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Understanding the Potential Impact of Different Drug Properties On SARS-CoV-2 Transmission and Disease Burden: A Modelling Analysis

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Summary: COVID-19 drug development to date has focused on reducing deaths among hospitalised patients, but greater public-health impact could come from drugs delivered to outpatients early in the course of disease, and that prevent hospitalisation and/or onwards transmission.

Abstract

Background

The public health impact of the COVID-19 pandemic has motivated a rapid search for potential therapeutics, with some key successes. However, the potential impact of different treatments, and consequently research and procurement priorities, have not been clear.

Methods

Using a mathematical model of SARS-CoV-2 transmission, COVID-19 disease and clinical care, we explore the public-health impact of different potential therapeutics, under a range of scenarios varying healthcare capacity, epidemic trajectories; and drug efficacy in the absence of supportive care.

Results

The impact of drugs like dexamethasone (delivered to the most critically-ill in hospital and whose therapeutic benefit is expected to depend on the availability of supportive care such as oxygen and mechanical ventilation) is likely to be limited in settings where healthcare capacity is lowest or where uncontrolled epidemics result in hospitals being overwhelmed. As such, it may avert 22% of deaths in high-income countries but only 8% in low-income countries (assuming R=1.35). Therapeutics for different patient populations (those not in hospital, early in the course of infection) and types of benefit (reducing disease severity or infectiousness, preventing hospitalisation) could have much greater benefits, particularly in resource-poor settings facing large epidemics.

Conclusions

Advances in the treatment of COVID-19 to date have been focussed on hospitalised-patients and predicated on an assumption of adequate access to supportive care. Therapeutics delivered earlier in the course of infection that reduce the need for healthcare or reduce infectiousness could have significant impact, and research into their efficacy and means of delivery should be a priority.

Introduction

The COVID-19 pandemic has led to >4.5 million deaths as of 1st September 2021, and placed substantial pressure on healthcare systems, with demand for oxygen, advanced respiratory support (ARS) and beds nearing or eclipsing availability in settings hit hardest. This impact has motivated significant efforts to identify and develop therapeutics aimed at treating the disease - a need that has become even greater with the emergence of SARS-CoV-2 variants able to evade prior immunity[1–3]. This has underscored the potential for the virus to become endemic[4] and the need for an integrated, long-term approach to combating COVID-19. Such an approach will require a range of therapeutic options, targeting a range of points across the disease's natural history.

To date, many clinical trials have been conducted to evaluate potential therapeutics for COVID-19, with initial focus centring on hospitalised patients. Dexamethasone has been shown to reduce mortality in both severely/critically-ill[5] and moderately-ill patients[6] and is now recommended for use by the WHO[7]. Evidence also indicates the potential efficacy of therapeutic anti-coagulation in some patients[8], as well as interleukin-6 receptor antagonists, such as tocilizumab and sarilumab[9]. Other candidates have included antivirals such as remdesivir, although its effect remains uncertain[10,11]. Recent months have also seen trials focussed on individuals who are not hospitalised, including those aiming to prevent progression to hospitalisation, such as for colchicine[12] and inhaled-budesonide[13,14]; as well as molnupiravir[15,16], peginterferon lambda[17] and monoclonal antibodies[18–20], which may also reduce transmission through reducing viral loads. Numerous other therapeutics aimed at treating early infection in the outpatient setting remain under active development[21].

These therapeutics have diverse epidemiological impacts (reductions in mortality, impacts on healthcare demand and community transmission) and vary in which patient populations they are administered to (hospitalised individuals or outpatients). Given these diverse properties, understanding the potential impacts of each, and how this is affected by other factors (such as epidemic trajectory and healthcare supply) is vital for guiding procurement and research priorities. Here we use a modelling approach to understand the impact of established and potential COVID-19 therapeutics on disease burden and how this is affected by epidemic context and healthcare resources. Our results highlight how limited healthcare resources can constrain this impact, limiting the benefits of existing therapeutics, and provide insight into the types of therapeutic properties that could be of greatest value.

