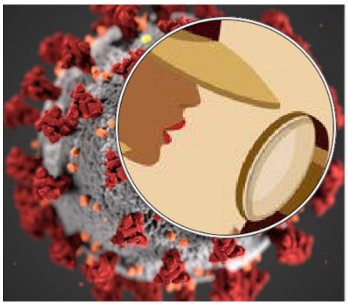
THE EPIDEMIOLOGY ADVENTURE: BEING A DISEASE DETECTIVE
25.3.2020



Episode 2: Basic measures "How contagious is the virus"?

Occurrence and cessation of an outbreak:

What is an epidemic or an outbreak? An epidemic is an unexpected increase in the incidence of a disease. When the disease affects a large number of people and crosses many frontiers it's called a pandemic. An epidemic will end or diminish when each case reproduces on average less than once. This can happen through immunization (natural immunization that happens when people actually catch the disease and become immune), treatment (vaccine), by removing the source of infection or by breaking the transmission cycle (isolating people, adopting personal protection measures like washing hands).

COVID-19 pandemic: Current Facts & Figures:

Since December 2019, the 2019 novel coronavirus disease (COVID-19), has caused a **pneumonia epidemic** in Wuhan. As of March 24^{nd,} 2020 COVID-19 touches over 196 countries and was officially classified a pandemic by the World Health Organization (WHO). The number of confirmed cases worldwide has exceeded **300'000**. It took more than 3 months to reach for the first 100'000 cases, but then **only 12 days** to reach the next 100'000**, less than a week** for the next 100'000. Many recent studies have looked at clinical and epidemiological characteristics of COVID-19 in Wuhan and mainland China:

- **Incubation**: The median of incubation period in China was 5-6 days [3-8] (Qian et al., 2020).
- **Symptoms**: Most common symptoms were fever (71%), cough (60%) and fatigue (43%).
- **Severity:** 3 patterns observed[2]:
    - mild illness with upper respiratory tract presenting symptoms,
    - non-life-threatening pneumonia,
    - severe pneumonia with acute respiratory distress syndrome that begins with mild symptoms for 7-8 days and then progresses to rapid deterioration, requiring life support.
- **Hospitalization & intensive care**: from the population that is infected (cases),
    - **80%** of the infections are mild or asymptomatic,
    - **15%** are severe infections and need hospitalization requiring oxygen
    - and **5%** needs intensive care requiring ventilation (WHO, OFSP).
- **Transmission**: COVID-19 is highly contagious and spreads rapidly through human-to-human transmissions[3]. We observe a direct transmission arising from close personal contact, which includes touching or inhaling the large respiratory droplets produced by sneezing, speaking or coughing by an infected person. Infected people produce a large quantity of virus. There are still many unknowns: the incubation period is ±5-6days but it is still not sure whether infectiousness starts before the onset of symptoms. Few clinical studies measured the presence of the virus in the blood and it might trigger transmission 1-2 days before onset of symptoms[4] . The duration of the infectious period still remains uncertain.

How contagious is the virus?

- **Contagiousness**: This can be illustrated using the basic reproduction number R_0. R_0 is the number of secondary infections, on average, that one infected individual will cause during

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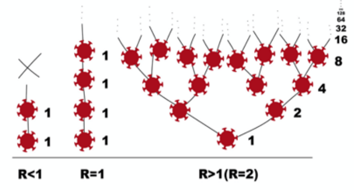
[2] WHO. https://doi.org/10.1016/ S0140-6736(20)30374-3)

[3] WHO. Coronavirus disease 2019 (COVID-19) outbreak. Feb 18 202. https://www.who.int/emergencies/diseases/novel-coronavirus-2019

[4] Anderson, R. M., Heesterbeek, H., Klinkenberg, D., & Hollingsworth, T. D. (2020). How will country-based mitigation measures influence the course of the COVID-19 epidemic?. *The Lancet*.

her infectious period in a base scenario where nobody has the disease. For COVID-19 R_0 is understood to be between 2 and 2.5[5]. Simply put, during an epidemic, one person infects a second person and once this individual infects more than one person, the number of infections will increase **exponentially** (FIGURE1). For example, if we put 1 infected person in a room with 100 non-exposed susceptible persons:

FIGURE 1 : R_0



R_0=2.0: 1 + 2 + 4 + 8 (15 infected cases)
R_0=3.0: 1 + 3 + 9 + 27 (40 infected cases)

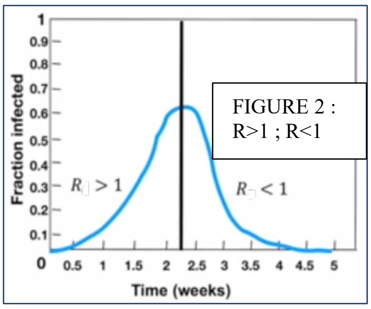


FIGURE 2 : R>1 ; R<1

- **The estimation of Basic R_0** is affected by several socio-behavioral and environmental factors and therefore is usually estimated with complex mathematical models. R_0 depends on the number of days persons are infectious, the number of susceptible people they meet and the chance that meeting leads to an infection (susceptibility). The interpretation is straightforward: an epidemic is expected to continue if R_0>1 and to end if R_0<1 (FIGURE 2). An exponential increase until the epidemic reaches a peak and then slows down (either due to immunization, vaccine or prevention measures).
- **Basic R_0 and Effective R**: R_0 does not indicate whether new cases will occur within 24h or months and does not give indications on severity. Moreover, in many situations the disease has already spread, therefore R_0 is not so predictive after the outbreak. After an outbreak, the more appropriate measure to use is the "effective" reproduction number R, which integrates the population's current susceptibility and is therefore likely to be lower than the basic R_0 depending on whether or not individuals in the population have immunity. The effective-R is an estimate based on a more realistic situation within the current population. Both numbers are situation-dependent and are additionally affected by demographics (population age), population density, but most importantly, **our behavior**. Individuals cannot affect demographics and population density quickly, but they can change their behavior. Simply having many people in the same room will often increase R_0. Due to how situation-specific R_0 and effective-R are, it then becomes clear why we can observe several estimates of R that change over time.

