Key International COVID-19 Science Issues for SAGE

28 January 2021

Background and purpose

This paper provides an update on the international COVID-19 epidemic, with a focus on current status, the distribution of mutations of concern, primary and secondary impacts, future distribution of vaccines and therapeutics, and related scientific uncertainty.

Summary

Epidemiology

Globally, more than 100m people have been reported infected by COVID-19, with over 2.1m deaths. The human and social costs are significant, with an estimated $544bn per month in global lost growth. An estimated 140 million additional people (2% global population) are living in extreme poverty, reversing the steady reductions seen over the past 7 years. Economic scarring will last for many years, with livelihoods damaged, asset accumulation depleted, investments paused, and human capital degraded.

In the past month significant increases in transmission and mortality have been reported in almost every region of the world. Whilst these increases may, in part, be due to behaviours during the festive period, the rapid increase is likely to be predominantly due to the emergence and spread of more transmissible variants (medium confidence, low evidence). This has significant implications for global control. For some variants, increased transmission may be a consequence of escape from naturally acquired immunity (low confidence, low evidence). If confirmed, this would have a major impact on future epidemiological trajectories.

Epidemic trajectories have differed significantly between regions and countries over the course of the pandemic, affected by varying age structures, co-morbidities, population density / connectivity, health system capacity, and strength, timing, and type of response implemented. Differences in capacity, scale and strategies for testing make direct comparisons in infection and mortality rates between countries challenging, particularly those at different income levels.

Under-ascertainment of cases and deaths remains a significant challenge, particularly in low- and lower-middle income countries (L/LMICs), with estimates of case under-ascertainment up to 250 times in L/LMICs in Q2 2020[i] (medium evidence, low/medium confidence). Novel mortality surveillance studies estimate that only 1-2% of COVID-19 deaths have been reported in a number of fragile and conflict affected contexts. (medium confidence, low/medium evidence).

Variants

The emergence of new genetic variants of concern highlights the critical importance of a strong global response to COVID-19, with dominant strains of concern including B.1.1.7 detected in 50+ countries, B.1.351 detected in 20+ countries, B.1.1.248 (P.1) detected 5+ countries, and B.1.1.248 (P.2) detected 9+ countries.

New variants have largely been identified in countries with high sequencing capacity or with dedicated research investigations. Despite substantial efforts to scale up SARS-CoV-2 sequencing capacity in L/LMICs, of the genomes submitted to the GISAID EpiCoV database, only 1.3% come from Africa and 1.2% from South America. This creates significant

[i] Differences in methodology, such as sampling design, choice of test, and timing, limit the ability to draw precise conclusions from comparing results.

blind-spots, which hinder the rapid identification of emerging variants globally (weak evidence, high confidence).

As the independent emergence and convergent evolution of specific mutations (and/or collection of mutations with similar functional effects) has demonstrated, there is a significant risk that new variants of SARS-CoV-2 with a potential for increased health impact will continue to emerge (medium confidence, medium evidence). These are likely in all global populations with high SARS-CoV-2 transmission and infection prevalence (high confidence, moderate evidence) including countries with no or low sequencing capacity. As countries start to achieve greater vaccine coverage, different selection pressures may apply.

In addition to resource and capacity constraints, **the risk of misplaced attributions of culpability and reactive measures** by other countries (e.g. travel bans) imposed on countries where variants are first detected may be a disincentive for increased global sequencing and/or transparent reporting. (weak evidence, moderate confidence). Yet the expanded coverage of sequencing is critical to an effective global response.

Early evidence on immune escape of variants B.1.351 and B.1.1.248[1,2] (and of significant transmission across the southern hemisphere) with a potential impact on vaccine effectiveness could exacerbate the challenge countries are facing in controlling transmission. Along with new, more severe waves of infection in settings that have experienced previous outbreaks, there is the risk of transmission in areas that have previously been less affected (e.g. more dispersed populations) (moderate confidence, low evidence)

Increased global genomic surveillance that supplements essential testing and surveillance regimes will be critical to understand mechanisms of viral strain replacement, especially in the context of widespread vaccine roll-out.

Vaccines

There are at least 237 vaccine candidates in development: 64 in clinical development; 16 in Phase 3 trials and 6 in Phase 2/3 trials with the front runners across four vaccine technology platforms. Novel RNA vaccines (e.g. Pfizer, Moderna) are highly efficacious, but less suitable for deployment at scale in lower income countries compared to viral vector vaccines (e.g. AstraZeneca), due to their temperature requirements, as well as unit price.

Global allocation of initial doses should be used to achieve health impact as well as equity[ii], **but the scale of globally available vaccines in 2021 remains an unknown**. The most optimistic (not risk adjusted) production forecast for 2021 is 19 billion doses with 9 billion of these reportedly secured.[4] High income and producer countries (especially US, EU, and China, as well as COVAX) have been most active in terms of securing or retaining vaccine volume. COVAX, the multilateral partnership which is buying vaccine on behalf of 191 countries for 2021, has secured 2.1 billion doses although supply is not guaranteed.[4] There is an intensifying scramble for bilateral doses, which complicates the multilateral approach.

Even with an historic level of speed and scale, vaccine roll-out in L/LMICs through COVAX will lag behind high-income countries (HICs) initially, and may worsen if boosters or periodic immunisation are needed. It is likely also that many countries will access a variety of vaccines from both COVAX and bilateral or regional arrangements. There is a risk that many people may receive only one dose of a vaccine schedule, or a mixed combination of first and second vaccine types, with varying gaps between doses.

[ii] For example, 2 billion doses equitably distributed avoids 61% deaths vs 33% of deaths with a HIC focus[3]

Rigorous evidence from the UK on the following could help inform global strategies:

1. The effectiveness of a single dose schedule of various vaccines (on both severe illness/death and transmission) (particularly for the Oxford/AZ vaccine).
2. Any potential risks for immune escape associated with the large-scale deployment of a partially effective vaccine (e.g. 50-60%)
3. Likely effectiveness and/or risks associated with different combinations of first and second vaccine types being deployed.

Global vaccine allocation strategies have been informed by modelling evidence that has considered how to achieve greatest impact on severe illness and death for vaccine in limited supply. This modelling suggests that optimum strategies should target the elderly and other high-risk groups. Particularly with the rise of new genetic variants of concern, and multiple approved vaccine candidates, additional modelling is needed to consider optimal approaches to distribution. Important questions include:

1. The likely public health benefit of a shift to the prioritisation of the large-scale delivery of the first vaccine dose, with the delayed delivery of second doses, versus a continued commitment to ensuring the per-protocol delivery of first and second doses.
2. The implications for future distribution of different assumptions about protection, vaccine effectiveness on transmission, and vaccine dosage (among others).

Countries face challenging health resource allocation decisions with difficult trade-offs between competing priorities across all health in a fiscally constrained environment. Maximising the health impact goes beyond averting COVID-19 infections and deaths, including maintaining essential health services, avoiding displacement of routine childhood immunisation, and averting health system strain.