Methods

Mathematical Model of SARS-CoV-2 Transmission

We extended a model of SARS-CoV-2 transmission[25] to include an updated representation of COVID-19 disease, healthcare capacity and the impact of potential therapeutics (**Appendix, Fig.1A** and **Supp Fig.1**). The model is age-structured and includes a detailed representation of disease severity and clinical care. Those with more serious symptoms deteriorate to the point of requiring hospitalisation - they progress to either moderate disease (requiring a general hospital bed and low/moderate-flow oxygen), severe disease (requiring an ICU bed and high-flow oxygen) or critical disease (requiring an ICU bed, high-flow oxygen and ARS) **(Fig.1B).** The model tracks healthcare resource use (beds, oxygen and ARS devices) to determine what care an individual actually receives **(Fig.1C)**. Individuals recover or die, with a probability determined by an individual's age, disease severity, and healthcare received (see Appendix for further information).

Model Parameterisation

Natural history parameters for SARS-CoV-2 infection were taken from the literature (**Supplementary Tables 1-3**). Clinical parameters surrounding duration of hospital stay were derived from a literature review of publications spanning 20 countries (**Supplementary Table 4**). To derive estimates for parameters not estimable from the literature, we convened a clinical panel of 34 medical professionals who have treated patients with COVID-19 in 11 countries (Argentina, Brazil, Colombia, Ecuador, India, Indonesia, Kenya, Thailand, United Kingdom, Venezuela and Zambia). This focused on determining the potential effect of dexamethasone under different assumptions of healthcare availability and the overall effect of healthcare resource unavailability (either lack of ARS, oxygen or beds) on COVID-19 mortality. See **Appendix** for collated responses.

Model Simulation

We simulated epidemics under varying degrees of healthcare availability and epidemic trajectories; first in a setting with a profile typical of lower-middle income countries (an age-structure equivalent to the LMIC with the median proportion >65 years and median hospital-beds per-capita) under two epidemic scenarios that reflected different extents of control: a scenario with a high reproduction number for a poorly mitigated epidemic (R=2), and another with a low reproduction number for a partially mitigated epidemic (R=1.35). We varied healthcare resource availability, exploring scenarios with i)unlimited healthcare, ii)where availability of ARS only is limited, iii)where ARS and oxygen availability are both limited; and iv)where ARS, oxygen and hospital/ICU beds are all limited. To evaluate the potential impact of different therapeutics, we consider 6 different types of therapeutic effects, each corresponding to a mode of action of at least one proposed therapeutic (see Table 1). For country-specific estimation, we fit our model to COVID-19 deaths data[22,23] using a Bayesian framework (see **Appendix**) and project the epidemic forwards under different assumptions of future control.

Results

Evaluating the Impact of Dexamethasone Under Different Assumptions of Epidemic Spread and Health System Capacity: We simulated an epidemic in a setting with a profile typical of LMICs under two epidemic scenarios (R=1.35 or 2.0). Our results highlight the substantial difference in the timing and intensity of healthcare demand resulting from epidemics of different sizes. Higher R epidemics (R=2, representing a poorly mitigated epidemic) lead to a smaller fraction of moderately ill patients (requiring a general hospital bed, **Fig.2A)** and severely/critically ill patients (requiring ICU-based care, **Fig.2B)** receiving the clinical care they need, with this disparity most pronounced for ICU-based care. A lower R reduces demand for healthcare, resulting in a higher proportion of individuals receiving the required care, but still leaves a high proportion not receiving the full ICU-based care they need. We next examine the 'Infection Fatality Ratio' (IFR, the probability of death given infection) that persons with SARS-CoV-2 face, arising from the joint effect of disease, healthcare capabilities and usage of dexamethasone. Our results highlight the pronounced impact of healthcare constraints on the IFR, which is significantly higher when healthcare resources (ARS, O_2 and beds) are limited (**Fig. 2D**: dots). This increase in IFR is most substantial for our high R scenario in which a higher fraction of individuals not receiving adequate care.

The therapeutic impact of dexamethasone (**Fig. 2D**: boxes) is strongly dependent on these same factors: there is a substantial reduction in mortality due to the drug when there are adequate healthcare resources, but a much smaller effect when these resources are unavailable. This is especially the case when a larger epidemic has overwhelmed resources **(Fig.2D)**. The reduced impact of dexamethasone in these circumstances is because fewer individuals are hospitalised and receive dexamethasone (due to shortages of beds) and fewer hospitalised individuals receive the other healthcare required (oxygen/ARS) to maximise the therapeutic benefit of

dexamethasone. As a result, prevailing healthcare resources in this typical setting allow only 45% (if R=1.35) or 28% (if R=2.0) of the maximum potential impact of dexamethasone (defined as the reduction in IFR achieved by the drug under a scenario with no healthcare resource constraints) to be realised (**Fig. 2E**).

