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Opinion

Strategies to minimize preventable morbidity and mortality resulting from pandemics like COVID-19

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Healthcare and preventable disease

The fundamental role of healthcare systems is minimisation of preventable morbidity and mortality in the population. Notwithstanding, despite their central role in promoting health and preserving and improving the well-being of society, budgetary constraints limit accessibility and services provided to the population, resulting in preventable disease (OECD, 2015).

Preventable morbidity and mortality not caused directly by the pandemic infectious agent

At times, for example, during the winter influenza season, health services may become overstretched, or even overwhelmed, due to a mismatch between case load and available capacity/resources. This does not usually lead to a significant reduction in routine and elective services. However, new infectious diseases, in particular those with unpredictable disease progression and outcomes and/or transmission characteristics, and that can lead to pandemics, may cause rapid and severe reductions in available capacity for routine clinical care: (i) health services may be re-focussed towards dealing primarily with the new health crisis, and (ii) frontline professionals can become infected and either become ill or need to self-isolate to minimize infection of others, thereby further reducing healthcare capacities. As a result, normal health services can become severely disrupted.

Moreover, the consequences of public health measures to interrupt infection chains, compounded by the perceived (or *de facto* existing) threat posed by pandemics, can exacerbate chronic and mental health-related conditions, and even trigger new ones (https://unsdg.un.org/sites/default/files/2020-05/UN-Policy-Brief-COVID-19-and-mental-health.pdf). Crucially, some measures may formally disincentivise patients from seeking urgent or non-urgent essential healthcare. Such measures and their accompanying public announcements may also create public anxiety (https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/technical-guidance/mental-health-and-covid-19) about risks of becoming infected/infecting others during visits to health centres, and thereby induce reluctance to undertake such visits (a behaviour that might be termed *clinical services hesitancy*), which may lead to deterioration of some conditions.

Pandemics entrain other hurdles to healthcare practice and access, such as disruption of supply chains for key medicaments and materials, and travel restriction measures that curtail vital health-related travel (of both patients and health professionals). Particularly worrying are prospects of increasing incidence of major endemic infectious diseases, such as tuberculosis, malaria and AIDS which, together, are responsible for annual deaths of ca. 2.4 million people, mostly in low- and middle-income countries (Editorial, 2020; Finn McQuaid *et al*., 2020; Glaziou, 2020; Sherrard-Smith *et al*., 2020). Recent reports suggest that 80% of care programmes for these three diseases have suffered severe disruptions to their activities (e.g. see Editorial, 2020; https://www.nytimes.com/2020/08/03/health/coronavirus-tuberculosis-aids-malaria.html?smid=em-share).

The combination of pandemic-induced re-prioritization of healthcare services, reductions in clinical capacities and availability of diagnostics and clinical supplies, hindrance of travel to care facilities, disincentives to seeking care, and *clinical services hesitancy*, creates a perfect storm that severely interrupts diagnosis-prevention-(early)treatment care services. This can lead to a

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subsequent and unnecessary wave of potentially serious new or worsening non-pandemic-related disease cases, of cancer (e.g. Sud *et al*., 2020), cardio-vascular disease, infectious disease, psychiatric disorders, and so forth (e.g. Reza *et al*., 2020; https://unsdg.un.org/sites/default/files/2020-05/UN-Policy-Brief-COVID-19-and-mental-health.pdf), that could otherwise have been managed more appropriately by routine health services.

Preventable morbidity and mortality caused directly by the pandemic infectious agent

We have previously discussed some of the logistical aspects of preventable morbidity and mortality (Timmis and Brüssow, 2020). In terms of disease-specific aspects, the notion of *preventable* will generally evolve during the course of a pandemic, as our understanding of the disease process grows.

The over-riding priorities in epidemics/pandemics is infection containment and the early treatment of infected individuals (https://www.who.int/emergencies/diseases/managing-epidemics-interactive.pdf). Transmission control and early diagnosis require as near as possible real-time epidemiological information to identify and characterize foci of infection, and inform about transmission dynamics, to enable immediate and effective action to contain and interrupt pandemics. At the time of writing, most virus testing currently carried out takes days before results become available to patients and public health monitoring facilities. Nevertheless, this is changing dramatically due to the recent development of rapid diagnostic tests (e.g. Broughton *et al*., 2020; Huang *et al*., 2020; Vogels *et al*., 2020). The deployment of such tests at airports and other points of entry into countries around the world is likely to simplify tracking and interruption of infection chains created by international travel, and at locations containing susceptible populations, like health centres, care homes, prisons and so on, will help reduce infection spread to and within such environments.