There is a high risk of re-allocation of resources from essential health services to enable roll out of COVID-19 vaccines (weak evidence, medium confidence), with a dearth of evidence to inform optimal decision making, including to consider the likely benefits and trade-offs between investment choices – for example, investment in COVID-19 vaccines versus sustaining rates of childhood immunisation.

The deployment of vaccines for adults will present novel challenges to many countries, with a need to identify and reach target groups, including marginalised and/ or remote populations. Vaccine hesitancy, alongside low trust in health systems, in some settings, may limit vaccine uptake and impact. Political science research suggests that corruption, organised crime and poor governance pose significant threats to COVID-19 vaccination, including increased potential for elite capture.

Testing and Diagnostics

Testing capacity remains highly centralised in many countries and is often insufficient to meet current demand. HICs are now conducting 252 daily tests per 100,000 people, in L/LMICs the rate is 10 times lower at 24 tests per 100,000 people.

Drugs that are available, affordable, easy to administer, and with manageable side-effects, are important in alleviating severity of disease globally, on top of the impact of vaccines and public health and social measures (PHSMs). Global equitable access and pricing for COVID-19 treatments has received less attention than vaccine access. Many drugs are not currently affordable or feasible for widespread use in L/LMICs (e.g. IL-6 inhibitors, mono-clonal antibodies). Dexamethasone has most current potential for L/LMIC treatment of severe illness, and recent emerging indications on potential effectiveness of colchicine is also

positive. Further evidence to demonstrate the effectiveness of dexamethasone in the absence of oxygen is likely to facilitate its expanded use.

Health systems in L/LMICs are facing severe impacts from COVID-19, both directly and indirectly. Specific areas of concern for health system delivery of the COVID-19 response that require greater attention include:

- Enhanced access to low cost, sustainable oxygen therapy delivered at scale.
- Systems to strengthen infection control, including strengthened procurement and provision of PPE (as well as more wearable options); safe options for disposal of contaminated material; potential options for expanded local production; and options for simple, effective decontamination and safe re-use.

Indirect impacts

The magnitude of global indirect impacts of COVID-19 globally, particularly in the poorest countries, is significantly exceeding direct impacts. An estimated 140 million additional people (2% global population) are living in extreme poverty, with many more temporarily falling below the poverty line. This is a reversal to the steady reductions in extreme poverty seen over the past 7 years. The economic scarring will last for many years to come, with livelihoods damaged, asset accumulation depleted, investments paused, and human capital degraded.

In many countries, the indirect impact of COVID-19 on health outcomes is highly likely to be greater than the direct impact in terms of cases and deaths. Over half of countries have reported scaling back service provision in response to COVID-19, including 70% of countries reporting disruption to routine immunisations.

Modelled estimates suggest service disruption in 118 L/LMICs could lead to a 9.8% - 44.7% rise in child deaths per month, and an 8.3% - 38.6% rise in maternal deaths per month. Lower fiscal space for health and re-allocation of health spending from non-COVID services to COVID-19 interventions, including roll-out of COVID-19 vaccines, risk worsening access to quality essential health services going forward.

Key International COVID-19 Science Issues for SAGE – Main Section

Epidemiology

Epidemiological Trends

1. **The pandemic has accelerated globally.** It took just over nine months to reach 1 million global reported deaths (29 September 2020), but only a third of that time to reach 2 million deaths earlier this month (16 January 2021). While some of this is due to increased surveillance and detection, and the aggregated effect of heterogeneous trends, there has been a clear overall trend in increasing growth.

2. **Epidemic trajectories within and between regions and countries have been highly heterogeneous over the course of the pandemic** (Fig. 1)**.** Many factors underlie these differences, including demographic, environmental, and differential testing capacity and disease control measures.

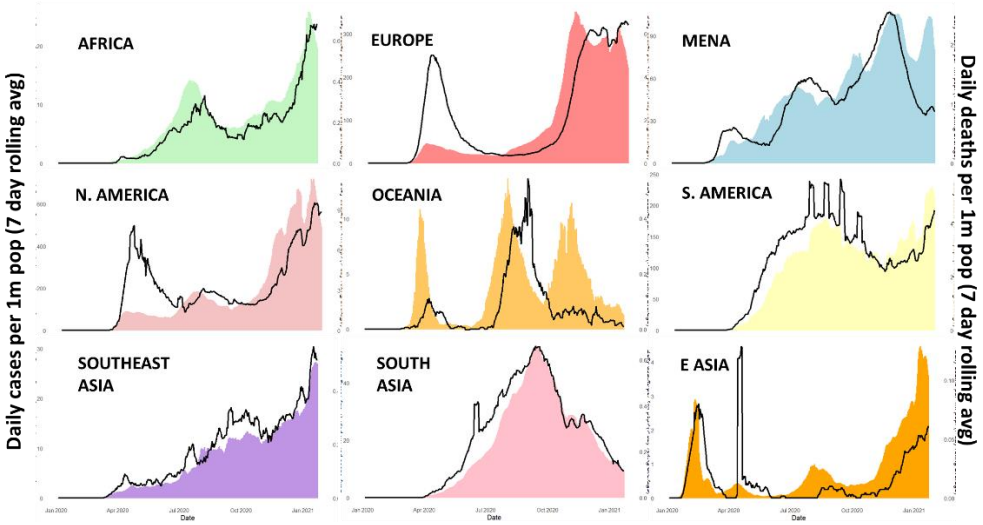

Figure 1: Daily cases (bars) and deaths (lines) (per 1M population), by region (Data: WHO)
Axes not to scale, both within region (cases/deaths) and between regions

3. **In the last month, significant increases in transmission and mortality have been reported in almost every region (Fig. 2),** despite the known heterogeneity between countries. Though these rises may in part be due to effects from the festive period, the emergence of more transmissible variants is also likely to be playing a significant factor though definitive evidence is not yet clear. Specific trends of importance include:
    a. **Sub-Saharan Africa is experiencing a continent-wide resurgence,** with a clear 'second' wave. While reported figures are being driven by South Africa, many countries have reached record numbers of new cases and deaths in recent weeks.
    b. **Countries across the southern hemisphere are seeing a rising trajectory despite being in the hemispheric summer period,** which would have some expectations of lower transmission.
    c. **Oceania has been the only region able to maintain low transmission**. Notwithstanding the insulated geographical nature of islands, New Zealand and Australia have had some of the greatest success in epidemic control.
    d. **Health systems have been overwhelmed across multiple regions.** In recent weeks, reports of health facilities reaching bed capacity have been registered across Europe, South America, and sub-Saharan Africa.

