What we know and don't know about COVID-19

Introduction

1. COVID-19 is the disease caused by the coronavirus SARS-CoV-2. A global pandemic has resulted since its emergence in Wuhan, China in late 2019. Although primarily a respiratory tract infection, it often causes gastroenteric symptoms and it is increasingly recognised as a disease affecting many tissues[1]. This note, aimed at policymakers, reviews some of what we do and do not know about the virus and the disease, and the implications this has for efforts to control the epidemic. It covers the main issues at the current time but is not an exhaustive synthesis of the evidence. It is likely that the picture will change, perhaps significantly, as new evidence emerges.

What we do and do not know about the disease

Infectiousness

2. SARS-CoV-2 is highly infectious. The basic reproduction number, R_0, is approximately 3 (compared to ~1.5 for influenza)[2]. This means that in a population where all are susceptible and no control measures are in place, each infected person will infect on average three others, causing exponential spread. With a serial interval (the time between symptom onset of successive infections) of as little as 3 or 4 days, this can happen very quickly, making the pandemic difficult to control.

Mortality and risk factors

3. The infection fatality rate (IFR, the proportion of infected individuals who die) of SARS-CoV-2 is probably around 0.5-1%[3] in the UK but potentially higher in countries with weak healthcare systems. This is low compared to, for example, SARS, a coronavirus which had a similar R_0. However, the infectiousness of SARS-CoV-2, and, unlike SARS, the potential for transmission by pre-symptomatic (and asymptomatic) individuals means that it has spread undetected and caused many more deaths.

4. Mortality rates vary considerably across the population. By far the most important risk factor is advancing age with risk increasing steadily for men age over 50 and women age over 60 years. At all ages, being male confers additional risk. Additional risk is associated with obesity and pre-existing disease of the liver, lung, heart, kidneys or diabetes but not asthma. High human-contact occupations are associated with increased risk of severe disease and death – see paragraph 36.

5. Young children are very unlikely to get severe COVID-19[4]. In the CO-CIN cohort of 55,394 people admitted to hospital, there were no hospital deaths among the 236 (0.4%) children under 5 years old or the 132 (0.2%) who were aged 5-15 years. Among the 83 young people aged 15-19 years admitted, 3 died, two of whom had severe underlying conditions and the third was immunosuppressed by chemotherapy. In contrast, hospitalised patients over 80 are approximately ten times more likely to die than those aged under 50 and those with obesity around one third more likely to die than those without[5]. While effective measures to shield high-risk groups and prevent transmission to and within elderly care homes has the potential to significantly reduce mortality, the risk to the general population at age over fifty and in particular people over 50 years old with underlying health conditions remains important in terms of years of life lost from COVID-19.

Ethnicity

6. People from ethnic minorities, particularly Black and South Asian, have higher rates of COVID-19 diagnosis, of admission to critical care and of death[6]. A complex, interconnected range of factors

may be involved, including the effects of inequalities and deprivation (which are associated with higher prevalence of common chronic diseases such as diabetes and heart disease); involvement in high contact/high risk occupations (see paragraph 37) and communal activities; household size and multigenerational living; differences in accessing healthcare; ineffectiveness or lack of trust in government messaging and potentially workplace discrimination.

7. These social and economic factors may not completely explain, however, why critical care admission is more common in South Asian, Black and Other Ethnic Minority people compared to white people even after adjusting for age, sex, deprivation, disease severity on admission to hospital and comorbidities. Underlying biological vulnerabilities other than comorbidities may therefore be involved, although given that increased risk is seen across different non-white ethnic groups it is unlikely to be a single biological risk factor.

Symptoms and testing

8. In a typical case of COVID-19, symptoms appear around 5 days after infection (range 1-14 days, with 25% on day 7 or later)[7]. Fever, a dry cough and runny nose/sneezing are the most common but are not always present – fever is often absent, limiting its utility for screening. Other symptoms can include anosmia (loss of sense of smell/taste), gastrointestinal problems, headache, sore throat and other aches and pains. The variable presentation of COVID-19, and its similarity to flu and other viral infections, means accurate diagnosis cannot be made based on symptoms alone. Diagnosis – and therefore also outbreak surveillance and test, trace and isolate programmes – rely on laboratory RT-PCR testing, usually from a nose and throat swab.

