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Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts

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摘要

- 本篇是由知名的倫敦衛生與熱帶醫學院的流行病學與感染學部門運用隨機運算數學模式來探討2019新冠肺炎(COVID-19)是否能經由與隔離案例(Isolation of cases) 控制接觸史追蹤(contact tracing)策略達成控制疫情爆發(outbreak)。而達到控制疫情傳播的定義是案例數在5000例以內或是在3個月內無新增案例。
- 主要影響的因子還是R0與無症狀傳染比率與症狀產生到隔離時間長短，如果一開始只有5個案例R0是1.5，而且如SARS絕大部分傳染是在有症狀時候，那接觸史追蹤比率就可以小於50%，疫情就能在3個月內成功控制。反之，如果一開始有20個案例，R0是3.5，無症狀感染比率又高的話，則需要更高接觸史追蹤比率(>90%)來控制疫情爆發如COVID-19。
- 作者建議隨著對於COVID-19傳染力，臨床症狀更多的了解，可以用這套數學模式來評估未來的疫情控制是否成功參考。

背景資料

- 一個新興傳染性疾病以接觸史追蹤與隔離案例是否成功端視該疾病是否在發病前就能傳染給他人以及其基本傳染力R0而定，如前所述絕大部分的SARS在有症狀之後方能傳染給其他人，所以最終能以此方法被根除。當然接觸史追蹤與隔離案例的這套方法也曾經使用於MERS Ebola傳染病控制。
- 除此之外，成功的接觸史追蹤與降低症狀出現到隔離案例的延遲也是很重要的，所以早期偵測與檢驗病人非常重要。

背景資料

- 不過這個前提是必須該傳染疾病不會在有症狀前就感染給別人，如果會有無症狀感染，那又需要額外的策略控制該疫情爆發。由於COVID-19的臨床症狀與病毒特性等仍有許多未知，所以該機構研發一套隨機演算數學模式，來探討究竟接觸史追蹤與隔離案例是否能夠成功控制疫情爆發。
- 作者會帶入不同模擬情境，例如:不同接觸史追蹤效能，不同爆發時案例數目，病人有症狀到被隔離時間不同等等因子。來幫助有COVID-19爆發風險國家評估以接觸史追蹤與隔離案例控制COVID-19疫情爆發是否可行。

