境條件及不同物體種類下，病毒數目會出現差異(ref)。
病毒RNA甚至在某些物體表面可持續存在數週(ref)。

"Characteristic" Infection Progression in a Single Patient

Basic reproductive number, R_0: typically 2-4, but varies further across space and time
(number of new cases directly generated from a single case)
Incubation period (median): ≈5 days (99% ≤ 14 days unless asymptomatic)
Diagnosis after ≈5 days
Latent period: ≈3 days
Infectious period: ≈4 days
Recovery: mild cases: ≈2 weeks
severe cases: ≈6 weeks
Case Fatality Rate: ≈0.8%-10% (uncorrected)
Infected Fatality Rate: ≈0.3%-1.3%
Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability (ref, ref).

Note the difference in notation between the symbol ≈, which indicates "approximately" and connotes accuracy to within a factor of 2, and the symbol ~, which indicates "order of magnitude" or accuracy to within a factor of 10.

感染病例的進程"特徵"

基本再生數, R_0: 普遍介於 2-4, 但此範圍並非固定，會隨著時間及地點改變
(此數字代表每個病例可直接造成的傳染人數)
症狀潛伏期 (中位數): ≈5 天 (99% 的病例不大於 14天，但無症狀者除外)
確診的時間 ≈5 天
傳染力潛伏期: ≈3 天
傳染力時期: ≈4 天
復原時期: 輕症病例: ≈2 週
重症病例: ≈6 週
病例死亡率: ≈0.8%-10% (未校正)
感染致死率: ≈0.3%-1.3%
各項數值在病例之間有極大的差異，而目前仍無法適當地描述該差異。這些數值是藉由中國大陸所收集的病例資料的中位數，經過模型推算所得，並無法得知病例間的差異(ref, ref).

請注意，符號≈ 及符號~ 代表不同程度的近似。符號≈ 為偏差在2倍之內; 而符號~ 為偏差在10倍之內。

Abstract

The current SARS-CoV-2 pandemic is a harsh reminder of the fact that, whether in a single human host or a wave of infection across continents, viral dynamics is often a story about the numbers. In this snapshot, our aim is to provide a one-stop, curated graphical source for the key numbers that help us understand the virus driving our current global crisis. The discussion is framed around two broad themes: 1) the biology of the virus itself and 2) the characteristics of the infection of a single human host. Our one-page summary provides the key numbers pertaining to SARS-CoV-2, based mostly on peer-reviewed literature. The numbers reported in summary format are substantiated by the annotated references below. Readers are urged to remember that much uncertainty remains and knowledge of this pandemic and the virus driving it is rapidly evolving. In the paragraphs below we provide "back of the envelope" calculations that exemplify the insights that can be gained from knowing some key numbers and using quantitative logic. These calculations serve to improve our intuition through sanity checks, but do not replace detailed epidemiological analysis.

摘要

SARS-CoV-2全球大流行就像一記響鐘，重重地敲在人們心上，提醒人們，無論是單一病人體內或是擴及世界各大陸的感染歷程，這些事件常常可用測量病毒本身的數據來解釋。我們收集及檢視SARS-CoV-2的研究，將研究所得的各項關鍵數據圖像化，力求簡單清楚，幫助大家了解現在這個造成我們恐慌的敵人。討論主要包含兩大議題：一是病毒本身的生物特徵，二是病毒感染人類的過程。而大部分的關鍵數據係來自經由相關領域科學家審查過的研究文獻，文獻出處也隨文附上，方便查閱。讀者務必認知到，關於這次的全球大流行及此致病病毒，現今的知識都會因未來研究而有所修正，許多不確定性仍然存在。我們會利用目前已知的數據，經由定量化的分析邏極，粗略計算，來呈現許多重要的觀念。我們展現的數據計算就像是簡單的檢驗，希望加深大家的認知，而不是要用來替代任何流行病學的分析。

1. How long does it take a single infected person to yield one million infected people?

If everybody continued to behave as usual, how long would it take the pandemic to spread from one person to a million infected victims? The basic reproduction number, R_0, suggests each infection directly generates 2-4 more infections in the absence of countermeasures like social distancing. Once a person is infected, it takes a period of time known as the latent period before they are able to transmit the virus. The current best-estimate of the median latent time is ≈3 days followed by ≈4 days of close to maximal infectiousness (Li et al. 2020, He et al. 2020). The exact durations vary among people, and some are infectious for much longer. Using R_0≈4, the number of cases will quadruple every ≈7 days or double every ≈3 days. 1000-fold growth (going from one case to 10^3) requires 10 doublings since $2^{10} \approx 10^3$; 3 days × 10 doublings = 30 days, or about one month. So we expect ≈1000x growth in one month, million-fold (10^6) in two months, and a billion fold (10^9) in three months. Even though this calculation is highly simplified, ignoring the effects of "super-spreaders", herd-immunity and incomplete testing, it emphasizes the fact that viruses can spread at a bewildering pace when no countermeasures are taken. This illustrates why it is crucial to limit the spread of the virus by social distancing measures. For fuller discussion of the meaning of R_0, the latent and infectious periods, as well as various caveats, see the "Definitions" section.

1. 一位病人造成一百萬人染病需要多久?

若每個人持續疫情爆發前的生活模式，染病人數從一到一百萬會需要多少時間呢?依據此病毒的基本再生數(R_0)，在沒有任何防治措施(如，保持社交距離)的情況下，每個感染病例可直接造成額外的2-4個感染。當某人感染到病毒，並不會馬上具有傳染他人的能力，這段時期稱作傳染力潛伏期。根據目前最佳的觀測結果，這段時期的中位數約3天，接著便是為期約4天的高傳染力時期 (Li et al. 2020, He et al. 2020)。每個人具有傳染力的時間因人而異，有人的是遠大於4天。假設R_0大約是4，病毒大約每7天就會造成4倍的染病人數，相當於每3天人數就會倍增。10個3天就是10次的倍增(2^{10})，而2^{10}=1024≈ 10^3，於是我們可以預計，從一人到一千人染病只需要一個月，而再過一個月便有一百萬人染病。也就是說單一病例出現後的一個月就會有一千例，兩個月後有一百萬例，而三個月就達到十億病例。不可否認地，我們簡化了整個情況，忽略了超級傳播者的存在、群體免疫的影響、以及檢測不普及的事實。但也正是如此，這個推算結果顯現出若沒有任何防治措施，新冠肺炎會以快到令人費解的速度傳播下去。並且點出了保持社交距離之於防堵疫情的關鍵地位。在後面有關"定義"的章節裡，關於 R_0、傳染力潛伏期、傳染力時期、以及許多需要釐清的觀念，提供了更全面的探討及解釋。

2. What is the effect of social distancing?

A highly simplified quantitative example helps clarify the need for social distancing. Suppose that you are infected and you encounter 50 people over the course of a day of working, commuting, socializing and running errands. To make the numbers round, let's further suppose that you have a 2% chance of transmitting the virus in each of these encounters, so that you are likely to infect 1 new person each day. If you are infectious for 4 days, then you will infect 4 others on average, which is on the high end of the R_0 values for SARS-CoV-2 in the absence of social distancing. If you instead see 5 people each day (preferably fewer) because of social distancing, then you will infect 0.1 people per day, or 0.4 people before you become less infectious. The desired effect of social distancing is to make each current infection produce < 1 new infections. An effective reproduction number (R_e) smaller than 1 will ensure the number of infections eventually dwindles. It is critically important to quickly achieve R_e < 1, which is substantially more achievable than pushing R_e to near zero through public health measures.

2. 保持社交距離的作用為何?

保持社交距離的必要性可以用相當簡單並數值化的例子清楚地告訴大家。假設你受到感染了，而每天你因為上班、通勤、或出門辦事等，會接觸到50人。為了方便計算，就再假設你傳染給這50人的可能性是2%。這樣一來，你每天有可能會感染1人，於是造成1個病例的新增。若你的傳染力維持4天，平均就有另外4人因你而染病。此一情境便是我們之前提到在沒有任何防治措施下，SARS-CoV-2目前基本再生數R_0的最大值。現在來看另一情境，假設你開始遵守保持社交距離的政令，因此每天遇到的人變成5人(最好可以更少)，這樣你每天可能造成的感染就變成了0.1人，而在你的傳染力下降前，你就僅傳染0.4人。保持社交距離就是為了使每個既存的病例造成少於1個的新病例。有效再生數(R_e) 在小於1的情況下，任何傳染病終將消退。可以想見，迅速地讓R_e小於1，對於防堵疫情有多麼重要，再者，相較於利用公衛措施讓R_0逼近0的訴求，讓R_e小於1實在是非常容易實現。

3. Why is the quarantine period two weeks?

The period of time from infection to symptoms is termed the incubation period. The median SARS-CoV-2 incubation period is estimated to be roughly 5 days (Lauer et al. 2020). Yet there is much person-to-person variation. Approximately 99% of those showing symptoms will show them before day 14, which explains the two week confinement period. Importantly, this analysis neglects infected people who never show symptoms. Since asymptomatic people are not usually tested, it is still not clear how many such cases there are or how long asymptomatic people remain infectious for.