However, tests for other segments of the population remain, for the most part, limited to symptomatic or high-risk groups. Rapid tests for symptomatic individuals will enable prompt clinical care and the minimisation of preventable morbidity and mortality. On the other hand, since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals can be infectious prior to symptom development (Arons, *et al*., 2020; Emory, *et al*., 2020; Gandhi *et al*., 2020), or remain asymptomatic but nevertheless infectious, a failure to screen asymptomatic groups has important consequences.

Firstly, tracing of contacts of newly symptomatic individuals is necessarily subject to crucial delays, during which significant further transmission can occur, so both transmission is increased and care of infected individuals delayed, with potentially poorer health outcomes as a result.

Secondly, while COVID-19 is primarily an infection of the lungs, it can also affect other organs, in particular the cardio-vascular system (e.g. Guzik *et al*., 2020) and have a myriad of long-term sequelae (e.g. see Gupta *et al*., 2020; https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/; Perez-Bermejo *et al*., 2020), the magnitude, nature and severity of which we are only beginning to appreciate. As our understanding of the causes of, and predisposing factors for, non-lung involvement and sequelae increases, so the evolution of prophylactic and therapeutic interventions to address these unmet needs will accelerate. However, for optimal effectiveness in reducing disease severity, these will need to be promptly instituted, which in turn requires early diagnosis and monitoring.

Thirdly, the institution of robust public health measures to contain transmission of new outbreaks can involve large-scale curtailment of civil liberties and disruption of local economies, both of which may lead to a rise in anxiety-related mental health issues, and an increase in household violence (e.g. Usher *et al*., 2020). Large-scale testing of particular groups/sub-populations of asymptomatic individuals provides much greater detail and granularity to an emerging epidemiological overview of new outbreaks. This in turn enables transmission prevention measures to be targeted more precisely and effectively to smaller regions/populations, resulting in less disruption to regional civil liberties and economies, and avoidance of unnecessary anxiety and stress.

Fourthly, at present we are largely blind to virus movement among asymptomatic individuals, so are hindered in anticipating where and when new outbreaks may arise, and how they will evolve. Information on asymptomatic virus carrier incidence in the population, viral loads and their dynamics in such individuals, and the frequency of asymptomatic carriage of SARS-CoV-2 that does not develop into symptomatic COVID-19 disease, is vital for epidemiological comprehension of a pandemic, the creation of accurate predictive tools, and the development of effective public health responses to minimize infections.

Fifthly, we do not yet know if there are potential long-term health consequences of asymptomatic infections with SARS-CoV-2 and, if so, what they might be. In order to be able to institute adequately powered follow-up studies, it is essential to rapidly identify a significant number of asymptomatic carriers for long-term monitoring.

The infection pandemic conundrum of healthcare systems

So, this is the conundrum: how to minimize a pandemic-specific disaster of an unpredictable magnitude without simultaneously precipitating major collateral damage of a more predictable but substantive magnitude?

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The current pandemic is undoubtedly a game changer for civil society and life changing for many individuals. But it is not over and current rising case numbers already suggest a second COVID-19 wave which, due to the absence of an effective vaccine, is once again leading to partial or full-scale lockdowns and may seriously postpone a return to normality in healthcare services. It is, therefore, crucial to confront the conundrum now, in order to identify and set in motion the measures needed to minimize preventable disease in this, and other pandemics that are sure to follow (https://www.who.int/emergencies/diseases/managing-epidemics-interactive.pdf).

Here we discuss three measures to increase the effectiveness of health system responses to pandemics and reduce unnecessary incidence or severity escalation of disease:

- firstly, to channel infection testing to autonomous diagnostic-speciality centres,
- secondly, to channel patients with mild–moderate severity infections to *Shelter Hospitals* for isolation,

in both cases, away from home and traditional hospitals where they can create new infection chains,

- and, thirdly, to urgently introduce rapid testing, and to substantially expand testing of the asymptomatic population, to reduce intervention lag times, and thereby lower the incidence and severity of pandemic cases, and their impact on the normal functioning of health services.