研究方法: Model structure 1

- 使用樹枝流程圖模式branching process model與negative binomial distribution負二項分布

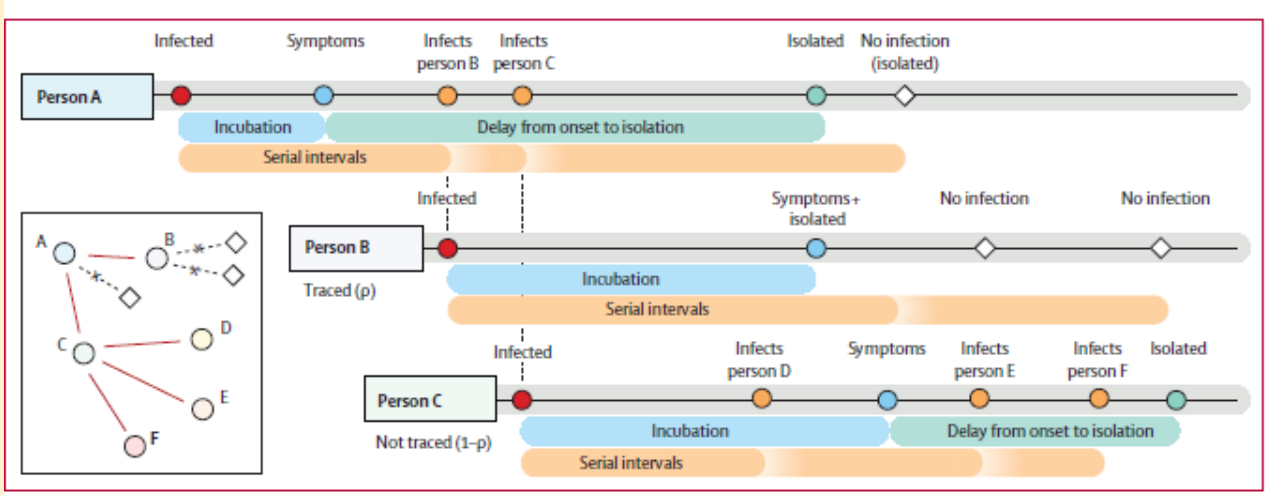

Figure 1: **Example of the simulated process that starts with person A being infected**
After an incubation period, person A shows symptoms and is isolated at a time drawn from the delay distribution table. A draw from the negative binomial distribution with mean reproduction number (R_0) and distribution parameter determines how many people person A potentially infects. For each of those, a serial interval is drawn. Two of these exposures occur before the time person A is isolated. With probability ρ, each contact is traced; with probability 1–ρ they are missed by contact tracing. Person B is successfully traced, which means that they will be isolated without delay when they develop symptoms. They could, however, still infect others before they are isolated. Person C is missed by contact tracing. This means that they are only detected if and when symptomatic, and are isolated after a delay from symptom onset. Because person C was not traced, they infected two more people (E and F), in addition to person D, than if they had been isolated at symptom onset. A version with subclinical transmission is given in the appendix (p 12).

研究方法: Model structure 2

- 以圖1模擬方式為例，R0是3，其序列時間(serial interval)如下:病人A感染本來要傳給3個人，後來在潛伏期症狀出現後沒有馬上被偵測而傳染兩個人B與C，A被隔離，就沒再傳染，A的R0為2。B病人有被追蹤到隔離，就沒再傳出去，B的R0為0。C再傳給D.E.F3個人，C的R0為3。再套入不同隨機演算數學模式。包括一開始的病例數目，基本傳染人數R0(這裡是3)，可以被追蹤到接觸史機率ρ。了解這樣的追蹤接觸史與隔離發病案例是否成功控制疫情爆發。而成功控制疫情爆發定義是案例數<5000例，或是12-16周後無新增案例。

研究方法: Model structure 3

傳染情境表

	Value	Reference
Sampled		
Delay from onset to isolation (short)	3·43 days (2·02–5·23)	Donnelly et al[20]
Delay from onset to isolation (long)	8·09 days (5·52–10·93)	Li et al[21]
Incubation period	5·8 days (2·6)	Backer et al[22]
Serial interval	Incubation period (2)	Assumed
Fixed		
Initial cases	5, 20, and 40	Public Health England[11] and Klinkenberg and colleagues[34]
Percentage of contacts traced	0%, 20%, 40%, 60%, 80%, 100%	Tested
Reproduction number (R_0: low, central, high estimate)	1·5, 2·5, 3·5	Kucharski et al[17] and Imai et al[18]
Overdispersion in R_0 (SARS-like, influenza-like)	0·16	Lloyd-Smith et al[19]
R_0 after isolation	0	Assumed
Cases isolated once identified	100%	Assumed
Isolation effectiveness	100%	Assumed
Subclinical infection percentage	0%, 10%	Tested

Data are median (IQR) or mean (SD), n, or %. Sampled values are probabilistically sampled during the simulation, and fixed values remain constant during the simulation. The mean of the short and long delays are 3·83 and 9·1, respectively. SARS=severe acute respiratory syndrome.

Table: Parameter values for the model

說明

- 共有1000個情境。如左表，一開始案例5, 20, 40；接觸史追蹤機率 0 ,20%, 40%, 60%, 80% 100%，R0: 1.5, 2.5, 3.5；等等；以及是短暫或是稍長延遲隔離案例；潛伏期5.8天，序列時間種種因子套入數學演算模式

