CROWN CORONATION: COVID-19 Research Outcomes Worldwide Network for CORONA virus mitigation

An international, multi-site, Bayesian platform adaptive, randomized, placebo-controlled trial assessing the effectiveness of candidate interventions in mitigating COVID-19 disease in healthcare workers.
What is the CROWN collaborative?

- An international, transdisciplinary, research network, established to assess rigorously and efficiently promising interventions for COVID-19

- Using a Bayesian, pragmatic, participant-level randomized, multi-center, and international placebo-controlled platform trial, assess candidate interventions that either
  - modify the host immune response or

- **Outcome**: prevention of symptomatic COVID-19 by using combinations of approved and safe agents, with complementary mechanisms of action.
An international network

Funded by the COVID-19 Therapeutics Accelerator
Why prophylaxis?

- SARS CoV2 is a significant threat to public health
  - No prior immunity
  - Rapid transmission
  - Wide spectrum of disease with potential for severe outcomes

- Limited proven pharmacological interventions
- Efforts underway to develop a specific vaccine but 1-2 years before roll out
- Need interventions that can be scaled up to at-risk populations
Why health care workers?

- HCWs are vulnerable to COVID-19 infection due to occupational exposure
  - Repeated exposures
  - Size of inoculum
  - Travel to and from work
  - PPE not infallible

- Potential for devastating impacts on already frail health care systems in LMIC
  - E.g. Ebola crisis in W. Africa
A pivot away from Chloroquine

- Concerns about futility rather than safety
- Several NDAs cancelled CQ trials
- NHP and animal model data suggested no in vivo activity
- In vitro data suggests cell type may be important for entry into cells
- Very small protective effects in two PEP trials
- Potential interaction with remdesivir
A novel platform trial approach

PROGRESSION OF CROWN CORONATION PLATFORM

ADDITION OF AGENTS IN FULL-FACTORIAL DESIGN

STAGE 1:
A) Live attenuated vaccine (MMR/MR) vs placebo injection

STAGE 2:
A) MMR/MR vs placebo injection
B) Antiviral-X (e.g. Nitazoxanide) vs placebo
C) Antiviral-X PLUS MMR/MR vs placebo

STAGE 3:
A) MMR/MR vs placebo injection
B) Antiviral-X vs placebo
C) Antiviral-X PLUS MMR/MR vs placebo
D) Antiviral-Y vs placebo
E) Antiviral-Y PLUS MMR/MR vs placebo
F) Antiviral-Y PLUS Antiviral-X vs placebo
G) Antiviral-Y PLUS Antiviral-X PLUS MMR vs placebo
Selecting potential interventions

Vs. either the virus or the host response with the goal to prevent infection or mitigate severity of disease
MMR vaccine - rationale

- Non-specific effect of live attenuated vaccines lead to reduced all-cause mortality benefit of specific prevention

Cross-reactive protection (antigen mediated function of adaptive immune system)

Trained immunity (augmentation of innated immune system)

Exposure-induced tolerance (inhibition of inappropriate inflammatory response)

Trained innate immunity

Unchallenged cells: Limited responses to infection

- Pattern recognition receptor
- Resting metabolic activity
- Glucose → Pyruvate → ATP
- Acetyl-CoA
- Oxaloacetate → Citrate
- Succinyl-CoA → α-KG
- TCA cycle

Closed chromatin: Little accessibility
- Low gene expression

Trained immunity: Enhanced responses to infection

- Stimulus that induces trained immunity
- Increased metabolic activity
- Glucose → Lactate → ATP
- Cholesterol synthesis
- Lipid synthesis
- Glutamine
- Acetyl-CoA → Oxaloacetate → Citrate
- TCA cycle

Open chromatin: High accessibility
- Enhanced gene expression

EPIGENETIC REPROGRAMMING – Transcription factors and genes for immune response are more readily accessible subsequent to first challenge.

FUNCTIONAL REPROGRAMMING – Metabolic pathways remain upregulated beyond response to first challenge.

Netea MG, et al. Cell 2020 May 4
Exposure-induced tolerance

- Non-specific effect of live attenuated vaccines lead to reduced all-cause mortality benefit of specific prevention
MMR – evidence vs. SARS CoV2

- Observed lower prevalence in children <10 years
- Observed lower disease severity in vaccinated naval recruits
- Ecological associations between areas of MMR use and COVID19 severity
- Induced rubella antibodies from vaccination correlate inversely with severity in those hospitalised
Why a non-specific vaccine?

- Inexpensive
- Readily available
- Simple to administer – no adherence requirements
- Safe and well-tolerated

- Potential to be used in combination with specific vaccines?
A novel platform trial approach

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G) Antiviral-Y PLUS Antiviral-X PLUS MMR vs placebo
Considerations for selecting agents for chemoprophylaxis

Safety profile
Adherence
Cost
Access
Scalability

Modified from Guy RK et al. Science 22 May 2020
Conclusions

• SARS CoV2 is a novel coronavirus that poses a significant ongoing threat to public health

• Prophylaxis remains an important strategy as a bridge to SARS CoV2 specific vaccine development and deployment

• Repurposing drugs and interventions provides an opportunity to identify and deploy interventions for high risk populations rapidly

• The CROWN Coronation platform trial is an agile approach that uses a novel adaptive design to generate robust data about potential prevention interventions

... we look forward to launching in SA in the coming weeks!
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