3. 為何隔離期是14天?

從感染病毒到症狀出現的時期稱作症狀潛伏期。在SARS-CoV-2例子裡，該潛伏期為5 天(Lauer et al. 2020) 。每個人的潛伏期長短其實相當不同。而有症狀的人裡，大約99% 會在14天內出現病徵，這也就解釋了為何要限制活動範圍長達14天。更重要的是，這些研究都沒有包含無症狀患者。因為沒有病徵，這些人通常都沒有被檢驗，於是乎究竟有多少無症狀患者以及他們的傳染力持續多久，目前都是未知數。

4. How do N95 masks block SARS-CoV-2?

N95 masks are designed to remove more than 95% of all particles that are at least 0.3 microns (μm) in diameter (NIOSH 42 CFR Part 84). In fact, measurements of the particle filtration efficiency of N95 masks show that they are capable of filtering ≈99.8% of particles with a diameter of ~0.1 μm (Regnasamy et al. 2017). SARS-CoV-2 is an enveloped virus ~0.1 μm in diameter, so N95 masks are capable of filtering most free virions, but they do more than that. How so? Viruses are often transmitted through respiratory droplets produced by coughing and sneezing. Respiratory droplets are usually divided into two size bins, large droplets (> 5 μm in diameter) that fall rapidly to the ground and are thus transmitted only over short distances, and small droplets (≤ 5 μm in diameter). Small droplets can evaporate into "droplet nuclei," remain suspended in air for significant periods of time and could be inhaled. Some viruses, such as measles, can be transmitted by droplet nuclei (Tellier et al. 2019). At present there is no direct evidence showing SARS-CoV-2 transmission by droplet nuclei. Rather, larger droplets are believed to be the main vector of SARS-CoV-2 transmission, usually by settling onto surfaces that are touched and transported by hands onto mucosal membranes such as the eyes, nose and mouth (CDC 2020). The characteristic diameter of large droplets produced by sneezing is ~100 μm (Han J. R. Soc. Interface 2013), while the diameter of droplet nuclei produced by coughing is on the order of ~1 μm (Yang et al 2007). Therefore, N95 masks likely protect against several modes of viral transmission.

4. N95口罩如何阻擋SARS-CoV-2?

依據N95口罩的設計，只要直徑0.3 micron(微米)以上之懸浮粒子，超過95%都無法穿透過此口罩(NIOSH 42 CFR Part 84)。而實測結果顯示，對於直徑~0.1微米之懸浮粒子，N95口罩的過濾程度≈99.8% (Regnasamy et al. 2017)。SARS-CoV-2具有外套膜，其直徑~0.1微米，顯而易見地，N95口罩足以過濾掉懸浮於空中的病毒顆粒，但其實N95口罩能阻擋的還要更多。飛沫依其大小分成兩類，直徑大於5微米的在被噴灑出來時，很快就墜落於地面，所以僅造成近距離的傳染。而直徑不大於 5 微米的飛沫會形成"飛沫核心"，在被噴灑出來後可以懸浮於空氣中，持續存在相當長的時間，於是可能被吸入人體。就像麻疹病毒，有些病毒正是利用飛沫核心造成傳染 (Tellier et al. 2019)。目前尚未有直接證據指出SARS-CoV-2傳染是由飛沫核心。倒是將主要的傳染途徑指向較大的飛沫。這些飛沫先是坐落於物體表面，然後經由雙手碰觸該物體，雙手碰觸人體的黏膜部位，好比眼睛、鼻子、及嘴巴等，引起感染(CDC 2020)。打噴嚏所噴灑出來的飛沫~100微米 (Han J. R. Soc. Interface 2013)，而那些由咳嗽產生的則~1 微米上下 (Yang et al 2007)。 由此可知，N95口罩及有可能阻絕多種的SARS傳播途徑。

5. How similar is SARS-CoV-2 to the common cold and flu viruses?

SARS-CoV-2 is a beta-coronavirus whose genome is a single ≈30 kb strand of RNA. The flu is caused by an entirely different family of RNA viruses called influenza viruses. Flu viruses have smaller genomes (≈14 kb) encoded in 8 distinct strands of RNA, and they infect human cells in a different manner than coronaviruses. The "common cold" is caused by a variety of viruses, including some coronaviruses and rhinoviruses. Cold-causing coronaviruses (e.g. OC43 and 229E strains) are quite similar to SARS-CoV-2 in genome length (within 10%) and gene content, but different from SARS-CoV-2 in sequence (≈50% nucleotide identity) and infection severity. One interesting facet of coronaviruses is that they have the largest genomes of any known RNA viruses (≈30 kb). These large genomes led researchers to suspect the presence of a "proofreading mechanism" to reduce the mutation rate and stabilize the genome. Indeed, coronaviruses have a proofreading exonuclease called ExoN, which explains their very low mutation rates (~10^{-6} per site per cycle) in comparison to influenza (≈3×10^{-5} per site per cycle (Sanjuan et al. 2010)). This relatively low mutation rate will be of interest for future studies predicting the speed with which coronaviruses can evade our immunization efforts.

5. SARS-CoV-2 和普通感冒病毒及流感病毒有多相似?

SARS-CoV-2是beta屬的冠狀病毒，其基因組為長度≈30 千鹼基對的單股RNA。流感則是由完全不同科的RNA病毒引起，稱作流感病毒。流感病毒的基因組較小 (≈14 千鹼基對)，含有8條不同的RNA，並且該病毒傳染人類的途徑有別於與冠狀病毒的。而普通感冒則是由數種不同的冠狀病毒及鼻病毒所引起。其中，有些冠狀病毒 (比如，OC43 及 229E 病毒株)具備和SARS-CoV-2非常相似的基因組長度 (相差10%以內) 以及基因組成，但從序列(彼此僅≈50% 的核苷酸一樣)及感染嚴重程度，則有所不同。冠狀病毒有個令人興味的特徵，那就是在任何RNA病毒中，它們擁有的基因組最大 (≈30 千鹼基對)。此一特徵不禁使研究人員懷疑，該病毒必須具有"校讀機制"，用來降低突變，好保持基因組的穩定。確實在後來的研究中，發現冠狀病毒有個稱作ExoN 的核酸外切酶，具有校讀功能。這也解釋了為何它們的突變率(每次複製週期裡每個核酸位點的突變率為~10^{-6})相較流感病毒(每次複製週期裡每個核酸位點的突變率為≈3×10^{-5} (Sanjuan et al. 2010))來得低。再者，此一相對低的突變率會是未來針對該病毒多快可以產生躲避免疫反應的研究重點。

6. How much is known about the SARS-CoV-2 genome and proteome?

SARS-CoV-2 has a single-stranded positive-sense RNA genome that codes for 10 genes ultimately producing 26 proteins according to an NCBI annotation (NC_045512). How is it that 10 genes code for >20 proteins? One long gene, orf1ab, encodes a polyprotein that is cleaved into 16 proteins by proteases that are themselves part of the polyprotein. In addition to proteases, the polyprotein encodes an RNA polymerase and associated factors to copy the genome, a proofreading exonuclease, and several other non-structural proteins. The remaining genes predominantly code for structural components of the virus: (i) the spike protein which binds the cognate receptor on a human or animal cell; (ii) a nucleoprotein that packages the genome; and (iii) two membrane-bound proteins. Though much current work is centered on understanding the role of "accessory" proteins in the viral life cycle, we estimate that it is currently possible to ascribe clear biochemical or structural functions to only about half of SARS-CoV-2 gene products.

6. 關於SARS-CoV-2的基因組及蛋白質體，有多少已知的資訊?

