


INVITED REVIEW ARTICLE

Model-informed drug repurposing: A pharmacometric approach to novel pathogen preparedness, response and retrospection

Michael Dodds¹ | Yuan Xiong¹ | Samer Mouksassi¹ | Carl M. Kirkpatrick²  |
 Katrina Hui^{1,2} | Eileen Doyle¹ | Kashyap Patel^{1,2}  | Eugène Cox¹ |
 David Wesche¹ | Fran Brown¹ | Craig R. Rayner^{1,2} 

¹Certara, Princeton, NJ, USA

²Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia

Correspondence

Craig R. Rayner, Certara, 100 Overlook Center, Princeton, NJ, 08540, USA.
 Email: craig.rayner@certara.com

Funding information

Bill and Melinda Gates Foundation

During a pandemic caused by a novel pathogen (NP), drug repurposing offers the potential of a rapid treatment response via a repurposed drug (RD) while more targeted treatments are developed. Five steps of model-informed drug repurposing (MIDR) are discussed: (i) utilize RD product label and in vitro NP data to determine initial proof of potential, (ii) optimize potential posology using clinical pharmacokinetics (PK) considering both efficacy and safety, (iii) link events in the viral life cycle to RD PK, (iv) link RD PK to clinical and virologic outcomes, and optimize clinical trial design, and (v) assess RD treatment effects from trials using model-based meta-analysis. Activities which fall under these five steps are categorized into three stages: what can be accomplished prior to an NP emergence (preparatory stage), during the NP pandemic (responsive stage) and once the crisis has subsided (retrospective stage). MIDR allows for extraction of a greater amount of information from emerging data and integration of disparate data into actionable insight.

KEYWORDS

clinical pharmacology, COVID, infectious diseases, model-informed drug development, pandemic, pharmacometrics, repurposing

1 | INTRODUCTION

Unlike endemic diseases, a pandemic triggered by a novel pathogen (NP) may be a quickly moving target defined by outbreaks of unknown duration, location and severity. Traditional drug development for new molecular entities tailored to an NP takes too long to be considered as first-line treatment. In contrast, drug repurposing is well suited to the pandemic situation because the repurposed drugs (RD) are often well characterized and usually available as marketed products. Use of approved drugs is advantageous as there is usually a lower risk of failure due to safety reasons particularly during efficacy trials, a shorter time-frame needed for drug development and less investment required.¹

Pandemic pathogens are generally either bacterial or viral, with viral pathogens greatly outnumbering their bacterial counterparts. While the approaches are likely applicable to both, the work presented focuses on viral pandemics which are currently the principal issue.

The presented strategy for model-informed drug repurposing (MIDR) can facilitate prioritization and decision making during a pandemic. An MIDR strategy is described that is independent of the NP of interest, though case examples related to SARS-CoV-2 are presented in the Supplementary Materials for illustration. This strategy is presented in two arrangements. The first arrangement relates to increasingly deeper analytical activities that unfold as information is gained about the NP. The second arrangement relates to parsing these analytical activities by what can be done prior the

emergence of an NP, what can only be done during the pandemic, and what incremental improvements should be considered after the pandemic has passed. Both arrangements are valid perspectives on the same approach.

2 | MODEL-INFORMED DRUG REPURPOSING

2.1 | Overview

At the start of a pandemic there is very little information about the NP. Information on mechanism of infectivity and site of action (SOA) of infection are obtained, followed by testing in vitro potency of compounds that have shown efficacy against similar pathogens with the clinical isolates of the NP. In vitro potency information is compared against reported clinically achievable exposures, providing estimation of probability of achieving clinically effective concentrations (Step 1, Figure 1). While the translatability of the in vitro systems to

clinical outcome might be questionable, these data define the extent of actionable information. For RDs that appear promising, clinical pharmacokinetics (PK) could be explored in order to develop recommendations on optimal posology (Step 2, Figure 1) as there is no reason, a priori, to believe that a posology developed for a labelled indication will be optimal for treatment of an NP. In such cases, the suitability of the available safety data may need to be reassessed prior to progressing to clinical trials.

The passage of time yields data: information about NP viral kinetics becomes available. These data are used to build a viral kinetic (VK) model that links events in the viral life cycle to PK of the RD (Step 3, Figure 1), guiding clinical trial design.

Later in the pandemic, greater experience with RD interventions allows comparison, contrast and synthesis. As clinical response data emerge, exposure–response (E-R) analysis can be used to assess adequate exposure in the patient population and to understand factors that drive response (Steps 4, Figure 1). This data can loop back to the early in vitro data, and questions around dose and regimen specific to the NP can be addressed.

