

The SARS-CoV-2 ‘perfect storm’: from humble betacoronavirus to global pandemic



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Abstract. The novel betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global pandemic unprecedented in modern times. Understanding the key features that have enabled this virus to propagate so widely in the global community is critical to current and future clinical and public health efforts. High proportions of mild disease and peak viral loads at, and likely prior to, symptom onset have hindered efforts to identify and isolate infected persons effectively, facilitating undetected spread of the virus. In countries with limited diagnostic and/or contact tracing capabilities, population-wide transmission escalated beyond a critical threshold, challenging even well-developed healthcare systems. This ‘perfect storm’ for transmissibility has led to widespread outbreaks and deaths in many regions around the world. Extensive testing and contact tracing, together with Australia’s geographic advantage, tightening of international travel restrictions, physical distancing and public health messaging measures, have contributed to limiting the extent of coronavirus disease 2019 (COVID-19) spread in the country, but recent case escalation in Victoria highlights the country’s vulnerability to future outbreaks due to low population immunity.

Introduction

Since December 2019, the global population has been impacted by a pandemic unparalleled in scale and geographical extent since the influenza pandemic of 1918. The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel

betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with respiratory tract infections of varying severity, from an asymptomatic or mild influenza-like illness to severe pneumonitis, acute respiratory distress syndrome and multiorgan failure. Kawasaki disease-like post-infectious hyperinflammatory syndromes (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS]) and severe coagulopathies have also been reported in certain subpopulations^{1–4}. Understanding the key virological, clinical and population health features of COVID-19 is critical to mitigating the effects of this pandemic as well as preparing for future outbreaks.

Betacoronaviruses

Coronaviruses are enveloped single-stranded RNA viruses, named for their crown-like appearance under electron microscopy, due to spike (S) proteins that protrude from their spherical lipid bilayer membrane (Figure 1). Mammals, primarily bats, are the natural reservoir of these viruses. The S protein plays a key role in viral entry by binding to angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine protease (TMPRSS2) receptors on host epithelial and endothelial cells⁵.

Coronaviruses are transmitted by droplets and contaminated surfaces or fomites via the mucous membranes of a susceptible host. The common seasonal beta- and alpha-coronaviruses (OC43, HKU-1, 229E and NL63) have been circulating in human populations and primarily cause upper respiratory tract infections. SARS-CoV-2 shares 88% sequence homology to two zoonotic coronaviruses in bat populations (bat-SL-CoVZC45 and