Hence, what makes R_0 useful in Public Health, in the current COVID-19 epidemic?

- **Public Health perspective:** A key issue for epidemiologists is helping policy makers decide the main objectives of mitigation in order to flatten the epidemic curve while we wait for vaccine development. These strategies comprise quarantine, stopping mass gatherings, closing of educational institutes or places of work and isolation of households, towns or cities. If we practice social distancing, we can reduce the transmission rate, reduce the value of R_0, and slow down the "doubling time" of the disease, hence slowing the rate of infection.

***Example** : Currently for Switzerland, as of 24/3/2020 the "DOUBLING TIME" is down to around 4 days. Let's do a hypothetical calculation, starting with 100 infected persons (cases) in a susceptible, non-immunized population, with R0=2.0:*

Day 4	*100+200=300*
Day 8	*300+400=700*
Day 12	*700+800=1'500*
Day 16	*1'500+1'600=3'100*
Day 20	*3'100+3'200= **6'300***
Day 24	*6'300+6'400=12'700*
Day 28	*12'700+12'800= **25'500***

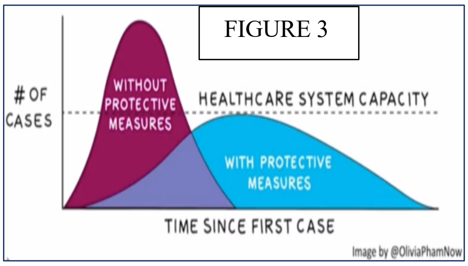
→ In less than a month (and from today only 8 days away) we have theoretically 25'500 cases, out of which on average 20% needs hospitalization: 15% hospitalzation requiring oxygen (3'825) and 5% needs intensive care (1'275).

→ Even for robust economies with large hospital infrastructures this becomes a stretch for the health care system…

[5] WHO, situation report 6 March 2020

- We need to **"flatten the curve",** to prevent everyone from getting sick at once (FIGURE 3). Without a widespread test available to all persons in communities or cities we cannot know who is infected and who is not. During the exponential growth phase, the majority of people with a COVID-19 infection don't know they have it. We all can adopt the mitigation strategies to **stop the "exponential growth**" such as: isolating the infected (exposed), staying home (except for essential trips) and adopt the personal protective measures (handwashing, coughing in the elbow etc.). The problem is that even a small number of people not following the strategy results in the continued spread of the infection, meaning that the good actions of hundreds can be undone by one infected person. According to Prof Lipsitch[6]: *"We need a breakthrough to make effective treatments, vaccines, available at scale. But for the short term, there are two options for Covid-19 at the moment: social distancing or overwhelmed health care systems.* ***We need to buy time*** *with social distancing".*

FIGURE 3



- **Please let's do our individual part to decrease $R_0 < 1$:**
    ➡ **Stay Home, Save Lives & apply Personal Protective Measures**

Now that we have become new experts on R_0:

- If a COVID-19 vaccine was available, how would this affect the basic-R_0?
    - *A bit tricky question…. Vaccination campaigns reduce the proportion at risk for infection and the removal of susceptible people from a population will reduce the number of potential new cases. But technically this will not reduce the basic-R_0 value because the definition of R_0 includes the assumption of a complete non-exposed susceptible population. When examining the effect of vaccination, the more appropriate measure is "effective-R". In our situation vaccination could potentially end an epidemic if effective-R can be reduced <1.*
- Can basic R_0 or effective R be used to calculate the % infected and the immunization needed in a population?
    - *Yes, basic-R_0 (but not effective-R!) can be used to estimate the proportion of the population that must be vaccinated to eliminate an infection from the population. Here the fact that R_0 is calculated in a susceptible population free of any immunization allows to estimate the appropriate amount of protection at population-level.*
    - *A large theoretical literature[7] shows how to derive the theoretical threshold for immunization coverage $1-(1/R_0)$. If $R_0=2.26$, then $1-(1/R_0)=56\%$; therefore you hear experts mentioning that around 60% of the population needs to be immunized. But in practice Public Health is to aim for 100% coverage, which, while never achievable, strives to reach whatever the "real" threshold.*

    ➡ ***About "population immunization", more to come in a next episode of the Epidemiologist Disease Detective***

Please excuse any oversights I may be blind to
and feel free to contact me and let me know
of any "errors and omissions" in this article

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[6] Marc Lipsitch, D.Phil., is professor of epidemiology at the Harvard T.H. Chan School of Public Health and director of Harvard's Center for Communicable Disease Dynamics

[7] Fine, P., Eames, K., & Heymann, D. L. (2011). "Herd immunity": a rough guide. *Clinical infectious diseases*, *52*(7), 911-916