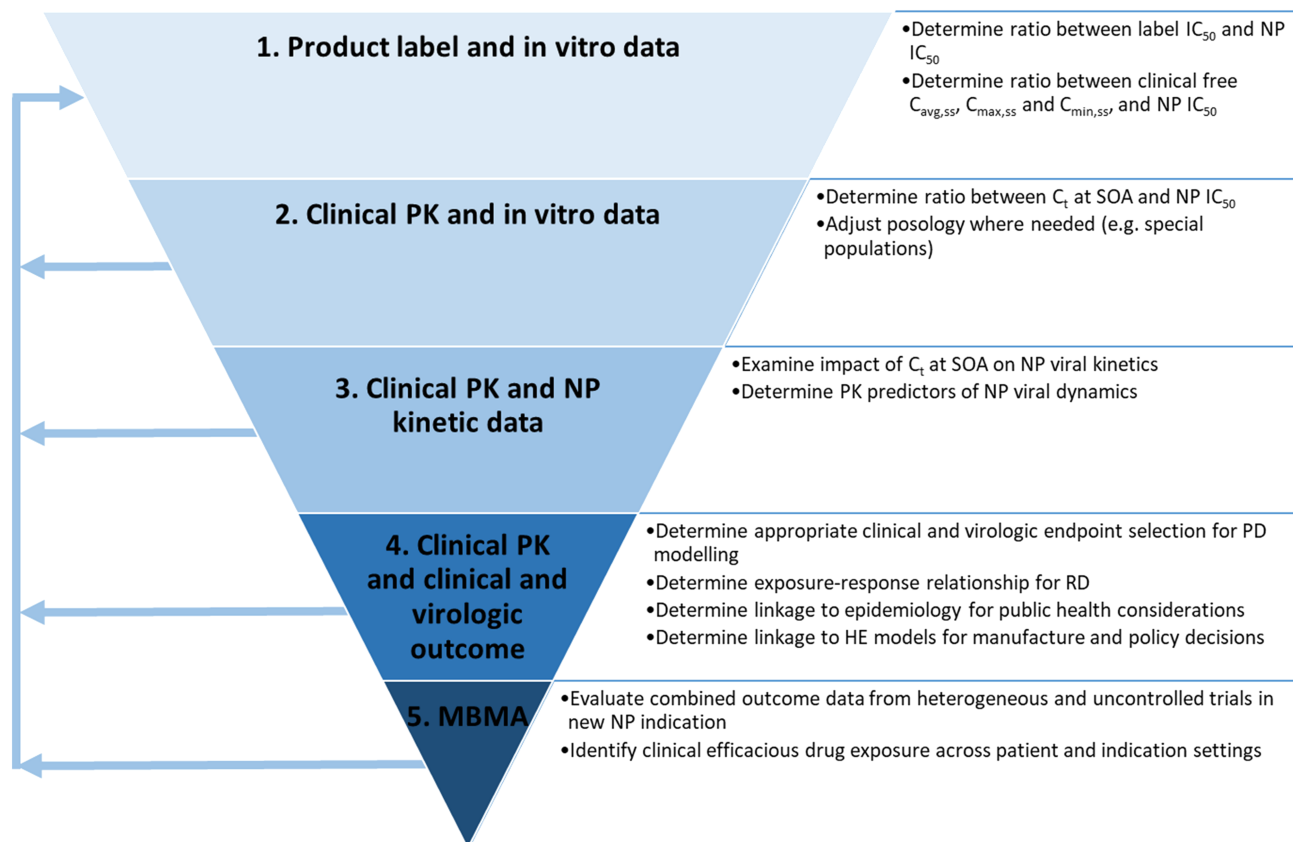


FIGURE 1 MIDR strategy arranged by increasing analytical depth and knowledge generation with increasing novel pathogen understanding $C_{avg,ss}$, average steady state concentrations; $C_{max,ss}$, maximum steady state concentration; $C_{min,ss}$, minimum steady state concentration; C_t , tissue concentration; IC_{50} , half maximal inhibitory concentration; HE, health economic; MBMA, model-based meta-analysis; NP, novel pathogen; PK, pharmacokinetics; RD, repurposed drug; SOA, site of action. Notes: The amount and quality of information is indicated by shade of colour (lighter shade equals least amount of information and lower quality information, darker shade equals most amount of information and higher quality information). Arrows indicate that the learnings from each step can be used to update and refine the activities of the previous steps. It is also critical that the same concentration units (e.g., μM) be calculated for all concentration values, including IC_{50} values, in all steps

After clinical trials are performed, large volumes of information are available, but comparisons are difficult and seeming contradictions are evident. Model-based meta-analysis (MBMA) can be employed to extract the most information from these trials to quantitatively assess drug treatment effects (Step 5, Figure 1).

Each of these steps is intended to facilitate action: should further time and resources be invested in a specific RD? Critically, compounds are not necessarily *rejected* with these tools; they are *prioritized*, thereby facilitating decision making whilst keeping in mind fundamental PK and PD principles including exposure at the target SOA, binding to the pharmacological target and expression of pharmacology.² The steps are arranged so more insightful analyses are performed as more information about the NP becomes available (Figure 1) with focus on RDs that are prioritized higher as guided by the results from earlier steps. Early activities are not less useful than later activities; they are pragmatic and represent what can be accomplished with the information available at that moment in the pandemic arc. Later activities update and refine the findings from earlier activities.

A complementary arrangement of this MIDR strategy is made by considering what can be done in preparation for a pandemic, what must be done during the pandemic, and what should be done after the pandemic. Table 1 delineates activities from Figure 1 by these stages.

In each step of the MIDR process, particular data are needed, and specific assumptions must be made. Below is a discussion of each of the MIDR steps described in Table 1 and Figure 1.

2.2 | Step 1. Repurposed drug product label and in vitro data

RD information from the product label and publications is mined and compared to in vitro data generated for the NP, providing initial assessment of potential for use of the RD against the NP.

The suitability of the labelled posology is considered by two quantitative methods (Figure 1, Step 1) using a readily available in vitro parameter such as IC_{50} : (1) comparing the ratios of in vitro IC_{50} of the RD for approved marketed indication(s) relative to that of the NP and (2) comparing the ratio of the average, maximum and minimum steady-state RD free concentration at the approved clinical regimen to the NP IC_{50} .³ Both steps offer initial assessments of whether concentrations near or above the NP IC_{50} can be achieved (see Case Example 1 in the Supplementary Materials). For most antivirals, exposures higher than IC_{50} are likely to be required to eradicate the infection. Whilst IC_{90} would be preferred, it is not as commonly

TABLE 1 MIDR strategy arranged by activities performed before, during and after the pandemic

| MIDR steps | Preparatory stage (developing infrastructure) | Responsive stage (move quickly once NP is identified) | Retrospective stage (reflect and update) |
|---|---|--|--|
| 1. Product label and <i>in vitro</i> data | <ul style="list-style-type: none"> - Obtain label IC_{50} for potential RDs - Obtain molecular weight for potential RDs - Obtain f_u and compute free $C_{avg,ss}$, $C_{min,ss}$ and $C_{max,ss}$ at the approved clinical dose | <ul style="list-style-type: none"> - Obtain ratio of RD IC_{50} to NP IC_{50} - Obtain ratios of RD free $C_{avg,ss}$, $C_{min,ss}$ and $C_{max,ss}$ to NP IC_{50} | <ul style="list-style-type: none"> - Addition of new potential RDs to this list - Review translatability of results, including cell lines used to determine IC_{50} |
| 2. Clinical PK and <i>in vitro</i> data | <ul style="list-style-type: none"> - Determine tissue concentrations for RD - Develop a real-time simulation platform for RDs based on PopPK/PBPK models | <ul style="list-style-type: none"> - Obtain ratio of RD tissue concentrations to NP IC_{50} - Refine models and simulations as in vitro data for NP become available | <ul style="list-style-type: none"> - Update model and simulations as new data related to the NP emerges |
| 3. Clinical PK and NP kinetic data | <ul style="list-style-type: none"> - Develop a real-time simulation platform which integrates general VK models with PopPK/PBPK models | <ul style="list-style-type: none"> - Refine VK models and simulations as NP viral kinetic data become available | <ul style="list-style-type: none"> - Update VK model and simulations as new data related to NP emerge |
| 4. Clinical PK and clinical and virologic outcome | <ul style="list-style-type: none"> - Develop best practice, highly efficient trial study design guidance for future pandemics focusing on clinical pharmacology to establish optimal dosing of RD and combination RD regimens | <ul style="list-style-type: none"> - Conduct highly efficient clinical pharmacology focused trials using adaptive designs to optimize RD dosing and potential combination RD treatments for an emerging pathogen | <ul style="list-style-type: none"> - Refine and update study design guidelines |
| 5. Model-based meta-analysis (MBMA) | <ul style="list-style-type: none"> - Set up processes for efficient/automated data capture - Develop routines for a standardized or automated NMA/MBMA | <ul style="list-style-type: none"> - Update databases and conduct MBMA simulations to translate NMA/MBMA analyses to facilitate decision making - Develop web-based graphical interface or application specific to the NP | <ul style="list-style-type: none"> - Review data capture and analysis processes (efficiency, quality) |