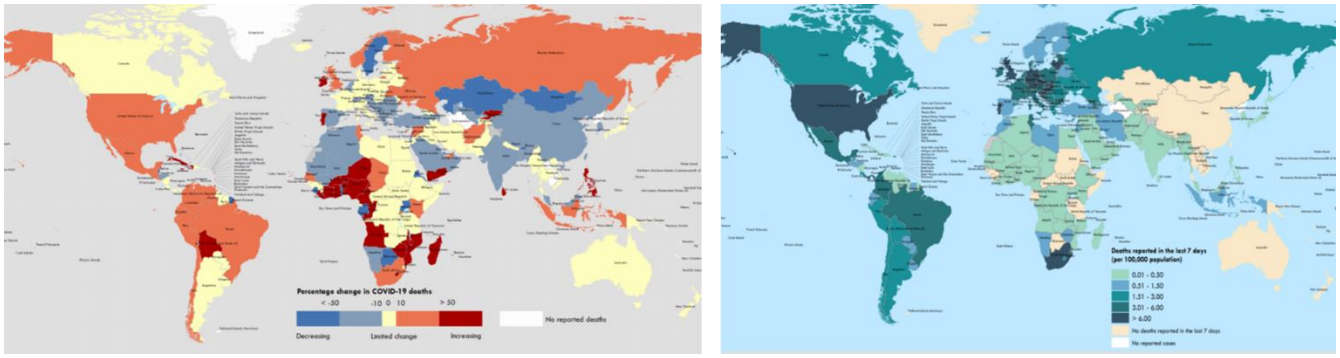

Figure 2: a) % change in weekly COVID-19 deaths, last 7 days; b) new deaths per 100k population, last 7 days (Data: WHO)

4. **Well-documented risk factors for COVID-19 infection and severity are based on a wealth of evidence in HICs, with more limited evidence from L/LMICs.** As with most work on COVID-19 thus far, there is limited rigorous data documenting the epidemiology and specific risk factors across L/LMICs. While some aspects are broadly generalisable, a limited understanding of differences across populations is likely to result in challenges with parameterisation of modelling approaches, and the inappropriate application of interventions (including drugs and vaccines) to populations where the infection and course of disease may differ.

Under-ascertainment of cases

5. **Many L/LMICs have had comparatively fewer reported cases to date.** For example, despite having 17% of the world's population, Africa has had only 4% of confirmed cases. By contrast, Europe has 10% of the world's population and almost 30% of confirmed cases. Several factors led to early analyses projecting the greater transmission in L/LMICs, including: high occupancy, multi-generational living with shared facilities; high levels of absolute poverty and reduced social protection enabling self-isolation or quarantine; and weak health systems with limited infection prevention and control measures.

6. **Contextual differences and under-ascertainment are likely to influence difference in reported cases seen between L/LMICs and HICs.** Higher under-ascertainment will occur, both due to the lack of testing capability, as well as the effect of younger demographics resulting in fewer severe cases and so lower detection. Some have suggested that in many African countries, both early lock-downs and a more effective, community-led public health response (drawing on the experience and systems developed for polio, Ebola, etc.) benefited their response to COVID-19; however, such response performance is difficult to analytically evaluate. Separately, some authoritarian regimes without a free media may be more likely to underreport their COVID-19 cases and deaths[5], whether through wilful underreporting or avoidance of data collection and/or reporting. Media repression and statistical manipulation have also been observed.

7. **Under-ascertainment of cases in L/LMICs is likely to be up to 10-50 times greater than in HICs.** While seroprevalence in HICs has been estimated to be up to 10 times the number of reported cases[6]), serosurveys in L/LMICs have reported estimates on an order of magnitude of 10-100[7,8]). However, the dearth of systematic, high-quality studies (e.g. appropriate sampling design, timing, sensitive tests) conducted in L/LMICs limits the representativeness of seroprevalence estimates.

Under-ascertainment of deaths

8. **Many L/LMICs have also had fewer reported deaths to date**. A significant driver of this is the age profile of populations in these countries compared to HICs, with the median age in Africa 19.3, compared to 37.9 in North America and 41.4 in Europe (in 2015). The risk

of death is estimated to double approximately every eight years of age, leading to estimates of overall infection fatality ratios ranging from 0.23% (0.14% - 0.42%) in a typical LIC with a population structure skewed towards younger individuals, to 1.15% (0.78% - 1.79%) in a typical HIC with a greater concentration of elderly individuals.[9] Lower prevalence of co-morbidities associated with higher mortality are also likely to play a role.

9. **Under-ascertainment also contributes to the difference in reported deaths between L/LMICs and HICs. Excess mortality analyses can be used to estimate the true mortality associated with COVID-19, but has limitations for causal attribution.** The inability to distinguish direct and indirect impacts, as well as potential inaccuracy of baseline mortality estimations, restricts its usage in understanding true disease severity for L/LMICs without further context. Excess mortality estimates include combined effects (direct / indirect and increased / decreased impact), which confounds the true picture. Further methodological differences limit the validity of between-country comparisons, though within-country sub-national comparisons can be used to illustrate the impact of contextual factors (e.g. system capacity, social norms).

10. **Without sufficient routine data, a range of novel approaches has been used in L/LMICs to assess excess mortality and suggests significant under-ascertainment.** While more systematic, national initiatives are underway (e.g. in selected African countries[iii]), other singular analyses have identified indirect methods or mortality proxies for resource-limited environments, including satellite imagery of graveyards, mortuary data, and social media data, which have shown 1-2% of COVID-19 deaths were reported in a selection of fragile and conflict affected contexts.[10–12]

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11. **Challenges of mortality reporting in L/LMICs are not limited to COVID-19**. For example in Africa, only 12% of countries have complete reporting of deaths, and high-quality cause of death data is only available in less than one-third of countries.[13] There are significant barriers to capturing data from the full range of the health system (e.g. private providers), including in impoverished areas. Death certification faces further challenges, both with and without civil registration systems – data from India suggest that only 22% of deaths in CRVS have a medically certified cause of death.[14] Existing challenges in mortality reporting have been exacerbated during the COVID-19 pandemic. Lack of testing capacity (both operational and logistical) have impacted accurate clinical and post-mortem diagnostics, especially under the pressure of PHSMs and reduced services**.**

Genetic variants – international trends and potential global scenarios

12. **The emergence of new genetic variants of concern highlight the critical importance of a strong global response to COVID-19.** Four variants recently identified (lineages B.1.1.7[15], B.1351[16], and B.1.1.248 [P.1[17]/P.2[18]]) have been detected in a combined over 50 countries thus far. However, most of the detection following identification of these variants has been reactive (e.g. screening individuals with travel history from initial countries of detection), with limited broader analysis. A systematic approach to sequencing is necessary to avoid biased data and subsequent misinterpretation of the results.

[iii] South Africa, Somalia, and Uganda (Africa Centres for Communicable Disease Control and Prevention / Vital Strategies) and Togo, Burkina Faso, Ghana, Liberia, and Sierra Leone (African Field Epidemiology Network, AFENET).