Do-it-yourself medical centres: Permanent advanced diagnostics infrastructure

We have previously proposed the creation of essentially autonomous, local *digital medical centres* (dMCs), initially in numbers and locality similar to current community primary care centres (Timmis and Timmis, 2017). They are clinically supervised, do-it-yourself (DIY) facilities – available 24/7 – featuring an array of easy-to-use self-diagnostic routine medical services, and a mini-pharmacy. They are artificial intelligence (AI) driven and digitally networked to a patient data storage and processing centre of the health system that integrates patient data and current best clinical practice, to facilitate precision medicine (diagnostics, prevention and treatment), as well as optimal personal lifestyle recommendations, such as precision nutrition.

dMCs were initially conceived to increase accessibility to, and reduce pressure on, primary care services, promote engagement of patients in their own healthcare and co-incidentally improve health-disease literacy in society, incentivize the development of an AI-enabled comprehensive (nationwide/worldwide) integration of evidence-based medicine and patient data that would accelerate the implementation of individualized care, and steer future evolution of healthcare systems towards greater coherence and fiscal sustainability (Timmis and Timmis, 2017). However, since they are in essence centres of advanced diagnostics, and modular in design, it would be straightforward to include a highly protective/isolated 'pandemic testing-pathway', both walk-in and drive-through where possible, that would accommodate any rapid test, and separate pandemic-specific testing from patients visiting the dMCs for routine primary healthcare. Testing could be either DIY or professionally-conducted high through-put, or both, depending on requirements at the time. Optimized ventilation, airflow and air filtration, the use of robots (Yang *et al*., 2020) and so on, for frequent analysis and cleaning of surfaces, and the presence of minimal clinical personnel (nurse, pharmacist, on-call clinician), would essentially prevent disease transmission within the facility and to healthcare professionals. The concentration of pandemic diagnostics in dMCs would divert potential infection sources away from secondary and, crucially, tertiary clinical services, while not affecting the DIY primary healthcare services provided by the dMCs (Fig. 1).

Importantly, dMCs would be available in all communities, so the *de novo* creation of diagnostic centres and necessary infrastructure in response to pandemic emergencies, with all the inherent planning and logistical effort needed, and the delays these entrain in getting adequate testing up and running, would be averted. Once a test became available, it would simply be integrated with the dMCs' existing arsenal of tests in the appropriate diagnostic pathway. Equally importantly, their focus on rapid tests would enable 'while-you wait' results and immediate result-dependent patient instructions, such as prompt quarantining in *Shelter Hospitals*.

Temporary shelter hospitals: Channelling pandemic patients away from traditional hospitals

In most countries, standard procedures for patients with COVID-19 infections has been to send them home to self-isolate, in the case of mild–moderate symptomology, or to refer to hospital, in the case of moderate–severe symptomology. The former transports the virus into the home where it can be transmitted to other members of the household, and thereafter the community; the latter transports the virus into the hospital where it can be transmitted to other patients and hospital personnel, some major consequences of which have been alluded to above.

In the case of home isolation, the monitoring of compliance with isolation regulations by responsible authorities is logistically challenging, and patient anxiety about infecting loved ones is often problematic. Moreover, the monitoring of the health status of home isolation patients

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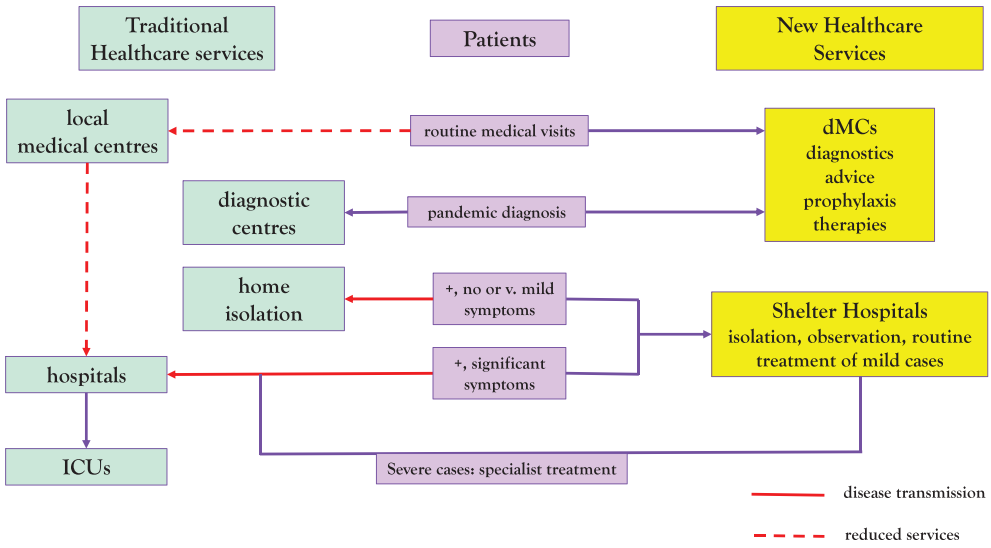


Fig 1. Protecting healthcare services in an infection pandemic.