9. Even with an effective test, accurately identifying COVID-19 cases for test and trace will be very difficult from November to March when the high background level of influenza and other respiratory tract infections will all trigger the system. Even with careful screening of cases no more than 20% (as low as 1% in some surveys) of those who are symptomatic test positive for SARS-CoV-2. Encouraging people to get tested faces multiple challenges such as the difficulty of reaching high-risk but marginalised groups, the economic disincentives against self-isolation and the risk of stigmatisation.

10. The current RT-PCR test has a high specificity, with very few false positive. Sensitivity is however lower: a significant proportion (up to 20%) of negative tests of positive cases may be false negatives, which may be due to ineffective swabbing or low viral levels or both. Caution is therefore required if contacts of known cases in test and trace, or health care workers with symptoms, were to be released from isolation on the basis of single negative test result. Testing twice (or more) on different days can reduce the potential for false negatives[8].

11. RT-PCR tests can detect virus 1-2 days before onset of symptoms; virus levels peak around the onset of symptoms, then gradually decline[9]. Symptoms normally persist for around a week, during which time infectious virus can be recovered, although a minority of cases will be infectious for longer, hence the isolation period of one week from symptom onset is extended if symptoms persist. Household members are required to isolate for a further week to allow symptoms to appear if they have been infected. Individuals can test positive by RT-PCR for weeks after symptoms resolve, but this test detects viral RNA, not live virus, and so it is not necessarily an indicator of infectivity[10].

12. Whereas the RT-PCR test (also known as a "swab" or "antigen" test) detects the presence of viral RNA, antibody testing indicates whether a person has been previously infected. Antibodies that react to SARS-CoV-2 proteins can be detected in most individuals from 10-14 days after symptom onset[11] and there is some evidence that someone who is antibody positive but still PCR positive is unlikely to be shedding live virus[12].

Severe disease and long-term effects

13. In most cases, symptoms resolve in around a week but in some cases a form of pneumonia develops, or a complex array of inflammatory and prothrombotic processes[13]. This can lead to a form of acute respiratory distress syndrome (ARDS) and eventually death, usually within 14 days of hospitalisation[14]. It is not yet clear what causes this progression and how it relates to predisposing factors or other variables. Therapies targeting the progression of the disease rather than the virus itself, such as immunomodulators, may reduce mortality – dexamethasone is a recently proven treatment of this type[15].

14. Some patients experience symptoms for many weeks after infection, including neurological, cardiac, thromboembolic (blood vessels blocked by clots) and other effects beyond the respiratory system. SARS-CoV-2 enters a variety of tissues beyond the respiratory system and long-term research is required to understand the full range of effects, and why and for how long they persist. Although children are in general rarely affected by severe COVID-19, in a small minority a severe multisystem inflammatory syndrome has followed, typically 1 to 4 weeks after the end of symptomatic infection.[16] Why this happens is not yet known.

Pre-symptomatic and asymptomatic transmission

15. One of the greatest challenges for interrupting the spread of SARS-CoV-2 is the transmission by pre-symptomatic and asymptomatic individuals. Although symptoms usually appear around 5 days after infection, transmission can occur up to 2 days before this and some infected individuals never notice any symptoms. Estimates of the proportion of asymptomatic cases vary considerably, from below 10% to over 50%, and even as high as 80%[17]. Current surveys (ONS, REACT, UK Biobank) that repeatedly swab test the general population, as well as antibody testing to show who has been infected without realising, should help to establish the true level of such cases.

16. Pre-symptomatic individuals are often infectious, and it has been estimated that as much as 44% of transmission may occur in the day or two before symptom onset. Asymptomatic individuals can also be infectious, though it is not clear whether all are, and whether they are as infectious as those with symptoms – indeed it is not known whether infectiousness varies more generally, what factors may be associated with this, or what dose of virus leads to infection. Household and contact tracing studies may help to resolve this.

Children

17. There is some indication that young children, who on the whole experience milder disease (see paragraph 5), are less likely to be infected but the evidence is mixed and more is needed before a definitive conclusion can be reached[18,19]. If they are less infectious and/or less susceptible to infection then the impact on R of re-opening schools would be less than otherwise. There are some indications that “vertical” transmission from mother to baby (that is transmission in utero, rather than after birth) can occur but this appears to be very rare[20].

Immunity

18. An important area of uncertainty is the extent to which infection confers immunity to reinfection – whether immunity is whole or partial (i.e. whether reinfection is either not possible, or possible but with reduced symptoms and/or infectiousness), how long immunity lasts, how variable it is and whether this correlates with the severity of disease or other factors such as age, sex and ethnicity[21].