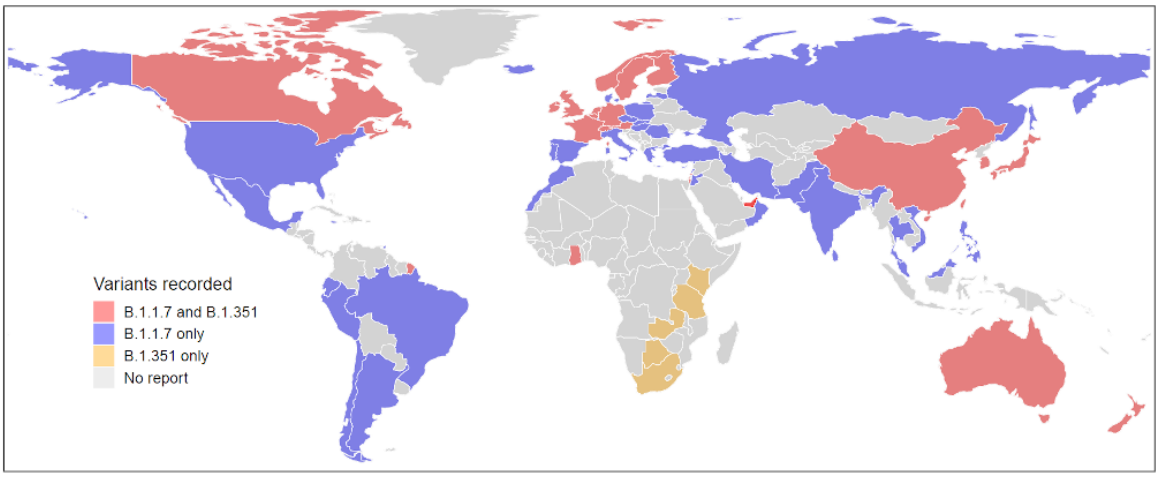

Figure 3: Global spread of SARS-CoV-2 variants (lineage B.1.1.6 and B.1.351), as of 24/January 2021[19] *(**Note**: does not show B.1.1.248)*

13. **Early, open international cooperation is critical to preventing further domestic and international spread of variants of concern,** and understanding the extent of their implications on human and population health. This has been exemplified by collaboration between colleagues in South Africa and COG-UK to understand the B.1351 lineage, engagement in international partnerships like the WHO Virus Evolution Working Group, and regular cooperation between research groups and government scientists across countries in many capacities.

14. **Low global sequencing capacity (both proactive and reactive) greatly endangers the ability to pre-emptively understand epidemiological shifts and viral evolution, and to adjust response strategies accordingly.**[20] Genomic sequencing has been massively scaled up during the COVID-19 pandemic compared to normal standards and previous epidemics. However, few countries currently perform sufficient regularised, systematic sequencing of either representative samples or targeted sub-populations to maximise the benefit of sequencing as a timely disease surveillance tool.

15. **Some countries have used genomic sequencing to great effect when well-integrated within the public health response.** This has been both to detect genomic changes of potential significance or to inform public health interventions (e.g. contact tracing) in real time to break chains of transmission and prevent further disease spread.
    - *Japan*: Regular sequencing activity at airports between March – Sep 2020 captured 129 genomes from the 782 cases identified through testing travellers.[21] This screening measure also led to the recent detection of the B.1.1.148 lineage (P.1 variant) in Japan when testing travellers from Brazil.
    - *The Netherlands*: Sequencing during initial stages of the pandemic supported transmission analysis and informed further public health measures.[22]
    - *UK*: As the global leader in sequenced genomes, large-scale surveillance has been performed regularly through the support of the COG-UK consortium. This has facilitated regular systematic analysis, especially for VOC 202012/01[23], as well as informing enhanced outbreak control strategies such as investigations of nosocomial COVID-19 infections.[24]

16. **L/LMICs may have limited laboratory capacity and few (if any) dedicated resources to conduct genomic sequencing**. As a crude illustration of this differential, of the over 380,000 genomes submitted to the GISAID (Global Initiative on Sharing All Influenza Data) EpiCoV database[25,26] to date (excluding low coverage samples), only 1.3% have come

from African countries despite covering 17% of the world's population (Fig. 4). These samples represent 0.1% of Africa's total reported COVID-19 cases. Comparatively, over 44% of GISAID genomes are from the UK. It is likely that a significant volume of the global viral genomic evolutionary history is unrepresented in current repositories due to the limited sequencing in many countries.

	AFRICA		EUROPE		SOUTH AMERICA		GLOBAL
	TOTAL	South Africa	TOTAL	UK	TOTAL	Brazil	
Population, % of global	**16.9%**	**0.8%**	**10.8%**	**0.9%**	**2.0%**	**2.7%**	**100%**
SARS-CoV-2 genomes in GISAID	**5,002**	**2,740**	**250,187**	**169,256**	**4,465**	**1,865**	**387,386**
(% of region)	*(100%)*	*(54.8%)*	*(100%)*	*(67.7%)*	*(100%)*	*(41.8%)*	-
(% of global)	*(1.3%)*	*(0.7%)*	*(64.6%)*	*(43.7%)*	*(1.2%)*	*(0.5%)*	*(100%)*
Before 14/Dec., 2020*	**4,063**	**2,395**	**156,647**	**118,060**	**2,038**	**982**	**252,516**
(% of region)	*(100%)*	*(58.9%)*	*(100%)*	*(75.4%)*	*(100%)*	*(48.2%)*	-
(% of global)	*(1.6%)*	*(0.9%)*	*(62.0%)*	*(46.8%)*	*(0.8%)*	*(0.4%)*	*(100%)*
Cumulative reported COVID-19 cases	**3,266,451**	**1,346,936**	**29,378,632**	**3,433,498**	**14,663,539**	**8,488,099**	**94,467,624**
(% of global)	*(3.5%)*	*(1.4%)*	*(31.1%)*	*(3.6%)*	*(15.5%)*	*(9.0%)*	*(100%)*
(% of global, pop.-standardised)	*(2.6%)*	*(0.01%)*	*23.3%)*	*(0.3%)*	*(26.0%)*	*(0.5%)*	*(100%)*
Before 14/Dec., 2020*	**2,393,426**	**860,964**	**20,985,792**	**1,849,407**	**11,933,214**	**6,880,127**	**71,145,903**
(% of global)	*(3.5%)*	*(1.4%)*	*(31.1%)*	*(3.6%)*	*(15.5%)*	*(9.0%)*	*(100%)*
(% of global, pop.-standardised)	*(5.4%)*	*(0.5%)*	*(49.2%)*	*(0.9%)*	*(10.0%)*	*(1.0%)*	*(100%)*
% of reported cases sequenced (GISAID genomes to cases)	**0.1%**	**0.2%**	**0.9%**	**4.9%**	**0.03%**	**0.02%**	**0.4%**
Before 14/Dec., 2020*	**0.2%**	**0.3%**	**0.7%**	**6.4%**	**0.02%**	**0.01%**	**0.4%**

***Figure 4**: SARS-CoV-2 genomes in GISAID and reported COVID-19 cases, by region and country (selected), as of 23 January 2021. (Data sources: GISAID, WHO; Independent analysis: FCDO)*
**14/Dec: date of first public report of VOC 202012/01*

17. **Significant efforts have been made to scale up SARS-CoV-2 sequencing capacity in L/LMICs through surveillance networks**, including regional expanded laboratory network initiatives in Africa (led by Africa CDC)[27,28] and the Americas (led by PAHO-WHO)[29], and specific country-led operations (e.g. South Africa[30], India). Internationally supported partnerships in L/LMICs to facilitate sequencing and analysis are critical to manage sequencing gaps, exemplified by work from Zimbabwe, Kenya, and South Africa characterising lineages and sources of transmission.[31–33] However, many L/LMICs still have considerable resource allocation needs that hinder prioritising sequencing. Further reluctance is generated by concerns of misplaced attribution of culpability and reactive measures (e.g. travel bans) imposed on countries where variants are first detected.