研究方法: Model structure 4

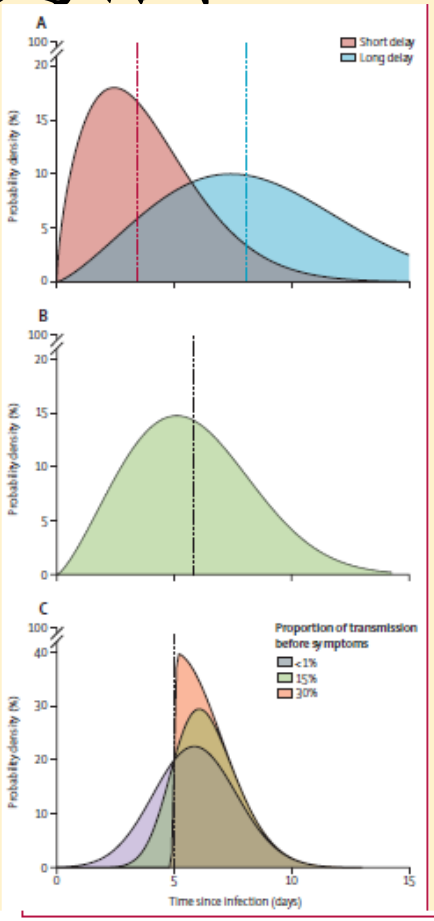

Figure 2: **Probability distributions used in simulations**
(A) The short and long delay distributions between the onset of symptoms and isolation (mean marked by line). Parameter values and references are given in the table. (B) The incubation distribution estimate fitted to data from the Wuhan outbreak by Backer and colleagues.[21] (C) An example of the method used to sample the serial interval for a case that has an incubation period of 5 days. Each case has an incubation period drawn from the distribution in (B), their serial interval is then drawn from a skewed normal distribution with the mean set to the incubation period of the case. In (C), the incubation period was 5 days. The skew parameter of the skewed normal distribution controls the proportion of transmission that occurs before symptom onset; the three scenarios explored are less than 1%, 15%, and 30% of transmission before onset.

- 圖2顯示按照上面表格，模擬情境下的機率 (A) 紅色的是指症狀開始到隔離時間為短的而藍色為症狀開始到隔離時間為長的。 (B) 潛伏期為Backer等人敘述武漢地區爆發情境機率。 (C) 潛伏期為5天而無症狀傳染力分別為0%(紫色) 15%(綠色) 30 %的機率(紅色)

研究方法: Model structure 5

- 作者選擇以如下條件呈現結果: R0為2.5，一開始案例數目為20，從有症狀可以傳染他人到隔離時間為短的模式(新加坡SARS模式)。
- 綜合以上，要能夠控制疫情爆發，是否以接觸史追蹤與隔離案例能夠成功，要看以上因子，除此之外，如果有無症狀傳染者更增加控制疫情難度，如要增加舉措，將付出更多成本，如有旅遊史著須居家檢疫。相對的，，當案例數目多到一個程度，接觸史追蹤會很困難。。

結果 1

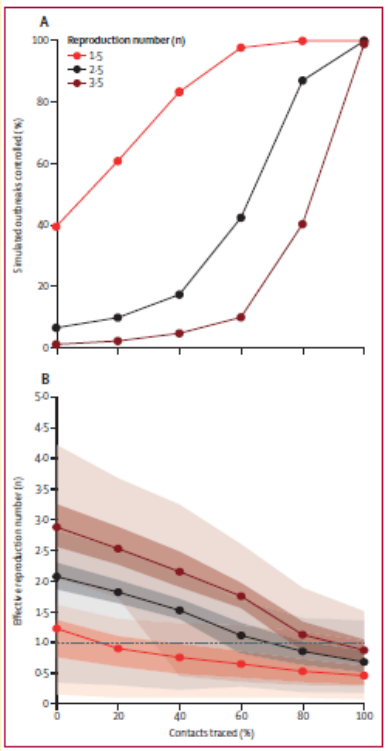

Figure 3: Effect of isolation and contact tracing on controlling outbreaks and on the effective reproduction number
(A) The percentage of outbreaks that are controlled for scenarios with varying reproduction number (R_0), at each value of contacts traced. The baseline scenario is R_0 of 2·5, 20 initial cases, a short delay to isolation, 15% of transmission before symptom onset, and 0% subclinical infection. A simulated outbreak is defined as controlled if there are no cases between weeks 12 and 16 after the initial cases. Other scenarios are presented in the appendix (p 2). (B) Effective reproduction number in the presence of case isolation and contact tracing. Median, and 50% and 95% intervals are shown.