f_u , free fraction of drug; $C_{avg,ss}$, average steady state concentration; $C_{max,ss}$, maximum steady state concentration; $C_{min,ss}$, minimum steady state concentration; IC_{50} , half maximal inhibitory concentration; MBMA, model-based meta-analysis; NMA, network meta-analysis; NP, novel pathogen; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; PopPK, population pharmacokinetics; RD, repurposed drug; VK, viral kinetics

reported as IC_{50} . Therefore, in these initial steps IC_{50} is used to provide some early indication as to whether the repurposed drug demonstrates potential activity against the target virus.

Furthermore, consider that an NP IC_{50} two orders-of-magnitude higher than the IC_{50} for the approved marketed indication(s) suggest a substantial increase in dose would be required to bring the RD concentration into an effective range against the NP. In order to be repurposed, the candidate must have safety coverage at the proposed posology.

The minimum ratio for initial prioritization for repurposing should be >1 for both evaluation metrics. Ratios of <1 could be acceptable if there is clear evidence from existing safety data that there is sufficient scope for a proportional increase in dose to achieve (or exceed) the desired target ratio >1 while not experiencing concentration-dependent side effects. Again, the purpose here is to *rank* potential RDs, so these ratios should be thought of as down-selection and up-selection (prioritization) tools.

Activities such as generating a master list of RD label IC_{50} s, f_u , $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$ can all be performed in the preparatory stage (Table 1, Step 1). Activities around the NP IC_{50} in this step must be performed rapidly after the NP is identified. Review and curation of the potential RD list, including new additions for future pandemic preparedness, should take place in the retrospective stage. Additionally, the translatability of cell lines (discussed further in Step 2 and the Supplementary Materials) and other methods to determine RD potency against the NP should be considered and recorded for future pandemics.

2.3 | Step 2. Repurposed drug clinical PK and in vitro data

Once initial assessment that the RD has the potential to reach effective concentrations has been achieved, the potential for the RD to be optimized can be further evaluated. Investigations at this stage include determining (or predicting) NP exposure at the SOA, considering the predicted RD concentration within its therapeutic window (including safety margins), adjustments of posology to account for the acute nature of the NP, and making assumptions about the interaction between NP and RD at the SOA.

This step (Figure 1, Step 2) considers the potential for differences in the SOA between the indication with marketing approval and the NP. Free drug concentration can be a useful surrogate for tissue concentration. If available, PK studies that directly measure RD concentration in target tissues are ideal. If not, mathematical modelling such as physiologically-based pharmacokinetic models (PBPK) may be utilized to account for altered partitioning, transporter utilization and tissue metabolism.^{2,3}

Through experience during the current pandemic, we recommend that the ratio of free drug tissue (SOA) concentration vs. IC_{50} is the key metric for consideration and should ideally be greater than 1. Repurposed drugs that achieve or exceed this target can undergo posology optimization for use against the NP. During posology

optimization, differences in methodology utilized for the in vitro IC_{50} measurement must be taken into account^{3,4} (see Case Example 2 in the Supplementary Materials). For example, in vitro tests of repurposed anti-viral compounds are often performed in cell culture assays with low ($<20\%$) or no protein in the assay. Human plasma has significant circulating proteins, so free RD concentration in situ may be vastly different from that observed in an in vitro assay (as was seen in SARS-CoV-2 with ivermectin).^{5,6}

Additionally, cell culture systems may not mimic normal cell function to an extent that allows determination of the true tissue concentration ratio, so the in vivo IC_{50} may differ from that observed in vitro.^{7,8} Additional complexities of active metabolites or intracellular activation play a role and should be considered for a specific RD with those features. Moreover, the RD may have a posology that is well suited for chronic administration but should be adjusted for the acute NP case. For example, drug accumulation over the course of multiple days to an effective concentration is appropriate for long-term treatment or prophylaxis, but would be suboptimal in the context of an acute infection by an NP in a pandemic setting. Likewise, long-term safety data should also be interpreted in light of differences in duration of therapy between licensed indication and use as an RD (e.g., safety signals emerging at 1 year of treatment may not be relevant for a proposed RD 14-day treatment). Therefore, due diligence must be undertaken, particularly for older drugs, with regard to safety.

In Step 2, a real-time simulation platform for RD exposure could be developed. For many newer drugs, the dose-exposure relationship would have been studied through PopPK and/or PBPK analyses during the drug development process. For older drugs, this information may be less readily available, though published models could be used where available. While the PopPK model is relatively straightforward to implement in simulations, most analyses focus on plasma or serum concentrations only, and lack a direct link to the SOA (e.g., lung tissues). Whilst PBPK modelling is perfectly suited to describe drug distribution across different organs, tissues, SOAs and drug exposures in special populations (e.g., paediatric, geriatric, critically ill), de novo implementation of this approach during a pandemic is challenging. Both approaches can be modified to provide accurate prediction of RD free concentration at an NP's SOA, and both approaches can largely be implemented using pre-pandemic data.