18. **As the independent emergence and convergent evolution of specific mutations (and/or collection of mutations with similar functional effects) has demonstrated, further new variants of SARS-CoV-2 with a potential for increased impact on health are almost certain to continue arising globally.** Genetic variants are likely to arise in all global populations with high SARS-CoV-2 transmission and infection prevalence. However, they are most likely to *identified* in countries with high sequencing capacity or with dedicated research investigations. As demonstrated by under-ascertainment, there are also likely to be L/LMICs at risk for emergent variants without the accompanying capacity to detect them.

19. **Increased genomic surveillance that supplements essential testing and surveillance regimes will be critical to understand global mechanisms of viral strain replacement, especially in the context of widespread vaccine roll-out**. Though some evidence exists from the 1918 influenza pandemic[34,35] and modelling of seasonal and pandemic influenza strains, short-term applicability to the COVID-19 pandemic is limited. Further global data from the current pandemic are critical to understand the likelihood, risk,

and implications of vaccine-induced strain replacement. This not only includes genomic sequencing, but also antigenic surveillance to inform timely vaccine development.

20. **Possible antigenic drift (with an impact on vaccine effectiveness) will also significantly affect under-resourced countries** struggling to control transmission with public health measures and limited vaccine supply. Early evidence suggests immune escape of 501Y.V2, including laboratory data that indicate resistance to neutralisation by convalescent plasma (~11-33 fold) and vaccinee sera (~6.5-8.6 fold)[1], with similar implications for the B.1.1.248 lineage variants.[1,2] Epidemiological data also suggest that large resurgences in South Africa and Manaus, Brazil[36] occurred against a background of high seroprevalence. A high likelihood of reinfections would have significant considerations for control, especially in L/LMIC contexts given the current extent of spread.

21. **The potential role of immunocompromised patients with chronic SARS-CoV-2 infections in promoting viral evolutionary pressure has significant implications for HIC and L/LMIC populations alike.** With the very limited but compelling evidence of strong selective pressure for escape mutants in immunosuppressed individuals receiving antibody treatments[37,38], clinical protocols will need to be considered in the context of patient profiles and available drugs. There may be further implications in populations with high prevalence of undetected and/or untreated HIV.

Vaccines, Diagnostics & Therapeutics

Vaccines – demand and supply

22. **The COVAX Advance Market Commitment (AMC) aims to supply** fully subsidised doses for 92 L/LMICs[iv] (subject to funding) for 20% population coverage in 2021. There is low likelihood of additional supply in 2021 and AMC countries would need to self-finance doses (at COVAX negotiated price) and delivery. The AMC has secured $2.4bn plus up to $4bn (US) of donor funding, with at least an additional $2bn - $3bn needed in 2021 for further procurement and delivery (higher, to reach above 20% population coverage)**.** COVAX AMC will supply small-scale but meaningful quantities before the end of March 2021, scaling up to: i) the end of June (est. 480m doses, 240m people) sufficient for 6% population coverage; and ii) the end of 2021 (est. further 1.36bn doses), all subject to approvals and supply.

23. **COVAX AMC supply for 20% coverage in 2021 will be sufficient to reach countries' priority populations**. Countries under constrained supply may pursue 'protection' strategies. Many will likely prioritise health care workers who are both exposed to COVID-19 and at risk of transmitting infection, in addition to a focus on high-risk populations for severe disease (e.g. elderly, HIV and TB). **Different population age structures will also require further consideration of strategies**. For example, 3% of Africa's population is above 65 years old. 60% coverage against average African age structure would include 15-year olds in immunisation cohorts.

24. **Demand for vaccines will outstrip supply in 2021.** Timing of supply volumes is uncertain and dependent on: phase 3 clinical trials still underway to identify leading candidates with the potential to supply high volumes[v]; timing between national and

[iv] Forty–six (46) of these are in Africa. AMC countries also include 12 IDA eligible UMICs which are mostly small island states.

[v] For example, Novavax and J&J

regional regulatory processes and deployment, with additional time needed for WHO evaluation for global supply[vi]; and manufacturer over-estimation of early supply volumes[vii].

25. **There is continuing and intensifying scramble for bilateral doses which complicates the space for the multilateral approach through COVAX**. This has been fuelled by second epidemic waves in most regions and concerns over new genetic variants. Early supply volumes of these bilateral deals are likely to be relatively small, irregular, and politically symbolic rather than transformational. For developing countries, especially LICs, the main supplier will remain the COVAX Advance Market Commitment (AMC) and separate deals secured by the African Union, with the bulk of supply in the second half of 2021.

26. **The rush for vaccines, particularly early doses, may likely result in vaccine nationalism.**[39] A few supplier countries may be able to restrict exports of finished products or manufacturing impacts, disrupting plans for global distribution. Similarly, there is a risk of vaccine diplomacy, where access to vaccines is used to secure political or economic benefits for supplier countries.

27. **Limited evidence to date on roll-out strategies suggests differential approaches based on available supply, vaccine effect, and current incidence of disease (among others).** Countries face challenging health resource allocation decisions with difficult trade-offs between competing priorities across all health needs in a fiscally constrained environment. Maximising the health impact goes beyond averting COVID-19 infections and deaths, including maintaining essential health services, avoiding displacement of routine childhood immunisation and averting health system strain.
    a. **Vaccines that reduce both transmission and disease severity will have the greatest population effect**. Modelling evidence suggests that for a vaccine in limited supply (<20% coverage), optimum strategies should target the elderly and other high-risk groups. However, as supply increases, maximum benefit is gained from targeting high-transmitting populations (e.g. younger and middle-aged workers) to provide indirect protection.[40–42]
    b. **The effectiveness of these strategies depends on immunological and epidemiological factors**, including naturally acquired immune duration, epidemic trajectory, and healthcare capacity.
    c. **Initial global allocation strategies have been designed to deliver significant mortality reduction, by distributing doses in proportion to countries' population size**[40], (as a proxy for the size of high-risk populations).
    d. **The rise of new genetic variants of concern and multiple approved vaccine candidates highlight the importance of modelling that reflects the current landscape** to consider optimal approaches to distribution, including with a range of scenarios for protection, vaccine effectiveness on transmission, and vaccine dosage (among others).