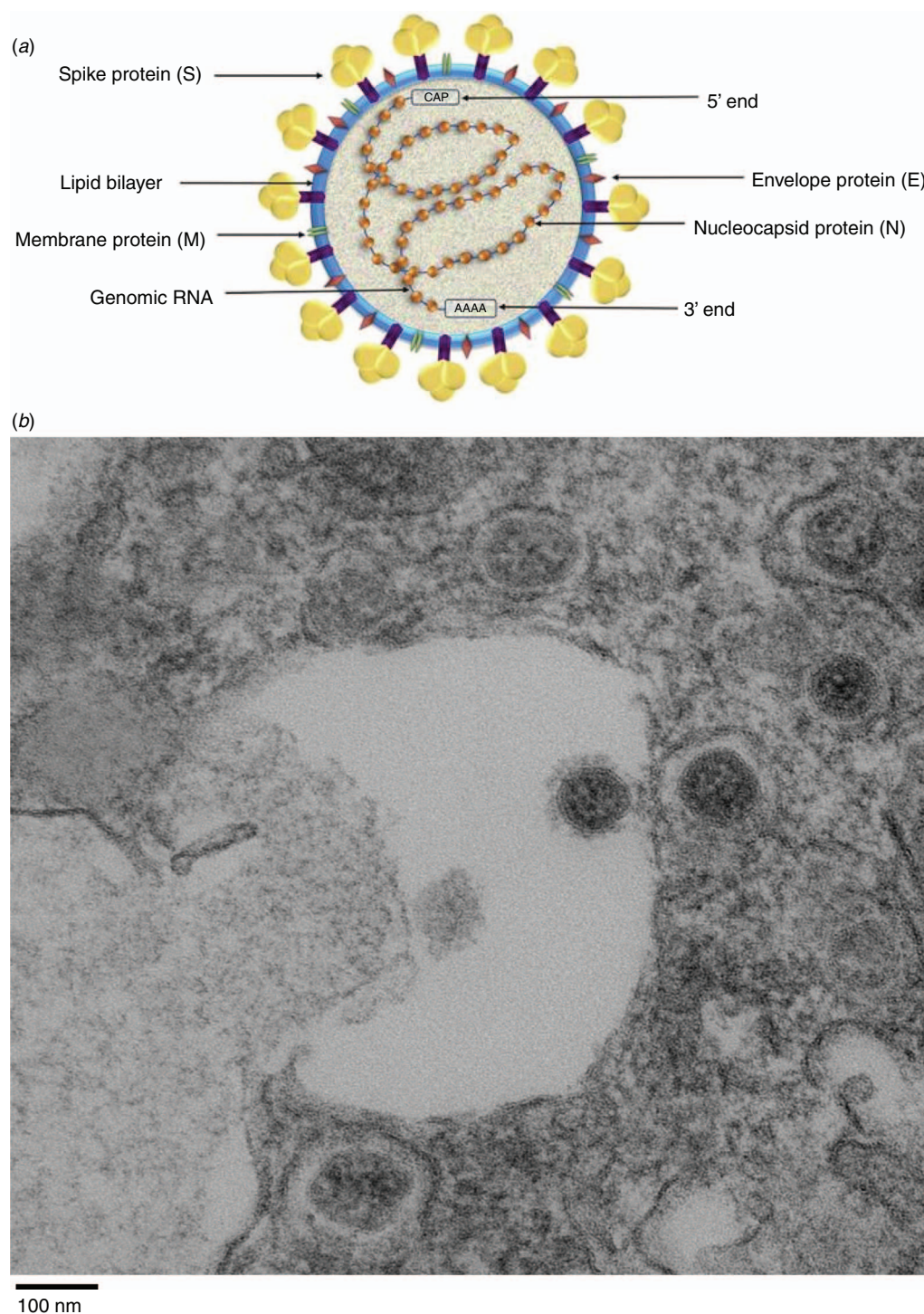


Figure 1. (a) Cross-sectional schematic of SARS-CoV-2 structure including spike (S), envelope (E) and nucleocapsid (N) proteins (reprinted from *Arch. Med. Res.*, Sartarker and Nampoothiri, Structural proteins in severe acute respiratory syndrome coronavirus-2, doi: 10.1016/j.arcmed.2020.05.012, Copyright (2020), with permission from Elsevier)⁵; and (b) transmission electron micrograph image of SARS-CoV-2 virus particles.

bat-SL-COVZXC21) and 80% and 50% similarity to severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) respectively, the betacoronaviruses responsible for previous epidemics in 2003 and 2012 (Figure 2)⁶.

Lessons from earlier epidemics: SARS-CoV-1, MERS-CoV and A(H1N1)pdm09 influenza

Up to 2020, the most likely pathogen expected to cause the next pandemic was influenza virus. Influenza viruses share similar