We distinguish two layers of uncertainty in characterizing the effect of dexamethasone: the magnitude of the effect when supportive care is available, and the extent to which these effects would persist in patients not receiving such case. The second is not well understood but we constructed three alternative scenarios (based on clinical input described in the **Supplementary**) for the extent to which patients without supportive care may benefit from dexamethasone. We find only a small extra impact (60% of potential drug impact realised under R=1.35 scenario, and 52% under R=2scenario) if it was assumed that individuals for whom supportive care could not be provided still benefited to some degree from dexamethasone **(Supp Fig.3).**

Evaluating the Potential Impact of Dexamethasone Globally: Our results suggest that limitations in healthcare capabilities that reduce dexamethasone's impact are likely to be most severe in LMICs. Under scenarios where extensive mitigation of transmission is achieved globally (R=1.35 scenario**, Fig.3A**), we expect a median of 28%, 43%, 91% and 100% of dexamethasone's maximum potential impact to be achieved across LICs, LMICs, UMICs and HICs respectively **(Fig.3B)**, corresponding to averting 8%, 13%, 20% and 22% of total deaths. Under scenarios where epidemics are less controlled (R=2, **Fig.3C**), this reduces to 18%, 26%, 43% and 71% of dexamethasone's maximum potential impact (5%, 7%, 13% and 18% of deaths averted) **(Fig.3D)**.

Exploring the Potential Impact of Different Treatments and Drug Properties: We divide the spectrum of potential effects of the therapeutics currently under investigation into six types (**Table 1**) and explore their impact on COVID-19 mortality (**Fig.4A** and **Supp Fig.4**). The impact of therapeutics administered to hospitalised patients (types 1, 2 and 3) have a lower overall impact in reducing deaths, even when efficacy and coverage are high, because they suffer from the limitation that their therapeutic benefit is dependent on similar healthcare capabilities (such as oxygen and ARS) described above for dexamethasone **(Fig.4A, top row)**. Therapeutics that reduce severity of disease (Type 2) or reduce the duration of hospitalisation (Type 3) do have an indirect effect in alleviating healthcare demand, but this is minimal because demand for healthcare resources outstrips supply by such a wide margin, even under comparatively well-controlled epidemics (low R scenario). In these scenarios, a slightly faster throughput of patients therefore does not substantially reduce the number of individuals unable to access healthcare due to a lack of availability.

Therapeutics that are not administered in hospitals (and so do not suffer the same limitations) and address patients at an earlier stage of disease progression have a potentially greater impact, even after allowing for the lower coverages that may be achieved **(Fig.4A, bottom row)**. Type 4 therapeutics (which reduce likelihood of severe disease and hospitalisation) have both a direct effect (reducing mortality) and an indirect effect (reducing healthcare demand and enabling greater access to healthcare for others) - and avert a significant fraction of COVID-19 mortality. For our low R scenario, there is an even greater effect from Type 5 therapeutics (which reduce infectiousness). Through reducing community transmission, they lead to reductions in the overall number of people infected with SARS-CoV-2 during the epidemic and alleviate demand for healthcare resources. This would be especially the case if therapeutics are administered before onset of symptoms (Type 5b), although the coverage that could be achieved with such therapeutics would be expected to be lower than for therapeutics administered following symptom onset (Type 5a). It follows that the estimates of impact are influenced by R and healthcare resources (see **Supp Fig 4** in SI) - for Type 5 therapeutics, relative impact is higher under the low R scenario, and lower in the high R scenario (though still comparable with the best performing hospital administered therapeutics); for our high R scenario, Type 4 therapeutics were predicted to have the greatest

benefit in the range of indicative coverages and efficacies explored **(Supp Fig 4B).** If healthcare needs do not eclipse resources, the direct effect of hospital-delivered therapeutics is greater than otherwise, although the overall impact on mortality from Types 4, 5a and 5b remains high.