28. **Roll-out of vaccines is likely to raise several significant challenges at global and national levels.** These include:
    a. **Even with an historic level of speed and scale, vaccine roll-out in L/LMICs through COVAX may lag behind high-income countries (HICs)** during initial immunisation rounds, and may worsen if boosters or periodic immunisation are needed.

[vi] WHO Emergency Use Listing or Prequalification needed before COVAX procurement. Pfizer has been given WHO Emergency Use Listing (EUL), with AZ and Moderna expected to follow in February. Three Chinese vaccines and one Russian vaccine are seeking WHO EUL/PQ, with decisions not expected before March.

[vii] For example, delays to Pfizer production in Europe, AZ production in various locations including Russia and India, and the uncertain timing of international supply by China

b. **Rapid access at scale is needed globally**. Well-targeted early doses are inherently more valuable – these protect health systems and reduce social and economic losses, a critical need when the pandemic is costing an estimated $544bn per month in global lost growth. Vaccine hesitancy alongside low trust in health systems and fuelled by weak pharmaco-vigilance may limit take up and impact of vaccines.
c. **The availability of multiple vaccines (from both COVAX and bilateral or regional arrangements) increases the risk of irregular dosage uptake.** Many people may receive only one dose of a vaccine schedule, or a mixed combination of first and second vaccine types and with varying gaps between doses. The impact of this is unclear, and could have implications on individual vaccine efficacy and future emergence of variants.

29. **Vaccine deployment will be particularly challenging for countries without routine adult vaccination programmes at scale** (most L/LMICs). Such limitations reduce the ability to identify, engage and reach non-routine cohorts (e.g. informal health workers, undiagnosed high-risk groups), poorer and/or marginalised sub-groups, and those in more remote locations. **Further challenges and delays will arise in the absence of established regulatory pathways, indemnification, and liability approaches.** Weak in-country supply chains also place such a high-value product at risk of diversion, loss, wastage or damage. Additional low capacity for pharmacovigilance or post-marketing trials demands a critical need for low-cost reporting system for SAEs. **LIC/LMICs will need to balance efforts to address significant supply, delivery and uptake challenges** from end to end, reducing friction for all actors in the system.

Vaccines – social and behavioural

30. **Widespread vaccine hesitancy and a lack of population trust, acceptance, and intended uptake**, **enhances the risk of insufficient coverage globally.** Vaccine hesitancy was identified as one of the top 10 threats to global health even before the pandemic[43].
31. **Although some countries have seen a rise in vaccine acceptance, recent evidence suggests that it has dropped in most countries**. World Economic Forum-Ipsos survey data[44] indicate an increase in intent to be vaccinated in countries where vaccine rollout is already substantially underway (e.g. UK, US). However, most scores were much lower, highlighting the need to avoid false optimism from positive domestic figures on vaccination intent.

32. **Community engagement, behaviour change, improving the enabling environment, and countering mis-/disinformation are paramount, especially in relation to vaccine rollout**. As has been demonstrated throughout the pandemic and in other international public health outbreaks (e.g. Ebola[45]), tailored and locally delivered solutions are required. A 'one size fits all' blueprint approach for behaviour change interventions will not be effective, especially considering cultural, political, and religious concerns as drivers for vaccine hesitancy and socio-demographic differences within countries. Given lower capacity to perform such social sciences research and sustained engagement, L/LMICs are likely to struggle the most in this area.

33. **The challenge of accurate, effective public messaging during a disease outbreak has fostered an environment for mis-/disinformation to thrive**. The cognitive difficulty of accepting and adhering to public health guidance based on complex, unfamiliar, and often inconsistent scientific concepts increases this risk.
    a. **There may be both a 'virtuous' and 'vicious cycle' between the effectiveness of public messaging and trust in leaders.** Trust in authority and the role that political and scientific leaders (and health professionals)[46,47] play in communicating messages have a significant effect on vaccine acceptance and individual decision-making.[48,49] Pre-pandemic trust has also been affected (both positively and negatively) by perceived

effectiveness of leaders during the crisis, including examples where trust in political leaders was enhanced[50 51].

b. **Exposure to mis-/disinformation is substantial across global populations, and may induce a fall in vaccine intent.** Recent survey research has shown 68% of adults in South Korea reporting exposure to at least one misinformation item[52], almost half of adults in the UK being exposed to misinformation in the last week[53], and 19% of adults in Hong Kong reporting seeing claims suggesting smoking/drinking alcohol could protect against COVID-19[54]. For one such study, in those who would otherwise "definitely" vaccinate, intent fell by 6.4% (UK) and 2.4% (US), with even greater decreases in intent to vaccinate to protect others[55].

c. **L/LMICs may need to focus their limited resources** and efforts on those who are undecided or 'on the fence' to ensure uptake. This may include making it as normative, quick, cheap, and easy as possible for people to get their vaccinations, as well as reinforcing continued adherence to other protective behaviours to prevent transmission.

34. **L/LMICs have limited capacity to undertake critical localised rapid research to identify specific barriers and drivers for maximising vaccine uptake.** Social science-informed strategies have all highlighted the need for applying and integrating behavioural considerations into the design of vaccination programmes to improve acceptance and uptake. Such conclusions are unique to the population and must be locally informed to maximise effectiveness. However, ability to carry out these investigations is dependent on strong governance and ample resources for assessment.

Vaccines – governance

35. **Corruption, organised crime and poor governance pose significant threats to COVID-19 vaccination,** including increased potential for elite capture and becoming a conflict driver (e.g. politicised targeting, exacerbating inter-communal tensions)**.** As outlined in a UN policy paper[56], vaccination is operating on an unparalleled scale for global manufacturing and distribution. While there are safeguards around donor-funded vaccines through COVAX (which still pose a risk of being breached), it is not clear whether these will be effective on bilaterally procured supply.

36. **It is highly likely that vaccine roll-out will multiply existing cracks in governance systems**. Corruption, crime, and political risks will be as important as finances, epidemiology, and logistics in dictating if and when desired coverage will be achieved. 'Fast, flat, flexible structures' are necessary to account for poor governance, including lack of transparency, dismantling of accountability structures, and unwillingness or inability to adapt in a timely manner in the face of changing evidence.