For the PopPK or PBPK-based simulations to provide practical information in a pandemic, a real-time simulation platform should be developed during the preparatory stage (Table 1, Step 2, see Case Example 2 in the Supplementary Materials). Once an NP and RD are identified, real-time PK simulations using published PopPK and/or PBPK models can be developed quickly. Results will then be available for comparison as NP in vitro data emerge, with necessary adjustments made for SOA, population characteristics or other relevant covariates. During a pandemic, the models and simulations can be updated as new NP data, and relevant disease-related changes (e.g., to drug distribution across different organs or tissues), become available.

2.4 | Step 3. Repurposed drug PK and novel pathogen kinetic data

With the PK of the RD determined and initial NP viral kinetic (VK) data emerging, efforts should focus on understanding the effect of RDs on the viral kinetics of the NP. Once an NP is identified, integrating VK models with PopPK/PBPK models is crucial to understanding where and when an RD could have the largest impact (see Case Example 3 in the Supplementary Materials). A critical prerequisite for understanding viral kinetics is the development of a new, reliable, sensitive assay to measure the NP across the time course of the infection.

Viral kinetic data provide an understanding of the infection characteristics, which differ by virus: latency period, virus generation time and duration of infectiousness.^{9,10} For influenza and respiratory

syncytial virus (RSV), the time between clinical symptom onset (1 and 3 days, respectively) and peak viral load (2 and 6 days, respectively) is short relative to the start of infection.^{9,11–13} In contrast, symptom appearance and corresponding diagnosis is considerably longer (range 5–24 days)¹⁴ following SARS-CoV-2 infection, and may occur just prior to or near the time of maximal viral load.¹⁵ Consideration of the time window between infection at the SOA and symptom onset is crucial to developing effective therapies and the optimal timing of their administration. Most antiviral drugs are designed to inhibit infectivity or free virion production, and are only active prior to peak viral load (Figure 2). If diagnostic tools are available and the time between infection and symptom onset is short (<3–5 days), drug repurposing using established replication inhibitors may be effective for treatment and prophylaxis. If the time between infection and symptom onset is longer (>5–10 days, as

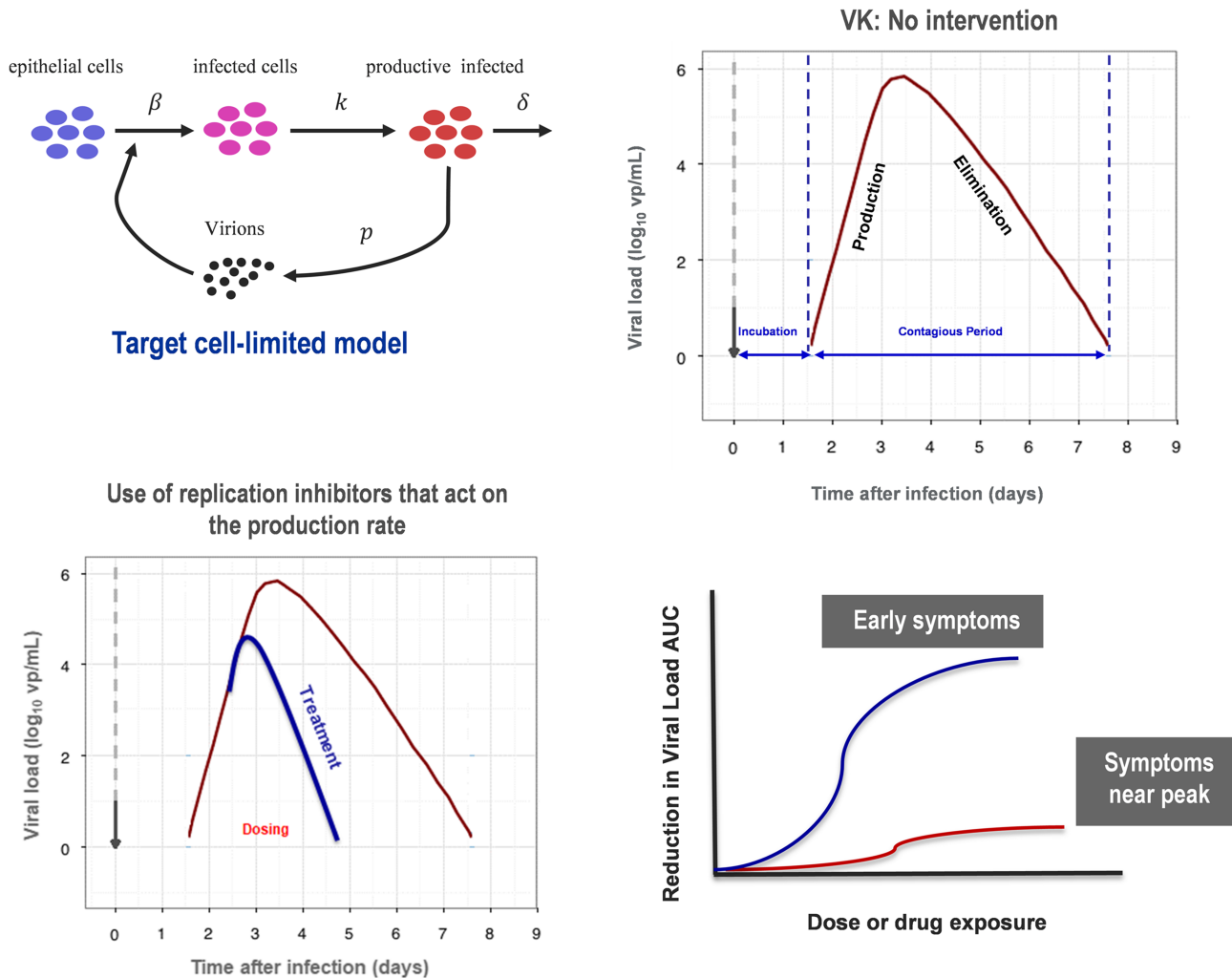


FIGURE 2 Schematic showing the relationship between peak viral load, symptom onset and possible exposure–response relationships AUC, area under the curve; VK, viral kinetics. Notes: The schematic presents the typical structure of a target cell-limited model (top left) with the expected viral kinetic profile in the absence of drug intervention (top right). Bottom panels illustrate the mechanism of action of viral replication inhibitors that act on the production rate (bottom left). If symptom onset and corresponding treatment occurs prior to the peak viral load, these replication inhibitors may produce a favourable exposure–response relationship (bottom right). In contrast, late symptom onset (at or near the peak viral load) is unlikely to provide viral load inhibition

seen with SARS-CoV-2), combination with replication inhibitors and immune modulators or other effectors of the viral life-cycle may be more effective, improving viral kill rates and enhancing infected cell clearance.^{16,17}