Discussion

Understanding the contexts in which COVID-19 treatments are likely to be most effective is essential for guiding research and procurement. Here, we utilise a modelling approach to evaluate the potential impact of COVID-19 treatments under a range of different assumptions about healthcare availability and epidemic trajectory. Our results show that effect sizes for therapeutics estimated in clinical trials will not necessarily provide a guide to their 'real-world' impact on COVID-19 disease burden as 'real-world' impact also crucially depends on prevailing healthcare constraints, the trajectory of the epidemic and the extent to which benefits persist in the absence of supportive care. We find that the impact of the main therapeutic currently recommended by the WHO (dexamethasone) could be considerable in well-resourced settings with an epidemic under control (averting almost a quarter of deaths), but far smaller in settings where resources are limited and/or there is large epidemic (averting fewer than 10% of deaths). Whilst our focus here is on dexamethasone, these results would apply similarly to other therapeutics for which clinical benefit is dependent on the presence of supportive care such as oxygen or ARS.

Our results highlight that treatments with different types of effect can yield vastly different scales of population-level impact. In particular, the results show that substantial impact could be achieved with therapeutics delivered to persons not in hospital that either reduce the duration of infectiousness (and hence transmission) or disease severity (preventing hospitalisation, reducing healthcare strain), in-keeping with recent work highlighting the need for effective COVID-19 treatment for early infection in the outpatient setting[21]. Indeed, our results highlight that even modest levels of treatment efficacy or coverage could achieve high levels of impact, although the exact level of impact will likely be determined by a complex interplay of baseline transmission, household structure, quarantining practices, and the background of other control measures being implemented – factors only crudely considered here through our modulation of the reproduction number. However, because of the nature of their administration (delivered in the community) and the effects of these therapeutics (which depend only minimally on the availability of constrained healthcare resources), our results suggest their potential impact would also be less affected during larger epidemics.

Although most trials to date have focussed on evaluating treatments aimed at critically ill, hospitalised patients, there are promising results from some trials. Several individual/combination monoclonal antibody treatments have shown an impact on viral loads and hospitalisation[18–20]; however significant challenges related to delivery (the need for intravenous infusions) and their high cost likely preclude widespread utilisation in resource-poor settings. Numerous repurposed therapeutics have also been or are currently being evaluated as part of large scale adaptive trials: these include PRINCIPLE (evaluating azithromycin[24], doxycycline[25] and inhaled budesonide[13] in outpatient populations, amongst other drugs), ANTICOV (led by the Drugs for Neglected Diseases Initiative, evaluating a number of different therapeutics in 13 countries across Africa[26]), and the ACTIV-6 platform, which is testing a number of repurposed drugs[27]. Whilst some of these (e.g. inhaled budesonide) have shown promise, the majority of drugs assessed through these platforms aim to reduce duration and severity of symptoms in those with mild disease (a Type 4 property), rather than transmission (Type 5). It is in this context that results from the trials of orally administered antiviral molnupiravir (which has shown preliminary evidence of potentially both properties) are eagerly anticipated[15, 16].

Whilst the impact of drugs delivered in the outpatient setting are less dependent on prevailing in-hospital healthcare resources, this would need to be balanced by the ability of healthcare systems to deliver therapeutics in the community (including health worker capacity and distribution channels) and the costs of doing so. There therefore remain numerous factors that will modulate their effectiveness that warrant discussion here. Perhaps most crucially is the need for rapid, widely-available COVID-19 testing to identify persons infected early and hence maximise reductions in onwards transmission achieved by drugs with Type 5 properties (and to a lesser degree, ensuring Type 4 drugs are delivered to individuals before significant disease progression). Testing capacity thus represents a crucial determinant of the effectiveness of these drugs, but this remains inadequate in many parts of the world: for instance, recent results from a post-mortem surveillance study in Lusaka, Zambia suggest that the majority of COVID-19 deaths (>70%) had occurred without any test having been conducted. A related limitation is that we assume levels of healthcare-seeking within the population such that all individuals with COVID-19 requiring hospitalisation will seek care. Numerous studies have highlighted the disparities in access to healthcare that exist globally (e.g.[28,29]), and that cost of care (if borne privately) can be a key determinant[30]. To the extent that not all of those in need seek care in-hospital, the limitations we have found for therapeutics for hospitalised patients and the potential benefits of therapeutics for non-hospitalised patients would be even greater than our results show. More generally, whilst our results have highlighted that only modest levels of coverage among patient populations with these therapeutics is required for significant impact, such levels are likely impractical for therapeutics requiring infusion such as monoclonal antibody therapies. The current cost of these therapies is also substantial and may prove prohibitive in all but the most well-resourced settings. Achieving levels of coverage required for substantial impact may be more feasible for orally delivered, low-cost therapeutics.