37. **Vaccine rollout is a 'perfect storm' for corruption, and serious organised crime (SOC) presents a serious risk to global vaccine deployment**. In December, Interpol issued an orange notice[i] on the SOC threat to COVID-19 vaccines, alerting global law enforcement to prepare for organised crime networks targeting vaccines, both physically and online. Researchers have indicated that vaccines present an even greater threat from corruption, fraud and organised crime[56] than that of the previously established high risk to supplies (e.g. public procurement of PPE[57]). COVID-19 vaccines are a high-demand product that: (uniquely) have a high street value; have extremely restricted supply and no legal competition (e.g. elites cannot buy their own), fuelling illegal markets, political capture, and manipulation for political ends; and have a high potential to drive inequality and conflict. The political and social cohesion impacts for corruption within the vaccine response are likely to be particularly high, because of the direct impact on the public as well as visibility and salience.[56]

38. **There is <u>no</u> current system/financing in MICs/LICs to deliver annual/periodic vaccination (with adapted vaccines) if needed,** especially in light of possible escape variants. Such a scenario would demand regional manufacturing capacity, long-term pharmaceutical partnerships, and sustainable financing for product and delivery innovation (e.g. low-cost vaccines without significant delivery challenges).

<u>Diagnostics and therapeutics</u>

39. **Despite the introduction of Ag RDTs in September 2020, testing capacity remains highly centralised in many countries, and often insufficient to meet the current demand.** This is especially true in L/LMICs, where fragile health systems and exclusive reliance on global supply chains have often left healthcare providers unable to access urgently needed tests. While HICs are now conducting 252 tests per 100,000 people each day, in L/LMICs the rate is 10 times lower at just 24 tests per 100,000 people.[58]

40. **Limited access to laboratories exacerbates the issue of populations in remote areas with the need for rapid results to avoid multiple journeys.** The ACT-Accelerator estimates that 500 million COVID-19 diagnostic tests are needed in LMICs during 2021, 75% of which must be deployed in decentralised settings (i.e. primary healthcare, community-level care, hospital triage). Ag RDTs are the primary diagnostic test for detection of active SARS-CoV-2 infection in decentralised settings where timely molecular testing is not available.

41. **Evaluation and application of diagnostics beyond direct testing has further benefit to the public health response.**[59] While the most urgent, obvious need is for diagnostics to inform the understanding of disease spread, more consideration is needed to explore the varying use cases of different diagnostic tools including outside the health sector (e.g. travel, screening). Challenges in accessing point-of-care tests and the potential usage of less reliable rapid diagnostics (highlight this need. Work supported by FIND and other global initiatives is critical to further progress.

42. **There are limited existing therapeutic options, especially those that could be feasibly used in low-resource settings, suggesting that vaccines and PHSMs may be the most effective current options for limiting severe outcomes of COVID-19 in L/LMICs.** Few drugs have yielded strong evidence for effectiveness against a range of clinical endpoints. Many therapeutics which are currently approved for use or may be in the near future, such as remdesivir or monoclonal antibody preparations, will not be cost-effective or feasible for widespread use in L/LMICs.

43. **Drugs that are available, affordable, easy to administer, and with manageable side-effects hold the greatest value in alleviating severity of disease globally.** While drugs that require well-resourced healthcare settings for delivery may have increased clinical effectiveness, other options suitable for simpler settings can be applied to a wider population and have potential for multiple use cases. Ongoing clinical trials can make most effective use of compounds where efficacy has been demonstrated, with enhanced R&D to ensure suitable treatments for L/LMIC settings – as demonstrated by work supported by CEPI and the WHO Solidarity trials.

44. **Whilst dexamethasone is likely to be an effective treatment for severe cases of COVID-19 (by mode of action), with or without supplemental oxygen, there is a lack of direct evidence for severe COVID-19 cases who do not have access to oxygen** (though evidence has shown no benefit in, and potentially harm, in non-severe COVID-19 cases who did not *require* oxygen)**.** in most data demonstrating effectiveness[60], patients who benefited from dexamethasone were those with “severe/very severe illness” defined as “on oxygen/ventilation”. Whilst this definition is applicable in HICs (as most severe

cases receive oxygen), it is less so in L/LMICs where many severe cases do not have access to oxygen. This has led to challenges of dexamethasone application in contexts where severe COVID-19 cases do not have access to oxygen. Accordingly, ongoing clinical trials are now underway to define the best use of dexamethasone and similar corticosteroids in such settings, with further results awaited.

45. **The continuously changing epidemiology and understanding of the pandemic in L/LMICs demands flexible platforms of research which can pivot quickly to emerging data**. Significant unknowns around transmission, viral mechanisms of infection, and the role of the (maladaptive) host response in generating severe clinical outcomes necessitate upstream efforts to broaden and accelerate adaptable options.

46. **Recent trial results for colchicine** also have potential for promising impact, with indications that use of colchicine in newly diagnosed SARS-CoV-2 infection reduced hospitalisations by 25%, the need for mechanical ventilation by 50%, and deaths by 44% (n = 4488 patients).[61] While this appears promising, data is preliminary with further details necessary to verify and to understand the absolute effect size.

Indirect impacts – global

47. **Indirect impacts of COVID-19 in developing countries will likely be far higher than direct impacts**. The combination of direct and indirect impacts has potential to set development progress back significantly, leaving a legacy that will last far beyond the acute phase of the pandemic.

Poverty, livelihoods and economic scarring

48. **COVID-19 is likely to have resulted in over 140 million additional people living in extreme poverty ($1.90 per day) in 2020 – around 2% of the global population.** Results from internal forecasting suggest that COVID-19 has reversed development progress on global poverty by about 7 years, with the world's population of extreme poor now being similar to their level in 2013.[viii] Before the pandemic, we estimated that 8.7% of the global population would be living below the $1.90 extreme poverty line in 2020, rising to 10.6% once the long-term impacts of COVID-19 are considered. Equivalently, the estimated population of global extreme poor has risen from 657 million pre-pandemic to 797 million, with many more likely in 2021. These figures are likely to be underestimates, not accounting for the complex short-term impacts on livelihoods, asset depletion, nutrition, education, and health caused by PHSMs.

49. **COVID-19 restrictions have placed significant immediate impacts on livelihoods across developing countries.** Recent research on the impact of COVID-19 on rural households in Kenya found declining employment opportunities, especially for youths, with one-third of agricultural small- and medium-sized enterprises surveyed saying they hired less labour due to COVID-19.[62] Findings also highlighted a worsening gender gap as the increase in unpaid care responsibilities and school closures have pushed women out of the productive economy, erasing decades of advancement in women's economic empowerment. There are further implications for the ability of rural economies to effectively recover from the COVID-19 crisis, risking eroding years of progress in improving access to inputs, finance, services, and markets for farmers. Drying revenue streams and capital markets have led to a cash crunch, negatively impacting the innovative business models that have fuelled progress in this area.

