SRA 2020 Symposium Proposal: Data and models for dose-response relationships for SARS-CoV-2

Jointly Sponsored by Dose-Response and Microbial Risk Analysis Specialty Groups

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Symposium Description

Knowledge of relationships governing human responses to viral pathogens continues to accumulate for the COVID-19 pandemic caused by a novel corona virus (SARS-CoV-2). A tremendous amount of data on pandemic cases was made available very quickly worldwide through preliminary manuscripts and expedited commentaries and journal review processes. Some full-text open-source studies provide raw data estimating viral loads for a few individuals from hospital admission through recovery using reverse transcription polymerase chain reaction (RT-PCR) and droplet digital PCR (ddPCR). However, sparse information is provided characterizing method performance for many studies, particularly unspecified limits of detection and quantitation critical to evaluating dose-response relationships across studies. Four perspectives relevant to dose-response assessment are emphasized by the invited speakers. First, the available data on animal dose-response models from a previous pandemic caused by a related corona virus is introduced. Next, available data from the NY City metropolitan area will be examined in light of dose-severity effects. Third, a summary is presented for the available data in the literature on viral loads of SARS-CoV-2 over time, including meta-data from a data-call-in administered through QMRA Wiki. The symposium closes with a presentation of data and analysis of time- and dose-dependent severity for SARS-CoV-2. To encourage wider deliberation of the data, analyses, and implications for microbial risk analysis, a Round Table Panel discussion will follow and a perspectives article will be prepared for submission to Risk Analysis.

Speakers	**Affiliations**	**Titles**
1. Mark Weir	Ohio State University	Assessment of the Dose-Response and its Use for Quantifying Safe Shift Procedures for Healthcare Workers During the COVID-19 Pandemic
2. Madeline Lewis and Mark Weir	Ohio State University	Exploratory Modeling of Cumulative Dose Exposure to Determine Impacts on Severity of Outcome for COVID-19
3. Jade Mitchell	Michigan State University	Meta-data uploaded on QMRA Wiki for dose-response assessment of SARS-CoV-2 viral loads documented in human cohorts
4. Peg Coleman and Gene McClellan	Coleman Scientific Consulting and Applied Research Associates	Human data for time- and dose-dependent severity of SARS-CoV-2

Speakers	Title and Abstract
1. Mark Weir	**Assessment of the Dose-Response and its Use for Quantifying Safe Shift Procedures for Healthcare Workers During the COVID-19 Pandemic** **Background:** The COVID-19 pandemic has demonstrated a significant lack of preparedness, sustainability and resiliency in our healthcare and public health systems. Part of this is a lack of knowledge on the best and most protective means of healthcare worker shifts during surge and non surge conditions. Therefore, we have developed a QMRA model to simulate working conditions within surge and non surge settings to determine what a "safe shift" is computationally. **Methods:** We used preexisting data on healthcare worker movement to model what surfaces they come in contact with during their time in a patient room. From these data we optimized a discrete time Markov chain to simulate their movement and surface contacts in the room. We then assessed healthcare worker risks based on proper and improper PPE doffing and hand-washing compliance. We developed a candidate does response from pooled coronavirus data to assess the risks. **Results and Discussion**: Our results demonstrate that based on the best available dose-response with limited data, that healthcare worker safety can become a major concern during surge conditions. Further to abate these risks, PPE doffing and hand hygiene compliance are vital. Further we show that simple adjustments to the behavioral modeling component of the exposure model, that a wide array of simulations can be developed and automated in R. **Conclusions and Implications:** Whilst it sounds simple to recommend hand hygiene and PPE compliance these are vital notes and recommendations. PPE compliance is not a simple task especially when healthcare workers are fatigued and may forget a step in PPE doffing compliance. Further hand hygiene compliance rates in general are quite low, and can easily be forgotten. This means that something as simple as a communication and education or compliance monitoring and assessment campaign can be health protective.
2. Madeline Lewis and Mark Weir	**Exploratory Modeling of Cumulative Dose Exposure to Determine Impacts on Severity of Outcome for COVID-19** **Background:** Human hosts are not exposed to single bolus doses such as those used in dose- response experiments, but rather cumulative exposures of typically smaller doses. Therefore using this knowledge and prio r cumulative dosing data for another pathogen, we present a concept for a model that can assess likely exposure locations and cumulative dose exposure based on epidemiological data. Further, such a modeling framework can allow for a connection between mechanistic risk modeling and epidemiological risk modeling. **Methods:** We simulate a spectrum of severe and moderate cases of COVID- 19 in an urban population. From this simulated population and using the candidate dose- response model, we simulate the likely dose that this synthetic population was exposed to. Then from this likely dose, we use knowledge and models of environmental contamination and exposure to simulate the likely sets of doses that lead to that cumulative dose. **Results:** Results are still developing, but are expected to be an outline of likely exposure that an urban population such as in NYC would have developed a cumulative dose of SARS- CoV- 2. These results will be presented appropriately as synthetic data from a simulated population. Therefore, a major component of the results that we are focusing on is the uncertainty and variability of the estimates and model variables. **Conclusions/Discussion:** Because the pandemic is developing as we are learning more about outbreaks with severe outcomes outside the known pre- existing conditions and age groups, this type of exploratory modeling is needed. This allows us to experiment in- silico with multiple social distancing and environmental controls outside of lock down methods. Further, due to the issues agent based and epidemiological model can have converging with mechanistic risk modeling, this method will be a value added to the field.