– sometimes in their hundreds of thousands – may in some cases present problems, especially during periods of rapidly-evolving crisis. As a result, deterioration in the health status of patients may not always be promptly detected and the transfer of such patients to hospital may experience significant delays that result in poorer health outcomes.

In the case of referral to hospital, when R_0 is high, the bed capacity in hospitals in most countries rapidly becomes saturated. When all available beds are occupied, non-critically ill-patients are sent home where their conditions may worsen. And, under such circumstances, clinical professionals responsible for the care of the COVID patients typically become exhausted, physically and mentally.

To avoid or minimize these problems, and to respond to the urgent need for rapid massive expansion of pandemic care facilities, Fangcang Shelter Hospitals (FSHs) were created in Wuhan in the early days of the COVID-19 pandemic (Chen *et al*., 2020; Fang *et al*., 2020). The philosophy of FSHs was not to provide overspill capacity for traditional hospitals but, in contrast, to create an additional, *temporary* healthcare facility to specifically deal exclusively with the pandemic. COVID patients were channelled to FSHs, away from the home and traditional hospitals, thereby reducing household and community transmission, importation of the infection into hospitals, and bed occupation (Fig. 1).

FSHs are created by conversion of existing public venues that meet criteria of capacity, infrastructure (adequate power, sewage, ventilation, etc.), adequate inside and outside space, accessibility, proximity to traditional hospitals, etc. They constitute a rapidly established and massive additional capacity (e.g. the first 3 FSHs created in Wuhan were completed in 29 h and provided 4000 beds; soon thereafter 13 more were completed, providing a further 12,000 beds), are inexpensive compared with the *de novo* creation of additional traditional hospitals, temporary, and rapidly and inexpensively reconverted to their original function when no longer required (Chen *et al*., 2020).

FSHs have five functions: isolation, triage, basic medical care, frequent monitoring of key disease parameters and prompt referral to traditional hospitals when disease progresses to severe, and recreational activities and social engagement (Chen *et al*., 2020; Fang *et al*., 2020). Clinical care in FSHs is such that 'no patient is unattended or untreated', and the transfer of patients with deteriorating parameters to traditional hospitals within hours rather than days, allows prompt specialist treatment and enables best possible outcomes. It is reported that the normal short-term stay in an FSH alleviates patient anxiety of infecting loved ones at home, and the community activities, social engagement and mutual support of the 'community of patients', all having the same infection, promotes well-being and contributes to recovery.

FSHs are typically created in large-scale public venues located in urban areas near traditional hospitals, so logistics are favourable. Such venues are typically well served by public transport and have ample outdoor space required for entry and evacuation, the set-up of temporary auxiliary stations (command centres, administration, etc.), and the accommodation of supplementary specialist mobile services, like imaging, laboratory services and so on. Smaller cities and towns, with lower case incidences, could usefully repurpose smaller venues. A key feature of the FSH strategy is that the explosive spread of a

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pandemic which triggers fear of an imminent and unpreventable overwhelming of health systems, also triggers immediate prohibition of large public gatherings. This simultaneously frees up large public venues, allowing them to be repurposed into FSHs within hours, thereby avoiding breakdown of healthcare systems and services. The search for new sites for *de novo* construction, and associated planning issues, is avoided.

Planning for emergencies, such as pandemics and other catastrophes, is the remit of different agencies, including civil protection organizations (see e.g. Federal Office for Civil Protection: babs.admin.ch/en/verbund.html). In future, it is essential that civil protection organizations be involved in deliberations concerning planning permission for public venues, not only with regard to public safety aspects, but also to assess whether or not a new venue could/should serve as a potential FSH and, if so, how it should be designed to enable rapid and efficient reconfiguration into a FSH, with ventilation, sewage, logistics, etc. in mind: 'one investment, comprehensive disaster prevention' (Fang *et al*., 2020).

The key role of rapid tests and result reporting in real time

A key challenge in pandemics is to be able to monitor the epidemiology in as close to real time as possible, in order to enable rapid public health responses to contain the infection. Inadequate testing, and long-time intervals between sampling and analysis, means that it has been challenging for many countries to get ahead of the pandemic. However, as a result of enormous efforts worldwide, considerable progress has been made towards development of rapid and reliable diagnostic tests for infection with SARS-CoV-2 (https://www.finddx.org/covid-19/pipeline/), based, for example, on reverse transcription loop-mediated isothermal amplification (RT-LAMP) approaches (Broughton *et al*., 2020; Huang *et al*., 2020).