[viii] Based on FCDO Chief Economist's Office forecasts, and similar to those assessed by the World Bank

50. **As well as the severe global economic downturn in 2020, there are risks of longer-term economic scarring occurring via lower investments, labour degradation and behavioural changes.** In the UK, after two previous recessions, unemployment took seven years to return to pre-crisis levels. Since the COVID-19 crisis began, five countries have defaulted on their debt while further groups of countries remain at high-risk. The resultant decline in per capita incomes is expected to set average living standards back a decade in one quarter of sub-Saharan Africa countries.[63,ix]

51. **The latest IMF assessments of global economic growth in 2020 and 2021 set out significant uncertainties in economic recovery prospects, and it is expected that previous progress in convergence will be undermined.** The IMF project an upgrade of 0.3 percentage points for 2021[64], reflecting the positive effects of vaccination onset and stronger policy responses in some countries. However, the strength of projected recovery varies significantly. With advanced economies generally expected to recover faster, progress made towards convergence over the last decade is at risk of reversal. Between 2020-2022, over 50% of emerging markets and developing economies converging towards advanced economies per capita income over the last decade are now expected to diverge.

Stability and state responses

52. **Government responses to the pandemic have varied in the degree to which they respect democratic standards, with observations generally in line with pre-pandemic state behaviour.** Tracking from the V-Dem Institute Pandemic Violations of Democratic Standards Index (PanDem) shows that in Q4 2020, some major violations of democratic standards persisted in 69 countries, most of which were already autocratic before the pandemic. Recent responses in many countries appear to be more in line with standards than those taken during the first wave, with the situation improving in 26 countries in Q4 2020 compared to the previous quarter.[65] This suggests that the so-called 'authoritarian turn' predicted by some[65] at the onset of the crisis has not yet materialised – however, careful monitoring is necessary as indirect impacts that are likely to impact political elites and social cohesion continue to emerge. It also highlights the need to embed context-specific guidance into future crisis preparedness.

53. **In some L/LMICs, the pandemic and country responses have enabled an increase in violence against civilians by state forces**. Tracking from the Armed Conflict Location and Event Data (ACLED) project showed that between March and May 2020, the enforcement of NPIs offered an opportunity for some governments to crack down on opposition and minority groups.

54. **Government responses have, in some cases, facilitated serious and organised crime, often as an unintended consequence rather than as an intended outcome.** The impact on governance and conflict globally is wide-ranging, as exemplified in a forthcoming detailed review.[66]

Indirect impacts on health

55. **COVID-19 has disrupted the supply of health services and weakened already low resilience in L/LMICs to cope with rising patient numbers.** Service delivery has been impacted by: insufficient healthcare workers (due to redeployment, fear, sickness or travel restrictions); insufficient PPE[67,68,69]; and lack of availability of diagnostic tests, therapeutics and vaccines[70]. Over half of countries surveyed by WHO report implementing policies to scale back service provision in response to COVID-19. Lower fiscal space for health and re-allocation of health spending from other services to COVID-19 interventions, including

[ix] For 45% of countries the set back is 1-4 years. For 30% of countries the set back is 5-9 years

roll-out of COVID-19 vaccines, risk worsening access to quality essential health services going forward. Specific impacts on services between May and July 2020 include:

a. 70% of countries reported disruption to routine immunisations;
b. 68% disruption to family planning services and 56% disruption to antenatal care;
c. 52% disruption to child-health services;
d. 75% disruption to non-communicable disease (NCD) treatment services.[71]

56. **Lower demand for essential health services is also reported in many countries**, due to fear of contracting COVID-19, inability to afford out of pocket payments[72], movement restrictions[73], and isolation / quarantine despite symptoms of other illnesses.

57. **The disruption to health systems is highly likely to reverse the progress made by many countries toward the health-related Sustainable Development Goals (SDGs) in recent years.** There is still limited empirical data on the impact of reductions in health service availability and utilisation, but emerging evidence highlights increases in maternal and newborn mortality, and stillbirth, in specific settings.[74,75] Modelled estimates suggest that across 118 L/LMICs, reduction in coverage of key essential health services of 9.8% - 51.9% and a rise in wasting of 10% - 50% would result in a 9.8% - 44.7% rise in under-5 child deaths and an 8.3% - 38.6% increase in maternal deaths per month.[76] Other work suggests that the pandemic may set us back by up to 25 years in progress on vaccine coverage.[77] It is likely to be some time before the full health impacts are understood.

58. **Severe direct and indirect impacts on health systems jeopardise appropriate and effective service delivery.** Areas requiring greater attention specific to the health system delivery of the COVID-19 response include:
    a. Enhanced access to low cost, sustainable oxygen therapy delivered at scale.
    b. Infection control and prevention measures, including strengthened procurement and provision of PPE (as well as more wearable options); safe options for disposal of contaminated material; potential options for expanded local production; and options for simple, effective decontamination and safe re-use.

59. **Indirect impacts on mental health, gender-based-violence, nutrition, and water and sanitation (WASH) are likely to have both short-term and long-term consequences:**
    a. Significant increases in mental ill-health have been reported among health care workers and within the general population (e.g. a three-fold increase in prevalence of depression in affected areas of Ethiopia).[78]
    b. UNFPA modelled estimates suggest approximately 15 million more cases of sexual and gender-based-violence will occur for every 3 months of lockdown globally.[79] Other analysis suggests 85 million more children worldwide may be exposed to physical, sexual and/or emotional violence over three months as a result of lockdowns [80,81]
    c. In countries and regions where COVID-19 is exacerbating existing humanitarian crises, UNICEF projects that 10.4 million may suffer from acute malnutrition in 2021, with potential for famine conditions in DRC, northeast Nigeria, South Sudan and Yemen.[82] Severe nutritional shocks impact both maternal and child mortality and long-term health and economic outcomes.
    d. Added pressure on WASH systems in L/LMICs have seen a 10-15% rise in demand for water at the household level.[83] This also limits the delivery of quality essential health services, with half of health care facilities lacking basic water services and 60% lacking any sanitation services.[84]

Indirect impacts on education:

60. **The learning losses associated with pandemic-related disruptions to education will have long-lasting impacts on future health and economic outcomes.** 1.6 billion children were affected by school closures at the peak of global lockdowns in March / April

2020. Models suggest that children in L/LMICs could lose more than a year's learning from a three-month school closure.[85,86] (Data from Pakistan's 2005 earthquake shows 1.5 years of learning were lost from a 3-month schooling disruption.[87])The OECD predicts that a loss of one-third of a schooling year will lower a country's GDP by an average of 1.5% over the remainder of the century.[88] The World Bank has estimated a $10 trillion earning loss for this student generation over their working life.[89]

61. **Long-term effects are driven in part by the significant proportion of learners who will not return to education.** UNESCO estimates that 24 million students are at risk of not returning to education institutions, with tertiary (a 3.5% decline) and pre-primary (2.8% decline) education most affected.[90] Potential factors for drop out include increased early marriage[91], pregnancy[92] and gender-based violence - as well as parental concerns for school safety. Rapid survey data in Ethiopia, India, Nigeria and Pakistan shows 4% of girls unlikely to return to school.[x]

62. **Education disruption will affect the most marginalised disproportionately, widening existing educational inequalities.** Recent data from L/LMICs shows disparity in access to basic learning materials and caregiver support, with parental education levels being a buffer for negative impact on students learning. This includes evidence of a large 'digital divide' between and within countries.

[x] Malala Fund, 2020, unpublished.

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