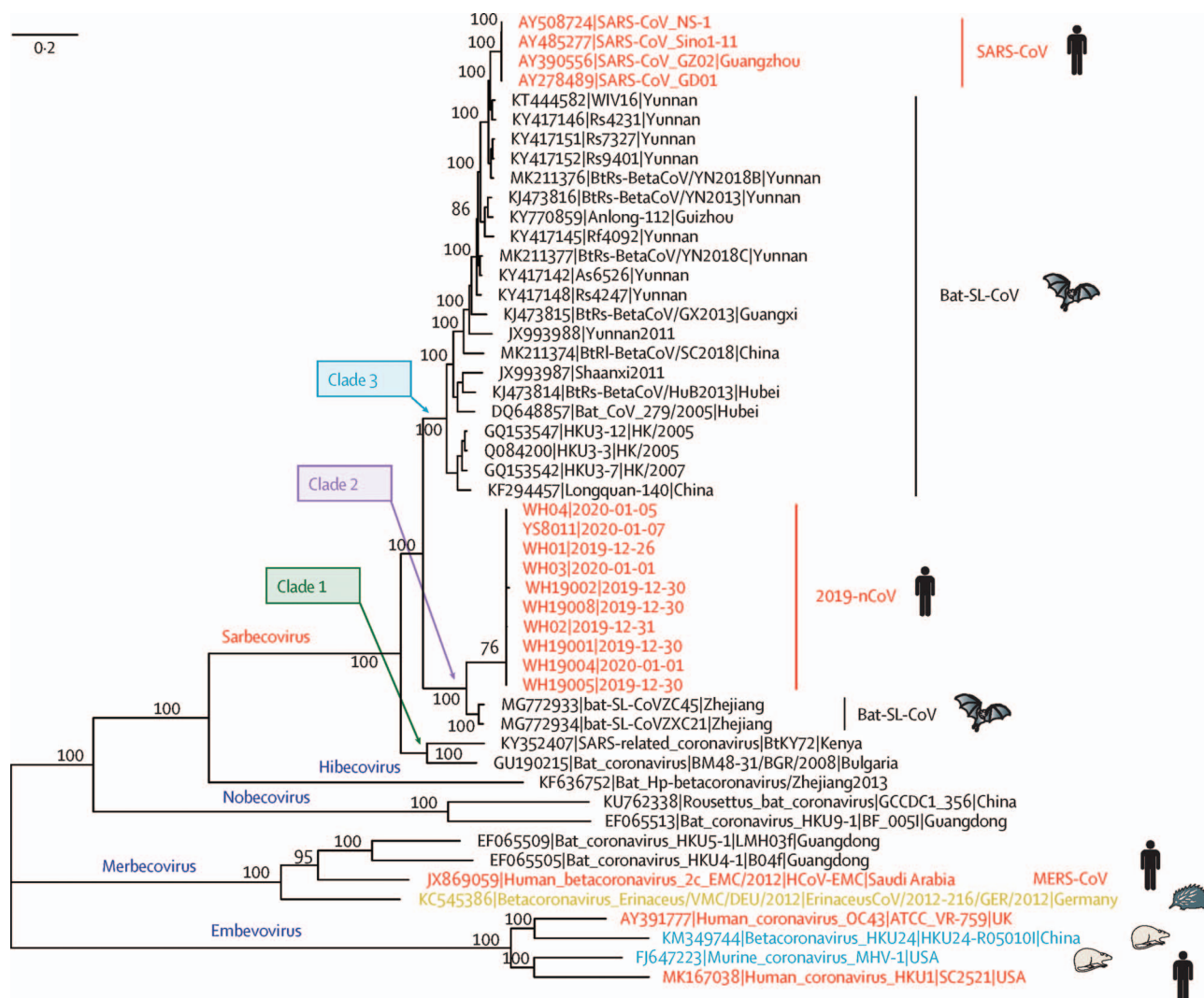


Figure 2. Phylogenetic analysis of full-length genomes of SARS-CoV-2 (2019-nCoV) and other representative betacoronaviruses (reprinted from *The Lancet*, 395, Lu *et al.*, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, 565–574. Copyright (2020), with permission from Elsevier)⁶.

droplet-based transmission dynamics with the coronaviruses and a broad spectrum of illness severity. As with SARS-CoV-2, influenza's relatively low case fatality rate (CFR) of 0.2% enables establishment of unrecognised transmission in communities. Indeed, the pandemic potential of the A(H1N1)pdm09 influenza strain was attributed to its high rates of asymptomatic and mild infections but ready transmission from infected persons⁷.

The COVID-19 pandemic is the third betacoronavirus outbreak over the past two decades (Table 1). These three novel coronaviruses (SARS-CoV-2, MERS-CoV and SARS-CoV-1) infect the lower as well as the upper respiratory tract and are capable of causing severe pneumonitis with acute respiratory distress syndrome, at times associated with widespread multiorgan failure. The mortality rates of these three viruses significantly exceed that of seasonal coronaviruses, and the emergence of each has led to major concern for potential widespread health impacts. Notwithstanding this, the SARS-CoV-1 and MERS-CoV outbreaks were

largely contained and pandemics did not ensue. The virus and host-based transmission parameters of SARS-CoV-2 are therefore distinct from those earlier coronaviruses in critical aspects that have enabled its global spread.