3. Jade Mitchell	**Meta-data uploaded on QMRA Wiki for dose-response assessment of SARS-CoV-2 viral loads documented in human cohorts** **Background:** Crowdsourcing has evolved over the past decade to address a number of societal issues. At the same time pressures from public funding agencies and peer-reviewed publication requirements have necessitated better data management and sharing from researchers. Data repositories exists in many well-established subjects for specific data-types. However, such methods or sources have not been widely utilized in risk assessment especially for dose-response data. COVID19 highlights both a need and opportunity implement such methods. **Methods:** The QMRAWiki (qmrawiki.org) was developed as a knowledge repository for microbial risk assessment and has been instrumental in provided archival dose-response data and models. In order to support, the understanding of the dose-response relationship for SARS-CoV-2, a data-call was issued via the QMRAWiki to quickly assemble data sets for meta-analysis. Data was requested to evaluate viral loads in patients tested for COVID19 by blood serum with additional meta data. **Results and Discussion:** This talk will discuss the quantity and quality of data obtained using this method; its value for understanding the dose-response relationship for SARS-CoV-2; and challenges and methods for synthesizing disparate data. We will also present remaining needs and approaches to standardize collection of certain data types to make such analysis more feasible. **Conclusions and Implications:** The success of this approach and lessons learned for future crowdsourcing and data sharing for rapid meta-analyses in microbial risk modeling will be discussed.
4. Peg Coleman and Gene McClellan	**Human data for time- and dose-dependent severity of SARS-CoV-2** **Background**: The WHO reported crude fatality ratios that varied greatly both temporally and spatially in the 2020 pandemic (range in China from 21.9% in the most susceptible population near the epicenter of the first outbreak in Wuhan to 0.7% elsewhere in China). Fatality estimates were influenced by local scenarios documented in generally small cohorts of cases admitted to major hospitals around the world (including Beijing, Hong Kong, and Nanchang, China; Munich, Germany; Seoul, Korea). **Methods**: Data for viral load and biomarkers of disease severity over time were obtained from published studies and from meta-data provided through the data-call-in via QMRA Wiki. Study-specific and pooled data were analyzed for time- and dose-dependencies building on prior approaches for aerosols of a bacterial pathogen and other microbial dose-response studies. **Results**: Multiple patient cohort studies reported positive correlations between mean viral load upon admission and disease severity. One study quantified significantly higher mean viral loads in nasopharyngeal swab samples from 30 severe cases compared to those from 46 mild cases ($p<0.00001$, Mann-Whitney test). Results of such individual studies will be extended by established dose-response assessment methods using meta-data obtained from the data-call-in. **Interpretation**: Quantitation of viral load is a useful biomarker for severe disease. Further characterization of dose- and time- dependencies using established dose-response assessment approaches can enhance reliability of early diagnostics and assist in prioritizing/optimizing therapeutic interventions to prevent severe disease outcomes. Such integrated knowledge is essential to understanding viral dynamics and managing responses so that outbreak curves around the world flatten and decline with minimal secondary waves of transmission as social distancing controls are relaxed.