根據NCBI提供的資訊，SARS-CoV-2的基因組為單股正鏈RNA，共編碼了10個基因，可產生26的蛋白質(NC_045512)。這為數10個的基因如何產生超過20個蛋白呢? 其中一個稱作orf1ab的基因，有著頗長的基因長度，會產生一個多蛋白，而多蛋白會被蛋白酶切斷，形成16個蛋白質，這個蛋白酶也是多蛋白的一部分。除此蛋白酶，多蛋白還包括RNA聚合酶、其他幫助複製基因組的蛋白質、具有校讀功能的核酸外切酶、以及一些非結構蛋白。剩下的基因主要是負責產生組成病毒的結構蛋白: (i) 與人類及動物細胞上相對應受器結合的棘蛋白; (ii) 組裝基因組的核蛋白; 以及(iii) 兩個膜連型蛋白。目前，許多研究著重於了解那些"輔助性"蛋白在病毒生活週期所扮演的角色，但我們估計，大約僅半數的SARS-CoV-2基因產物，其生化或結構方面的功能有著清楚的了解。

7. What can we learn from the mutation rate of the virus?

Studying viral evolution, researchers commonly use two measures describing the rate of genomic change. The first is the evolutionary rate, which is defined as the average number of substitutions that become fixed per year in strains of the virus, given in units of mutations per site per year. The second is the mutation rate, which is the number of substitutions per site per replication cycle. How can we relate these two values? Consider a single site at the end of a year. The only measurement of a mutation rate in a β-coronavirus suggests that this site will accumulate ~10^{-6} mutations in each round of replication. Each round of replication cycle takes ~10 hours, and so there are 10^3 cycles/year. Multiplying the mutation rate by the number of replications, and neglecting the potential effects of evolutionary selection and drift, we arrive at 10^{-3} mutations per site per year, consistent with the evolutionary rate inferred from sequenced coronavirus genomes. As our estimate is consistent with the measured rate, we infer that the virus undergoes near-continuous replication in the wild, constantly generating new mutations that accumulate over the course of the year. Using our knowledge of the mutation rate, we can also draw inferences about single infections. For example, since the mutation rate is ~10^{-6} mutations/site/cycle and an mL of sputum might contain upwards of 10^7 viral RNAs, we infer that every site is mutated more than once in such samples.

7. 我們能從病毒的突變率獲取什麼資訊?

普遍來說，病毒演化的研究會利用兩個觀測值，來形容病毒基因組的變化速率。首先是演化速率，其定義為，每年裡該病毒株平均置換了多少核酸，這些置換必須持續出現在後代每個病毒顆粒體內，也就是這樣的突變成為該病毒株的新特徵，使用的單位便是每年每個基因組位點的突變數目。 再者便是突變率，表示每次複製週期裡每個位點的核酸置換數目。這兩個數值彼此有何關係呢? 以單一位點在一年裡產生之變化為例，根據目前唯一的相關研究，β屬冠狀病毒的突變率可能造成單一位點在每次複製週期時有~10^{-6}個突變。而每次複製週期有~10小時，所以一年就發生了10^3次的複製。我們先忽略演化上的天擇及漂變造成的效應，直接將突變率乘上複製次數，可推知每年單一位點有10^{-3}突變發生，而此一推算結果與由不同冠狀病毒已解碼之基因組序所推算的演化速率相符合。藉由這筆數值的一致性，我們推測此病毒在自然環境裡，幾乎可以不間斷地完成複製，持續產生突變並於一整年的過程裡累積起來。另外，我們從突變率也能獲取有關單次感染的資訊。比如，因為每次複製週期中單一位點的突變率是~10^{-6}，而一毫升具有感染性的痰裡可能含多達10^7個病毒RNA，我們結合這兩項事實，便可以知道此種檢體裡的病毒在單一位點產生了多次的突變。

8. How stable and infectious is the virion on surfaces?

SARS-CoV-2 RNA has been detected on various surfaces several weeks after they were last touched (Moriarty et al. 2020). In the definitions we clarify the difference between detecting viral RNA and active virus. The probability of human infection from such exposure is not yet characterized as experiments to make this determination are very challenging. Nevertheless, caution and protective measures must be taken. We estimate that during the infectious period an undiagnosed infectious person touches surfaces tens of times. These surfaces will subsequently be touched by hundreds of other people. From the basic reproduction number R_0 ≈2-4 we can infer that not everyone touching those surfaces will be infected. More detailed bounds on the risk of infection from touching surfaces urgently awaits study.

8. 存在於物體表面的病毒顆粒能夠多麼地穩定且感染性?

在被汙染的數週後，仍有多種物體表面可偵測到SARS-CoV-2 的RNA (Moriarty et al. 2020)。在有關定義的章節裡，我們會清楚地指出偵測到病毒RNA與具活性的病毒之間所代表意義的差別。因為有關實驗極度困難，目前尚無法確切地決定人類經由接觸這些污染物體而感染的可能性。但相對應的警示及保護措施，必須要付諸行動。我們估計，在感染力時期，一位尚未確診但具感染力的人碰了有數十個物體。然後，這些物體的表面會再被數百個其他人所接觸。從基本再生數R_0 為≈2-4，我們可知並非所有碰了這些汙染表面的人都會被感染。於是，關於接觸物體而感染的風險研究，實在是當務之急。

Glossary

詞彙表

Clinical Measures

Incubation period: time between exposure and symptoms.
Seroconversion: time between exposure to virus and detectable antibody response.

臨床測量

症狀潛伏期: 從暴露於病原到病徵出現的時間
血清轉換: 從暴露於病毒到足以偵測抗體免疫反應的時間

Epidemiological Inferences

R_0: the average number of cases directly generated by an individual infection.
Latent period: time between exposure and becoming infective.
Infectious period: time for which an individual is infective.
Interval of half-maximum infectiousness: the time interval during which the probability of viral transmission is higher than half of the peak infectiousness. This interval is similar to the infectious period, but applies also in cases where the probability of infection is not uniform in time.

流行病學的推估

基本再生數: 每個病例可直接造成的傳染人數的平均數
傳染力潛伏期: 從暴露於病原到具有傳染力的時間
傳染力期: 具有傳染力的時間
高於半最大傳染力的時期: 傳播病毒的可能性達到大於最高傳染力的一半之期間。這個時期類似於傳染力期，但亦適用於傳染力會隨著時間變化的例子。

Viral Species

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. A β-coronavirus causing the present COVID-19 outbreak.
SARS-CoV-1: β-coronavirus that caused the 2002 SARS outbreak in China.
MERS: a β-coronavirus that caused the Middle East Respiratory Syndrome outbreak beginning in Jordan in 2012.
MHV: Murine herpes virus, a model β-coronavirus on which much laboratory research has been conducted.
TGEV: Transmissible gastroenteritis virus, a model α-coronavirus which infects pigs.
229E and OC43: two strains of coronavirus (α- and β- respectively) that are cause a fraction of common colds.

病毒種

SARS-CoV-2: 嚴重急性呼吸道症候群冠狀病毒2。引起目前COVID-19爆發的 β屬冠狀病毒。
SARS-CoV-1: 引起2002年 SARS在中國爆發的 β屬冠狀病毒。
MERS: 引起2012年起始於約旦之中東呼吸症候群的爆發。
MHV: 鼠肝炎病毒，為實驗室環境下研究β屬冠狀病毒所使用的模式生物。
TGEV: 傳染性腸胃炎病毒, 感染豬隻α屬冠狀病毒的模式生物。
229E and OC43: 引起部分普通感冒的兩株冠狀病毒 (分別為α及β屬)。

Viral Life-Cycle

Eclipse period: time between viral entry and appearance of intracellular virions.
Latent period (cellular level): time between viral entry and appearance of extracellular virions. Not to be confused with the epidemiological latent period described below.
Burst size: the number of virions produced from infection of a single cell. More appropriately called "per-cell viral yield" for non-lytic viruses like SARS-CoV-2.
Virion: a viral particle.
Polyprotein: a long protein that is proteolytically cleaved into a number of distinct proteins. Distinct from a polypeptide, which is a linear chain of amino acids making up a protein.