In the context of an emerging pandemic, mathematical modelling of viral infection dynamics (i.e., through a target-cell limited model) may help identify therapeutic strategies.¹⁸ These VK models can incorporate treatment effects that characterize the pharmacodynamic (PD) response profile of virus or downstream immune system and symptom effects.^{9,18} For NP, all kinetic components of the viral life-cycle (i.e., rates of infectivity, transition, infected-cell mortality, free virion production and virus elimination) should be considered potential target areas for drug therapy. For SARS-CoV-2, these activities suggest that targeting different stages of the viral life cycle yield different outcomes.¹⁶ Particularly, inhibiting the productivity of infected cells (e.g., using intracellular antivirals) and hastening infected cell death (e.g., using interferons) appear attractive targets.

In practice, VK models are developed and refined as information becomes available from the NP and can be useful to expedite the design of appropriate treatment designs. Simulation platforms can integrate VK models with RD PK models to generate viral response curves. Where RD concentration data are unavailable, kinetic-pharmacodynamic (K-PD) models may be used to characterize viral effect-time curves. These simulation tools probe the mechanism by which promising therapeutics may influence components of the viral life-cycle, aiding in decision making regarding which therapeutics to use at which times. Clinical trial simulations further establish the optimal time of initiation and duration of treatment, predicting the RD posology required to achieve the required level of potency and maximal effectiveness (Figure 1, Steps 2–3).

During the preparatory stage, platform-based simulation tools can be implemented that link a theoretical RD's PK, potency and mechanism-of-action (MoA) to a general class of VK model such as a target-cell-limited model¹¹ that is commonly used in the context of an acute infection. Simulation studies should be undertaken to study perturbations in the VK model (perhaps representing types of future NPs) and which MoA may be more or less effective against NPs with those characteristics. For example, simulations of the relationship between onset of symptoms and peak viral load, as discussed above, would help prioritize different MoAs and intervention timings. Updating the model with NP information as it unfolds is crucial to achieving predictive accuracy and can only take place in the responsive stage. Refining the NP VK model with the addition of clinical data allows assumptions to be replaced with data. For example, NP VK modelling may start with a general model with parameters fixed to assumed values. Model refinement via information addition leads to NP-specific parameter estimation and therefore RD ranking based on NP-specific therapeutic options. Finally, these simulations should be folded back into preparatory exercises for future pandemics. It is important to recognize that the optimal treatment MoA and timing for the next pandemic may be quite different.

2.5 | Step 4. Repurposed drug PK and novel pathogen clinical outcome data

Once the kinetics of the RD and the NP have been considered and evaluated, information gained from the aforementioned steps can be used to inform robust clinical trial designs that follow sound clinical pharmacology and model-informed principles. Furthermore, dose- and/or exposure-response analyses from these robust clinical trials can then be used to feed back into the previous steps. For this to occur effectively, informative virologic and clinical outcome measures need to be collected and rapidly returned for analysis and incorporation into the previously built models (Figure 1, Step 4).

Improving patients' morbidity and mortality is the key component of clinical efficacy when evaluating candidate therapeutics. For respiratory virus infections, a broad range of clinical endpoints may be considered. For example, in mild respiratory viral illnesses in ambulatory patients, endpoints could include individual symptom scores, temperature, tissue weight for nasal discharge or even oxygen saturation at room air,^{19,20} whilst in more severely ill patients endpoints could include time in ICU, need for mechanical ventilation and survival. Composite symptom scores for an NP may also be developed and validated during clinical development leading to a diversity of endpoints in clinical trials. See the recent publication by Dodd et al. on the statistical power for trial endpoints for COVID-19²¹ and Case Example 4 in the Supplementary Materials.

Knowledge about the NP VK must also be taken into account and linked to antiviral efficacy, specifically the alignment of peak-virus titre with symptom onset. Caution must be taken to avoid bias entering into analyses if there is imbalance in study interventions vs time since symptom onset. Viral kinetic parameters (area under the viral growth curve, slope of viral decline and log-change from baseline viral load) are all subject to influence of time since symptom onset. The right RD at the right time is critical for a clinical outcome to be informative.

The quantitative analytical approaches that can be applied are varied and dependent on the endpoints evaluated, and the form in which they are investigated. Importantly, endpoint analyses should be fit-for-purpose, depending on the nature of the data variables (continuous, discrete, ordinal and nominal) to be analysed and the intended clinical use of the intervention. Generally, dose-response (D-R) and exposure-response (E-R) approaches may boost information. Time-to-event analysis and longitudinal analysis, in general, offer richer information than landmark analysis.

It cannot be assumed that D-R and/or E-R determined for the RD's approved marketed indication(s) would be the same for the treatment of the NP. Clinical trials, informed by clinical pharmacology and model-informed principles (i.e., Steps 1–3) should evaluate dose, dose frequency, dose duration and endpoints in a way that identifies optimal dosing and parameters from both efficacy and safety. Well-designed dose-response studies using adaptive designs provide key safety information about the drug in the novel disease, and provide efficacy information and predictive biomarkers that can be pivotal in the submission of a supplemental new drug application.

Dose–response and/or E-R can be highly informative and, in an adequate and well-controlled clinical trial, can be considered pivotal. In the review process, the question of “do we have the right dose regimen” is of paramount importance, especially for drugs whose safety profile could impact decisions about risk–benefit.

Several layers of decisions are informed by MIDR. Dose/E-R modelling supports timing of dose start, dose selection and duration of therapy and the validation of endpoint selection. While these inform the optimal treatment for an individual, they also provide information on the percentage of the population that will require prophylaxis or treatment to reduce NP shedding in the community. Applying MIDR and linking time to cessation of viral shedding in patients with epidemiological and health economic models informs antiviral use in pandemics at the population level. These “pharmacology to payer” models could optimally position these repurposed antiviral treatment interventions for maximum “population health” benefit.²² Thus, the focus on virologic endpoints for both individual and population health elevates virologic endpoints alongside clinical endpoints when considering new therapeutics for NP pandemics.

