What Should Pathogen X Antiviral TPP Look Like?  
A clinician’s perspective  

WHO Meeting: Scientific strategies from recent outbreaks to help us prepare for Pathogen X  
August 29-30, 2022  

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Typical Target Product Profile (TPP) Considerations

1. Indication for use
2. Target population
3. Safety/tolerability
4. Efficacy
5. Treatment regimen
6. Route of administration
7. Product stability and storage
8. Interactions
9. Formulation
10. Accessibility
11. Registration and prequalification
Pathogen X: Draw on Recent Challenges

- Ebola
  - Contact, significant symptomatic rate, high mortality

- Zika
  - Vector born, teratogenicity

- SARS-CoV-2
  - Droplet, asymptomatic, 90+% do well, increased mortality in sub-groups
  - Non-infectious consequences – immune dysregulation, thrombosis

- Monkeypox
  - Contact, low mortality

- How novel is pathogen X?
  - Do we have experience and knowledge for the pathogen’s family?

Rothe C et al., *NEJM* 30Jan 2020
Defining Illness Pattern

When in Illness will an intervention have impact and on what?

- Prophylaxis
  - Pre-exposure prophylaxis (PrEP)
- Pre-emptive
  - Post-exposure prophylaxis (PEP)
- Empiric
- Treatment
  - Early
  - Late
- Transmission
Properties of the Therapeutic Product

Examples from SARS-CoV-2

- Prevention
  - Vaccines
- Treatments
  - Antivirals
    - Monoclonal antibodies
    - Small molecules
- Host modifiers
Forecasting mAb Utility
Integrate Several Lines of Evidence

• Pathogen and Variant of Concern (VOC)
• *in vitro* activity of mAb
• PK/PD of mAb
• Clinical safety data
• Clinical efficacy data
  • In general vs against the specific VOC
  • Tempo of availability
In 1929 Finland was asked by Dr. Nye to join his laboratory at the Thorndike. Thus began one of the most remarkable careers in the field of infectious diseases. The first studies conducted by Max and his associates dealt with pneumonia. At that time the only treatment for pneumococcal pneumonia was administration of type-specific antiserum. The process of treating patients was cumbersome, to say the least. A naso-pharyngeal swab was taken and placed in a tube containing culture medium. After a few hours of incubation when enough bacteria had proliferated, material from the culture was exposed to type-specific antisera. If there was a match between the antiserum and the chemical composition of the polysaccharide on the surface of the bacterium, the capsule would swell and it could be seen with an ordinary light microscope (known as the Quellung reaction). If Quellung occurred, the corresponding antiserum (horse or rabbit) was administered to the patient. The patients usually survived the infection, but they invariably suffered from serum sickness, which could be most unpleasant. Finland and his fellows did a series of studies on the treatment of pneumococcal infection conducted with meticulous care, a hallmark of Finland’s research throughout. When sulfonamides became available
Remdesivir

- **Gilead: Compassionate use** — NEJM 10Apr20
  - N=61, open label, hospitalized, hypoxemic. LD200/100mg for 9days

- **NIAID-ACTT-1** — NEJM 22May (prelim) and 5Nov20
  - N=1062, RCT-pbo, LD200/100mg 9days, hospitalized
  - **Time to recovery** —median 10 vs 15 days

- **Gilead: 5 or 10 days, Severe Covid** -- NEJM 27May2020
  - N=397, Randomized, open-label, hospitalized no IMV
  - Clinical status improvement d14 – 64% in 5D vs 54% in 10D

- **Gilead: 5 vs 10 days vs pbo, Moderate Covid** — JAMA 21Aug2020
  - N=596, RCT-pbo, hospitalized, O2>94%, LD200/100 for 5 or 10d (median 6d)
  - Clinical status d11 – 5d>pbo, 10d~pbo

- **WHO-Solidarity: Inpatient** — NEJM 11Feb2021, Lancet 02May2022
  - N= 2750 remdesivir (10d)+2708 SOC, RCT-SOC, hospitalized, moderate Covid
  - **Mortality** – 11.0% (14.5%) vs 11.1% (15.6%)

- **PineTree: Outpatient** — NEJM 27Jan2022
  - N=562, RCT, LD200/100 2days. Outpatients
  - Hospitalization/death – 0.7% vs 5.3%
Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients


Figure 1
Incidence of Hospitalization or Death Through Day 29 by Subgroup (Protocol 002 – Full Population)

<table>
<thead>
<tr>
<th>Baseline Antibody Status</th>
<th>Molnupiravir (N=709)</th>
<th>Placebo (N=699)</th>
<th>Risk Difference* (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>5/136</td>
<td>2/146</td>
<td>2.3 (-1.7, 7.1)</td>
<td>0.326</td>
</tr>
<tr>
<td>Negative</td>
<td>39/541</td>
<td>64/520</td>
<td>-5.1 (-8.8, -1.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Figure 2
Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population

Figure 13
Incidence of Hospitalization or Death Through Day 29 MITT Population (P002 Phase 3 IA)

6.8 percentage point reduction

95% CI: 2.4, 11.3

p=0.0012

Table 1
Efficacy Results in Non-Hospitalized Adults with COVID-19 (Protocol 002 – Full Population)