病毒生命週期

隱蝕期: 從病毒入侵宿主到宿主體內細胞產生病毒顆粒的時間。
潛伏期 (細胞階層): 從病毒入侵到產生細胞外病毒顆粒的時間。之後會提到流行病學的傳染力潛伏期，請勿混淆這兩個名詞。
病毒釋出數量: 受感染的單一細胞所釋出的病毒顆粒。對於如同SARS-CoV-2的非溶裂病毒，稱之為單一細胞產出的病毒數，較為適合。
病毒顆粒: 病毒粒子。
多蛋白: 長蛋白可經由蛋白分解而切斷，產生數個不同的蛋白質。多蛋白與多肽不一樣，多肽為胺基酸鍵結形成的鏈狀分子，之後會進一步組成蛋白質。

Human Biology

Alveolar Macrophage: immune cells found in the lung that engulf foreign material like dust and microbes ("professional phagocytes")
Pneumocytes: the non-immune cells in the lung.
ACE2: Angiotensin-converting enzyme 2, the mammalian cell surface receptor that SARS-CoV-2 binds.
TMPRSS2: Transmembrane protease, serine 2, a mammalian membrane-bound serine protease that cleaves the viral spike trimer after it binds ACE2, revealing a fusion peptide that participates in membrane fusion which enables subsequent injection of viral RNA into the host cytoplasm.
Nasopharynx: the space above the soft palate at the back of the nose which connects the nose to the mouth.

人類生物學

肺泡巨噬細胞: 肺部的免疫細胞，會吞噬像是灰塵及微生物等外來物 ("專業吞噬細胞")。
肺泡壁細胞: 肺部非免疫細胞。
ACE2: 血管緊張素轉化酶2，是SARS-CoV-2接合上哺乳類細胞表面的受器。
TMPRSS2: 跨膜絲胺酸蛋白酶2，是哺乳類細胞細胞膜上的絲胺酸蛋白酶，會在棘蛋白三聚體結合上ACE2之後切斷棘蛋白，使棘蛋白的融合肽鏈曝露出來，而此肽鏈參與病毒與宿主的膜融和，於是病毒RNA 直接注入宿主細胞質內。.
鼻咽: 鼻腔後方與口腔相接處之軟顎上方的空間。

Notation

Note the difference in notation between the symbol ≈, which indicates "approximately" and connotes accuracy to within a factor 2, and the symbol ~, which indicates "order of magnitude" or accuracy to within a factor of 10.

標記說明

請注意，符號≈ 及符號~ 代表不同程度的近似。符號≈ 為偏差在2倍之內; 而符號~ 為偏差在10倍之內。

More on definitions and measurement methods

更多與詞彙定義及測量方法相關的說明

What are the meanings of R_0, "latent period" and "infectious period"?

The basic reproduction number, R_0, estimates the average number of new infections directly generated by a single infectious person. The 0 subscript connotes that this refers to early stages of an epidemic, when everyone in the region is susceptible (i.e. there is no immunity) and no counter-measures have been taken. As geography and culture affect how many people we encounter daily, how much we touch them and share food with them, estimates of R_0 can vary between locales. Moreover, because R_0 is defined in the absence of countermeasures and immunity, we are usually only able to assess the effective R (R_e). At the beginning of an epidemic, before any countermeasures, $R_e \approx R_0$. Several days pass before a newly-infected person becomes infectious themselves. This "latent period" is typically followed by several days of infectivity called the "infectious period." It is important to understand that reported values for all these parameters are population averages inferred from epidemiological models fit to counts of infected, symptomatic, and dying patients. Because testing is always incomplete and model fitting is imperfect, and data will vary between different locations, there is substantial uncertainty associated with reported values. Moreover, these median or average best-fit values do not describe person-to-person variation. For example, viral RNA was detectable in patients with moderate symptoms for > 1 week after the onset of symptoms, and more than 2 weeks in patients with severe symptoms (ECDC 2020). Though detectable RNA is not the same as active virus, this evidence calls for caution in using uncertain, average parameters to describe a pandemic. Why aren't detailed distributions of these parameters across people published? Direct measurement of latent and infectious periods at the individual level is extremely challenging, as accurately identifying the precise time of infection is usually very difficult.

什麼是R_0、"傳染力潛伏期"、以及"傳染力期"?

基本再生數(R_0)是用來估計平均有多少新產生的感染是直接源自於同一傳染病例。下標的0顯示此為感染流行初期的再生數，在這個時期，沒有人具有免疫力去抵抗感染，於是都可能被傳染，且社會上也沒有應對的公衛防治措施。由於地理及文化因素影響我們每天碰到的人數，以及當中有多少人和我們產生肢體接觸或是共享食物，各地估計出的R_0都不盡相同。再者，其實R_0是指大家都還沒有免疫力也沒有防治措施時的再生數，我們通常能測得的只是有效再生數(R_e)。而在感染流行開始及防治措施尚未啟動時，這兩個再生數彼此相近($R_e \approx R_0$)。新的感染產生時，該病例通常在數天後才具傳染力。"傳染力潛伏期"之後便是數天的"傳染力期"，病毒於此時得以傳播。還請認知到一件重要的事實，這些估計值，都是收集那些受感染、有症狀、及死亡的病例數，將其套入流行病學既有的模式，進而模擬出來的。病例資料的收集以及模式擬合都是不完美，而各地收集的資料也大相逕庭，造成了此處提到的數值有著諸多的不確定性。還有一點，這些數值為全部病人資料的中位數或是平均最佳擬和數，並無法顯示出人與人之間的差異。好比，病徵出現超過一週，中度症狀的患者體內仍可測到病毒RNA，而重症者體內則是超過兩週(ECDC 2020)。雖然測到病毒RNA和測到具活性的病毒不能相提並論，但此一事證點出使用平均且不確定的參數去描述全球大流行的感染疾病，需要小心。那為何不發表仔細且確切的數值呢? 直接測出傳染力潛伏期以及傳染力期是非常困難的，因為通常很難準確地決定受感染的時間點。

What is the difference between measurements of viral RNA and infectious viruses?

Diagnosis and quantification of viruses utilizes several different methodologies. One common approach is to quantify the amount of viral RNA in an environmental (e.g. surface) or clinical (e.g. sputum) sample via quantitative reverse-transcription polymerase chain reaction (RT-qPCR). This method measures the number of copies of viral RNA in a sample. The presence of viral RNA does not necessarily imply the presence of infectious virions. Virions could be defective (e.g. by mutation) or might have been deactivated by environmental conditions. To assess the concentration of infectious viruses, researchers typically measure the "50% tissue-culture infectious dose" ($TCID_{50}$). Measuring $TCID_{50}$ involves infecting replicate cultures of susceptible cells with dilutions of the virus and noting the dilution at which half the replicate dishes become infected. Viral counts reported by $TCID_{50}$ tend to be much lower than RT-qPCR measurements, which could be one reason why studies relying on RNA measurements (Moriarty et al. 2020) report the persistence of viral RNA on surfaces for much longer times than studies relying on $TCID_{50}$ (van Doremalen et al. 2020). It is important to keep this caveat in mind when interpreting data about viral loads, for example a report measuring viral RNA in patient stool samples for several days after recovery (We et al. 2020). Nevertheless, for many viruses even a small dose of virions can lead to infection. For the common cold, for example, ~0.1 $TCID_{50}$ are sufficient to infect half of the people exposed (Couch et al. 1966).

代表病毒RNA和感染性病毒的測量值，彼此間有何不同?

各種不同方法用於感染病毒的診斷和病毒的定量。其中兩者都採用的，便是以定量反轉錄聚合酶鏈反應(RT-qPCR)，去決定環境中(如，物體表面)或是臨床檢體裡(如，痰)含有多少病毒RNA。這個方法測到的是病毒RNA分子數目。病毒RNA的存在並不一定就代表感染性病毒顆粒的存在。有些病毒顆粒可能具有缺陷 (好比，基因突變)，或者是被外在環境改變而失去活性。研究人員使用"半數組織培養感染劑量" ($TCID_{50}$)，來決定感染性病毒的數目。首先，他們將含病毒的待測樣品作不同程度的稀釋，然後這些稀釋過的病毒樣品分別加到已含有可被感染細胞的培養盤裡，每一個稀釋倍數都會用來感染數盤細胞，最後觀察哪個稀釋倍數會導致半數的培養盤產生感染。由$TCID_{50}$測得的病毒數目容易比RT-qPCR測得的少。這或許就是為何研究病毒RNA在物體表面存在時間的報導中，測量RNA數者(Moriarty et al. 2020) 發現的時間較測量$TCID_{50}$者(van Doremalen et al. 2020)來得長。重要的是，在解讀有關病毒含量的資料，如，在已康復數天的病人的糞便人仍測到病毒RNA (We et al. 2020)，要將這些測量技術導致的差異或限制謹記心中。然而，其實許多病毒都只需要極少病毒量便可造成感染，好比普通感冒，只要暴露於~0.1 $TCID_{50}$的致病病毒之下，就足以造成半數的人受感染(Couch et al. 1966)。

What is the difference between the case fatality rate and the infection fatality rate?