We are therefore now on the cusp of being able to implement mass testing of symptomatic and asymptomatic members of the population, as well as individuals identified in contact tracing procedures, with tests that provide reliable results in minutes. Nevertheless, the current logistics of selecting who-when-where, and the subsequent need for travel to testing centres, which might disincentivize some members of the public (disabled, non-drivers, distant work-places, etc.), indicate that community dMCs integrated in hubs of public transport networks would be preferable testing venues.

In future, the logistics of testing should be simplified further by the development of simple-to-use kits that can be employed in small mobile testing stations, for testing specific populations like those in schools, care homes, cruise ships (e.g. see Emory, *et al*., 2020), large public gatherings, commercial operations characterized by a high degree of handling of products that may mediate person-to-person transmission (e.g. shops, restaurants, meat processing facilities) and so on.

And most effective will be the simplification of tests such that they can be used for DIY testing at home. Figure 2 illustrates the simplicity of one of a number of DIY test systems currently in development. It involves simple sampling (swab) and adding the sample to a reaction tube that is subsequently maintained at a temperature of about 65°C (permissible temperature range: 58–68°C) for 30 min. Tube content colour changes would then be photographed via a dedicated app and automatically sent for analysis. Home DIY test kits are likely to be available in the near future.

Because the logistics associated with the use of well-designed home testing kits –they can be home delivered or collected from the local pharmacy – are considerably

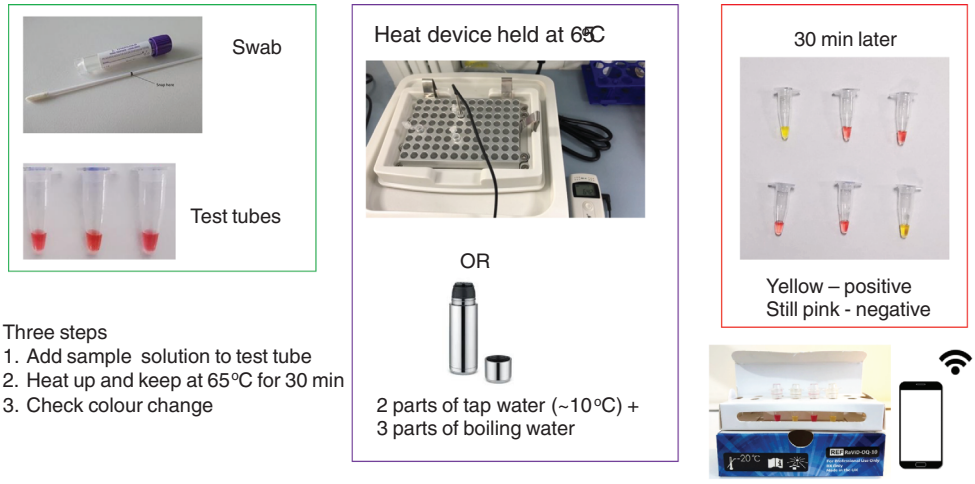


Fig 2. A simple DIY test system for SARS-CoV-2.

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simpler than those associated with testing in professional centres, they are likely to rapidly gain in importance for widespread testing. DIY kits will be particularly helpful for individuals who have impediments to leave the home, and those in care homes, prisons, and so on. They will also be invaluable for infected individuals in quarantine, enabling them to report the clearance of the virus/ending of infectiousness and to obtain authorisation for exit from quarantine, when it is safe to do so. This may be considerably earlier than the end of the standard self-isolation period, and thus enable a saving of days in the return to normality, with all the personal and professional benefits this can entail.

Platforms for development of rapid testing systems for future pandemics

Preparedness is crucial for emergency responses (e.g. see Timmis and Brüssow, 2020). To prepare for new pandemics/epidemics of infections with severe/lethal outcomes, it will be essential to establish rapid diagnosis platforms that can quickly design specific primers as soon as the genome sequence of the infectious agent is determined, and develop rapid diagnosis systems and kits, perhaps within a period as short as 2 weeks. Two distinct types of platform are needed, namely for professional testing and for DIY testing. The former will produce automated, large-scale high-throughput systems for rapid, accurate and quantitative detection of the infectious agent in diverse clinical samples. In normal times, the platforms will also evaluate new developments in detection/quantification, sampling/sample handling, signal processing/readoutinstrumentation, automationand so on, create state-of-the-art instrumentation and systems, and develop new diagnostics needed for non-pandemic infectious agents and biomarkers of other diseases. They will also develop validation protocols for evaluation of the performance of new tests, and prescribe everything needed for their immediate implementation in testing centres, such as sampling kits, enzyme kits, liquid handling, data capture, data processing algorithms, data sharing and clinical waste handling/disposal.