SARS-CoV-1 emerged from bat zoonotic hosts in China in 2002, and has a CFR of 15%¹¹. SARS-CoV-1's reproduction number (R0) of 2–4¹⁴ and household attack rate of 4–10%^{19–21} are consistent with other viruses transmitted by respiratory droplets. Overall, there were cases in 29 countries by the end of the epidemic in 2003¹⁴. Of note, peak viral shedding following SARS-CoV-1 infection occurs in the second week of illness at the time of severe symptomatic disease, and there was substantial nosocomial spread amongst healthcare workers (21% of all infected cases overall)¹¹. Minimal secondary transmission occurred if the index case was isolated within five days of illness onset¹¹. Hence, isolation of symptomatic patients could effectively curb the spread of SARS-CoV-1.

Table 1. Transmission parameters for SARS-CoV-2 compared to SARS-CoV-1 and MERS-CoV.

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Year of disease emergence in humans	2002	2012	2019
Number of countries affected	29	27	188
Number of cases ^A	8437 ⁸	2494 ⁹	16 762 605 ¹⁰
Number of deaths ^A	813 ⁸	858 ⁹	661 012 ¹⁰
Case fatality rate (CFR)	15% ¹¹	34% ⁹	1–5% ^{12,13}
Basic reproduction number (R0)	2–4 ¹⁴	0.3–1.3 ^{15–17}	2–3 ¹⁸
Household attack rate	4–10% ^{19–21}	4% ²²	12–17% ²³

^AFigures correct as at 29 July 2020.

MERS-CoV was first identified in Saudi Arabia in 2012, arising from bats via dromedary camels as the intermediary host. The household attack rate and estimated R0 of MERS-CoV is 4%²² and 0.3–1.3^{15–17}, respectively. As such, there is low likelihood of sustained person-to-person transmission, although there were large clusters with secondary transmission, including in nosocomial settings^{24,25}. Repeated animal-to-human transmission events as well as localised outbreaks were key factors in sustained transmission as well as spread across international borders via air travel¹⁶, eventually involving 27 countries¹⁴. The CFR of MERS-CoV is high (34%) as many cases involved elderly persons with pre-existing medical co-morbidities⁹, and most cases were severe enough to warrant medical attention. Viral shedding is maximal during the first week of illness, regardless of disease severity²⁶.

SARS-CoV-2 has a household attack rate of approximately 12–17%²³ and an R0 of 2–3¹⁸. The overall CFR is highly variable by geography – from 1.4% in Australia and New Zealand to over 5% in China and Europe^{12,27} – reflective at least in part of testing rates, number of infected persons and healthcare system capacities. In older populations, the CFR of COVID-19 is almost 15%; children and adults up to 50 years are relatively spared with CFRs under 0.4%^{27,28}. Additionally, viral shedding is maximal at symptom onset, and likely in the 24–48 h prior^{29,30}, enabling transmission of the virus from infected persons not yet identified or isolated. Of note, a point prevalence study in a skilled nursing facility showed that SARS-CoV-2 RNA could be detected and virus isolated in respiratory tract samples from infected persons up to seven and six days prior to the onset of symptoms, respectively³¹.

In comparison to MERS-CoV and SARS-CoV-1, the high proportion of mild cases of COVID-19 – with cases often not reaching threshold for medical attention and diagnosis – has in part contributed to SARS-CoV-2 becoming established in the community despite modest R0 and household attack rates. Furthermore,

peak viral shedding of SARS-CoV-2 at the time of diagnosis, and likely in the pre-symptomatic phase, greatly hinders containment efforts at a population level. These two factors are clear points of difference in the pathogenicity of SARS-CoV-2 compared to MERS and SARS-CoV-1 and likely drivers of the early exponential spread of this virus.