Global statistics on new infections and fatalities are pouring in from many countries, providing somewhat different views on the severity and progression of the pandemic. Assessing the severity of the pandemic is critical for policy making and thus much effort has been put into quantification. The most common measure for the severity of a disease is the fatality rate. One commonly reported measure is the case fatality rate (CFR), which is the proportion of fatalities out of total diagnosed cases. The CFR reported in different countries varies significantly, from 0.3% to about 10%. Several key factors affect the CFR. First, demographic parameters and practices associated with increased or decreased risk differ greatly across societies. For example, the prevalence of smoking, the average age of the population, and the capacity of the healthcare system. Indeed, the majority of people dying from SARS-CoV-2 have a preexisting condition such as cardiovascular disease

or smoking (China CDC 2020). There is also potential for bias in estimating the CFR. For example, a tendency to identify more severe cases (selection bias) will tend to overestimate the CFR. On the other hand, there is usually a delay between the onset of symptoms and death, which can lead to an underestimate of the CFR early in the progression of an epidemic. Even when correcting for these factors, the CFR does not give a complete picture as many cases with mild or no symptoms are not tested. Thus, the CFR will tend to overestimate the rate of fatalities per infected person, termed the infection fatality rate (IFR). Estimating the total number of infected people is usually accomplished by testing a random sample for anti-viral antibodies, whose presence indicates that the patient was previously infected. As of writing, such assays are not widely available, and so researchers resort to surrogate datasets generated by testing of foreign citizens returning home from infected countries (Verity et al. 2020), or epidemiological models estimating the number of undocumented cases (Li et al. 2020). These methods provide a first glimpse of the true severity of the disease.

病例死亡率和感染致死率有何不同?

全球有關新增病例及死亡率的統計資料，自許多國家不斷湧現，對於此疾病盛行的嚴重程度及演進程度提供了些許不同的觀點。而就政策制定來說，評估疾病盛行的嚴重程度，事關重要，於是力求將其數量化。病例死亡率(CFR)為一常用指標，顯示確診病例中的死亡比率。各國報告出來的CFR大相逕庭，從0.3%到大約10%的都有。而影響CFR的原因有數個，首先就是不同社會有著不同的人口組成及行為常規，造成情況的加劇或減緩。好比，抽菸的盛行，人口的平均年齡，以及醫療保健系統的強度。這也被證實在SARS-CoV-2死亡病例中，大部分病例都在染病前就有著特定狀況，如心血管疾病或是抽菸等(China CDC 2020)。而CFR的估計可能存在著偏差。比如，病症較嚴重者較易確診(選擇性偏差)，造成CFR的高估。反之，症狀出現之後一段時間才會導致死亡，這樣的時間延遲造成疫情初期對CFR的低估。但就算針對這些偏差做出校正，CFR仍無法提供完整的資訊，因為許多症狀輕微或是無症狀者並沒有接受檢測。由此可知，CFR必然高估了染病者的死亡率，也就是疾病致死率(IFR)。為此，隨機抽樣人群並測量其體內的抗病毒抗體量，常常被視為有效估計染病總人數的首選，因為抗體的存在代表著染病的事實，就算是過去發生的感染也能被偵測出來。筆者撰文之時，所述的抗體檢測及其資料並未普及，所以研究人員訴諸替代方案，其一便是針對從感染地區歸國之人民執行檢測的資料(Verity et al. 2020)，或是藉由流行病學模式去推算未被發現的病例數(Li et al. 2020)。藉此，我們得以初窺此一疫情真實的嚴重程度。

What is the burst size and the replication time of the virus?

Two important characteristics of the viral life cycle are the time it takes them to produce new infectious progeny, and the number of progeny each infected cell produces. The yield of new virions per infected cell is more clearly defined in lytic viruses, such as those infecting bacteria (bacteriophages), as viruses replicate within the cell and subsequently lyse the cell to release a "burst" of progeny. This measure is usually termed "burst size." SARS-CoV-2 does not release its progeny by lysing the cell, but rather by continuous budding (Park et al. 2020). Even though there is no "burst", we can still estimate the average number of virions produced by a single infected cell. Measuring the time to complete a replication cycle or the burst size *in vivo* is very challenging, and thus researchers usually resort to measuring these values in tissue-culture. There are various ways to estimate these quantities, but a common and simple one is using "one-step" growth dynamics. The key principle of this method is to ensure that only a single replication cycle occurs. This is typically achieved by infecting the cells with a large number of virions, such that every cell gets infected, thus leaving no opportunity for secondary infections. Assuming entry of the virus to the cells is rapid (we estimate 10 minutes for SARS-CoV-2), the time it takes to produce progeny can be estimated by quantifying the lag between inoculation and the appearance of new intracellular virions, also known as the "eclipse period". This eclipse period does not account for the time it takes to release new virions from the cell. The time from cell entry until the appearance of the first extracellular viruses, known as the "latent period" (not to be confused with the epidemiological latent period, see Glossary), estimates the duration of the full replication cycle. The burst size can be estimated by waiting until virion production saturates, and then dividing the total virion yield by the number of cells infected. While both the time to complete a replication cycle and the burst size may vary significantly in an animal host due to factors including the type of cell infected or the action of the immune system, these numbers provide us with an approximate quantitative view of the viral life-cycle at the cellular level.

什麼是病毒的釋出數量及複製時間?

病毒生活史的兩大重要特徵，一為產出新一代具感染性後代所需時間，二為單一受感染細胞所產出的病毒數目。對於新病毒顆粒的釋放數目，被溶裂型病毒所感染的細胞的產出量較易測定，這種病毒包括了感染細菌的病毒(噬菌體)。它們先是在細胞內複製，然後以溶解的方式破壞細胞，進而釋出其病毒後代，於是形成病毒產出數的"暴增"，相當便於檢測病毒數。而此情境下測量出的病毒數常稱作病毒釋出量("burst size")。SARS-CoV-2不會溶裂細胞，而是會持續地從細胞裡釋放出來 (Park et al. 2020)。既使沒有病毒"暴增"的現象，我們仍能針對每一個受到感染的細胞，估計出其產出的病毒顆粒平均數。但測量出體內真實的病毒複製時間及釋出數量，極其困難，於是研究人員會利用組織培養的實驗測定這些數值。儘管測量方式各式各樣，但有個普遍使用且相當簡單的方法，此方法利用了"一步"生長動態的概念，考慮病毒單一複製週期。其背後的關鍵準則便是，確保僅有一個週期被檢測。而為了達到此目的，標準做法便是用大量病毒顆粒，讓每一個細胞都被感染，杜絕再次感染同一個細胞的可能。假設病毒入侵細胞的時間很短(根據我們的估計，SARS-CoV-2只需10分鐘)，從將病毒加到細胞所處環境後，開始計時直至細胞內病毒顆粒出現，這段稱作"隱蝕期"的延遲，就相當於病毒產生後代所需的時間。隱蝕期並不是新病毒顆粒自細胞體內釋出所需的時間。而從病毒入侵細胞到釋出第一顆病毒至細胞外，病毒所花的時間稱作"潛伏期" (請見詞彙表，勿與流行病學中所使用的傳染力潛伏期搞混)，囊括了完整的病毒複製週期。在第一顆病毒釋出細胞外後，持續等待，直到不再有新病毒顆粒的產出，然後將這段時間所有產出的病毒顆粒數目除以感染的細胞數目，就可以估算出病毒釋出數量。儘管因為受感染的細胞種類及免疫系統的反應等各種因素的不同，動物宿主體內測到的病毒複製週期時間及釋出數量可能和上述的估計值有著明顯差異，由這些估計值，我們仍可對病毒在細胞層次上的生活史有些量化的概念。

References and excerpts

Note that for about 10 out of 45 parameters, the literature values are from other coronaviruses. We await corresponding measurements for SARS-CoV-2.