One of the challenges to robust clinical trials is patient recruitment. As seen with the COVID-19 pandemic, the number of cases fluctuates from country to country as the pandemic progresses, which could result in prolonged or underpowered studies. In a special communication, Hartman *et al.* seek to address this through standardization of informative endpoints and accessibility to master protocols.²³ Therefore, in the preparatory stage, best practice and highly efficient trial designs or master template protocols should be developed, focusing on establishing optimal dosing of RDs and combinations of RDs (Table 1, Step 4). Without central organization and access to readily available protocols, disparate, non-comparative, unaligned and underpowered studies will spring up to fill that void, as seen throughout the COVID-19 pandemic. This dilutes information early in the pandemic and slows our understanding of the effect of the RD on the NP. A minimum set of core outcomes to guide decision making, prioritization and comparison of RDs could be put in place, similar to the work done by the COMET initiative during the COVID-19 pandemic.²⁴ During the responsive phase, efficient trials should be executed in a transparent manner and the results communicated quickly to shape new and adapt ongoing trials.²³ Finally, in the retrospective stage, trial design best practices should be updated based on the learnings from the pandemic and implemented in preparation for the next NP.

2.6 | Step 5. MBMA and clinical outcome data

As a pandemic progresses, clinical trials that evaluate drug interventions against the NP appear, and model-based meta-analysis (MBMA) approaches can be employed to maximize the information which emerges from them (Figure 1, Step 5). Initially, trials will focus on RDs, with trials of *de novo* anti-NP treatments (e.g., vaccines, novel antibody therapies, convalescent plasma) appearing later. Earlier trials are likely to be small, uncontrolled proof-of-concept studies in well-specified populations, with larger, confirmatory studies occurring later.

This variability in patient demographics and study conduct will further increase as the pandemic spreads. Moreover, the standard-of-care (SoC) will be geographically diverse and will evolve over time. The NP itself may also change (mutations, changes in virulence factors, differential effects by geography).

This creates a huge potential to obtain insights into the impact of drug treatment on the course of disease, vital signs and biomarkers. These insights help identify the likelihood of success of RD interventions and will also provide directions to increase the efficiency of future clinical trials. It may identify enriched populations for initial proof-of-concept trials, before embarking on larger studies in all-comer populations. It can also support efficient study design by providing accurate estimates of both treatment effect and variability (between or within trials) for adequate statistical power, and optimize treatment duration.

In order to provide a quantitative, probabilistic assessment of drug treatment effects, an adequate statistical analysis framework needs to be constructed. A network meta-analysis (NMA) of the data from multiple trials can address variability in offset of response (e.g., placebo, SoC) between trials and to identify indirect treatment effects of drug interventions (difference from offset) across trials. Risk factors that impact drug treatment effects may be identified in a subsequent network meta-regression analysis or MBMA.²⁵

The main opportunity of meta-analysis is the wealth of information from combining outcome data from many clinical trials, including numerical information (large number of trials, patients) and variability in relevant patient risk factors (covariates). Heterogeneity between trials is a common challenge in meta-analysis. Analysis strategies to address this include evaluating known/reported covariates (meta-regression analysis) or unknown/unreported drivers (random effects) of drug effect. This is particularly relevant in a pandemic situation like COVID-19, where many intervention studies are retrospective, non-randomized or even uncontrolled. With such variability between trials, it would be impossible to explicitly identify the effect of an intervention within one study. However, meta-analysis strategies developed to handle variability across uncontrolled studies in other indications such as oncology could be used here.^{26–28} Randomized controlled studies provide statistical control of variability between trials and can strengthen the assessment of treatment and risk factors. However, observational or cohort studies in a real-world setting may be more relevant, and using MBMA of a large and heterogeneous data set of clinical outcome data to evaluate correlations between endpoints could be more informative.

As with any data analysis strategy, the quality of the clinical trial outcome data is a key driver of the quality of the inferences obtained from the analysis. In the case of meta-analysis of published (aggregate) data, such control over the data quality may be limited. However, MBMA applies routine procedures as set out by guidances (e.g., PRISMA checklists^{29,30}), which include assessments of bias, often in the form of funnel plots. This minimizes the risk of bias in the estimated drug treatment effect, or of missing the potential of a promising repurposed drug, or unnecessarily exposing future patients to an ineffective drug.

Given the context of a pandemic, a time-efficient data science strategy that organizes and analyses the data, and evaluates the implications of the analysis results is needed. Much of these efforts can be accomplished in the preparatory stage (Table 1, Step 5). Likewise, analysis routines to standardize or automate NMA/MBMA could be developed. Clinical trial registries provide a global public source of trial data, which can only be performed in the responsive stage of the pandemic. Model-based simulations will translate these complex analyses into simple, meaningful implications that will facilitate decision making in the management of an NP. Timely dissemination of these results is important, and web-based graphical interfaces can provide this functionality. Finally, in the retrospective stage, MBMA analysis can assist future analysis and also comment on the effectiveness of clinical trial designs (Step 4) to enable crisp decision making.

3 | DATA QUALITY

Data quality and quantity are concerns in all stages of MIDR due to the time-sensitive nature of a pandemic. Early *in vitro* and *in vivo* studies are less likely to be generated under Good Laboratory Practice standards. Similarly, quality concerns regarding clinical trial data where restrictions to monitoring or data collection are to be expected. For example, patients may need to self-swab or conduct at-home sampling (e.g., via dried blood spots), or to visit a clinic less often to reduce transmission opportunities. Different assays, with differing sensitivities and specificities, may be used to measure PK and VK samples, some of which have not undergone adequate validation steps. The decrease in sample availability opens the door for model-based analyses, where fewer samples are collected from each patient, which can be pooled in an *in silico* analysis. Although quantitative modelling efforts are sensitive to the quality of data and sample collection should be optimized, *in silico* models can incorporate differences in experimental measurement (i.e., through residual error models). Model-based approaches can also utilize data from early stages of a pandemic to explore potential outcomes and the associated uncertainty. Weighting schemes can also be employed to address the variability in data quality, as seen in MBMA where studies are commonly weighted based on sample size. This could be expanded to *in vitro* or preclinical studies, where potency information from multiple data sources is weighted with consideration to data quality and validity, particularly as the quality of data improves throughout the duration of a pandemic. Importantly, as data quality improves and *in silico* models are refined, analyses which pool data from early and late stages of the pandemic could address these changes in a quantitative manner, and further guide decision making.