Public health aspects of SARS-CoV-2 transmission

In many countries across Europe, the Americas, Asia, and now Africa, transmission of SARS-CoV-2 was already well established in the community before public health systems were effectively activated (Figure 3a). Asymptomatic or mild influenza-like symptoms predominated in these early cases, often not reaching diagnostic thresholds; only patients with severe disease presenting to hospital *in extremis* were diagnosed with COVID-19. Diagnostic assays and testing algorithms take time to establish, as do efficient networks for contact tracing. By the time these resources were readily available, SARS-CoV-2 was largely endemic in many countries, such as the United States of America, Italy and the United Kingdom. The public health response then turned to mitigation with universal social isolation measures aimed at limiting onward transmission. The full extent of the pandemic could not be accurately determined in real time, though future serological studies will retrospectively inform our understanding of the true attack rate of the first wave of SARS-CoV-2.

In countries such as Australia and New Zealand – where early warnings were apparent from the experiences of other countries, international borders were tightened in a timely manner and extensive testing and public health measures were rapidly instituted – initial suppression of the COVID-19 pandemic was achieved (Figure 3b). This monumental effort involved comprehensive identification and isolation of infected persons (of all levels

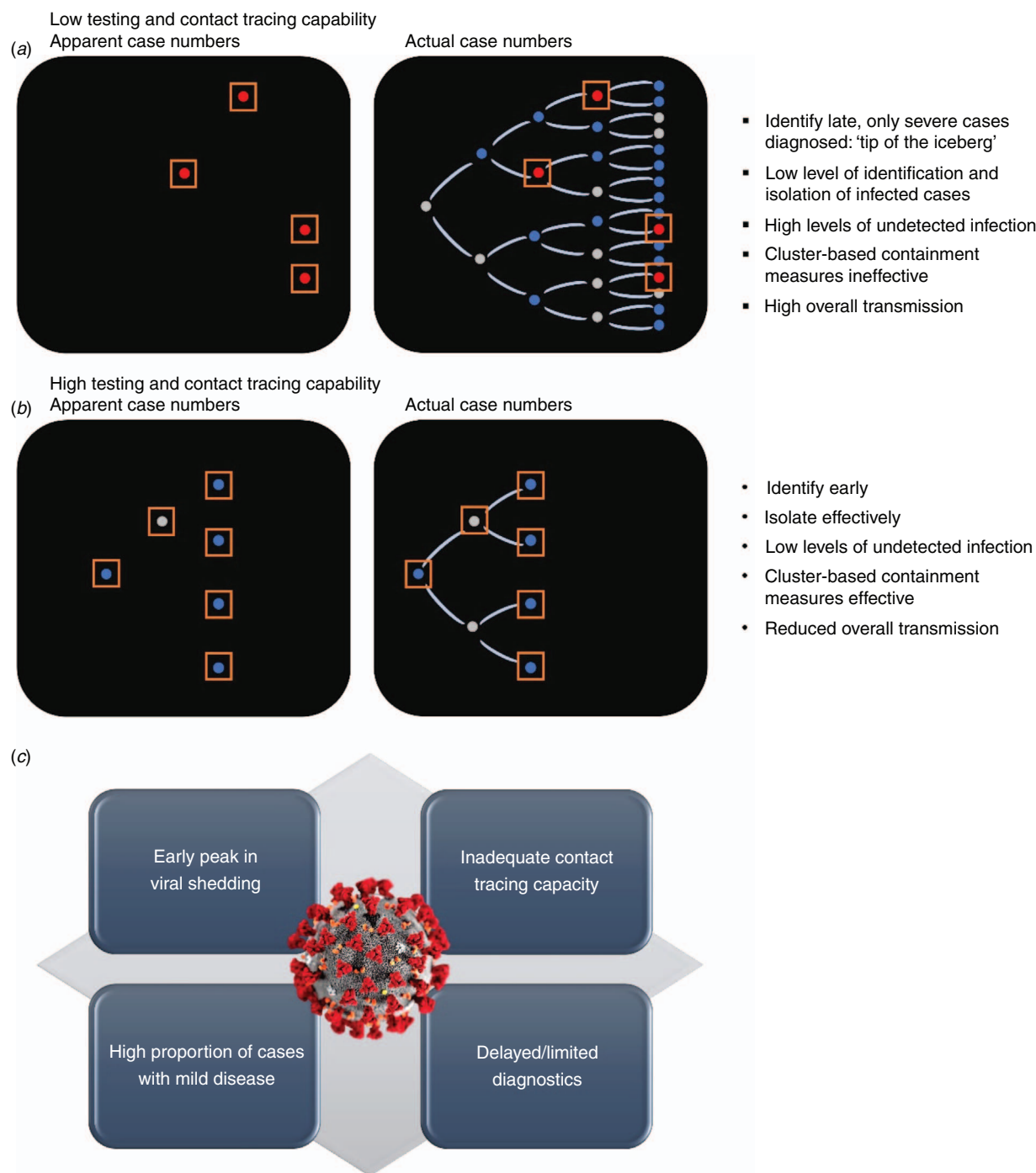


Figure 3. Schematics of viral transmission chains of SARS-CoV-2 in settings with (a) low testing and contact tracing capability, versus (b) high testing and contact tracing capability, and (c) key pathogenicity and health system factors enabling pandemic spread of SARS-CoV-2 and potential future pathogens. Grey = asymptomatic cases; blue = mild cases; red = severe cases; orange box = positive case identified and isolated.

of disease severity) and their close contacts, clear public health messaging and strict physical distancing measures with enormous societal ramifications. Our largely seronegative and therefore susceptible population remains vulnerable to future waves and the rapid identification and quarantining of infected persons and thorough contact tracing efforts will be an ongoing public health priority to limit further transmission of the virus.

At the time of writing, recent escalation in case numbers in Victoria has highlighted the susceptibility of our population and

the rapidity with which public health capacity can be tested to its limits. Ongoing containment of the pandemic will rely on the enduring wisdom of public health officials, strong political resolve, meaningful financial commitment to medical and public health capacity building including planning for surge capabilities, and long-term engagement and cooperation across all sectors of society. Future clusters will not be unexpected and long-term collaboration and trust amongst all stakeholders will be essential to suppress viral transmission with each wave of