參考文獻及其摘錄部份

請注意，45個參數當中有10個是依據其它冠狀病毒所得，我們仍在等待SARS-CoV-2的相關測量值。

Size & Content

Diameter: (Zhu et al. 2020) - *"Electron micrographs of negative-stained 2019-nCoV particles were generally spherical with some pleomorphism (Figure 3). Diameter varied from about 60 to 140 nm."*
Volume- Using diameter and assuming the virus is a sphere
Mass: Using the volume and a density of ~ 1 g per mL
Number of surface spikes trimers: (Neuman et al. 2011) - *"Our model predicts ~90 spikes per particle."*
Length of surface spikes trimers: (Zhu et al. 2020) - *" Virus particles had quite distinctive spikes, about 9 to 12 nm, and gave virions the appearance of a solar corona."*
Receptor binding affinity (K_d): (Walls et al. 2020) - Walls et al. reports K_d of ≈1 nM for the binding domain in Table 1 using Biolayer interferometry with k_{on} of ≈1.5×10^5 M^{-1} s^{-1} and k_{off} of ≈1.6×10^{-4} s^{-1}. (Wrapp et al. 2020) - Wrapp et al. reports K_d of ≈15 nM for the spike (Fig.3) and ≈35 nM for the binding domain (Fig.4) using surface plasmon resonance and bio-layer interferometry respectively, with k_{on} of ≈1.9×10^5 M^{-1} s^{-1} and k_{off} of ≈2.8×10^{-3} s^{-1} for the spike and k_{on} of ≈1.4×10^5 M^{-1} s^{-1} and k_{off} of ≈4.7×10^{-3} s^{-1} for the binding domain. The main disagreement between the studies seems to be on the k_{off}.
Membrane (M; 222 aa): (Neuman et al. 2011) - *"Using the M spacing data for each virus (Fig.6C), this would give ~1100 M2 molecules per average SARS-CoV, MHV and FCoV particle"*
Envelope (E; 75 aa): (Godet et al. 1992) - *"Based on the estimated molar ratio and assuming that coronavirions bear 100 (Roseto et al., 1982) to 200 spikes, each composed of 3 S molecules (Delmas and Laude, 1990) it can be inferred that approximately 15- 30 copies of ORF4 protein are incorporated into TGEV virions (Purdue strain)."*
Nucleoprotein (364 aa): (Neuman et al. 2011) - *"Estimated ratios of M to N protein in purified coronaviruses range from about 3M:1N (Cavanagh, 1983, Escors et al., 2001b) to 1M:1N (Hogue and Brian, 1986, Liu and Inglis, 1991), giving 730–2200 N molecules per virion."*

大小及組成

直徑: (Zhu et al. 2020) - *"Electron micrographs of negative-stained 2019-nCoV particles were generally spherical with some pleomorphism (Figure 3). Diameter varied from about 60 to 140 nm."*
體積- 假設病毒為球體，利用上述的直徑所求得
質量: 利用上述體積以及考慮密度為每毫升 ~ 1 克所求得
表面棘蛋白三聚體的數目: (Neuman et al. 2011) - *"Our model predicts ~90 spikes per particle."*
表面棘蛋白三聚體的長度: (Zhu et al. 2020) - *" Virus particles had quite distinctive spikes, about 9 to 12 nm, and gave virions the appearance of a solar corona."*
受體結合親和力 (K_d): (Walls et al. 2020) - Walls等人利用生物膜層表面干涉(Biolayer interferometry)，測得 k_{on} 常數為每秒每莫耳濃度≈1.5×10^5，k_{off}常數為每秒≈1.6×10^{-4}，進而估測棘蛋白的受體結合域的K_d 為≈1 奈米莫耳濃度，這些數值列於表1。 (Wrapp et al. 2020) - Wrapp等人利用表面電漿共振(surface plasmon resonance)測量棘蛋白的K_d，以及利用生物膜層表面干涉(Biolayer interferometry)測量棘蛋白受體結合域的K_d。對於棘蛋白，他們測到 k_{on} 為每秒每莫耳濃度≈1.9×10^5而k_{off}為每秒≈2.8×10^{-3}，可知K_d 為 ≈15 奈米莫耳濃度(圖3)。對於受體結合域，他們測到 k_{on} 為每秒每莫耳濃度≈1.4×10^5而k_{off}為每秒≈4.7×10^{-3}，於是K_d 為 ≈35奈米莫耳濃度(圖4)。不同研究間的差異似乎主要來自 k_{off}的測量值。
膜蛋白 (M; 222 個胺基酸): (Neuman et al. 2011) - *"Using the M spacing data for each virus (Fig.6C), this would give ~1100 M2 molecules per average SARS-CoV, MHV and FCoV particle"*
外套膜蛋白 (E; 75 個胺基酸): (Godet et al. 1992) - *"Based on the estimated molar ratio and assuming that coronavirions bear 100 (Roseto et al., 1982) to 200 spikes, each composed of 3 S molecules (Delmas and Laude, 1990) it can be inferred that approximately 15- 30 copies of ORF4 protein are incorporated into TGEV virions (Purdue strain)."*
核蛋白 (364 個胺基酸): (Neuman et al. 2011) - *"Estimated ratios of M to N protein in purified coronaviruses range from about 3M:1N (Cavanagh, 1983, Escors et al., 2001b) to 1M:1N (Hogue and Brian, 1986, Liu and Inglis, 1991), giving 730–2200 N molecules per virion."*

Genome

Type: (ViralZone) +ssRNA *"Monopartite, linear ssRNA(+) genome"*
Genome length: (Wu et al. 2020) - *Figure 2*
Number of genes: (Wu et al. 2020) - *"SARS-CoV-2 genome has 10 open reading frames (Fig. 2A)."* or (Wu et al. 2020) - "The 2019-nCoV genome was annotated to possess 14 ORFs encoding 27 proteins".
Number of proteins: (Wu et al. 2020) -*"By aligning with the amino acid sequence of SARS PP1ab and analyzing the characteristics of restriction cleavage sites recognized by 3CLpro and PLpro, we speculated 14 specific proteolytic sites of 3CLpro and PLpro in SARS-CoV-2 PP1ab (Fig. 2B). PLpro cleaves three sites at 181–182, 818–819, and 2763–2764 at the N-terminus and 3CLpro cuts at the other 11 sites at the C-terminus, and forming 15 non-structural proteins."*
Evolution rate: (Koyama et al. 2020) - *"Mutation rates estimated for SARS, MERS, and OC43 show a large range, covering a span of 0.27 to 2.38 substitutions ×10-3 / site / year (10-16)."* Recent unpublished evidence also suggest this rate is of the same order of magnitude in SARS-CoV-2.
Mutation rate: (Sanjuan et al. 2010) - *"Murine hepatitis virus … Therefore, the corrected estimate of the mutation rate is* $\mu_{s/n/c} = 1.9x10^{-6} / 0.55 = 3.5 \times 10^{-6}$."
Genome similarity: For all species except pangolin: (Wu et al. 2020) - *"After phylogenetic analysis and sequence alignment of 23 coronaviruses from various species. We found three coronaviruses from bat (96%, 88% and 88% for Bat-Cov RaTG13, bat-SL-CoVZXC12 and bat-SL-CoVZC45, respectively) have the highest genome sequence identity to SARS-CoV-2 (Fig. 1A). Moreover, as shown in Fig. 1B, Bat-Cov RaTG13 exhibited the closest linkage with SARS-CoV-2. These phylogenetic evidences suggest that SARS-CoV-2 may be evolved from bat CoVs, especially RaTG13. Among all coronaviruses from human, SARS-CoV (80%) exhibited the highest genome sequence identity to SARS-CoV-2. And MERS/isolate NL13845 also has 50% identity with SARS-CoV-2."* For pangolin: (Zhang et al. 2020) - Figure 3