4 | DISCUSSION

Drug repurposing has the potential to identify effective treatments in an emerging pandemic while more specific treatments and preventions are developed. A five-step process of MIDR to screen and

prioritize compounds for use as a first response to an NP is suggested. Organized around the increasing level of information about the pandemic's pathogen, these steps are as follows.

In the early stages of a pandemic, little information is available and so what has worked before provides some guidance; treatments for similar viruses are considered, a similar life-cycle for the NP as other viruses in its class is assumed, and a priority list of compounds that might be effective (at least *in vitro*) are developed. This information is funnelled through to population PK and PBPK models that may be leveraged to adjust posology to meet acute treatment needs or special populations. As the pandemic spreads, the scientific community gains access to clinical viral isolates. Predictors of viral dynamics are determined by studying the NP. At the height of the pandemic, well-designed clinical trials with informative endpoints are executed. Results of these trials can be channelled into various modelling efforts, providing VK predictions, dose/E-R relationships, and posology recommendations, much of which can be fed back to updating and refining earlier models, and further refining clinical trial design. The pandemic is expected to move quickly, and MBMA can be used to handle incomplete data from many trials that, together, may paint a clearer picture of the disease and its weaknesses. The MIDR strategy proposed in this manuscript, will allow not only the retrospective evaluation of drug effects for drug repurposing, but will also allow tools and strategies to be developed in preparation for future pandemic events.

These steps can also be organized around implementation relative to the NP's emergence. Benjamin Franklin offered the advice that "an ounce of prevention is worth a pound of cure".²³ This axiom is assumed to relate to health, but in fact it was put forward as advocacy for fire awareness and prevention. More broadly, his advice relates to disaster preparedness and advocates, as do these authors, performing as much work as feasible ahead of the disaster.

Keys to success include setting up global alliances (examples for the current SARS-CoV-2 pandemic include the Accelerating COVID-19 Therapeutics Interventions and Vaccines [ACTIV] public-private partnership, covidpharmacology.com and COVID-19 Therapeutics Accelerator) and infrastructure prior to NP emergence (preparatory stage), streamlining the activities that must occur during an NP pandemic (responsive stage), and learning and confirming once the crisis has subsided (retrospective stage). Notably, much of the efforts described herein can (and should) be conducted in the preparatory stage, stripping the activities performed in the responsive stage down to the bare minimum.

In the preparatory stage, infrastructure and tools are developed. As outlined in Table 1, many activities can take place without regard to the NP. Relationships between laboratories can be established, so that once an NP is identified and clinical isolates are obtained, RD can be shipped immediately for Step 1 analysis. Investments can be made in physiologically based pharmacokinetic (PBPK) models, such that accurate predictions of RD concentrations at specific SOAs (Step 2) can be made once the NP's SOA is determined. Viral kinetic models can be implemented, and "what-if" scenarios can be considered for a variety of NP phenotypes (Step 3). Trial protocols can be developed,

particularly so-called “platform trials” within which multiple treatments are evaluated in parallel, and readied for deployment when an NP is identified (Step 4). The statistical framework for a network meta-analysis (NMA) or MBMA can be put in place without regard to the NP, facilitating Step 5 execution once trials are under way.

Steps in the responsive stage must be carried out rapidly after an NP is identified, as the utility of any repurposed drug must be assessed in the context of its ability to inhibit a specific event caused by the NP. These steps leverage work done in the preparatory stage to reduce time for data acquisition and afford the ability to rank candidates for repurposing. Aspects of Steps 1–5 occur in the responsive stage; the key is to front-load as much as possible into the preparatory stage to identify promising RD as quickly as possible.

In the retrospective stage, reflection suggests updates to preparatory activities seeking continuous improvement. This includes reviewing translatability of results (e.g., suitability of cell lines), updating models (popPK, E-R, VK), refining clinical outcome choices and streamlining study design (e.g., platform trial design).

5 | CONCLUSION

Model-informed drug repurposing has the ability to streamline treatment-to-patient decisions and logistics in response to a pandemic. By breaking the process into steps, the available information at any given stage is used to prioritize plausible treatments into clinic. Decision making and prioritization can be improved by integrating RD PK and in vitro data, NP VK, clinical endpoints and learnings from MBMA. This model-informed drug repurposing strategy provides a framework for an actionable, pharmacometric approach to novel pandemic preparedness, response and retrospection.

ACKNOWLEDGEMENT

This work has been supported and funded by the Bill and Melinda Gates Foundation.

COMPETING INTERESTS

At the time of writing and submission, M.D., Y.X., S.M., E.D., K.P., E.C., D.W., F.B. and C.R.R. work for, and are remunerated (some holding stock) by Certara, a consulting firm in integrated drug development, and have directly consulted with a variety of not-for-profit global health organizations, biotechnology, pharmaceutical companies and governments with an interest in medical countermeasures against respiratory virus infections. K.H. is a fellow funded by Certara and MTPConnect. C.M.K. is an employee of Monash University and has consulted with industry and governments in the area of respiratory viruses.

CONTRIBUTORS

All authors were involved in the concept development, and application, of the MIDR approach during the recent COVID-19 pandemic. M.D., C.M.K., K.H. and E.D. were involved in the initial drafting of the overall manuscript. S.M. and C.K. were involved in the drafting of Step

1. Y.X. was involved in the drafting of Step 2. K.P. was involved in the drafting of Step 3. C.R., D.W. and F.B. were involved in the drafting of Step 4. E.C. was involved in the drafting of Step 5. All authors were involved in important intellectual revision and final manuscript writing and submission, response to reviewers and approval of the completed manuscript.