infection – with the aim of avoiding preventable COVID-19 deaths resulting from potential health system overload – while also mitigating the societal impacts that are undoubtedly profound.

Risk factors for future pandemics

Pathogens most likely to trigger future pandemics will likely share key pathogenicity and transmissibility features with SARS-CoV-2 (Figure 3c). Large proportions of mild cases in the population and viral shedding with high infectivity in the pre- or early symptomatic period of infection are key risk factors. These two features enable undetected viral spread in a population prior to establishment of robust systems for diagnosis, isolation and contact tracing. Early public awareness regarding symptoms of concern and the importance of prompt diagnosis and medical assessment, as well as readiness of government to instigate population-wide containment measures, will obviate some of this risk. Nonetheless, the rapid development of diagnostics and contact tracing capacity are critical to containing pathogen spread before the disease becomes established in a community. This is particularly important in susceptible, unimmunised populations. As part of preparedness, governments must continue to invest in these systems to ensure pandemic response structures are robust and poised for activation in case of a novel outbreak. Equally important is the ongoing investment into upstream surveillance systems (such as at the animal-human interface) to predict and prevent spill-over events.

Conclusions

The COVID-19 pandemic has led to a substantial number of deaths worldwide and unprecedented population-wide measures to limit viral transmission within communities and between countries. Worldwide travel has ground to a halt, economies have been forced into recession and schools, workplaces and aged care settings have been closed or locked down with immense social, economic and broader health implications. From the drastic impacts of COVID-19, lessons must be learned to inform future pandemic preparedness. The establishment of COVID-19 as a sustained global pandemic has been enabled by two key virological features of SARS-CoV-2: (1) a high proportion of mild disease in the population; and (2) peak viral shedding with high infectivity prior to or at the time of diagnosis. Ongoing high-level commitment to maintaining robust detection, contact tracing and public health communication systems will be critical to obviate future waves of infection from this or other emerging pathogens.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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Biographies

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