19. Immunity to a virus, whether elicited by a vaccine or by infection, does not always completely prevent infection, but can prevent or attenuate clinical disease and may reduce infectiousness. Natural immunity to the four endemic human coronaviruses, as well as SARS and MERS, wanes after

1 to 3 years allowing frequent re-infection[22]. There have been reports of cases where antibodies against SARS-CoV2 wane in as little as three months[23] but to confirm this and to quantify whether re-infection occurs and how often, large longitudinal cohort studies are needed, stratified by factors such as age and pre-existing medical conditions that may affect immunity.

20. While nearly all individuals infected with SARS-CoV2 produce an antibody response, it is not yet clear whether a positive antibody test is proof of protective immunity. This is because not all antibodies that reacts to viral proteins will block viral activity, and immunity may involve other parts of the immune system, such as T cells. Immunity tests are being developed but none are currently available, which has implications for the concept of immunity passports. It is likely however that antibody positivity is associated with some degree of protection, and transfer of anti-SARS-CoV-2 antibodies in animal models has been shown to protect against disease[24]. There is also some indication that asymptomatic or mildly symptomatic cases may generate a similar level of antibody response as symptomatic cases.

21. ONS survey data from antibody tests found that, as of 29th June, 6.3% tested positive for antibodies to SARS-CoV-2 in England[25]. This suggests that there is relatively little immunity in the current population that might otherwise reduce the risk of a significant second peak of transmission. Public perceptions of immunity and testing, and their impact on behaviour, are important for controlling the epidemic. There is evidence that people who believe they have had COVID-19, whether tested or not, have relaxed their adherence to distancing measures[26]. Similar attitudes could for example adversely affect future uptake of vaccination.

Viral mutation and genomic studies

22. One reason why individuals can become susceptible to reinfection is if mutation or recombination in the viral genome change the antigens that the immune system recognises. Changes can also alter symptoms or cause diagnostic tests to stop working. Sequencing the viral genome from patients allows changes to be monitored as the epidemic progresses. Many sequence changes in SARS-CoV-2 have been detected, although it mutates at a much slower rate than the influenza virus. The impact on antigenicity and immunity is currently unknown although changes in animal coronaviruses have been linked to loss of immunity.

23. Variability in the viral genome means, however, that it is possible to track individual viral strains and trace the origins of outbreaks. For example, a sequencing study in care homes found different clusters of viral strains that suggested multiple separate introductions into the same facility[27]. Sequencing studies also suggest that at the beginning of the epidemic there were multiple (>1000) independent introductions of SARS-CoV-2 into different parts of the UK, mainly in March and from other European countries, particularly Spain, France and Italy, rather than China[28].

What we do and don't know about transmission and how to prevent it

24. Transmission of SARS-CoV-2 is thought to occur via three routes: at close range to an infected person via respiratory droplets and aerosols, which are generated by breathing, talking, coughing or sneezing; via contact with contaminated surfaces (known as fomites); and without close contact via aerosols[29]. The contributions of each route to transmission are unclear. The likelihood of infection depends on both the amount of virus present and the duration and type of exposure. Viral RNA is also detectable in faeces and urine – such that waste water sampling can be used for monitoring outbreaks – but there is little evidence that they contain infectious virus[30].

Time and distance

25. The risk of short-range transmission through aerosols or droplets increases with time of exposure but decreases with distance. The highest risks are where people are in close proximity indoors over extended periods. There is evidence that 2m is a distance where risk drops to low level for face-to-face interactions under most conditions. The risk at 1m is estimated to be 2-10x that at 2m. For example, a 6s exposure at 1m is comparable to a 1min exposure at 2m. Many real-world close contacts (e.g. passing someone in the street) will be even shorter than this. Countries that specify a separation distance below 2m generally already have a very low incidence of infection and mandate other mitigation measures, for example some form of face covering.

26. Exposure to cough is theoretically significantly riskier than exposure to someone talking; exposure to 1 cough at 2m is comparable to talking for 1 minute at 1m distance and talking for 30 minutes at 2m distance[31]. Several large outbreaks have been associated with choirs and religious services, which may suggest that certain "loud" activities such as singing, especially if they occur in crowded and/or poorly ventilated spaces, increase risk of transmission[32].

27. Virus is stable in the air for more than 3 hours but in a well-ventilated space is unlikely to pose a risk for more than 30 minutes. Lengthy exposure in a poorly ventilated place or a shorter period of very high aerosol concentration could result in infection; improving ventilation for poorly ventilated indoor (or outdoor) areas where it is technically feasible to do so may be helpful[33]. There is no evidence of long-range aerosol transmission (e.g. between rooms).