Additional caveats to the framework developed here includes lack of waning immunity or the possibility of novel SARS-CoV-2 variants able to partially evade protective immunity (as in Brazil[2], South Africa[31] and many other countries), nor how emergence of new variants may erode efficacy of previously effective therapeutics (such as bamlanivimab in the case of the Delta[32]). We further consider only country-level outcomes, which indicates broad trends, but which masks important sub-national variation in the availability of healthcare resources (e.g. as highlighted in recent work across Indonesia[33] and Brazil[34]) that would likely see mortality concentrated in areas with the least capacity– nor do we take into account the COVID-19 death underreporting that is likely concentrated in resource-poor settings with the least developed civil and vital registration capacity, and would result in inference of more mature epidemics and higher degrees of population-level immunity. The modelling also does not consider the judgments that may be made about how available resources are allocated among different patients, in view of their varying needs, risk of complications (including "long COVID"), and likelihood of success of different treatment options, which may mitigate to some small extent that effect of the constraints indicated.

Despite these caveats, our results highlight that low health system capacity in LMICs will likely limit the impact of many of the COVID-19 therapeutics currently being used to treat hospitalised patients (such as dexamethasone) and underscore the crucial need for effective COVID-19 therapeutics targeting outpatients with mild-to-moderate disease, early in the disease course. However, we also highlight important logistical and practical challenges to achieving the significant impact possible with these therapeutics, underscoring the importance of accompanying clinical trials with operational research in order to ensure mechanisms for drug delivery to affected communities can occur in a way that maximises their potential benefit.

NOTES

Contributions

CW & TBH conceived the study. CW, OJW and PGTW undertook the modelling and data analysis, with input from TBH, ACG, AH, HT, PW and AQ. All other authors contributed to forming modelling assumptions and interpreting results in a clinical panel or assisted in the setting up of the clinical panel. CW & TBH produced the first draft of the manuscript. All authors contributed to the final draft.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

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None of the authors have potential conflicts.

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FIGURE LEGENDS

Figure 1: Mathematical modelling approach used to evaluate potential COVID-19 treatment impact. (A) Schematic representation of the natural history of SARS-CoV-2 infection and COVID-19 disease in the model. **(B)** Description of the different disease states included in the model and the associated healthcare requirements. **(C)** Decision-tree diagrams illustrating the conditional delivery of healthcare components according to disease severity and availability. There is excess mortality associated with not receiving the full set of required healthcare components.

Figure 2: Projected impact of dexamethasone on COVID-19 mortality under different scenarios of epidemic progression and healthcare availability. (A) Daily general hospital bed demand under an epidemic scenario with a high reproduction number (R = 2, orange) or a low reproduction number (R = 1.35, green). Dashed lines indicate availability of different healthcare resources, and the right hand panel describes the proportion of patients that require oxygen and a general hospital bed who receive complete (bed and oxygen), incomplete (bed only) or no healthcare (neither). **(B)** As for **(A)**, but describing demand and healthcare received for severely and critically ill patients requiring an ICU bed, oxygen and advanced respiratory support (ARS). **(C)** Schematic illustration of the impact assumed for dexamethasone on COVID-19 mortality in different patient populations (moderate, severe or critical illness), and according to the care received (complete, incomplete or none) **(D)** The impact of dexamethasone on the COVID-19 infection fatality ratio under different assumptions for R (low, green or high, orange) and healthcare availability (unlimited, limited ARS, limited ARS and oxygen or limited ARS, oxygen and beds). In all panels, black points show the IFR without dexamethasone, and the boxplots show the modelled IFR using the assumed dexamethasone clinical benefit estimates described in **(C)**. **(E)** The percentage of maximum potential dexamethasone impact (defined as the reduction in IFR achieved by dexamethasone under a situation of unlimited healthcare) achieved in each of the different scenarios for healthcare availability. Orange and green bars refer to high and low R scenarios respectively, with the shading indicating the extent of imposed healthcare constraints, coloured as for **(D)**.