基因組

類型: (ViralZone) +ssRNA "*Monopartite, linear ssRNA(+) genome*"
基因組長度: (Wu et al. 2020) - 圖2
基因數目: (Wu et al. 2020) - "*SARS-CoV-2 genome has 10 open reading frames (Fig. 2A).*" 或是 (Wu et al. 2020) - "*The 2019-nCoV genome was annotated to possess 14 ORFs encoding 27 proteins*".
蛋白數目: (Wu et al. 2020) -"*By aligning with the amino acid sequence of SARS PP1ab and analyzing the characteristics of restriction cleavage sites recognized by 3CLpro and PLpro, we speculated 14 specific proteolytic sites of 3CLpro and PLpro in SARS-CoV-2 PP1ab (Fig. 2B). PLpro cleaves three sites at 181–182, 818–819, and 2763–2764 at the N-terminus and 3CLpro cuts at the other 11 sites at the C-terminus, and forming 15 non-structural proteins.*"
演化速率: (Kovama et al. 2020) - "*Mutation rates estimated for SARS, MERS, and OC43 show a large range, covering a span of 0.27 to 2.38 substitutions ×10-3 / site / year (10-16).*" 近期未發表的研究也推測 SARS-CoV-2演化速率和此處報導的結果，相差僅10倍以內。.
突變率: (Sanjuan et al. 2010) - "*Murine hepatitis virus … Therefore, the corrected estimate of the mutation rate is* $\mu_{s/n/c} = 1.9x10^{-6} / 0.55 = 3.5 \times 10^{-6}$."
基因組相似度: 針對除了穿山甲以外的物種: (Wu et al. 2020) - "*After phylogenetic analysis and sequence alignment of 23 coronaviruses from various species. We found three coronaviruses from bat (96%, 88% and 88% for Bat-Cov RaTG13, bat-SL-CoVZXC12 and bat-SL-CoVZC45, respectively) have the highest genome sequence identity to SARS-CoV-2 (Fig. 1A). Moreover, as shown in Fig. 1B, Bat-Cov RaTG13 exhibited the closest linkage with SARS-CoV-2. These phylogenetic evidences suggest that SARS-CoV-2 may be evolved from bat CoVs, especially RaTG13. Among all coronaviruses from human, SARS-CoV (80%) exhibited the highest genome sequence identity to SARS-CoV-2. And MERS/isolate NL13845 also has 50% identity with SARS-CoV-2.*" 對穿山甲而言: (Zhang et al. 2020) -圖3

Replication Timescales

Virion entry into cell: (Schneider et al. 2012) - "*Previous experiments had revealed that virus is internalized within 15 min*" and (Ng et al. 2003) - "*Within the first 10 min, some virus particles were internalised into vacuoles (arrow) that were just below the plasma membrane surface (Fig. 2, arrows). … The observation at 15 min postinfection (p.i.), did not differ much from 10 min p.i. (Fig. 4a)*"
Eclipse period: (Schneider et al. 2012) - "*SARS-CoV replication cycle from adsorption to release of infectious progeny takes about 7 to 8 h (data not shown).*" and (Harcourt et al. 2020) - Figure 4 shows virions are released after 12-36 hrs but because this is multi-step growth this represents an upper bound for the replication cycle.
Burst size: (Hirano et al. 1976) - "*The average per-cell yield of active virus was estimated to be about 6–7× 10² plaque-forming units.*" This data is for MHV, more research is needed to verify these values for SARS-CoV-2.

複製時程及複製量

病毒進入細胞所需的時間: (Schneider et al. 2012) - "*Previous experiments had revealed that virus is internalized within 15 min*" 和 (Ng et al. 2003) - "*Within the first 10 min, some virus particles were internalised into vacuoles (arrow) that were just below the plasma membrane surface (Fig. 2, arrows). … The observation at 15 min postinfection (p.i.), did not differ much from 10 min p.i. (Fig. 4a)*"
隱蝕期: (Schneider et al. 2012) - "*SARS-CoV replication cycle from adsorption to release of infectious progeny takes about 7 to 8 h (data not shown).*" 和 (Harcourt et al. 2020) - 圖4 顯示病毒顆粒在12-36小時之後釋放出來，但此結果來自多個複製週期(multi-step growth)，其所代表的是複製週期的上限。
病毒釋出數量: (Hirano et al. 1976) - "*The average per-cell yield of active virus was estimated to be about 6–7× 10² plaque-forming units.*" 這筆是 MHV的資料，而對於SARS-CoV-2，尚待研究中。

Host Cells

Type: (Shieh et al. 2005) - "*Immunohistochemical and in situ hybridization assays demonstrated evidence of SARS-associated coronavirus (SARS-CoV) infection in various respiratory epithelial cells, predominantly type II pneumocytes, and in alveolar macrophages in the lung.*" and (Walls et al. 2020) - "*SARS-CoV-2 uses ACE2 to enter target cells*" and (Rockx et al. 2020) - "*In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and mucous glands of the nasal cavity….In the upper respiratory tract, there was focal 5 or locally extensive SARS-CoV-2 antigen expression in epithelial cells of mucous glands in the nasal cavity (septum or concha) of all four macaques, without any associated histological lesions (fig. 2I).*"
Type I and Type II pneumocyte and alveolar macrophage cell number: (Crapo et al. 1982) - Table 4 *and* (Stone et al. 1992) - Table 5
Epithelial cells in mucous gland cell number and volume: (ICRP 1975) - surface area of nasal cavity, (Tos & Mogensen, 1976) and (Tos & Mogensen, 1977) - mucous gland density, (Widdicombe 2019) - mucous gland volume, (Ordoñez et al. 2001) and (Mercer et al. 1994) - mucous cell volume. We divide the mucous gland volume by the mucous cell volume to arrive at the total number of mucous cells in a mucous gland. We multiply the surface density of mucous glands by the surface area of the nasal cavity to arrive at the total number of mucous glands, and then multiply the total number of mucous glands by the number of mucous cells per mucous gland.
Type II pneumocyte volume: (Fehrenbach et al. 1995) - "*Morphometry revealed that although inter-individual variation due to some oedematous swelling was present, the cells were in a normal size range as indicated by an estimated mean volume of 763 ± 64 μm³*"
Alveolar macrophage volume: (Crapo et al. 1982) - "*Alveolar macrophages were found to be the largest cell in the populations studied, having a mean volume of 2,491 μm³*"

宿主細胞

類型: (Shieh et al. 2005) - "*Immunohistochemical and in situ hybridization assays demonstrated evidence of SARS-associated coronavirus (SARS-CoV) infection in various respiratory epithelial cells, predominantly type II pneumocytes, and in alveolar macrophages in the lung.*" 和 (Walls et al. 2020) - "*SARS-CoV-2 uses ACE2 to enter target cells*" 和 (Rockx et al. 2020) - "*In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and mucous glands of the nasal cavity….In the upper respiratory tract, there was focal 5 or locally extensive SARS-CoV-2 antigen expression in epithelial cells of mucous glands in the nasal cavity (septum or concha) of all four macaques, without any associated histological lesions (fig. 2I).*"
第一型及第二型肺泡壁細胞和肺泡巨噬細胞的數目: (Crapo et al. 1982) - 表4 和 (Stone et al. 1992) - 表5
黏膜腺體的表皮細胞數目: (ICRP 1975) - 鼻腔表面積, (Tos & Mogensen, 1976) 和 (Tos & Mogensen, 1977) - 黏膜腺體密度, (Widdicombe 2019) - 黏膜腺體體積, (Ordoñez et al. 2001) 和 (Mercer et al. 1994) - 黏膜細胞體積。我們將黏膜腺體體積除以黏膜細胞體積，得到黏膜腺體內的黏膜細胞數目。我們將黏膜腺體表面密度乘以鼻腔表面積，得到鼻腔內黏膜腺體的總數，接著將此腺體總數乘以單一黏膜腺體內的黏膜細胞數目。
第二型肺泡壁細胞的體積: (Fehrenbach et al. 1995) - "*Morphometry revealed that although inter-individual variation due to some oedematous swelling was present, the cells were in a normal size range as indicated by an estimated mean volume of 763 ± 64 μm³*"
肺泡巨噬細胞的體積: (Crapo et al. 1982) - "*Alveolar macrophages were found to be the largest cell in the populations studied, having a mean volume of 2,491 μm³*"

Concentration

Nasopharynx, Throat, Stool, and Sputum: (Woelfel et al. 2020) - Figure 2. and (Kim et al. 2020) - Figure 1 and (Pan et al. 2020) - Figure. We took the maximal viral load for each patient in nasopharyngeal swabs, throat swabs, stool or in sputum.