DIY test kit platforms will focus on the development of generic intuitive kits that are easy-to-use at home/in care homes/in mobile diagnostic stations and so on. These will include self-sampling materials and brief, straightforward instructions for safe use and disposal of samples and kit materials, and be complemented with mobile phone apps that capture and transmit results.

Though dMCs will typically feature DIY testing, in pandemic situations with a need for the testing of large numbers of people, they would also provide facilities for high throughput professional testing by trained personnel.

High- versus low-cost centres

Traditional secondary (medical specialist) and tertiary (hospital) healthcare facilities are designed to treat wide diversities of disease/disease presentation, and are personnel and diagnostic/therapeutic instrumentation intensive. They are high-cost centres, typically consuming approximately 40% of healthcare budgets (https://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_expenditure_statistics#Healthcare_expenditure_by_function). dMCs and Shelter Hospitals not only have important commonalities, such as being highly adaptable to evolving situations and not requiring a large overhead; they also synergistically establish a pandemic patient isolation pathway. Channelling pandemic patients into low-cost dMCs for virus testing, with rapid transfer of positively tested patients to low-cost Shelter Hospitals for isolation and treatment of mild-to-medium disease severity, significantly diverts pressure away from, and therefore mitigates interruption of, high-cost secondary and tertiary health services, and hence minimizes unnecessary morbidity and mortality that inevitably would have resulted from insufficient capacity.

Conclusions and recommendations

The public health mantra for epidemics/pandemics is *containment through interruption of infection chains*. Sending infected people to self-isolate at home or to hospital might briefly interrupt existing infection chains (e.g. in the workplace, in schools) but, by the same token, may create new ones, because of the infection susceptibility of people in these settings and the heterogeneity of effectiveness of containment measures possible and practiced in different home and hospital environments. Effective containment of infection foci requires other strategies that ensure better management of transmission and compliance with regulations.

It is often stated that the diverse measures instituted by governments in response to the pandemic are to prevent overwhelming of the health system. What is usually meant by ‘overwhelming’ is rapid saturation of available beds – especially in the ICUs – and the capacity to treat pandemic patients, with the ensuing dilemma of determining who receives recommended best practice care and who does not. However, since the primordial function of health systems is to minimize preventable disease, we would argue that the severe reductions in routine care and the inevitable increases in otherwise preventable morbidity and mortality, as a result of the refocusing of services to deal with the pandemic, constitute a *de facto* overwhelming of the health system. It might be considered analogous to an attempt to prevent the overwhelming of a supermarket by panic shoppers (e.g. Sim

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et al., 2020), through refocusing the product spectrum and restricting stock on offer to toilet paper only. In both cases, though the facilities remain open and receive customers/patients, their core function – of being a *one-stop shop* – has been abandoned.

We argue here that a strategy to better manage infection chains, and enable health systems maintain routine care services, would be the prompt implementation of rapid testing, including app/internet-enabled home testing as soon as these become available and have been validated, extension of testing to targeted large groups of asymptomatic individuals, such as communities in tourist destinations, in cities experiencing new outbreaks and so on, combined with the channelling of pandemic-related care of patients without severe symptoms away from traditional healthcare services and to pandemic-dedicated services: dMCs for diagnosis, and Shelter Hospitals for isolation/quarantine and treatment of mild–moderate disease (Fig. 1). Since both of these new care facilities are low-cost settings, and serve to protect the traditional hospital high-cost settings, they also afford economic benefits.

As a consequence, we recommend the following:

1. Rapid creation of a nationwide network of easily accessible dMCs, and the necessary informatic infrastructure (see also Keesara *et al*., 2020).
2. Development of a coherent plan and the capacity to create Shelter Hospitals at very short notice.
3. Commitment to maximal reduction of lag times between sampling, testing and result analysis
4. Commitment to extensive testing of selected asymptomatic groups, now and for future pandemics.
5. Incentivization of development of rapid DIY diagnostics, and of multiple generic rapid diagnostic development platforms.

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Conflict of interest

Wei E. Huang is involved in the development of rapid test systems for SARS-CoV-2.

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