Figure 3: The global impact of dexamethasone on COVID-19 mortality under different assumptions for future transmission and epidemic spread. (A) The percentage of maximum potential dexamethasone impact (defined as the reduction in IFR achieved by dexamethasone under a situation of unlimited healthcare) achieved for each country under an epidemic scenario of extensive mitigation control (R = 1.35). **(B)** The percentage of maximum dexamethasone impact achieved in each country. Each dot is the result for a single country, coloured according to the World Bank strata that country belongs to, with the boxplot presenting summary statistics for the modelled countries in aggregate. **(C)** As for A, under an assumption of an epidemic scenario characterised by uncontrolled spread (R = 2). **(D)** As for B, under an assumption of an epidemic scenario characterised by uncontrolled spread (R = 2).

Figure 4: Impact of different therapeutic product effects on COVID-19 disease burden. (A) For an epidemic with an R of 1.35, the proportion of COVID-19 deaths averted as a function of therapeutic efficacy and therapeutic coverage, for 6 different types of potential effects (Table 1). These include reducing COVID-19 disease mortality (Type 1); preventing deterioration and worsening of disease in hospitalised patients (Type 2); reducing duration of hospitalisation (Type 3); preventing hospitalisation due to COVID-19 (Type 4) and reducing duration of infectiousness, either among symptomatics (Types 5a) or all infected-persons (Type 5b). Inset boxes indicate the range of plausible values of coverage used to generate the estimates in **(B). (B)** Disaggregation of therapeutic effect type impact by whether this is direct or indirect. Bars are coloured according to the type of impact (direct reduction in mortality, indirect reduction in mortality due to reduced pressure on healthcare or indirect reduction in mortality due to reductions in community transmission), with error bars indicating the maximum and minimum proportion of deaths averted under the range of coverage and effectiveness values considered for each effect type (indicated by the boxes in **(A)** and **Table 1**).

Table 1: Potential COVID-19 therapeutic effects and their impacts. (Note: Inclusion in this list indicates that studies are underway to test for this property, and not that evidence has been found.

Effect	Description	Target Population	Epidemiological Impact	Examples of Therapeutics Which May Have This Property*	Indicative Potential Efficacy Range	Indicative Potential Coverage Range
Type 1	Reduce COVID-19 mortality	Hospitalised patients (moderately, severely or critically ill)	Reduced mortality	Dexamethasone (moderately[5] & severely/critically ill patients[5,6]). Remdesivir (moderately ill patients[10,11], per the meta-analysis of the two trials) Tocilizumab and Sarilumab (severely/critically ill patients[9]) Therapeutic anticoagulants (moderately ill patients[8])	20-45% relative reduction in mortality	90-100%
Type 2	Reduce COVID-19 severity (in hospitalised patients)	Hospitalised patients (moderately, severely or critically ill)	Reduced mortality and healthcare pressure	Possibly therapeutic anticoagulants (moderately ill patients[8])	20-45% relative reduction in hospitalised patients requiring ICU stay	90-100%
Type 3	Reduce duration of hospitalisation with COVID-19	Hospitalised patients (moderately, severely or critically ill)	Reduced healthcare pressure	Remdesivir (moderately ill patients[11]).	20-45% decrease in duration of hospitalisation	90-100%
Type 4	Prevent hospitalisation due to COVID-19	Post-symptom onset. Mildly symptomatic individuals in the	Reduced mortality and healthcare pressure	Monoclonal antibodies[18–20] Molnupiravir[15,16]	25-75% reduction in chance of hospitalisation	25-50%

		community		Inhaled Budesonide[13,14] Possibly Colchicine[12]		
Type 5a	Reduce duration of infectiousness	Post-symptom onset. Mildly symptomatic individuals in the community	Reduced mortality, healthcare pressure and transmission	Postulated for Monoclonal antibodies due to effect on viral loads[18–20] Possibly Molnupiravir[15,16] Possibly Peginterferon-Lambda[17]	25-75% reduction in duration of infectiousness	25-50%
Type 5b	Reduce duration of infectiousness	Post-exposure. All individuals exposed to risk of infection, irrespective of symptoms	Reduced mortality, healthcare pressure and transmission	Postulated for Monoclonal antibodies due to effect on viral loads[18–20] Possibly Molnupiravir[15,16] Possibly Peginterferon-Lambda[17]	20-75% reduction in duration of infectiousness	10-25%