病毒濃度

鼻咽、咽喉、糞便、和痰: (Woelfel et al. 2020) - 圖2、和(Kim et al. 2020) - 圖1、和 (Pan et al. 2020) - 圖。資料來自病人的鼻咽採檢拭子、咽喉採檢拭子、糞便、和痰，我們取用各部位檢測到的病毒最大含量。

Antibody Response - Seroconversion

Seroconversion time (time period until a specific antibody becomes detectable in the blood): (Zhao et al. 2020) - "*The seroconversion sequentially appeared for Ab, IgM and then IgG, with a median time of 11, 12 and 14 days, respectively*" and (To et al. 2020) - "*For 16 patients with serum samples available 14 days or longer after symptom onset, rates of seropositivity were 94% for anti-NP IgG (n=15), 88% for anti-NP IgM (n=14), 100% for anti-RBD IgG (n=16), and 94% for anti-RBD IgM (n=15)*"
Maintenance of antibody response to virus: (Wu et al. 2007) - "*Among 176 patients who had had severe acute respiratory syndrome (SARS), SARS-specific antibodies were maintained for an average of 2 years, and significant reduction of immunoglobulin G–positive percentage and titers occurred in the third year.*"

抗體免疫反應 - 血清轉換

血清轉換時間 (產生專一性抗體，直至其含量可在血液中被檢測到，所需時間): (Zhao et al. 2020) - "*The seroconversion sequentially appeared for Ab, IgM and then IgG, with a median time of 11, 12 and 14 days, respectively*" 和 (To et al. 2020) - "*For 16 patients with serum samples available 14 days or longer after symptom onset, rates of seropositivity were 94% for anti-NP IgG (n=15), 88% for anti-NP IgM (n=14), 100% for anti-RBD IgG (n=16), and 94% for anti-RBD IgM (n=15)*"
抗病毒抗體免疫反應的維持: (Wu et al. 2007) - "*Among 176 patients who had had severe acute respiratory syndrome (SARS), SARS-specific antibodies were maintained for an average of 2 years, and significant reduction of immunoglobulin G–positive percentage and titers occurred in the third year.*"

Virus Environmental Stability

Half life on surfaces: (van Doremalen et al. 2020) - For half-lives we use Supplementary Table 1. For time to decay from ~10^4 to ~10 $TCID_{50}/L^{-1}$ air or mL^{-1} medium, we use the first time titer reached detection limit in Figure 1A for surfaces. For aerosols, we use ten half-life values (1000-fold decrease from 10^4 to 10, meaning 10 halvings of concentration) from Supplementary Table 1. More studies are urgently needed to clarify the implications of virion stability on the probability of infection from aerosols or surfaces.
RNA stability on surfaces: (Moriarty et al. 2020) - "*SARS-CoV-2 RNA was identified on a variety of surfaces in cabins of both symptomatic and asymptomatic infected passengers up to 17 days after cabins were vacated on the Diamond Princess but before disinfection procedures had been conducted (Takuya Yamagishi, National Institute of Infectious Diseases, personal communication, 2020).*"

病毒在環境中的穩定性

在各種物體表面的半衰期: (van Doremalen et al. 2020) - 我們使用補充表1所提供的資料去估計半衰期。而對於從每公升的空氣或是每毫升的培養液$TCID_{50}$~10^4 衰退至~10所需時間，我們利用圖1A裡各種物體表面測得的資料中，取用第一個到達偵測限度的時間點。但對於氣溶膠環境，我們則是利用補充表1的半衰期資料，估計經過10次半數衰退(從10^4 到10為減弱1000倍，相當於連續地減半濃度長達10次)所需時間。目前，仍亟需更多研究去探討病毒顆粒在氣溶膠或各種物體表面的穩定性與感染疾病的可能性之間存在著如何的關聯，。
在各種物體表面的RNA穩定性: (Moriarty et al. 2020) - "*SARS-CoV-2 RNA was identified on a variety of surfaces in cabins of both symptomatic and asymptomatic infected passengers up to 17 days after cabins were vacated on the Diamond Princess but before disinfection procedures had been conducted (Takuya Yamagishi, National Institute of Infectious Diseases, personal communication, 2020).*"

"Characteristic" Infection Progression in a Single Patient

Basic reproductive number, R_0: (Li et al. 2020) - "*Our median estimate of the effective reproductive number, Re—equivalent to the basic reproductive number (R0) at the beginning of the epidemic—is 2.38 (95% CI: 2.04–2.77)*" and (Park et al. 2020) - "*Our estimated R0 from the pooled distribution has a median of 2.9 (95% CI: 2.1–4.5).*"
Latent period (from infection to being able to transmit): (Li et al. 2020) - "In addition, the median estimates for the latent and infectious periods are approximately 3.69 and 3.48 days, respectively." and Table 1 and (He et al. 2020) - We use the time it takes the infectiousness to reach half its peak, which happens two days before symptom onset based on Figure 1b. As symptoms arise after 5 days (see incubation period), this means the latent period is about 3 days.
Incubation period (from infection to symptoms): (Lauer et al. 2020) - "*The median incubation period was estimated to be 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection. These estimates imply that, under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine.*" and (Li et al. 2020) - "*The mean incubation period was 5.2 days (95% confidence interval [CI], 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days.*"
Infectious period (partially overlaps latent period): (Li et al. 2020) - "*In addition, the median estimates for the latent and infectious periods are approximately 3.69 and 3.48 days, respectively*." and Table 1 and (He et al. 2020) - We quantify the interval between half the maximal infectiousness from the infectiousness profile in Figure 1b.
Disease duration: (WHO 2020) - "*Using available preliminary data, the median time from onset to clinical recovery for mild cases is approximately 2 weeks and is 3-6 weeks for patients with severe or critical disease*"
Time until diagnosis: (Xu et al. 2020) - We used data on cases with known symptom onset and case confirmation dates and calculated the median time delay between these two dates.
Case Fatality Rate: (ECDC geographic distribution of cases from 29/03/2020) - We use data from all countries with more than 50 death cases and calculate the uncorrected raw Case Fatality Rate for each country. The range represents the lowest and highest rates observed.

Infected Fatality Rate: (Verity et al. 2020) - *"We obtain an overall IFR estimate for China of 0.66% (0.39%,1.33%)"* and (Ferguson et al. 2020) - *"The IFR estimates from Verity et al.12 have been adjusted to account for a non-uniform attack rate giving an overall IFR of 0.9% (95% credible interval 0.4%-1.4%)."*

感染病例的進程"特徵"

基本再生數 R_0: (Li et al. 2020) - *"Our median estimate of the effective reproductive number, Re—equivalent to the basic reproductive number (R0) at the beginning of the epidemic—is 2.38 (95% CI: 2.04–2.77)"* 和 (Park et al. 2020) - *"Our estimated R0 from the pooled distribution has a median of 2.9 (95% CI: 2.1–4.5)."*
傳染力潛伏期 (從受感染到能夠傳染他人): (Li et al. 2020) - *"In addition, the median estimates for the latent and infectious periods are approximately 3.69 and 3.48 days, respectively."* 及 Table 1，和 (He et al. 2020) -我們採用達到半最大傳染力所需的時間，根據圖1b此時約是病徵出現的前2天，因為受感染後5天才會出現病徵 (請見症狀潛伏期)，於是可知傳染力潛伏期大約3天。
症狀潛伏期 (從受感染到病徵出現): (Lauer et al. 2020) - *"The median incubation period was estimated to be 5.1 days (95% CI, 4.5 to 5.8 days), and 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection. These estimates imply that, under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine."* 和 (Li et al. 2020) - *"The mean incubation period was 5.2 days (95% confidence interval [CI], 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days."*
傳染力時期 (與傳染力潛伏期會有部分重疊): (Li et al. 2020) - *"In addition, the median estimates for the latent and infectious periods are approximately 3.69 and 3.48 days, respectively."* 及表1，和 (He et al. 2020) - 根據圖1b的傳染力曲線圖(infectiousness profile)，我們定量維持至少半最大傳染力的時間區間。
染病時期: (WHO 2020) - *"Using available preliminary data, the median time from onset to clinical recovery for mild cases is approximately 2 weeks and is 3-6 weeks for patients with severe or critical disease"*
確診前空窗期: (Xu et al. 2020) - 我們比較已知症狀的出現時間和病例確診時間，去計算兩筆資料在時間上延遲的中位數。
病例死亡率: (ECDC geographic distribution of cases from 29/03/2020) - 我們收集所有國內超過50例死亡病例的國家的資料，計算每個國家的非相關原始病例死亡率，將計算結果的最大及最小值作為範圍區間。
染病致死率: (Verity et al. 2020) - *"We obtain an overall IFR estimate for China of 0.66% (0.39%,1.33%)"* 和 (Ferguson et al. 2020) - *"The IFR estimates from Verity et al.12 have been adjusted to account for a non-uniform attack rate giving an overall IFR of 0.9% (95% credible interval 0.4%-1.4%)."*

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