ORCID

Carl M. Kirkpatrick  <https://orcid.org/0000-0002-5715-1534>

Kashyap Patel  <https://orcid.org/0000-0002-8790-906X>

Craig R. Rayner  <https://orcid.org/0000-0001-7755-6419>

REFERENCES

1. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*. 2019;18(1):41-58. <https://doi.org/10.1038/nrd.2018.168>
2. Morgan P, Van Der Graaf PH, Arrowsmith J, et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov Today*. 2012;17(9-10):419-424. <https://doi.org/10.1016/j.drudis.2011.12.020>
3. Baker EH, Gnjidic D, Kirkpatrick CMJ, Pirmohamed M, Wright DFB, Zecharia AY. A call for the appropriate application of clinical pharmacological principles in the search for safe and efficacious COVID-19 (SARS-CoV-2) treatments. *Br J Clin Pharmacol*. 2020. <https://doi.org/10.1111/bcp.14416>
4. Morrisette T, Lodise TP, Scheetz MH, Goswami S, Pogue JM, Rybak MJ. The pharmacokinetic and pharmacodynamic properties of hydroxychloroquine and dose selection for COVID-19: putting the cart before the horse. *Infect Dis Ther*. 2020;9:561-572. <https://doi.org/10.1007/s40121-020-00325-2>
5. Peña-Silva R, Duffull SB, Steer AC, Jaramillo-Rincon SX, Gwee A, Zhu X. Pharmacokinetic considerations on the repurposing of ivermectin for treatment of COVID-19. *Br J Clin Pharmacol*. 2020. <https://doi.org/10.1111/bcp.14476>
6. Bray M, Rayner C, Noël F, Jans D, Wagstaff K. Ivermectin and COVID-19: a report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Res*. 2020;178:104805. <https://doi.org/10.1016/j.antiviral.2020.104805>
7. Gonçalves A, Bertrand J, Ke R, et al. Timing of antiviral treatment initiation is critical to reduce SARS-CoV-2 viral load. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(9):509-514. <https://doi.org/10.1002/psp4.12543>
8. Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature*. 2020;585:584-587. <https://doi.org/10.1038/s41586-020-2558-4>
9. Canini L, Carrat F. Population modeling of influenza A/H1N1 virus kinetics and symptom dynamics. *J Virol*. 2011;85(6):2764-2770. <https://doi.org/10.1128/jvi.01318-10>
10. Ferguson N, Cummings D, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature*. 2005;437:209-214. <https://doi.org/10.1038/nature04017>
11. Baccam P, Beauchemin C, Macken CA, Hayden FG, Perelson AS. Kinetics of influenza A virus infection in humans. *J Virol*. 2006;80(15):7590-7599. <https://doi.org/10.1128/jvi.01623-05>
12. DeVincenzo JP, Wilkinson T, Vaishnav A, et al. Viral load drives disease in humans experimentally infected with respiratory syncytial virus. *Am J Respir Crit Care Med*. 2010;182(10):1305-1314. <https://doi.org/10.1164/rccm.201002-0221OC>
13. El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, DeVincenzo JP. Respiratory syncytial virus load, viral dynamics, and disease severity

- in previously healthy naturally infected children. *J Infect Dis.* 2011; 204(7):996-1002. <https://doi.org/10.1093/infdis/jir494>
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
 15. Zhou B, She J, Wang Y, Ma X. Duration of viral shedding of discharged patients with severe COVID-19. *Clin Infect Dis.* 2020;71(16):2240-2242. <https://doi.org/10.1093/cid/ciaa451>
 16. Dodds MG, Krishna R, Goncalves A, Rayner CR. Model-informed drug repurposing: viral kinetic modeling to prioritize rational drug combinations for COVID-19. *Br J Clin Pharmacol.* 2020. <https://doi.org/10.1111/bcp.14486>
 17. Patel K, Dodds M, Gonçalves A, et al. Using in silico viral kinetic models to guide therapeutic strategies during a pandemic: an example in SARS-CoV-2. *Br J Clin Pharmacol.* 2020. <https://doi.org/10.1111/bcp.14718>
 18. Canini L, Perelson AS. Viral kinetic modeling: state of the art. *J Pharmacokinetic Pharmacodyn.* 2014;41(5):431-443. <https://doi.org/10.1007/s10928-014-9363-3>
 19. Nicholson KG, Aoki FY, Osterhaus A, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet.* 2000;355(9218):1845-1850. [https://doi.org/10.1016/S0140-6736\(00\)02288-1](https://doi.org/10.1016/S0140-6736(00)02288-1)
 20. DeVincenzo JP, McClure MW, Symons JA, et al. Activity of oral ALS-008176 in a respiratory syncytial virus challenge study. *N Engl J Med.* 2015;373(21):2048-2058. <https://doi.org/10.1056/NEJMoa1413275>
 21. Dodd LE, Follmann D, Wang J, et al. Endpoints for randomized controlled clinical trials for COVID-19 treatments. *Clin Trials.* 2020;17(5):472-482. <https://doi.org/10.1177/1740774520939938>
 22. Kamal MA, Smith PF, Chaiyakunapruk N, et al. Interdisciplinary pharmacometrics linking oseltamivir pharmacology, influenza epidemiology and health economics to inform antiviral use in pandemics. *Br J Clin Pharmacol.* 2017;83(7):1580-1594. <https://doi.org/10.1111/bcp.13229>
 23. Hartman D, Heaton P, Cammack N, et al. Clinical trials in the pandemic age: What is fit for purpose? *Gates Open Res.* 2020;4(58). <https://doi.org/10.12688/gatesopenres.13146.1>
 24. Comet Initiative. Core outcome set developer's response to COVID-19. Secondary core outcome set developer's response to COVID-19 2020. <https://www.comet-initiative.org/Studies/Details/1538>
 25. Mandema JW, Gibbs M, Boyd RA, Wada DR, Pfister M. Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond. *Clin Pharmacol Ther.* 2011;90(6):766-769. <https://doi.org/10.1038/clpt.2011.242>
 26. Stroh M, Green M, Cha E, Zhang N, Wada R, Jin J. Meta-analysis of published efficacy and safety data for docetaxel in second-line treatment of patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol.* 2016;77(3):485-494. <https://doi.org/10.1007/s00280-015-2957-7>
 27. Leahy J, Thom H, Jansen JP, et al. Incorporating single-arm evidence into a network meta-analysis using aggregate level matching: assessing the impact. *Stat Med.* 2019;38(14):2505-2523.
 28. Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. *Res Synth Methods.* 2020;11(3):443-456.
 29. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
 30. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Dodds M, Xiong Y, Mouksassi S, et al. Model-informed drug repurposing: A pharmacometric approach to novel pathogen preparedness, response and retrospection. *Brit Jnl Clinical Pharma.* 2021;87(9):3388-3397. <https://doi.org/10.1111/bcp.14760>