<table>
<thead>
<tr>
<th></th>
<th>Molnupiravir (N=709)</th>
<th>Placebo (N=699)</th>
<th>Risk Difference* (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospitalization or death through Day 29</td>
<td>48 (6.8)</td>
<td>68 (9.7)</td>
<td>-3.0 (-5.9, -0.1)</td>
<td>0.0218</td>
</tr>
<tr>
<td>Hospitalization†</td>
<td>48 (6.8)</td>
<td>67 (9.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.1)</td>
<td>9 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown‡</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Talbye, B.S.N., Anise Gardner, M.P.H., M.S.P.T., Paula Almu, Ph.D., Wei-Yang Sun, Ph.D., Wayne Womack, M.D., Maryam Baradk, Ph.D., Victoria M. Hendrik, M.S.C., Bharat Daru, Ph.D., Abraham Simon-Campos, M.D., Rishi Poppida, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-CHR Investigators

A. Outcomes According to Time Since Onset of Covid-19 Symptoms

<table>
<thead>
<tr>
<th>Treated ≤3 days after Onset of Symptoms (modified intention-to-treat population)</th>
<th>Treated ≤5 days after Onset of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nirmatrelvir + ritonavir</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Patients with event — no. (%)</td>
<td>5 (0.72)</td>
</tr>
<tr>
<td>Hospitalization for Covid-19</td>
<td>5 (0.72)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0</td>
</tr>
<tr>
<td>Average time at risk for event — days</td>
<td>27.29</td>
</tr>
<tr>
<td>Average follow-up — days</td>
<td>27.43</td>
</tr>
<tr>
<td>Estimated percentage with event (95% CI) — %</td>
<td>0.72 (0.30 to 1.73)</td>
</tr>
<tr>
<td>Difference (AE) from placebo — percentage points</td>
<td>-3.81 ± 1.01</td>
</tr>
<tr>
<td>95% CI of difference</td>
<td>-7.78 to -3.84</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

B. Covid-19-Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset

C. Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nirmatrelvir + ritonavir</th>
<th>Placebo</th>
<th>Difference from Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8/1039</td>
<td>66/1046</td>
<td>-5.62 (-7.21 to -4.03)</td>
</tr>
<tr>
<td>Time since symptom onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 days</td>
<td>5/897</td>
<td>44/882</td>
<td>-5.81 (-7.78 to -3.84)</td>
</tr>
<tr>
<td>≥4 days</td>
<td>3/142</td>
<td>22/164</td>
<td>-5.22 (-7.91 to -2.55)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>7/908</td>
<td>46/900</td>
<td>-4.35 (-5.91 to -2.79)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>1/131</td>
<td>20/137</td>
<td>-13.99 (-20.07 to -7.90)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4/520</td>
<td>41/540</td>
<td>-6.95 (-8.32 to -5.58)</td>
</tr>
<tr>
<td>Female</td>
<td>4/519</td>
<td>25/506</td>
<td>-4.28 (-6.79 to -2.16)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>1/209</td>
<td>9/207</td>
<td>-3.88 (-4.83 to -0.94)</td>
</tr>
<tr>
<td>25 to ≤30</td>
<td>3/438</td>
<td>28/466</td>
<td>-5.68 (-7.75 to -3.63)</td>
</tr>
<tr>
<td>≥30</td>
<td>4/371</td>
<td>29/373</td>
<td>-6.60 (-8.82 to -4.37)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2/121</td>
<td>13/127</td>
<td>-5.51 (-10.51 to 0.52)</td>
</tr>
<tr>
<td>No</td>
<td>6/913</td>
<td>57/919</td>
<td>-5.64 (-10.30 to -0.90)</td>
</tr>
<tr>
<td><strong>Relative SARS-CoV-2 serology status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>7/487</td>
<td>59/505</td>
<td>-10.25 (-15.28 to -5.21)</td>
</tr>
<tr>
<td>Positive</td>
<td>2/740</td>
<td>58/57</td>
<td>-1.34 (-2.45 to -0.23)</td>
</tr>
<tr>
<td><strong>Recombinant-insect-derived SARS-CoV-2 monoclonal antibody treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1/70</td>
<td>7/69</td>
<td>-1.51 (-6.40 to 3.37)</td>
</tr>
<tr>
<td>No</td>
<td>8/1039</td>
<td>66/1046</td>
<td>-5.62 (-7.21 to -4.03)</td>
</tr>
</tbody>
</table>
Reflections

- **Determine risk/benefit ratio of the novel therapy in different clinical settings**
- Must rapidly define key aspects of the biology of pathogen X to determine prevention/treatment opportunities
- Need to carefully consider what we want the intervention to do
  - Preventing mortality, overwhelming of healthcare system - important
  - Impact on illness and transmission - worthy
- Must (re-)define efficacy as epidemic parameters change over time
- Leverage emerging biotechnological advances
  - Diagnostics, mAbs, pre-clinical models
- Understand scalability
  - In a timeframe relevant to the speed of the pathogen
- Develop a global regulatory framework
- Must be globally deployable
  - Develop local capacity