- 如圖3:要成功控制疫情必須將R0變成<1，
- 所以在R0 2.5要達到90%機率控制爆發，需成功追蹤80%接觸史。
- 相對的R0 1.5 則只需成功追蹤<50%接觸史
- R0 3.5就需要>90%左右成功追蹤接觸史
- 也就是說R0越低越可以只靠隔離案例達成控制疫情

結果 2

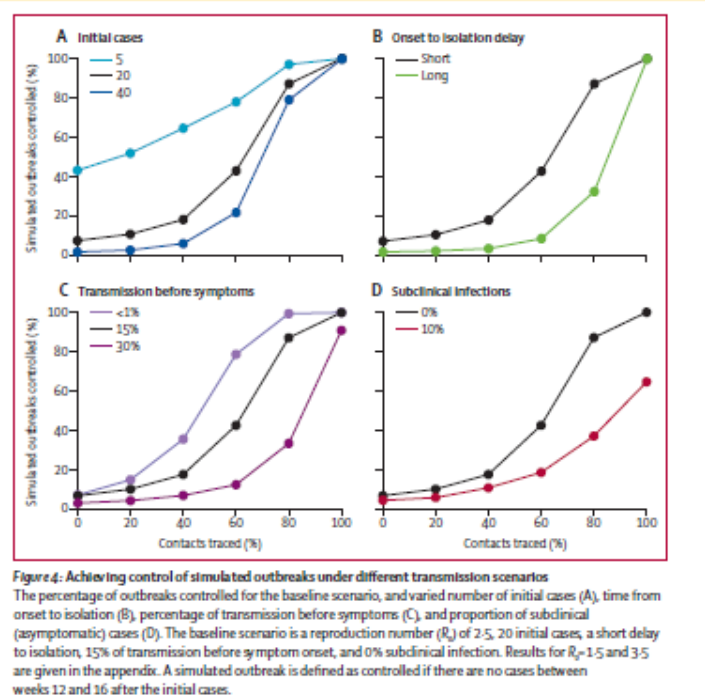

Figure 4: **Achieving control of simulated outbreaks under different transmission scenarios**
The percentage of outbreaks controlled for the baseline scenario, and varied number of initial cases (A), time from onset to isolation (B), percentage of transmission before symptoms (C), and proportion of subclinical (asymptomatic) cases (D). The baseline scenario is a reproduction number (R_0) of 2·5, 20 initial cases, a short delay to isolation, 15% of transmission before symptom onset, and 0% subclinical infection. Results for R_0=1·5 and 3·5 are given in the appendix. A simulated outbreak is defined as controlled if there are no cases between weeks 12 and 16 after the initial cases.

- 圖4 顯示不同模擬傳染情境下的狀況:
- (A)為不同起始案例數，案例數少容易控制疫情爆發。
- (B) 為潛伏期到隔離時間之短或長情境,越短越容易控制疫情爆發。