Surfaces

28. Preliminary analysis suggests surface contacts are likely to be a significant transmission route. Evidence to date suggests virus can persist on surfaces at a level that may pose a risk for up to 48 hours. Cleaning and hygiene measures, particularly hand-washing, are therefore a very important mitigating. Further research is needed into the survival of the virus on surfaces in realistic conditions including outdoors[34].

Outdoors vs indoors

29. Evidence suggests that transmission risk outdoors is significantly lower than indoors[35] except at close proximity. Dilution by air movements means that aerosol risk from respiratory sources is very low outdoors and there is evidence from laboratory simulations that bright sunlight (i.e. summer conditions) rapidly reduces viral stability to a half-life of a few minutes. Cold weather will tend, however, to mean more people clustering indoors, which, coupled with the likely increase in virus survival in cold temperatures, will add to the challenges of managing the epidemic in winter.

Face coverings

30. There is good evidence that properly worn surgical-grade masks or respirators in high-risk environments where close contacts are made, such as hospitals, have a significant effect on transmission. The evidence on effectiveness of masks in the community, both for stopping infectious people from infecting others and for protecting the mask wearer from becoming infected, is weak, although evidence that it encourages risk-taking is absent. Overall, the evidence that exists is marginally positive for the use of masks. Cloth masks have therefore been recommended in certain higher-risk settings where masks could be at least partially effective for preventing onward transmission from asymptomatic individuals, such as enclosed spaces where strict social distancing is not possible consistently, creating a risk of close social contact with multiple parties the person does not usually meet (for example public transport and some shops, if crowded). However, other measures such as hand washing are based on stronger evidence and larger effects[36]. If it is

confirmed that the proportion of asymptomatic individuals is high, and that they are generally infectious, the case for face coverings strengthens.

Transmission hot-spots, superspreading and high-contact individuals

31. As the epidemic has progressed in the UK, it emerged that there were, in effect, three epidemics – in hospitals, in care homes and in the community – that interact and feed into each other. As community transmission decreases, hospitals and care homes have accounted for an increasing proportion of the overall number of cases, and these settings have driven transmission elsewhere[37]. Significant outbreaks have also been associated with close communal living such as workers' dormitories, hostels for the homeless, prisons and ships, and certain work environments such as call centres and food processing factories[38]. High-risk settings, especially those that involve vulnerable people such as the elderly and homeless, are therefore a priority for testing and preventive and mitigation measures. It is already apparent that the incidence of infection and numbers of deaths are higher in health and social care workers than in the general population[39]. Mortality rates also appear to be elevated in high-contact rate occupations including security guards, taxi drivers and chauffeurs, bus and coach drivers, chefs, and sales and retail assistants[40]. In contrast, infection rates are lower in those who can work from home.

32. While the mechanics of transmission are understood to a degree, we still do not know exactly where and how people are catching the virus. With quarantining in place, a significant proportion of infections are likely to occur in the home. There is evidence for superspreading events where a small number of people infect large numbers of others over a short period in time. These often occur in indoor environments where there are prolonged interactions in close proximity, such as parties, bars, nightclubs, religious services, conferences and restaurants. It is unclear whether superspreading events are entirely due to environmental factors or whether some individuals have higher viral shedding which may be a factor. Detailed analysis of individual cases and outbreaks is required, including backwards tracing of chains of transmission supplemented by viral sequencing.

33. Locations, occupations and activities associated with high contact rates are priorities for surveillance for detecting and monitoring outbreaks, but this needs to be done sensitively to avoid anxiety, stigma or discrimination. Additional mitigation measures are required, such as frequent cleaning of high-contact surfaces, testing, or extra distancing measures or other changes to workplace practices, as well as raising awareness of people in these situations as to what they need to do at work and at home to reduce transmission[41].

Avoiding creation and linking of networks

34. The primary aim of social distancing measures is to minimise the number and duration of close contacts between individuals from different households, but these are not the only considerations. From an epidemiological perspective, it is also important that, where contacts do occur, they avoid (re-)connecting subnetworks that interventions have otherwise been separated. For example, a family with children in different schools can potentially connect allow transmission between these two networks[42].

Encouraging adherence

35. Ensuring long-term adherence to measures is an important challenge. It requires clear communications and guidance that is fair, feasible and co-created with affected communities, supported by actions to enable positive behaviours and mitigate negative impacts, including practical (and possibly financial) support. Both the effectiveness and impacts of measures need to be carefully monitored[43].

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