(C) 為無症狀就可以傳染比率，比率越低越容易控制疫情爆發。

(D) 無症狀或輕症感染比率.比率越低越容易控制疫情爆發。

結果 3

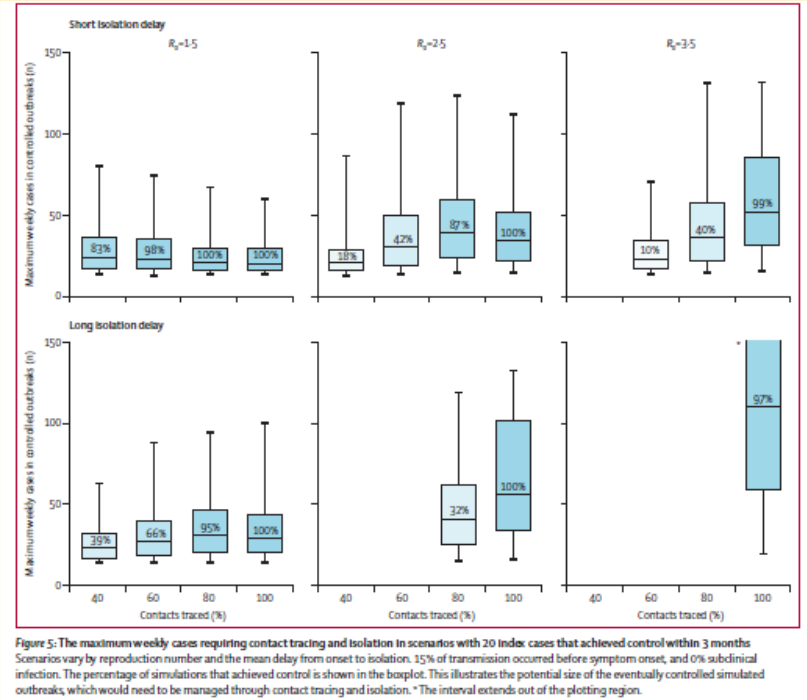

Figure 5: **The maximum weekly cases requiring contact tracing and isolation in scenarios with 20 index cases that achieved control within 3 months**
Scenarios vary by reproduction number and the mean delay from onset to isolation. 15% of transmission occurred before symptom onset, and 0% subclinical infection. The percentage of simulations that achieved control is shown in the boxplot. This illustrates the potential size of the eventually controlled simulated outbreaks, which would need to be managed through contact tracing and isolation. * The interval extends out of the plotting region.

- 圖5顯示的是在症狀前傳染力15%，0%無輕症感染的條件下，一開始病人數20人，採取追蹤接觸史與隔離案例策略，(橫軸是接觸史追蹤達成率縱軸是疫情控制所需周數)。在三種R0 條件分別為1.5 2.5 3.5下，與從產生症狀到隔離案例延遲短或長兩種模式(短為新加坡SARS模式，長為武漢模式)，達成3個月無新增案例定義之控制疫情所需要的周數。顯然R0 越大，延遲越長，需要接觸史追蹤比率越高，而且控制周數越長，有的甚至超過縱軸範圍。

討論

- 本研究主要是希望針對以追蹤接觸史以及隔離發病案例策略,是否足夠控制COVID-19爆發的評估。
- 據此要達成R0 為2.5 ，潛伏期到隔離時間為短的模式(新加坡SARS模式)，無症狀傳染比率15%下，能在90%機率成功控制疫情，亦即3個月內無新增病例，必須達成成功80%追蹤接觸史以及隔離發病案例方為可能。
- 綜觀結果顯示，R0 越低，一開始案例數越少，從潛伏期到隔離時間越短，無症狀傳染比率越低，輕症(subclinical case)越少，越容易控制疫情。

討論

- 除了嚴格的執行接觸史追蹤，發病個案隔離外，其他的呼吸道與手部衛生也有幫助疫情控制。
- 降低fomite 也幫助降低傳播病毒以幫助疫情控制。
- 還有無症狀傳染部分，作者提到應提升民眾對於前驅症狀的健康識能。如倦怠fatigue,輕微發燒等可能是COVID-19症狀，這樣或許無症狀的比率就不是真的這麼高。這個策略在SARS時期有使用過。而幫助疫情控制。

結論

- 該研究顯示:在大部分的疫情爆發情境下，僅僅案例隔離與接觸史追蹤不足以控制疫情爆發。而且就連接近完美的接觸史追蹤也不足以控制疫情爆發，而需要採取進一步的措施才能達成控制疫情。
- 快速而有效的接觸史追蹤能夠降低一開始案例數目，以幫助疫情容易受到控制。有效的案例隔離與接觸史追蹤有助於降低疫情爆發的整體規模，或者是說能有助於在較長一點時間下讓疫情得到控制。